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European Journal of Endocrinology Prize Winner

The *European Journal of Endocrinology* Prize is awarded to a candidate who has contributed significantly to the advancement of knowledge in the field of endocrinology through publication. This year's recipient is Dr Miguel Lopez who will receive his prize and deliver his lecture as part of the ECE 2017 Opening Ceremony on Saturday 20 May 2017. Further information on the prize can be found at http://www.ese-hormones.org/prizes/.

Dr. Miguel López received his PhD in Molecular Biology (2002) from the University of Santiago de Compostela (USC, Spain) and made his postdoctoral training (2002–2006) in the Department of Clinical Biochemistry in the University of Cambridge (UK). Currently, Dr. Miguel López is Associate Professor in Department of Physiology at the School of Medicine and the Research Centre of Molecular Medicine and Chronic Diseases (CIMUS) of USC. Since the beginning of his PhD, he has focussed his research on the regulation of energy balance and obesity, with his current interest on hypothalamic energy sensors in the modulation of energy balance and metabolism. He has published around 150 peer-reviewed papers. He currently serves on the editorial board of *Endocronology, Journal of Molecular Endocrinology, Molecular Metabolism, Journal of Endocrinology*, several *Frontiers journals* and *PLoS ONE*, and as a reviewer for several international biomedical journals and funding agencies. For his work in this area, Dr. López received the awards for Basic Research in Obesity from *Spanish Endocrinology and Nutrition Society* (*SEEN*, 2006 and 2009) and the *Spanish Society for the Study of Obesity* (*SEEDO*, 2009), *Spanish Award on Neuroendocrinology* (2012), as well as the *European Association for the Study of Obesity* (*EASO*) Young Investigator Award for Basic Science (2008; first Spanish citizen to be awarded with that price) and the *European Journal of Endocrinology Prize* for the *European Society of Endocrinology* (2017). He has been PI of 12 national and international grants, among them an *ERC Starting Grant*. He teaches Endocrinology in the Schools of Medicine and Pharmacy of USC. He has supervised 14 Master Thesis and 10 PhD Thesis.

The European Journal of Endocrinology Prize Lecture

EJE1

Hypothalmic AMPK: a golden target against obesity?

Miguel López
Spain.

AMP-activated protein kinase (AMPK) is a cellular gauge that is activated under conditions of low energy, increasing energy production and reducing energy waste. Centrally, the AMPK pathway is a canonical route regulating energy homeostasis, by integrating peripheral signals, such as hormones and metabolites, with neuronal networks. Current evidence links hypothalamic AMPK with feeding, brown adipose tissue (BAT) thermogenesis and browning of white adipose tissue (WAT), as well as muscle metabolism, hepatic function and glucose homeostasis. The relevance of these data is interesting from a therapeutic point of view since several agents with potential anti-obesity and/or antidiabetic effects, some currently in clinical use, such as nicotine, metformin and liraglutide are known to act through AMPK, either peripherally or centrally. Furthermore, the orexigenic and weight-gaining effects of the worldwide use of antipsychotic drugs, such as olanzapine, are also mediated by hypothalamic AMPK. Overall, this evidence makes hypothalamic AMPK signaling an interesting target for drug development, with its potential for controlling both sides of the energy balance equation, namely feeding and energy expenditure via defined metabolic pathways.

DOI: 10.1530/endoabs.49.EJE1

Geoffrey Harris Prize Winner

The prestigious Geoffrey Harris Prize is awarded to an established researcher in the field of neuroendocrinology and is the first of its kind in Europe. This years recipient is Professor Matthias Tschöp who will receive his prize and deliver his lecture as part of the ECE 2017 Opening Ceremony on Saturday 20 May 2017. Further information on the prize can be found at http://www.ese-hormones.org/prizes/.

Professor Matthias H. Tschöp received his M.D. from Ludwig-Maximilians Universität in Munich, where he also trained as a physician in internal medicine. In 1998 he accepted an invitation for a postdoctoral fellowship at the Eli Lilly Research Laboratories in Indianapolis, USA before returning to Europe in 2002 to establish his independent research laboratory at the German Institute of Human Nutrition (DIfE) Potsdam. He later returned to the United States where he joined the University of Cincinnati to ultimately serve as the Director of the Diabetes and Obesity Center of Excellence and Arthur Russell Morgan Endowed Chair of Medicine. In 2011 Prof. Tschöp accepted the position as Scientific Director of the Helmholtz Diabetes Center at Helmholtz Center München and was named Chair of the Division of Metabolic Diseases at Technische Universität München. Prof. Tschöp is the first German physician to receive the prestigious Alexander-von-Humboldt Professorship (2012). He was elected into the German National Academy of Science (Leopoldina) in 2013 and one year later was named adjunct Professor at Yale University, USA. He started the peer-reviewed open access journal Molecular Metabolism, which he leads as the Editor-in-Chief (first impact factor 2016: 5.4). In 2016 Matthias Tschöp received an honorary doctorate of the University of Leipzig and was named Director for Biomedicine of the Helmholtz Pioneer Campus in Munich, which he co-founded.

The Geoffrey Harris Prize Lecture

GH1

Toward hormone-based precision medicines for metabolic diseases

Matthias Tschöp
Germany.

After decades of research unraveling complex metabolic control networks, medicines capable of a safe reversal of morbid human obesity and type 2 diabetes are still not available. Historically, complex diseases have repeatedly proven to be defiant to the best mono-therapeutic approaches. Several examples of combination therapies have largely overcome such challenges, notably for the treatment of severe hypertension and tuberculosis. Obesity and its consequences, such as type 2 diabetes, have proven to be equally resistant to therapeutic approaches based on single medicines. Appropriate management of type 2 diabetes often requires adjunctive medications, and the recent registration of a few compound mixtures has set the precedent for combinatorial treatment of obesity. On the other hand, double or triple therapeutic combinations are more difficult to advance to regulatory approval. Following an improved understanding of the molecular basis for metabolic benefits following bariatric surgery interventions, several classes of novel unimolecular or independent combination therapeutics were discovered. These new classes of drug candidates are based on gastrointestinal hormones, offer efficacy superior to currently prescribed options and seem to have potential to fully reverse human obesity and type 2 diabetes. Moreover, gut peptide-based cell-specific targeted delivery of small molecules offer additional potential for novel metabolic precision medicines and reduced systemic side effects. In this presentation the discovery, pre-clinical validation and first clinical test of peptide hormone poly-agonist drug candidates as well as of combinatorial single molecule therapeutic candidates will be summarized, including previously unpublished observations.

DOI: 10.1530/endoabs.49.GH1

European Hormone Medal Lecture

The European Hormone Medal is awarded to an international scientist who has made significant contributions to the field of basic or clinical endocrinology. This year's recipient is Professor Evi Diamanti-Kandarakis who will receive her prize and give her lecture as part of the European Congress of Endocrinology (ECE), beginning on the 20th May. Further information on the prize can be found at http://www.ese-hormones.org/prizes/.

Dr. Evanthia Diamanti-Kandarakis is professor of Internal Medicine-Endocrinology & Metabolism and Chairman of the Endocrine Department of Euroclinic Athens. She received her MD from Medical School of Athens and her PhD in experimental Endocrinology on the effects of androgens in hypophysectomised rats, from the same University. She was trained in Internal Medicine in England (1974–1980), and in Endocrinology-Diabetes, Metabolism & Obesity in USA (1980–1986). Her research interests have focused for the last 25 years on clinical, molecular and environmental aspects of metabolic & hormonal abnormalities in obesity Diabetes and Polycystic ovarian syndrome. This work has generated 181 publications and more than 12000 citations, classifying her among the 27 worldwide best Greek scientists and the first Greek woman endocrinologist with the greatest international contribution. In 2016 she has received the award of the best teacher in endocrinology in Greece. Dr. Diamanti-Kandarakis has been invited by the international academic community as a speaker and Tutor and has given more than 250 lectures, in Europe, Asia, Africa, North & South America.

European Hormone Medal Lecture

EHM1

Endocrine disruptors: Is it all Greek to us?

Evi Diamanti-Kandarakis

The main achievement at present, on Endocrine-Disruptors (EDCs) effects on human health and disease development, is that it becomes a less ≪of a foreign language≫ issue. The widespread distribution of environmental chemicals in the atmosphere and the detection of these substances within human body, converge to the concept that humans are continually exposed to EDCs. This presentation will focus on the possible role of the most common and studied environmental toxins in female reproductive disorders and especially in PCOS. Exposure to endocrine disrupting chemicals (EDCs) such as plasticizers, bisphenol A (BPA) or phthalates, and food toxins like advanced glycation end products (AGEs), which may affect women's health in everyday, industrialized life, will be discussed. Acute or prolonged exposure to EDCs and AGEs may result in destabilization of the hormonal and metabolic homeostasis and lead to disruption of reproductive functions in females. Strategies and strong recommendations should be considered to protect present and future generations from their adverse health effects. Understandably, Rachel Carson, said in an international language: 'In nature nothing exists alone.'

DOI: 10.1530/endoabs.49.EHM1

Clinical Endocrinology Trust Lecture

The Clinical Endocrinology Trust (CET) Award is given for clinical research that addresses aspects of endocrinology at the forefront of clinical practice. This year's recipient is Professor Renato Pasquali who will receive his prize and give his lecture as part of the European Congress of Endocrinology (ECE), beginning on the 20th May. The award is sponsored by the Clinical Endocrinology Trust and further information can be found at http://www.ese-hormones.org/prizes/.

Renato Pasquali is full professor of Endocrinology at of University Alma Mater Studiorum of Bologna (UNIBO), Italy. In the 90's In 2000 he established the division of Endocrinology in the S. Orsola-Malpighi Hospital of Bologna (who was not present before), and served for a long period of time as Director. In addition, he was director of the School of Specialization in Endocrinology and Metabolism of UNIBO for fifteen years. Its clinical activity has covered over the years, all the major areas of Endocrinology and Metabolic diseases. He is a member of numerous national and international scientific societies and of the editorial boards of international journals. His scientific work was dedicated, in particular, to (i) the pathophysiology and treatment of the polycystic ovary syndrome, and (ii) the endocrinology of obesity (sex hormones, the hypothalamic-pituitary-adrenal axis, and the endocannabinoid system). He has authored 285 original papers and review articles published in international journals (PubMed) (HI 51) and 18 chapters in international textbooks. In particular, he participated as co-author, to the writing group of Clinical Guidelines in "Position" and "Consensus" statements.

Clinical Endocrinology Trust Lecture

CET1

Prospects for a new assessment of polycystic ovarian syndrome

Renato Pasquali
Italy.

PCOS is the most common hyperandrogenic disorder, with a high prevalence of metabolic comorbidities, including obesity and central fat distribution, insulin resistance and the metabolic syndrome. With this background, it should be accepted that androgen excess must be present in all women with PCOS. Thanks to the advance in measuring blood androgen levels by LC-MS/MS, it has become clear that almost all typical cases of PCOS have a variable pattern of androgen excess. An androgen profile including all major androgens should therefore be used for research purposes and clinical practice. The phenotype characterized by menses abnormalities and polycystic ovarian morphology but without androgen excess should be regarded as a separate entity. The presence of a dysmetabolic profile should also be used in the characterization of PCOS, specifically insulin resistance, which is commonly present in obese PCOS women but can also be detected in their normal-weight counterpart. In fact, there is evidence that androgen excess may play a crucial role in disrupting the metabolic pathway, in favouring aberrant visceral fat morphology and function, in favouring the development of insulin resistance and in increasing the susceptibility to develop glucose intolerance states and type 2 diabetes. Hirsutism is common in PCOS, however its correlation with blood androgen levels is weak or absent. Apart from the opportunity to use more objective methodologies to define it, much more research is needed on the potential role of cutaneous androgens. Finally, due to the relevant impact of obesity on PCOS and the fact that in many developed countries most PCOS women are obese, it can be suggested that a secondary form of PCOS related to obesity may exist. The concept of secondary PCOS can be extended to other pathological entities, particularly to the severe insulin resistant states, but also to other endocrinopathies and, finally, to specific drugs (particularly antiepileptics). As with other endocrine syndromes, we should therefore consider that PCOS, precisely because it is a ‘syndrome’, may include many different phenotypes, ranging from the classic to milder forms, and that a secondary PCOS may occur. Additional mild phenotypes without well defined androgen excess may have different pathophysiological mechanisms.

DOI: 10.1530/endoabs.49.CET1

IPSEN1

Redefining neuroendocrinology: stress, sex and cognitive and emotional regulation

Bruce McEwan
USA.

Abstract unavailable.

Plenary Lectures

The Fantastical World of Hormones

P1

The fantastical world of hormones

John Wass
USA.

We all know that endocrinology is the most amazing specialty. However although some of the discoveries in the last 3–400 years have been amazing, some of the wrong turns have exhibited opportunism and quackery. Perhaps we should start with testosterone and the effects of castration. We know that removal of the testes before puberty has irreversible affects and that in 16th and 17th centuries these were exploited for music. Popes did not come out of this covered in glory and the last papal castrato was singing in the Sistine Chapel choir in the early 1900s. In the late 1840s Berthold a German physiologist in Göttingen experimented on capons showing that if he removed their testes and transplanted them into the abdomen, where they regained their blood supply, the effects of castration were not seen. He did not recognize the importance of his observation. Later in the late 1880s Brown-Séquard, the famous French neurologist, reported at the French Royal Society injecting himself with a mixture of the bloods from the testes of dogs and guinea pigs. His reported marked improvement in strength and stamina was a placebo effect because of the shorter half-life of testosterone. Thyroxine from sheep given to patients with hypothyroidism, again in the late 1880s had a remarkable effect in women with hypothyroidism because of the longer half-life of thyroxine. In the late 1880s the ovary was thought to be part of the nervous system. Oophorectomy at that time was used to treat conditions in women including hysteria and anorexia and anxiety and even nymphomania. Ernest Starling was the first person to coin the term 'hormone' and 'Ormao' is the Greek word to 'excite or stir up'. This was the founding of endocrinology. We have then gone from strength to strength with the discovery of insulin and more recent leptin, pioneered amongst others by Steve O'Rahilly and Sadaf Farooqi in Cambridge.

DOI: 10.1530/endoabs.49.P1

The Secret Life of FGF21

P2

The secret life of FGF21

David Mangelsdorf
USA.

Fibroblast growth factor 21 (FGF21) is an endocrine and paracrine factor that is produced in many tissues in response to metabolic stress, including several nutrient and dietary conditions. In addition to its physiologic role in regulating the adaptive response to these conditions, pharmacologic administration of FGF21 to obese animals causes weight loss and improves insulin sensitivity. The diverse actions of FGF21 are mediated through a unique receptor complex that is composed of a classic FGF receptor and the novel co-receptor, βeta-Klotho. Investigation of the tissue-specificity of this FGF21 signaling pathway has revealed the existence of a complex peripheral and neural endocrine circuit that regulates metabolism, nutrient preference, and reward behaviors. We have also found an unexpected role for FGF21 in the exocrine pancreas as a secretagogue that protects acinar cells from proteotoxicity.

DOI: 10.1530/endoabs.49.P2

Update on Regulation of Steroidogenesis by Aberrant Hormone Receptors

P3

Update on regulation of steroidogenesis by aberrant hormone receptors

Andre Lacroix
Canada.

The mechanisms regulating cortisol production when ACTH of pituitary origin is suppressed in primary adrenal causes of Cushing's syndrome (CS) include diverse genetic and molecular mechanisms. These can lead either to constitutive activation of the cAMP system and steroidogenesis or to its regulation exerted by the aberrant adrenal expression of several hormone receptors, particularly G-protein coupled hormone receptors (GPCR) and their ligands. Screening for aberrant expression of GPCR in bilateral macronodular adrenal hyperplasia (BMAH) and unilateral adrenal adenomas of patients with overt or subclinical CS demonstrates the frequent co-expression of several aberrant receptors. In addition, the aberrant GPCR can also exert their activity by regulating the paracrine secretion of ACTH or other ligands for those receptors in BMAH or unilateral tumors. The molecular mechanisms underlying the abnormal tissue-specific expression of the aberrant GPCR remains unclear but may be secondary to dedifferentiation of progenitor cells at the origin of hyperplasia or tumors or to specific genetic alterations. The aberrant expression of hormone receptors is not limited to primary adrenal CS but can be implicated in other endocrine tumors including primary aldosteronism (aldosteronoma or bilateral idiopathic hyperaldosteronism) and Cushing's disease. Targeted therapies to block the aberrant receptors or their ligands have been effective in selected limited cases to date, but development of novel specific antagonists could become useful in the future.

DOI: 10.1530/endoabs.49.P3

The Role of Brain Insulin Resistance for the Development of Prediabetic Phenotypes

P4

The role of brain insulin resistance for the development of prediabetic phenotypes

Hans-Ulrich Häring
Germany.

Abstract Unavailable

Browning of Adipose Tissue and Metabolic Regulation

P5

Browning of adipose tissue and metabolic regulation

Jan Nedergaard
Sweden.

In most countries in the world, an increasing number of people suffer from the metabolic syndrome, normally defined as obesity, high blood sugar, high blood fats and high blood pressure. The new understanding that adult humans possess active brown adipose tissue has led to hope that a (re)activation of this tissue (browning) may be helpful in ameliorating the metabolic syndrome. Brown adipose tissue has the ability to combust (extra) food intake in a direct way, due to the unique presence in this tissue of the UnCoupling-Protein-1 (UCP1). Thus, if activated – normally through the release of norepinephrine from the sympathetic nervous system – the tissue will burn away food energy, leaving only heat, water and CO_2. Thus, it protects against the development of obesity. When the tissue is chronically activated, the stored lipid reserves in the tissue will not suffice for continued heat production, and the tissue will take up large amounts of sugar from the circulation, through a unique adrenergic mechanism, leading to lowering of blood sugar levels through a large glucose disposal. It will similarly activate the synthesis of lipoprotein lipase, leading in parallel to a large increase in lipid uptake from the circulation, diminishing blood triglyceride levels. During prolonged stimulation, the constant burning of food in the tissue will lead to the mobilization of the body's lipid reserves (the white adipose tissue) that will be broken down and the released fatty acids will be transported to the brown adipose tissue for combustion, i.e. the brown adipose tissue is slimming (and all these effects together will likely also result in lowering of blood pressure). Although the acute activity of the tissue is determined by norepinephrine, it would seem that sex hormones (positively) and glucocorticoids (negatively) can affect the tissue. The tendency to a worsening of the metabolic syndrome with age could then partly be explained by a diminished sex hormone stimulation and an unaltered but increasingly dominating negative effect of glucocorticoids, together leading to brown adipose tissue inactivity, and thus to obesity.

DOI: 10.1530/endoabs.49.P5

Thyroid Oncology in the Crossroads of Precision and Narrative Medicine

P6

Thyroid oncology in the crossroads of precision and narrative medicine

Manuel Sobrinho Simões
Portugal.

Thyroid cancers are the solid tumours of mankind with the lowest mutational load. This holds particularly true for papillary carcinomas (PTC) whose pathogenesis appears to be understandable by a limited number of genetic alterations (That is why they are so frequently multifocal). The utilization of NGS allowed the establishment of three molecular subtypes of well differentiated thyroid carcinomas: BRAF-life (Conventional and tall cell PTC, mainly), RAS-like (Follicular variant PTC and follicular carcinoma) and No BRAF/No RAS. Precision medicine is playing a major role in thyroid oncology but its shortcomings are becoming evident. Somatic copy number alterations play also a role in some tumour subtypes and, furthermore, one is progressively aware of the important role played by host factors: Stromal reaction (including extracellular matrix characteristics, subsets of fibroblasts and degree of desmoplasia), 'social' RNAs, immune cells, hormones, growth factors. The data brought in by the latter narrative medicine approach is turning easier the diagnosis and treatment of thyroid cancer patients.

DOI: 10.1530/endoabs.49.P6

Symposia

Clinical Updates in Hypoparathyroidism

S1.1

Congenital hypoparathyroidism

Agnes Linglart
France.

The most common causes of hypoparathyroidism in children are the lack of or the impaired development of the parathyroid glands due to genetic/chromosomal alterations and the abnormal signaling of the $Ca(^{2+})$-sensing receptor (CaSR). The latter refers to autosomal dominant hypocalcemia (ADH) mainly caused by heterozygous activating mutations in CASR encoding CaSR (ADH type 1), and exceptionally caused by activating mutations of GNA11 encoding the Gq/11 protein (ADH type 2). Hypoparathyroidism can also be caused by an autoimmune process, mainly in the context of AIRE mutations. However, in many children, the origin of the hypoparathyroidism remains undiscovered. In a recent national French survey gathering 142 children affected with hypoparathyroidism performed by MAC, 43% of the patients were diagnosed before the age of 1 year. The main causes of the PTH insufficiency were 22q1.1 deletion (31%), ADH1 (13%), AIRE mutations (10%) and cervical surgery (7%). The etiology is still unknown in 23% of the children. Due to the high calcium needs of the skeleton during infancy and childhood, hypoparathyroidism in children is often symptomatic and is diagnosed because of the clinical symptoms of hypocalcemia (muscle spasms, laryngospasm, seizures). Children may present with unspecific features such as cognitive and or motor delay, slowness, ungueal, dental and skin anomalies. In addition, clinical characteristics due to the disease itself causing the hypoparathyroidism may be present such as candidosis, conotruncal cardiac defect, renal and/or uterine malformation. Once hypoparathyroidism has been diagnosed in a child, a comprehensive work-up should be performed to identify the disease-causing defect. The investigations depends on the age of the child (neonate, child, adolescent), and on the clinical features associated with the hypocalcemia. The diagnosis is of importance for the management of follow-up and treatment. The management of hypoparathyroidism in children relies upon calcium supplements and vitamin D analogs. Following the initial period of profound hypocalcemia which may require IV infusion of calcium and high doses of vitamin D analogs (up to 4 μg/day of alfacalcidol), the conventional therapy should aim at absence of clinical symptoms, low-normal level of serum calcium (2–2.2 mmol/l), avoiding hyperphosphatemia and having normal urinary calcium excretion. In some children, this may be a challenging management requiring the use of thiazide diuretics, phosphate binders, calcium supplements and in refractory cases, recombinant PTH. It has become obvious in the past ten years that we need to i- obtain more data on the long-term evolution of children affected with hypoparathyroidism, ii- adjust our decision rules for the identification of the cause of hypoparathyroidism in the context of next generation sequencing and gene panels or whole exome sequencing, and iii- develop guidelines for the management of hypoparathyroidism in children including the specificity of ADH.

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S1.2

Acquired hypoparathyroidism

Fadil Hannan
Uk.

Hypoparathyroidism is characterized by absent or low circulating concentrations of parathyroid hormone (PTH), which results in hypocalcaemia, hyperphosphataemia and impaired renal reabsorption of calcium. Hypoparathyroidism has a prevalence of ~20–40 cases per 100 000 individuals, and anterior neck surgery accounts for around 75% of cases. Postsurgical hypoparathyroidism may arise in patients undergoing total thyroidectomy, radical neck dissection for head and neck malignancies, and after total parathyroidectomy. Hypoparathyroidism following surgery is caused by intraoperative trauma, and inadvertent gland removal or devascularisation. Transient postsurgical hypoparathyroidism, defined as lasting <6 months, affects 25–30% of patients following total thyroidectomy; whilst permanent postsurgical hypoparathyroidism, defined as lasting >6 months, affects up to 3% of patients after total thyroidectomy. Decreases in pre-operative serum calcium and 25-hydroxyvitamin D concentrations, reduced intraoperative PTH concentrations, and longer duration of surgery represent independent predictors of transient hypoparathyroidism. Permanent hypoparathyroidism following thyroid surgery is associated with: inability to identify ≥ 2 parathyroid glands during surgery; hypocalcaemia at 24-h post-surgery; and reoperation for bleeding. Occasionally, postsurgical hypoparathyroidism may have a delayed-onset and present several years after neck surgery. Autoimmune-mediated destruction of the parathyroids represents the next most common cause of acquired hypoparathyroidism and is considered in patients with a personal or family history of autoimmune diseases. Autoimmune acquired hypoparathyroidism may be associated with the presence of anti-parathyroid gland antibodies, and some patients harbor antibodies against the calcium-sensing receptor (CaSR). Acquired hypoparathyroidism may also be caused by hypomagnesaemia, which impairs PTH secretion; and can rarely be due to exposure to ionizing radiation, or result from infiltrative diseases affecting the parathyroids such as metastases or iron/copper overload.

DOI: 10.1530/endoabs.49.S1.2

S1.3

Clinical updates in hypoparathyroisism

Erik Fink Eriksen
Norway.

The spectrum of symptoms associated with hypoparathyroidism span from virtually none to severely debilitating fatigue, memory loss, muscle cramps, and paresthesia. Until recently disease management has focused on securing stable serum calcium values at the lower end of the reference range using potent active vitamin D analogues like Etalpha and Rocaltrol, together with calcium supplementation. Recently maintenance of adequate levels of 25(OH)D have also been mentioned as being important. Adequate intracellular magnesium levels seem to be pivotal for PTH secretion and action at the receptor level, and should therefore be kept at the upper end of the normal range if possible. It is one few endocrine diseases where supplementation of missing hormone was impossible about 10 years ago. Now we have access to recombinant PTH(1-34) and PTH(1-84), and I will review the potential use of and differences between these analogues in the treatment of hypoparathyroidism. In terms of symptomatic relief the results of controlled studies using these analogues as sc. injections have been disappointing. A more physiological pattern can be achieved with continuous subcutaneous infusion using insulin pumps, and I will review the results obtained with this technique so far.

DOI: 10.1530/endoabs.49.S1.3

Evolving Diagnostics in Adrenal and Neuroendocrine Tumours

S2.1

Role of genetic and biomarker tests for diagnosis of neuroendocrine tumours (NETs)

Raj Thakker
UK.

Neuroendocrine tumours (NETs) are a heterogeneous group of neoplasms that occur in different organs and give rise to tumours including carcinoids, pancreatic tumours (PNETs), pituitary adenomas, medullary thyroid carcinoma, and phaeochromocytomas. NETs usually occur as isolated non-familial tumours, but can also occur as hereditary and syndromic disorders, such as multiple endocrine neoplasia (MEN types 1–4), Von Hippel Lindau (VHL) and phaeochromocytoma/paraganglioma. Patients with NETs such as PNETs that do not secrete hormones (referred to as non-secreting or non-functioning PNETs) are often asymptomatic, and this may result in late diagnosis and presentation with metastases. Thus, there is an unmet need for new, reliable and specific biomarkers for early diagnosis that would improve patient survival and quality of life. Biomarkers, which are defined by the World Health Organisation as a substance, structure or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease, for non-secreting NETs include pancreatic polypeptide, chromogranins, carcinoembryonic antigen, α-foetoprotein, neuron specific enolase and synaptophysin. However, these current biomarkers have poor sensitivity and specificity for non-secreting NETs thereby limiting their use for clinical decision making. Recently, detection of germline mutations of the *MEN1* and *VHL* genes have been established as useful predictive biomarkers for the development of PNETs in families with these disorders. However, such familial mutations account for only approximately 3% of NETs. Additional biomarker development has also focussed on studying altered expression of the epigenome, transcriptome, proteinome and metabolome, as well as circulating DNA, microRNAs and tumour cells that can be released from tumours into the vasculature. These advances will be reviewed. Dr Kate E Lines, Dr Mark Stevenson & Professor Rajesh V Thakker.

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S2.2

Current status in morphological imaging in adrenal and gastrointestinal neuroendocrine tumours

Sundin Anders
Sweden.

Computed Tomography (CT) constitutes the basic technique for imaging of adrenal tumours and neuroendocrine tumours (NETs). The major work-load in adrenal imaging is characterisation of adrenal incidentalomas, i.e. adrenal tumours diagnosed on imaging performed for other reasons than adrenal disease. Myelolipomas, which have a typical appearance with areas of macroscopic fat, and simple cysts are easy to characterize and require no follow-up. Morphologically benign adrenal tumours (rounded, sharply delineated, homogenous internal structure) with an attenuation of $\leq$10HU in the native CT images are characterized as benign adrenocortical adenomas and require no additional imaging. With an attenuation $\geq$10HU, follow-up of tumour size is recommended for 6 months. In young ($<$40 years) patients this should preferably be performed by MRI. Calculation of contrast medium wash-out is no longer applied. For tumours $>$4 cm surgical resection is recommended unless in cases of a typical myelolipoma or cyst. CT is for NETs used for the initial localization of the primary tumour, for staging of the disease, detection of recurrence and for monitoring of therapy. It is also used in hybrid imaging in conjunction with PET (PET/CT) and SPECT (SPECT/CT). MRI is superior for imaging of liver, pancreas, brain and bone. In metastatic NETs, 68Ga-DOTA-somatostatin analogue PET/CT generally shows several additional lesions as compared to CT/MRI and small lesions such as lymph nodes may be characterized as metastatic/not metastatic lesions. Contrast-enhanced US is excellent for diagnosis and characterization of liver lesions and to guide the biopsy needle for the histopathological NET diagnosis. Endoscopic US is the best method for detection of pancreatic NETs.

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S2.3

Current status in functional imaging

Vickas Prassad
Germany.

Abstract unavailable.

From the Pituitary to the Periphery

S3.1

Implication of the prolactin receptor in humans

Nadine Binart
France.

While prolactin (PRL) is known as the pituitary hormone of lactation, accumulating evidence shows that PRL acts on many tissues and in many pathophysiological conditions. The major isoform, 23 kDa PRL, acts via a membrane receptor, the prolactin receptor (PRL-R), a member of the hematopoietic cytokine superfamily, and for which the mechanism of activation has been elucidated. The aim of this symposium is to present and discuss data supporting actions of PRL in hyperprolactinemia in the context of gonadotropic deficiency. High levels of PRL in humans may interfere with reproductive function mainly by actions at the hypothalamus. Our data suggest that Kisspeptin neurons appear to be the missing link between hyperprolactinemia and GnRH deficiency. Otherwise, germline *PRLR* mutations have been suspected to be a specific genetic cause of prolactinoma in humans. This will be discussed in light of our recent results.

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S3.2

GHR: are there benefits of endocrine defects?

John Kopchick
USA.

The effects of conditional mouse growth hormone receptor gene disruption or 'knock-out' on metabolic parameters and longevity will be presented. Tissues investigated include muscle, adipose, heart, and liver. Also, data on adult onset growth hormone gene disruption will be presented.

DOI: 10.1530/endoabs.49.S3.2

S3.3

Somatostatin receptors: news in the pituitary, lessons for the periphery

Justo Pastor Castaño
Spain.

The pituitary has been classically considered the 'Master Gland', owing to its ability to regulate the function of the other endocrine glands of the body. However, the hypophysis also served over the years as a master, guiding example to enlighten multiple fields of experimental biology and medicine, from classic physiology to modern cell biology, biochemistry and molecular biology. Somatostatin and its receptors (sst1-5) comprise a classic regulatory system, initially discovered and characterized at the hypothalamo-pituitary interface, which subsequently expanded to influence multiple bodily functions, from neurotransmission to digestive function and metabolic homeostasis, and also tumour biology. In this scenario, our group discovered an aberrantly spliced variant of sst5, sst5TMD4, which lacks 3 of the typical 7 transmembrane domains of GPCRs, but retains unique functional abilities and tisular and subcellular distribution. Initial studies revealed sst5TMD4 overexpression in pituitary tumors, particularly in acromegaly, where its presence is associated to a reduced response to somatostatin analogues, both *in vitro* and *in vivo*, and is linked to enhanced aggressiveness features, such as cell proliferation *in vitro* and tumor invasion *in vivo*. These findings led us to explore the possible presence and activity of sst5TMD4 in other hormone-related tumors. Interestingly, a series of collaborative studies demonstrated that this truncated receptor is overexpressed in multiple tumors and cancers, including, so far, breast cancer, pancreatic neuroendocrine tumors, poorly differentiated thyroid cancer, medullary thyroid carcinoma, and prostate cancer. In these pathologies, studies on patient samples and clinical features, an on tumor-derived primary cells or model cell lines have demonstrated that sst5TMD4 presence is directly linked to enhanced aggressiveness features, such as increased cell proliferation, migration and invasion, hormonal secretion, etc. Further analysis on the molecular underpinnings of these observed features have revealed a number of activated oncogenic or inactivated tumor-suppressing pathways and molecular players, some of which seem to be shared by most tumor types studied, whereas others seem to be unique for a given type of tumor/cancer. These results, coupled to our observation that other misspliced variants related to pituitary pathophysiology (namely, In1-grelin and GHS-R1b) are also present in the same tumors prompted us to study the splicing machinery. Of note, ongoing studies have revealed that the splicing machinery is dysregulated in these pathologies. Thus, the pituitary served, once again, to pave the way to scientific discovery for the periphery.

DOI: 10.1530/endoabs.49.S3.3

2nd Joint Global Symposium on Obesity – The Many Dimensions of the Childhood Obesity Problem

S4.1

Efficacy and effectiveness of physical activity and nutrition interventions in childhood obesity treatment

Hollie Raynor
USA.

While several organizations have recommended that multicomponent, behavioral family-based programs delivered at a moderate- to high-intensity contact frequency have a moderate to high rating of efficacy for improving weight status in children, these types of programs are difficult to translate into many practice-based settings. This presentation will review areas that have been identified within childhood obesity treatment programs that may assist with translation to practice-based settings, and discuss research that has been conducted that examine these factors. An example of a current randomized trial translating a multi-component,

behavioral family-based program into an integrated primary care setting in the USA will be provided.

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S4.2

The hunger genes: pathways to obesity

Sadaf Farooqi

Abstract unavailable.

S4.3

Can we prevent childhood obesity?

Tim Lobstein
UK.

Childhood obesity prevalence continues at a high level in most developed economies and is rising strongly in emerging middle-income countries. This rise in prevalence shows strong links to the exposure of populations to mass-marketed foods and beverages and the use of motorised transport. In Europe the prevalence tends to be higher, and rising faster, among children from lower-income households. The prevention of obesity is essential but clearly we are not doing very well – no country in Europe has successfully and sustainably reduced childhood obesity prevalence. We need to ask: What are the major social, commercial and political barriers which need to be overcome? What steps can we take to overcome these barriers and create a truly health-promoting society?

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Turn Your Face to the Sunshine

S5.1

Effects of maternal thyroid function on infant neurodevelopment

Tim Korevaar
The Netherlands.

In this talk I aim to provide a helicopter view of clinical studies on maternal thyroid function and child neurodevelopment and use this to pinpoint out how different viewpoints on the results can help to interpret the clinical relevance of the currently available data and provide handles to make personal but informed clinical decisions. It is well-established that thyroid hormone plays an important role during early stages of fetal brain development. Thyroid hormone-dependent stages of brain development occur from the 5th week of pregnancy onwards while the fetal thyroid is not functionally matured until week 18–20. This implicates that adequate maternal thyroid hormone concentrations are important for achieving optimal early fetal brain development. After the initial link between iodine deficiency and cretinism was first identified, a wide range of experimental studies further established underlying (patho)physiological mechanisms. Subsequently, clinical studies were set-up to translate these findings and quantify the extent of effects in humans. During this presentation I aim take the audience through a brief timeline of clinical studies published since the late 1990s until this year. The interpretation of clinical outcomes used to study the hypothesis that maternal thyroid hormones are important for fetal brain development, such as child IQ, will be discussed. The timeline of clinical studies together with the interpretation of the results of recent studies, including clinical trials, could help to weigh the potential clinical benefits and harms, and make for a better informed decision making.

DOI: 10.1530/endoabs.49.S5.1

S5.2

Vitamin D and rickets in African children

Vickie Braithwaite
UK.

Rickets is the most common non-communicable disease in low and middle income countries and is re-emerging in countries such as the UK where it was once thought to be eradicated. Rickets is a bone disease which affects growing children and is caused by the undermineralisaton of the growth plate of long bones. Rickets can lead to osteomalacia, disabling bone deformities of the lower-limbs, stunting, increased fracture risk and in severe cases circulating bone mineral disturbances can result in hypocalcaemic seizures and death. The majority of nutritional rickets worldwide is thought to be driven by vitamin D deficiency due to inadequate skin exposure to UVB-containing sunshine. In many countries in Africa however, 25-hydroxyvitamin D concentrations (the status marker for vitamin D) are above those generally associated with vitamin D deficiency thus indicating alternative causes of rickets. This presentation will explore some of our work on the role of the vitamin D-calcium-phosphate axis on nutritional rickets in a selection of African countries; highlighting the potential roles of calcium and iron deficiency. This presentation will also explore whether aetiology may differ depending on setting i.e. urban vs rural and the various treatment methods for rickets including surgical correction of bone deformities, nutritional supplementation and prophylactic treatment strategies for rickets prevention.

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S5.3

Carbohydrate metabolism in patients with Cushing disease: a glance at the incretin system

Lubov Matchekhina
Russia.

The relevance of carbohydrate metabolism studying in patients with Cushing disease (CD) and acromegaly can be explained by frequent occurrence of glucose metabolism disturbances on the one hand, and difficulties in glucose-lowering therapy in these patients on the other. The effectiveness of hyperglycaemia treatment may be reduced due to difficulties in remission/cure of the underlying disease, as well as to the use of specific drug-therapy, leading to hyperglycaemia. There is a growing interest in research aimed at studying the role of incretin system in the pathogenesis of secondary hyperglycemia associated with neuroendocrine diseases recently.

Aim of the study

To analyze the rhythm and levels of incretins and neuropeptides secretion in patients with CD and acromegaly and therefore to specify the pathogenesis of carbohydrate metabolism disturbances.

Methods

42 patients with Cushing disease and acromegaly were included; the mean age was 37.5 years. All of the patients were newly diagnosed with Cushing disease (using urinary free cortisol levels, evening saliva cortisol levels and low-dose dexamethasone suppression test) and acromegaly (in absence of GH suppression during OGTT and high IGF1 levels); none of them had a history of previous drug therapy, radiotherapy or pituitary surgery. All patients underwent OGTT, during which glucose, glucagon, GLP1, GLP2, GIP, ghrelin were measured at 0, 30 and 120 min respectively.

Results

During OGTT glucose levels were not significantly different in all groups. The mean HbA1c level was 5.8% (5.3–6.2). However the relevance of prediabetes was higher in CD patients. In CD patients glucagon levels were significantly higher at all cut off points compared to controls ($P=0.001$). In acromegaly patients, no significant differences were found. GIP secretion was slightly lower in CD patients; in acromegaly patients, no differences were found. Acromegaly group was characterized by inverse rhythm of GIP secretion, with no peak level at 30': GIP 0 min – 194.2 pg/ml, GIP 30 min – 178.8 pg/ml. GLP-1 levels were significantly higher in CD patients ($P=0.047$). In acromegaly group, no significant differences in GLP-1 secretion were found. GLP-2 levels were significantly higher in CD patients compared to acromegaly and controls ($P=0.001$). Ghrelin levels were significantly higher in CD ($P=0.013$) and acromegaly ($P=0.023$) patients.

Conclusion

More pleotropic actions of glucocorticoids can possibly explain higher relevance of carbohydrate metabolism disturbances in CD patients. This can be also explained by higher levels of glucagon secretion, which does not depend on type

of carbohydrate metabolism disorder and is stimulated by a direct action of glucocorticoids on glucagon receptor. GIP and GLP-1 secretion in CD and acromegaly patients are characterized by inverse rhythm with no peak levels which means that these hormones are not playing the crucial role in carbohydrate disturbances development in these patients. On the contrary, GLP-2 and ghrelin seem to influence and potentially regulate glucose homeostasis in CD and acromegaly patients.

DOI: 10.1530/endoabs.49.S5.3

Treatment of Hypothyroidism: What Have We Learned?

S6.1

What is the clinical relevance of deiodinase polymorphisms?

Antonio Bianco
USA.

Abstract unavailable.

S6.2

T4/T3 combination therapy: is there a true effect?

Wilmar Wiersinga
The Netherlands.

L-T4 monotherapy remains the standard treatment of hypothyroidism, as RCTs comparing T4 and T4 + T3 did not indicate superiority of the combination therapy. However, the issue is far from settled, as these RCTs can be criticized and 5–10% of patients on T4 have persistent complaints.
i) Has T4 + T3 therapy a true effect on serum thyroid hormones? Under T4 monotherapy serum FT4 is higher and serum FT3 is lower than in healthy subjects, giving rise to abnormal T3/T4 ratio's in 29% of patients. T4 + T3 therapy produces lower FT4 and higher FT3 values, and thereby T3/T4 ratio's are closer to normal values. There is conflicting data whether T3/T4 ratio's are related to SNPs (e.g. in DIO2) and to persistent complaints.
ii) Has T4 + T3 therapy a true effect on thyroid-hormone dependent actions? There is emerging but weak evidence that markers of thyroid hormone action (such as LDL-cholesterol, SHBG, bone alkaline phosphatase) are closer to normal under T4 + T3 therapy than under T4 monotherapy.
iii) Has T4 + T3 therapy a true effect on the clinical condition? Patients were asked for their preference in 4 RCTs. Preference for T4 was 25% and for T4 + T3 48%; no preference was expressed by 27%. Preference has been related to loss of body weight and to combined SNPs in MCT10 and DIO2.
iv) Has T4 + T3 therapy a true effect on clinical practice? Yes, absolutely. Many patients demand T4 + T3 therapy, sometimes in a aggressive manner. Prescription of T3 tablets have increased, and pharmacy has discovered the potentially big market for T3, among others resulting in a steep price increase of T3 tablets but also in availability of 5 microgram T3 tablets. Only the ETA published detailed guidelines how to start the still experimental T4 + T3 regimen (Eur Thyroid J 2012;1:55). The many unresolved issues call for many more clinical trials.of different designs.

DOI: 10.1530/endoabs.49.S6.2

S6.3

Rebuilding your own thyroid from stem cells; the future therapy of hypothyroidism?

Anthony Hollenberg
USA.

Advances in stem cell biology and thyroid development have opened up the possibility of developing tissue replacement therapy for hypothyroidism. Indeed, in this session the development from stem cells of functioning thyroid tissue in mice will be reviewed. In addition new insight into the development of this technology in human cells will also be discussed. Importantly, advances in this field may lead to new therapeutic options in congenital or post-surgical hypothyroidism.

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Crosstalk between Bone & Other Organ(ism)s

S7.1

Immune system

Patrizia D'Amelio
Italy.

The immune system has been recognized as one of the most important regulators of bone turnover and its de-regulation is implicated in several bone diseases as post-menopausal osteoporosis and inflammatory bone loss. The study of the relationship between immune system and bone metabolism is generally indicated under the term 'osteoimmunology', the vast majority of these studies have been performed in animal models, however several data have been confirmed also in humans. Post-menopausal osteoporosis (PMO) is the most frequent metabolic skeletal disease, it is characterized by reduced bone mineral density and micro architectural deterioration of bone with increased fracture risk. In PMO the uncoupling between osteoblast (OB)-mediated bone formation and osteoclast (OC)-mediated bone resorption results in bone loss. Estrogen deficiency is the main driver of post-menopausal bone loss: during estrogen depletion OCs formation and activity are increased, this increase is partially mediated trough the effect of estrogen deficiency on immune system. Estrogen deficiency influences immune response, in particular T cells, become more active and able to produce inflammatory and pro-osteoclastogenic cytokines as TNFα and RANKL. Despite of some inverse reports, the main body of literature firmly supports the essential role of activated T cells in regulating bone loss induced by estrogen deficiency, both in animal models and in humans. We recently demonstrated that immune system, and in particular T cells mediate the effect of PTH on bone turnover, in particular we demonstrated that during treatment with teriparatide for PMO T cells mediates osteoblastogenesis trough the production of Wnt10b, whereas primary hyperparathyroidism do not increase this molecule. Moreover we demonstrated that, both in mice and humans, continuous infusion of PTH and primary hyperparathyroidism increases the differentiation of T helper (TH) cells in TH17. These cells are responsible for increased OCs formation and activity both in inflammatory diseases and in PMO. In conclusion The interactions between immune system and bone are complex and play significant role in both health and disease, nevertheless not all the pathways discovered in animal models have been fully demonstrated in humans, and several challenging questions remains unsolved.

DOI: 10.1530/endoabs.49.S7.1

S7.2

Osteocalcin signaling in myofibers is necessary and sufficient to increase exercise capacity

Gerard Karsenty
USA.

The observation that circulating osteocalcin levels double during exercise in young mice suggests that this hormone might be a long sought after endocrine regulator of exercise capacity. We addressed this question by analyzing mice lacking either osteocalcin or its receptor in myofibers only. This analysis showed that osteocalcin signaling in myofibers enhances adaptation to exercise because it increases uptake and utilization of glucose into the tricarboxylic acid cycle and promotes fatty Osteocalcin signaling in myofibers favors adaptation to exercise through a second mechanism. Indeed it up-regulates the expression of Interleukin-6 a myokine that favors adaptation to exercise in part by signaling in bone to promote the production of bioactive osteocalcin. Acids utilization. In the course of these studies we noticed that circulating osteocalcin levels decline sharply before mid-life and do not increase during exercise in older mice. This observation raised the prospect that osteocalcin may also be sufficient to correct the age-related decline in muscle function. In support of this hypothesis, our experiments show that exogenous osteocalcin increases the exercise capacity of young wilt-type mice and confers to 15 month-old mice the exercise capacity of 3 month-old mice. This study uncovers an osteocalcin-interleukin-6 axis that increases muscle function during exercise and can reverse the age-induced decline in exercise capacity.

DOI: 10.1530/endoabs.49.S7.2

S7.3

Gut microbiota and bone metabolism

Klara Sjögren
Sweden.

The gut microbiota (GM), the commensal bacteria living in our intestine, performs numerous useful functions, including modulating host metabolism and immune status. Our recent studies demonstrate that the GM is also a regulator of bone mass and we propose that the effect of the GM on bone mass is mediated via effects on the immune system, which in turn regulates osteoclastogenesis. A role of the GM in bone metabolism is further supported by studies demonstrating that antibiotic, probiotic, and prebiotic treatments that impact GM composition regulate bone metabolism. Collectively, these studies suggest that the GM may be a novel therapeutic target for osteoporosis. Treatment with probiotics has already been shown to improve bone mass in rodent models of bone loss, but future randomized clinical trials are required to determine the possible effect of probiotics and other novel therapies modulating the GM composition on bone mass and fracture risk in patients with osteoporosis. Access to cheaper sequencing and improved bioinformatics tools will allow metagenomic sequencing for the analysis of the GM composition in large prospective clinical cohort studies. This can be used to evaluate the predictive value of the GM composition as a biomarker for low bone mass and fracture risk. In addition, metatranscriptomics and metaproteomics will most likely be used to identify the microbial genes and proteins that have an impact on bone mass and fracture risk. We propose a new cross-disciplinary GM–bone research field called 'osteo-microbiology', bridging the gaps between bone physiology, gastroenterology, immunology, and microbiology. Future studies are clearly warranted in this new research field to determine if the GM composition might be used as a biomarker for fracture risk prediction and to validate the GM as a possible novel therapeutic target for osteoporosis.

DOI: 10.1530/endoabs.49.S7.3

Predictors of Therapeutic Response in Functioning Pituitary Tumours

S8.1

Molecular profiling

Monica Gadelha
Brazil.

Abstract unavailable.

S8.2

MRI predictors of therapeutic response in GH-secreting pituitary tumours

Jean Francois Bonneville
Belgium.

The T2-weighted characteristics of GH-secreting pituitary adenomas have recently received particular attention from the research community. It now appears that somatotropinomas can be divided into groups with different behavior according to their T2-weighted signal. T2-hypointense adenomas are generally smaller, invade the cavernous sinus less frequently and are responsible for higher levels of GH-hypersecretion (Fig. 1). Treatment with somatostatin analogues, both before and after surgery, leads to different responses of T2-hypointense adenomas versus non-hypointense tumours. The T2-hypointense adenomas have higher GH and IGF1 decreases and more important tumour shrinkage rates (1). It is therefore interesting to have high quality T2-weighted MRI images at the diagnosis of acromegaly, as it allows to estimate disease evolution and to orient the management strategy.

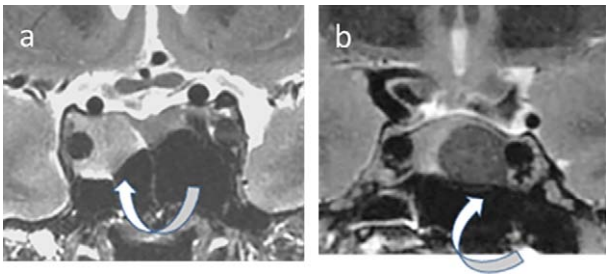

Figure 1 Hyperintense (a) and hypointense (b) GH-secreting adenomas on T2 W MRI.

Reference
1. Potorac, J et al. T2-weighted MRI signal predicts hormone and tumor responses to somatostatin analogs in acromegaly. *Endocr Relat Cancer* 23(11):871-881.

DOI: 10.1530/endoabs.49.S8.2

S8.3

Predictors of therapeutic response in functioning pituitary tumours

Marek Bolanowski
Poland.

Therapeutic response for medical therapy in hormonally functioning pituitary tumours is different in various types of tumours. While majority of prolactinomas respond well for medical therapy using dopamine agonists, in other tumours like somatotropinoma or corticotropinoma their response is significantly lower. In some case therapy resistance can occur. There are various factors determining the efficacy of medical therapy in patients harboring functioning pituitary adenomas. They are different for certain type of tumour. Among clinical aspects, gender, age and extent of hormonal hypersecretion are important factors. In general, response for the therapy in acromegaly is poor in younger male patients with larger tumours and greater GH hypersecretion. Pituitary imaging using MRI can show tumour size and invasiveness, together with T2 intensity. Histological and molecular analyses assess granulation pattern, somatostatin and dopamine receptors number and expression, Ki-67 index, mitotic activity, p53 immunoreactivity, AIP expression, genetic mutations and polymorphisms. The knowledge of possible factors influencing therapeutic response is important and may be helpful in the choice of optimal individualized therapy.

DOI: 10.1530/endoabs.49.S8.3

Novel Type 2 Diabetes Treatment: Beyond Glycaemic Control

S9.1

Experimental models

Jens Holst
Denmark.

One of the most surprising and inspiring experimental models for type 2 diabetes therapy is gastric bypass surgery. Recent 5-year results have demonstrated massive improvements in glycaemic control and body weight, lipids and quality of life after surgery compared to intensive medical therapy (the Stampede trial). Therefore, it is imperative to identify the responsible factors with a view to utilize this knowledge for future therapy without surgery. Substantial evidence suggests that increased secretion of gut hormones plays an important role for both weight loss (inhibition of appetite + food intake) and glucose metabolism (by stimulating glucose-induced insulin secretion). The appetite inhibition seems to involve hypersecretion of PYY, GLP-1 and perhaps CCK, oxyntomodulin, and neurotensin. Decreased secretion of ghrelin may also play a role. The improved glycaemic control is due to a combination of (i) dramatically improved insulin sensitivity (initially improved hepatic sensitivity in parallel with reduction in steatosis) and secondly peripheral sensitivity in parallel with general weight loss – and (ii) improved postprandial insulin secretion due to improved beta cell glucose sensitivity as well as a stronger glycaemic stimulus caused by accelerated glucose absorption. The latter is also the major driving force for postprandial release of the insulinotropic hormone GLP-1, whereas lipids (bile salts) may explain neurotensin secretion while protein derivatives drive CCK secretion. Further experiments using isolated primary gut cells and perfused gut preparations have identified certain bile salts to potently stimulate secretion while amino acids transporters including Pept-1 and basolateral calcium-sensing receptors are important for protein-induced secretioin. The most important lesson so far is that stimulated secretion predominantly depends on absorption of nutritional elements. Some of these elements may form the basis for new therapeutic approaches.

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S9.2

Clinical studies on GLP1 - cardiovascular outcomes

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The incretin hormone Glucagon-like peptide-1 (GLP-1) has various non-glycaemic properties. Among those, cardiovascular effects have been described in animal studies and in clinical studies in patients with type 2 diabetes that have been treated with GLP-1 receptor agonists (GLP-1RA). In animal studies, GLP-1 and GLP-1RA have lead to a decrease in ischaemic areas in artificial myocardial infarct models. Additionally, in some clinical studies, an improvement in left ventricular function was observed as well as a decrease for catecholamine requirement in post-surgical patients after coronary bypass graft surgery. The pathophysiological explanations for these effects are a possible improvement in substrate utilization of the myocardium as well as vascular effects mediated by the activation of cardiovascular GLP-1 receptors and a consecutive amelioration of hypertension. In recent years, randomized, prospective cardiovascular safety trials have been initiated or performed with GLP-1RA in patients with type 2 diabetes and concomitant cardiovascular disease or cardiovascular risk factors. Results from three of these studies have been published so far. In the ELIXA-trial, the short acting GLP-1RA lixisenatide was given as add on to a standard antidiabetic therapy in patients after an acute cardiovascular event. In comparison to an established diabetes therapy, lixisenatide demonstrated non-inferiority and cardiovascular safety. The LEADER-study performed with liraglutide in patients with type 2 diabetes and concomitant cardiovascular risk or disease showed a highly significant 13% relative risk reduction in the 3-point MACE (MACE = multiple adverse cardiovascular events; combined endpoint of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) after 54 months. This result was primarily driven by a significant reduction of cardiovascular death by 22%. Semaglutide, a long-acting GLP-1RA for once weekly injection that is not approved yet, lead to a significant 26% relative risk reduction in the 3-point MACE in its clinical phase III study programme. From these data, the hypothesis that the activation of the GLP-1 receptor has beneficial cardiovascular effects, is strongly supported and it has now been demonstrated in two studies, that patients with type 2 diabetes and cardiovascular disease may profit from a therapy with GLP-1RA regarding their cardiovascular outcomes.

DOI: 10.1530/endoabs.49.S9.2

S9.3

SGLT2 long term protective effects

Javier Escalada
Spain.

Abstract unavaialble.

The Challenges of Male Fertility

S10.1

Manipulating testicular androgen production to promote lifelong male health

Lee Smith
UK.

Abstract unavailable.

S10.2

Fertility preservation in pre-pubertal and young males

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The Netherlands.

Survival rates for patients with cancer have continuously increased over the past decade as a result of more advanced cancer treatment. As a consequence, adverse side effects of cancer therapy becomes an important health issue for these cancer survivors. Male sterility is a relative common side effect of cancer treatment. This adverse fertility effect is caused by gonadotoxic effects as the cancer treatments not only effectively kill cancer cells but also destroy the progenitors of sperm. Spermatogenesis is the process of sperm production starting from spermatogonial stem cells that are extremely sensitive to treatments with alkylating agents or irradiation. Damage to these stem cells results in temporary or permanent sterility depending on the doses. For this reason, adult men diagnosed with cancer are offered cryopreservation of semen before starting cancer treatment. However, for pre-pubertal and young boys, this is not an option as sperm is not yet produced in these boys. As spermatogonial stem cells are already present in the testis, these cells are a source for fertility preservation. A potential future clinical application to preserve fertility in these boys with cancer is to cryopreserve a small testis biopsy prior to cancer treatment for later isolation and propagation of spermatogonial stem cells from this biopsy and transplantation of these cells back after cure of cancer. Studies in animal models have provided evidence that this method indeed restores fertility. It is shown that spermatogonial stem cells can be transplanted to the testis, where they migrate to their niche and colonize the testis, giving full spermatogenesis of which sperm was able of fertilizing eggs and producing offspring. Using this transplantation as readout, spermatogonial stem cell characteristics could be studied in more detail, resulting in the establishment of a long term *in vitro* propagation system for mouse spermatogonial stem cells that upon transplantation could produce sperm to generate offspring. This presentation will give an overview on the state of art of the translation of these techniques to the human situation to establish a clinical application for fertility preservation in young boys suffering from cancer.

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S10.3

Pubertal induction and hormone replacement in young males

Nelly Pitteloud

Congenital gonadotropin-releasing hormone deficiency is a rare disorder characterized by incomplete or absent puberty and infertility. This condition is both clinically and genetically heterogeneous and presents with a broad spectrum of phenotypes ranging from mild to severe. This presentation will provide a review of hypogonadotropic hypogonadism, including the clinical presentation of HH, a rational approach to evaluating HH patients, and an update on treatment options. In particular, the speaker will focus on the choice of the most appropriate treatment in hypogonadotropic hypogonadism based on clinical presentation including the use of rFSH to enhance treatment outcome.

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New Roles for Nuclear Receptors

S11.1

Identification of nuclear receptors network in male fertility

David Volle
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Male fertility is controlled by complex interactions among the hypothalamus, pituitary, and testis. The major functions of the testis include production of spermatozoa (male gametes) and synthesis of testosterone. Testosterone is produced by the testicular Leydig cells and is responsible for the development of gonad, the attainment of puberty, and the maintenance of secondary sexual characteristics. It is also involved in the maintenance of of spermatogenesis and thus ensuring male fertility. Many studies have highlighted the complexity of the regulations of testicular homeostasis at both tissue and cellular levels. Among the involved molecular mechanisms, several nuclear receptors (NRs) have been identified as key regulators of testicular physiology. NRs are a family of transcription factors with a conserved structure that within testis control steroidogenesis and germ cell differentiation. Since several years, using both genetic and pharmacologic strategies, we have been implicated in the identification of the multiple roles of particular members of the NR superfamily. Here we will give an overview of our research highlighting the identification of a complex network showing the interactions of these NRs in the regulation of the exocrine and endocrine functions of the testis.

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S11.2

Crosstalk between estrogen signalling and DNA damage repair

Simak Ali
UK.

Estrogen receptors (ER) are expressed in the majority of breast cancers, are key drivers of breast cancer development and progression and hence therapies to inhibit their activities are a mainstay of treatment for breast cancer. A large proportion of patients develop resistance to these therapies, so determining the mechanisms of ER action is important for improving patient management and for identifying new therapies. In defining the mechanisms by which ER regulates gene expression, we and others find that proteins involved in DNA damage recognition and repair (DDR), including components of base excision repair (BER) and non-homologous end-joining (NHEJ) are central to the promotion of gene expression by ER. Most recently, we have demonstrated that the cytosine deaminase APOBEC3B (A3B) is recruited to the regulatory regions of estrogen-responsive genes in an ER-dependent manner. We have shown that A3B recruitment promotes transient C-to-U changes at ER/A3B binding regions, repaired by BER/NHEJ pathways, with the cytosine deamination and its repair facilitating chromatin remodeling that aids expression of ER target genes. Importantly, we have now extended these studies to demonstrate an important role for A3B in transcription regulation in ER-negative, as well as ER-positive breast cancer cell lines, indicating that A3B has a general role in regulating gene expression in human cells. These findings highlight the therapeutic potential of A3B inhibitors for the treatment of ER+ and ER-negative breast cancer. Recent reports have implicated A3B as the enzyme responsible for acquisition of mutations and tumour evolution in diverse cancer types, highlighting the inherent dangers associated with the cellular role of DNA damage and repair in the regulation of gene expression. These findings also raise the question of whether targeting of A3B to gene regulatory regions might promote non-coding mutations that modify gene enhancer function and provide further impetus for the development of A3B inhibitors for cancer.

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S11.3

The role of androgens in bone

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Abstract unavailable.

New Development in Graves' Orbitopathy

S12.1

The orbital fibroblast: a key player and target for therapy in graves' orbitopathy

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Graves' orbitopathy (GO) is characterized by orbital tissue inflammation, expansion, remodelling and fibrosis. Although the initiating trigger of GO is still indistinct, excessive orbital fibroblast activity is at the heart of its pathogenesis. Orbital fibroblasts are activated by cellular interactions with immune cells and the soluble factors they secrete as well as autoantibodies (e.g. TSH-receptor autoantibodies). Activated orbital fibroblasts produce inflammatory mediators thereby contributing to the inflammatory process in GO. Moreover, orbital fibroblasts exhibit robust proliferative activity and extracellular matrix (especially hyaluronan) synthesizing capacity and can differentiate into adipocytes and myofibroblasts with disease progression, thereby contributing to tissue expansion/remodelling and fibrosis in GO. Orbital fibroblasts, especially those from GO patients, exhibit a hyper-responsive phenotype when compared to fibroblasts from other anatomical regions, which may further contribute to GO pathogenesis. This presentation will address our current view on the role that orbital fibroblasts fulfil in GO pathogenesis as well as the potential of direct targeting of the orbital fibroblast in the treatment of GO.

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S12.2

Management of Graves orbitopathy

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Italy.

Management of Graves' orbitopathy (GO) depends on the severity and activity of the disease. Guidelines for the management of GO have recently been published by EUGOGO (European Group on Graves' Orbitopathy) (*European Thyroid Journal* 2016 **5** 9–26). Assessment of GO by standardized criteria is fundamental to determine the type of intervention. General measures for all patients with GO, irrespective of the degree of severity and activity, include restoration and stable maintenance of euthyroidism, refrain from smoking, use of local measures (e.g. artificial tears, ocular gels). All GO patients, except for the mildest cases, should be referred to specialists. Mild GO is not treated actively, except for a 6-month course of selenium supplementation, shown in a randomized clinical trial (RCT) to be more effective than placebo also in terms of prevention of progression to more severe forms of GO. Sight-threatening GO, due to dysthyroid optic neuropathy and/or corneal breakdown, is an endocrine emergency and should be treated immediately with very high doses of intravenous glucocorticoids (ivGCs) and measures to protect the corneal surface. If, however, response is absent or poor within 2 weeks, the patient should be promptly submitted to orbital decompression. Treatment of moderate-to-severe GO depends on disease activity. If GO is stably inactive, there is no place for medical treatment, and rehabilitative surgery (orbital decompression, squint surgery, eyelid surgery) can be performed, as needed. For moderate-to-severe AND active GO, ivGCs represent, for the time being, the first-line treatment. ivGCs are given as 12 weekly, slow infusions of methylprednisolone (MP). Most commonly, the cumulative dose of MP is 4.5 g, but the dose should be tailored to the patient conditions, avoiding a cumulative dose >8 g and a single dose >0.75 g, to minimize the risk of toxicity. If response is not satisfactory in terms of regression and inactivation of GO, second-line therapies include a second course of ivGCs, a course of oral glucocorticoids combined with either orbital radiotherapy or cyclosporine, treatment with rituximab. The choice of second-line treatments should be part of a shared decision-making process with the informed patient. In addition to rituximab, the effectivess and safety of which should be confirmed in larger RCTs, ongoing studies are investigating the effectiveness and safety of other biologics, including teprotumumab and tolicizumab. Results of these studies are not available yet.

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S12.3

How to predict progression in Graves orbitopathy?

Petros Perros
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Graves' orbitopathy (GO) is a relatively rare condition, but can cause significant morbidity, poor quality of life, socioeconomic cost and occasionally impaired vision. Some studies indicate that nearly all patients with Graves' hyperthyroidism, even those without overt GO, have subclinical eye disease. It is becoming increasingly evident that early recognition of GO and early interventions can affect the long-term outcome favourably. Predicting which patients will develop clinical manifestations of GO is therefore important. Clinical tools for early recognition of GO in a population of patients with Graves' hyperthyroidism attending endocrine clinics have been developed and are being further validated. A number of clinical and biochemical parameters have been shown to be associated with progression of GO and can be used clinically to identify such cases. They include age, gender smoking status, severity of thyrotoxicosis, dysthyroid status, use of radioiodine and the level of TSH receptor antibodies.

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Challenging Pituitary Diseases

S13.1

Hypophysitis

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Hypophysitis is a rare inflammatory condition of the pituitary gland. Its pathogenesis is poorly understood and new variants have been recently described. It can be primary (isolated inflammation of the gland, not related with medications, systemic inflammatory disorders, infections, or other diseases), or secondary (associated with systemic inflammatory processes (as sarcoidosis, Wegener's granulomatosis, Crohn's disease, Takayasu's arteritis, Cogan's syndrome), inflammatory cell proliferative disorders (Langerhans cell histiocytosis, Erdheim-Chester disease), infections (as tuberculosis, syphilis), tumour-associated inflammatory infiltrate (as in germinoma), immunotherapy (as medications targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4) or programmed cell death 1 (PD-1)), rupture of sellar cysts (Rathke's cleft cysts and craniopharyngiomas)). The histological subtypes are lymphocytic, granulomatous, xanthomatous, and plasmacytic (also termed IgG4-related hypophysitis which is often a manifestation of systemic disease). The inflammation may involve the anterior pituitary gland (adenohypophysitis), posterior gland and stalk (infundibulo-neurohypophystis), or entire gland (pan-hypophysitis). Patients with hypophysitis present with manifestations related to mass effect from the gland enlargement and hypothalamo-pituitary dysfunction. The severity of hormone deficiencies may be out of proportion to imaging findings. Radiological findings include homogenous enhancement of the pituitary, diffuse symmetric gland enlargement, midline stalk thickening, and absence of a posterior pituitary bright spot. The diagnosis is established by biopsy and pathological examination. There are no prospective controlled studies on the optimal management of hypophysitis and treatment remains controversial; potential options include surgery (if visual deterioration), glucocorticoids (at variable dosages and duration), immunosuppressive agents and radiotherapy. Spontaneous resolution of pituitary enlargement has been observed in a number of cases and improvement of pituitary hormone deficits may occur after the resolution of hypophysitis.

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S13.2

Empty sella

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Empty Sella (ES) represents a heterogeneous syndrome, with a completely unknown pathogenesis. Defects in the organogenesis or hypoplasia of the sellar diaphragm (associated with stable or intermittent variation of intracranial pressure and/or with pituitary volume variation) can facile the herniation of the arachnoid space into pituitary fossa and the consequently pituitary compression. ES can be the sequel of necrosis of pituitary adenomas, of hypophysitis or of brain/head trauma. In these condition, ES is defined secondary. In cases with unknown aetiology ES is defined Primary. However, actually, obesity, systemic hypertension, multiple pregnancies, diabetes mellitus and *pseudotumor cerebri* are considerate factor risks for the occurrence of primary ES (PES). In 50% of cases with PES a coexistent intracranial hypertension is associated, with the occurrence of neurological signs and symptoms. The clinical manifestation of PES can be insidious, with subclinical or severe symptoms, as headache or papilledema, as visual disturbance or diplopia or optic neuritis, as partial or complete hypopituitarism, also associated to hyper-prolactinemia. Pituitary Magnetic Resonance is crucial for the diagnosis and allow to distinguish between partial or complete empty sella. A complete pituitary function clinical and laboratory evaluation is required to identify and diagnose hypopituitarism condition, with basal and, if necessary, dynamic test. Moreover, measurement of intracranial pressure is suggested, though direct or indirect test, as lumbar puncture or optical nerve ultrasound to evaluate the thickness of the optic nerves. In ES affected patients, hormonal replacement therapy is required for the management of hypopituitarism. Moreover, treatment of intracranial hypertension is strongly suggested, though diuretic drugs, as acetazolamide. In cases of drug-resistant intracranial hypertension or in cases of neurological emergencies, intracranial hypertension neurosurgery treatment, as ventricular shunt placement, is recommended. A semestral or at least annual follow-up is suggested in these patients, with endocrinological, ophthalmological and neurosurgical clinical, laboratory and morphological evaluation. ES, in fact, represents a complex syndrome which requires a multidisciplinary and dedicated team, as to ensure integrated therapy charge and as to prevent the occurrence of the severe disease complications.

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S13.3

Imaging of sellar masses

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To date, magnetic resonance tomography is generally considered the imaging method of choice for its premium resolution of lesions and surrounding anatomic structures. This is mainly due to the improved soft tissue contrast this method offers. Other advantages are the possibility of direct multiplanar imaging in sagittal, coronal, and axial orientations and the avoidance of ionizing radiation. The goal of all imaging studies in this region is to indicate precisely the location, extent, and size of a sella region tumor. These features, along with signal characteristics, frequently not only allow us to determine the presence of a lesion but also indicate the nature of the lesion. For this purpose, its extension in relation to the various surrounding structures, its structure, and its enhancement pattern must be recognized in order to help in differential diagnosis and in treatment planning. A proper set of images is required. A stepwise analysis of the images is suggested. For various types of lesions, typical examples are shown. In this context, monitoring of treatment effects is shown by using repeat imaging with comparable data acquisitions. The common artifacts are discussed as well as enhancement of depiction of minute tumours. Of course, the common features that allow differential diagnosis, are presented.

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Searching for the Cause and Approach in Ectopic Hormone Syndromes

S14.1

Rare Cushing's

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Germany.

Ectopic ACTH syndrome accounts for approximately 20% of all cases of ACTH-dependent Cushing's syndrome. The most common causes are oat cell carcinomas, bronchial and foregut carcinoid tumors, pancreatic islet cell tumors and pheochromocytomas. Rarely, ectopic CRH-secretion occurs by peripheral tumors, especially carcinoids. Whereas the screening for hypercortisolism followed by analysis of ACTH is well established, the distinction between pituitary adenomas and ectopic sources in ACTH-dependent Cushing's syndrome is more challenging. Ectopic tumors producing ACTH with already suppressed pituitary ACTH levels do generally not respond even to high doses of glucocorticoids. Measuring response to CRH or vasopressin may also be useful in the differential diagnosis. Inferior petrosal sinus venous sampling allows definite identification of a pituitary source of ACTH, especially in combination with a CRH-test administered during catheterization. Localization of the source of ectopic ACTH secretion may be especially difficult. In addition to CT, MRI and endoscopic ultrasound, nuclear medicine techniques can help greatly in identifying the source of ectopic ACTH production. Treatment often requires a combination of different approaches, including surgery, medical therapies to control hypercortisolism and/or proliferation, local ablation techniques, and PRRT. As hypercortisolism may cause more clinical problems than the underlying tumor itself, bilateral adrenalectomy is performed in selected cases.

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S14.2

Searching for the cause and approach in ectopic hormone syndromes: rare acromegaly

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Acromegaly secondary to ectopic growth hormone-releasing hormone (GHRH) is rare accounting for less than 1% of cases of acromegaly. Less than 100 cases have been reported in the literature mainly as case reports, except for a nationwide French series of 21 cases. Ectopic acromegaly occurs more frequently in women who represent 2/3 of cases. Median age at diagnosis is 41 years but ranges from adolescence to elderly. GHRH secreting neuroendocrine tumors are usually well differentiated, originating in 90% of cases from pancreas or lung. Pheochromocytomas or paragangliomas have been reported in a small proportion of cases. Positive immunoexpression for GHRH is found in most tumors. Clinical and hormonal features of ectopic acromegaly are very similar to that of somatotropic adenomas and differentiating between both may be challenging. Pituitary may be normal or enlarged at MRI which may be difficult to interpret especially in MEN1 patients where the association of a microprolactinoma to a pancreatic tumor secreting GHRH may be misleading. GHRH plasmatic measurement has an excellent specificity for the diagnosis. Tumors are usually large and easy to localize by conventional imaging or somatostatin receptor scintigraphy. Prognosis is usually favorable, even in metastatic forms which represent 50% of cases. Surgical approach is recommended and, when a complete tumoral resection is feasible, results, in most patients, in long-lasting remission. In such cases, GHRH concentration is normalized and its increase is an accurate indicator of recurrence. In uncured patients, somatostatin analogs control GH secretion but inhibit, only partially, GHRH secretion. MEN1 mutation should be systematically investigated in patients with a pancreatic tumor.

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S14.3

Rare hypoglycemia

Kimberley Kamp
The Netherlands.

Abstract unavailable.

Metabolic Surgery Mechanisms to Clinical Results (*Endorsed by the European Journal of Endocrinology*)

S15.1

The upper gut anti-incretin theory

Geltrude Mingrone
France.

Abstract unavailable.

S15.2

The role of bile in metabolic surgery

Gilles Mithieux
France.

Gastric bypass surgery (GBP) promotes early benefits in energy homeostasis in obese diabetic patients, including decreased hunger and improved glucose control. A suggested mechanism associates a decrease in hepatic glucose production (HGP) with an enhanced intestinal gluconeogenesis (IGN), the latter promoting metabolic benefits in energy homeostasis. In addition, bile acids (BA) have emerged as key metabolic regulators, which might account for several anti-diabetic effects. Moreover, plasma bile acids are elevated after GBP and are known to inhibit gluconeogenesis. Bile diversions mimicking GBP in lean rats (re-insertion of bile in the mid-jejunum or the mid-ileum) promote an increase in plasma bile acids and a marked improvement in glucose control. Bile bioavailability modification is causal since a bile acid sequestrant suppresses the beneficial effects of bile diversions on glucose control. In agreement with the inhibitory role of bile acids on gluconeogenesis, bile diversions promote a blunting in HGP, whereas IGN is increased in the gut segments devoid of bile. In obese rats fed a high fat-high sucrose diet, bile diversions improve glucose control and dramatically decrease food intake. This is due to an acquired disinterest for fatty food, leading the animals to prefer starch-enriched diet. These data suggest a key role of bile and of gluconeogenesis in the favorable outcomes of metabolic surgery.

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S15.3

Long term effects of metabolic surgery

Josep Vidal
Spain.

Abstract unavailable.

Late-breaking: The PCSK9 Revolution

S16.1

Beyond LDL lowering: the pleiotropic roles of PCSK9

Bertrand Cariou
France.

Abstract unavailable.

S16.2

New strategies for inhibiting PCSK9

TBC

Abstract unavailable.

S16.3

PCSK9 inihibition in clinical practice: present and future

Alberico Catapono
Italy.

Abstract unavailable.

What Endocrinologists Should Know about the Genomics of Endocrine Tumors

S17.1

Clinical consequences of the recent genomics findings in thyroid cancer

Thomas Giordano

Abstract unavailable.

S17.2

Clinical implications of SDHx mutations

Anne-Paule Gimenez-Roqueplo
France.

Paragangliomas and pheochromocytomas (PPGL) are neuroendocrine tumors with a very strong genetic component. A germline mutation in one of the different susceptibility genes identified so far explains about 40% of all cases. Genetic testing is recommended in every affected patient and next-generation sequencing (NGS) is the ideal technology to screen the high number of PPGL susceptibility genes (1). The interpretation of genetic variants identified by NGS can be guided by the clinical presentation as well as by the secretory phenotype and by the immunohistochemical analysis of tumors (2). The diagnosis of an inherited form drives clinical management and tumor surveillance of the patient and relatives (1). While whole-exome sequencing studies showed that PPGL is characterized by a low mutation rate of 0.3 mutations per megabase similar to other neural crest-derived tumors, the first integrative genomic analysis of a large collection of 202 PPGL, carried out by the French COMETE network, demonstrated that mutation status in PPGL susceptibility genes is strongly correlated with multi-omics data and revealed the crucial role of predisposing mutations as being the main drivers of PPGL (3). PPGL subtypes can be defined by a set of unique genomic alterations that represent different molecular entities. Transcriptomic studies identified two main molecular pathways, activating either the hypoxic pathway (cluster C1) or the MAPkinase/mTOR signalling (cluster C2). This comprehensive analysis illustrated the functional interdependence between genomic and epigenomic dysregulations. Indeed, DNA methylation profiling uncovered a hypermethylator phenotype specific to the tumors related to a mutation in one of the PPGL susceptibility genes encoding for a protein of the tricarboxylic cycle. Besides, we demonstrated that succinate is acting as an oncometabolite, inhibiting 2-oxoglutarate-dependent dioxygenases, such as HIF prolyl-hydroxylases and histone/DNA demethylases, explaining noradrenergic secretory and metastatic phenotypes of PPGL classified in cluster 1A (4). A recently published novel comprehensive multi-platform analysis of 173 PPGLs led by TCGA has confirmed the COMETE data and identified recurrent fusions genes by RNA sequencing. Altogether those data suggested new therapeutic targets for patients with a metastatic PPGL as well as novel diagnostic and prognostic biomarkers. New 'omics'-based tests for PPGL are likely to be transferred from research laboratories to clinical practice in order to give the access to a precise molecular classification of every PPGL, after surgery, to practicing clinicians with the goal of establishing a personalized medical management.

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S17.3

Will genomics help to finally classify NET's?

Jean Yves Scoazec
France.

The genetic landscape of neuroendocrine tumors (NETs) is being rapidly uncovered. It has long been known that, like other endocrine tumors, NETs might occur in the context of familial predisposition syndromes, involving genes like *MEN1*, *VHL*, *TSC1/TSC2*, *NF1* and *CDKN1B*. Recently, several seminal papers have described the main molecular abnormalities underlying sporadic or apparently sporadic NETs. The results confirm that: (a) well differentiated NETs from various sites are genetically distinct; (b) well differentiated and poorly differentiated neuroendocrine neoplasms are genetically distinct and likely correspond to different entities. Pancreatic and lung well differentiated NETs are mainly associated with abnormalities in genes encoding proteins involved in chromatin regulation and telomere control (such as *MEN1, DAXX* and *ATRX* in pancreatic NETs, *MEN1* again and a number of genes of the SWI/SNF pathway in lung NETs); in addition, recent results have revealed the occurence of fusion transcripts involving *EWSR* in pancreatic NETs, uncovering a new perspective in the molecular mechanisms underlying pancreatic and perhaps other NETs. In contrast, in well differentiated small intestinal NETs, the molecular landscape appears to be heterogeneous, with a high frequency of chromosomal changes and a wide spectrum of mutations involving various signalling pathways (mTOR, SMAD). Taken together, these results suggest that in well differentiated NETs, several oncogenic mechanisms might be involved: epigenetic dysregulations due to chromosomal and genomic instability, alterations in intracellular signalling pathways, and production of oncogenic proteins. As regards the neoplasms morphologically classified as poorly differentiated neuroendocrine carcinomas, concurrent results show that they might be associated with three different molecular signatures: (a) typical 'high grade neuroendocrine' signatures, characterized by mutations in *TP53* and *Rb*, and corresponding to 'true' neuroendocrine carcinomas; (b) 'adenocarcinoma-like' signatures, corresponding to aggressive carcinomas maskerading as neuroendocrine neoplasms, (c) 'well differentiated NET' signatures, corresponding to highly proliferative well differentiated neuroendocrine neoplasms with an aggressive behavior. The molecular tools now available will clearly help to refine the classification of aggressive, high grade neuroendocrine malignancies, but their clinical and therapeutic impact remains to be evaluated. As for low grade neuroendocrine malignancies, the main interest of molecular profiling will probably be prognostic and predictive.

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Hyperandrogenism: Challenges in Clinical Management

S18.1

Hyperandrogenic states: pitfalls in diagnostic approach

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France.

Measuring total testosterone level is the first line approach to assess androgen excess in women. Most laboratories in Europe use direct testosterone immunoassay without prior extraction. In the near future, liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) will be commonly used for measuring testosterone, providing the best accuracy with low limit of detection. In all cases, testosterone norms must be standardized for normal premenopausal women values. Where testosterone is twice the upper limit of normal, it is recommended that DHEAS assay be performed. DHEAS is primarily of adrenal origin in women. Thus, a DHEAS level of over 600 µg/dl indicates a diagnosis of androgen-secreting adrenal carcinoma (often associated with hypercorticism). In this case, abdominal scan must be performed rapidly. Where testosterone is just above the normal upper limit, the most likely diagnosis is polycystic ovary syndrome (PCOS). However, screening should be performed for the nonclassic form of 21-hydroxylase deficiency (assay of 17OH-progesterone) and depending on the clinical setting, Cushing disease must be ruled. Normal testosterone levels in patients with clear clinical symptoms of hyperandrogenism must be interpreted with care. Indeed, T circulates in the blood tightly bound to sex-hormone binding-globulin (SHBG). Low SHBG is typically observed in overweight PCOS patients, in association to inflammatory state and metabolic syndrome, and contributes to lower total testosterone by increasing its clearance from the blood. Therefore, it is recommended, to measure SHBG for correct interpretation of total testosterone by calculating free testosterone index, awaiting direct free-T assay that is still not available. Δ4-androstenedione (A) has been studied comparatively with testosterone, and dissociations exist, with isolated elevation of A but no elevation of testosterone, particularly in the incident of reduced SHBG. In unusual circumstances, dexamethasone test to suppress androgens arising from a functional adrenal source and gonadotropin-releasing hormone (GnRH) agonist in identifying ovarian androgen secreting tumor and hyperthecosis, could be helpful. All these pitfalls should not discourage endocrinologist to challenge the diagnosis of hyperandrogenic states. Decision trees for evaluating the origin of androgen excess will be suggested and discussed during the session.

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S18.2

Metabolic perspectives for the non-classical CAH (NCAH)

Fahrettin Kelestimur
Turkey.

Congenital adrenal hyperplasia (CAH) is one of the most common autosomal recessive inherited endocrine diseases and is characterized by complete or partial impairment of adrenal steroidogenesis. 21-hydroxylase deficiency and 11β-hydroxylase deficiency account for 90% and 6–8% of cases of CAH, respectively. NCAH is the mild form of CAH and occurs in approximately 0.1–0.2% in the general population. The worldwide prevalence of NCAH among hyperandrogenic women is approximately 4.0%. Adrenal androgen secretion and its response to ACTH is increased in these cases. Patients with NCAH generally present with manifestations due to high androgen levels including hirsutism, acne and alopecia. Ovulatory and menstrual dysfunction are seen in more than 30–50% of

patients with NCAH. Polycystic ovarian morphology is recorded in at least 25% of the patients. The data regarding insulin resistance, diabetes, obesity and abdominal visceral adiposity in NCAH patients is scarce. Chronic androgen excess around puberty may favor abdominal visceral adiposity, insulin resistance and its metabolic consequences. Hyperinsulinemia and insulin insensitivity associated with high androgen levels were reported in untreated newly diagnosed patients with NCAH. Chronic glucocorticoid administration in a limited number of patients may also favor metabolic abnormalities. The frequency of type 2 diabetes was reported to be increased in NCAH patients. It seems that NCAH is associated with increased cardiovascular and metabolic morbidity. Therefore, screening metabolic abnormalities may be required in patients with NCAH.

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S18.3

Hyperandrogenism and cardiometabolic risk

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Slovenia.

Hyperandrogenism is the main characteristic of PCOS therefore hyperandrogenism in women is best addressed when studying this highly prevalent syndrome. Besides the clinical features of oligomenorrhea, hirsutism and infertility, PCOS patients are often insulin resistant (IR), obese, they have arterial hypertension, dyslipidemia, an increased pro-thrombotic state, impaired glucose tolerance or frank type 2 diabetes (T2D). The prevalence of metabolic syndrome is doubled as compared to non-PCOS population. Obesity, particularly of visceral origin, plays a crucial role in both the development and maintenance of PCOS and significantly influences the severity of cardiovascular risk profile. At least 30% of women with PCOS are obese, and in some series, up to 75% are obese. About 50–60% of women with PCOS have central body fat distribution. Metabolic disease in PCOS should be considered as a continuous variable, with metabolic dysfunction worsening with severity of androgen excess. Increasing androgen burden is associated with an adverse metabolic phenotype. Androstenedione (A) has been shown to be in better correlation with IR than testosterone (T) in PCOS women. Recent data suggest that biochemical androgen excess poses a higher risk of liver disease, IR, and subclinical atherosclerosis in PCOS compared with those women with anovulation and polycystic ovaries alone. Serum A is a more sensitive indicator of PCOS-related androgen excess than serum total T concentrations. Concurrent measurement of both A and T discovers a PCOS cohort that appears to be at the highest metabolic risk. The analysis of 2543 pre- and perimenopausal women in their 40s originally included in the SWAN study indicated that hyperandrogenemia but not oligomenorrrhoea was independently associated with the risk of prevalent metabolic syndrome. High prevalence of cardiovascular risk factors in PCOS is assumed to be associated with accelerated cardiovascular disease (CVD). However, clear data from large end point trials about cardiovascular morbidity and mortality in PCOS is currently lacking. Though, there is plenty of data on early occurrence of subclinical, potentially reversible atherosclerosis in women with PCOS. Endothelial dysfunction is associated with higher levels of androgens and with insulin resistance. This was observed even at very early ages, and with a trend of deterioration of endothelial function from lean to overweight and obese PCOS women. Recent systematic review has confirmed that carotid intima-media thickness was thicker in women with PCOS in comparison to controls. PCOS women have a greater prevalence and extent of coronary artery calcification, and that is independent of age and BMI.

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How to Incorporate the New Guidelines for Thyroid Cancer in my Clinical Practice

S19.1

Thyroid microcarcinoma: to treat or not to treat?

Paolo Vitti
Italy.

In the last 20 years, the incidence of thyroid cancer (TC) has more than doubled. Since 50% of the increase is related to papillary microcarcinomas (mPTC, <1 cm), it appears that an increased detection, due to the wide use of neck ultrasound (US), is the major factor driving this dramatic rise. Autoptic and histological studies after thyroidectomy (TX) show that 10 to 30% of adults harbor an undiagnosed mPTC. The disease-specific mortality of patients treated by surgery for mPTC is <1% and loco-regional and distant recurrence rates are 2–6 and 1–2%, respectively. Furthermore, 2 Japanese prospective clinical trials demonstrated a good outcome in more than 1,300 patients with biopsy-proven mPTC who were not submitted to TX. Thus, since only a minority of mPTC progress to a clinically overt disease, it is critical to re-evaluate the current management strategy that indiscriminately recommends thyroid surgery that is, although infrequently, burdened by complications. We retrospectively evaluated clinical data of 293 consecutive patients with mPTC, surgically treated at our Department. After 6 years of follow-up no patient had evidence of structural disease. This prompted us to obtain the approval by the ethical committee to offer patients an active surveillance instead of immediate surgery, when they had an intrathyroid nodule with a Thy4 or a Thy5 cytology, less than 1.3 cm of diameter, with no evidence at US of extrathyroid extension and cervical lymphnodes suspicious for metastasis. Out of 163 patients who choose active surveillance, 97 (59.5%) did not satisfied the inclusion criteria and 66 (40.5%) were enrolled in the protocol. With a median follow-up of 12 months (6–28) only 3/66 (4.5%) were addressed to surgery for the appearance of neck metastatic lymphnodes or an enlargement of the nodule. 7/66 (10.6%) patients withdrew from the study. In conclusion, the results of prospective studies will provide more precise data to build up a patient tailored approach for the management of mPTC.

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S19.2

When and how should we perform extensive surgery?

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USA.

Thyroid cancer is one of the most rapidly increasing cancer diagnoses worldwide. Thyroid cancers exhibit the full range of cancer behavior from the relatively indolent occult papillary thyroid cancer to the uniformly aggressive and lethal undifferentiated thyroid cancers. Surgical resection is the principal treatment for thyroid cancer and there are several important areas of controversy in the surgical management of thyroid cancer. Some of these controversies have arisen due to the increasing incidence of thyroid cancer, the variable biologic behavior of low-risk differentiated thyroid cancer, and because of the improved detection of persistent/recurrent disease. International Surgical and Medical Societies and Association have proposed guidelines to the surgical management of thyroid cancer and the level of evidence for these guidelines will be reviewed. Three critical areas in the surgical management of differentiated thyroid cancer remain controversial: the extent of thyroidectomy for differentiated thyroid cancer, need for prophylactic central neck lymph node dissection in patients with papillary thyroid cancer, and the need for completion thyroidectomy in patients who initially undergo hemithyroidectomy. A clinical, pathologic and molecular based approach to address these three controversial areas in the surgical management of differentiated thyroid cancer will be proposed to personalize surgical management decisions in patients with differentiated thyroid cancer.

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S19.3

Dynamic risk stratification in low-risk vs high-risk patients

Miguel Melo
Portugal.

In recent years, an increasing interest in an individualized approach for the care of patients with differentiated thyroid cancer has occurred. The cornerstone of individualized treatment is the existence of a proper risk stratification system that supports physicians' options regarding the treatment and follow-up of patients. Considering that the initial risk stratification systems account for only about 15–20% of the variability in the outcome they are trying to predict, it is now well recognized that risk stratification is a dynamic process. The input of clinical, biochemical and imaging data collected during follow-up, notably the response to the initial treatment, can dramatically change risk estimation and significantly improve its accuracy in predicting long-term outcomes. The use of this approach faces different problems in patients with low/intermediate risk and in patients with high risk of recurrence. Regarding the low/intermediate risk group, dynamic risk stratification was based in the assessment of response to an initial treatment that consisted in total thyroidectomy followed by radioiodine (RAI) treatment. However, lobectomy is now considered a reasonable approach for some low risk patients and the role of postsurgical RAI in the low/intermediate risk group is currently under debate. As a consequence, there are no well-established thyroglobulin (Tg) cut-off points to define categories (e.g. excellent response, biochemical incomplete response) in patients treated with lobectomy or total thyroidectomy without postsurgical RAI treatment. Nonetheless, different

thresholds for patients submitted to lobectomy or total thyroidectomy without RAI treatment have been included in clinical recommendations and recently validated in the low risk group. Apart from static Tg levels, the trend of both Tg and Tg-antibodies levels over time, with similar TSH values, has proven to be an effective way of assessing response to treatment. An increase of 20% seems to accurately predict structural disease recurrence. High-risk patients require a very individualized follow-up because most of the patients are expected to have persistent disease after the initial treatment. For these patients, the initial follow-up is mainly aimed at identifying those with progressive disease despite initial treatment. Nonetheless, most impact of dynamic risk stratification in this group occurs when an excellent response is found, precluding patients from an unnecessary aggressive follow-up strategy. In this session, different ways of implementing and refining dynamic risk stratification will be discussed, addressing the low, intermediate and high risk groups.

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Beta Cell Replacement and Plasticity (*Endorsed by Endocrine Connections*)

S20.1

Stem cells for β cell replacement in type 1 diabetes

Valeria Sordi
Italy.

Pluripotent stem cells (PSC), both embryonic and induced (iPSC), are the most promising cell sources for replacement therapies. In particular for a disease like type 1 diabetes (T1D), caused by the loss of a single specific cell type that does not need to be transplanted back in its originating site to perform its function, a stem cell-based cell replacement therapy seems to be the ideal cure. At present, however, a successful strategy for the use of PSC in patients with diabetes has still to overcome several important hurdles, including i) the development of *in vitro* differentiation protocol for β cell generation, efficient and reproducible in different cell lines in different labs, ii) the possible tumorigenicity of PSC-derived β cells, iii) the risk of allo- and auto-immune rejection upon transplantation into a subject with T1D and iv) the regulatory/economic issues associated to the use of iPSC in humans, starting from production of GMP iPSC lines. At present, the major challenge is how to avoid immune-rejection of stem cell-derived β cells. To overcome the risk of an alloimmune response we could (i) use autologous iPSC, but personalized cell therapy has big economic and safety limits or (ii) iPSC from a cell bank with a limited number of highly selected cell donors with homozygous HLA types, to enable HLA matching for a majority of potential recipients. These strategies, however, would not eliminate the recurrence of autoimmunity after a new exposure to β cell antigens of the immune system of the T1D recipient. The only possible solution consists into trying to 'hide' the transplanted cells from the immune system: we and others are exploring the possibility to achieve this goal through i) the setup of a new immunosuppressive regimen for PSC-derived β cells, able to contrast autoimmune response; ii) the microencapsulation of cells into inert biomaterials, iii) the macroencapsulation of cells into specific devices able to protect them from allo- and auto-immune response while allowing oxygen, nutrients, and insulin exchange and iv) the genetic manipulation of the cells to escape immune recognition. If the limit of immune rejection is solved, a successful translation to the clinical practice of stem cell therapy for diabetes will be closer.

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S20.2

New Strategies for beta cell replacement

Stefan Bornstein
Germany.

Abstract unavailable.

S20.3

Induction of pancreatic beta-like cell neogenesis

Patrick Collombat
France.

The recent discovery that genetically-modified α-cells can regenerate and convert into β-like cells *in vivo* holds great promise for diabetes research. However, to eventually translate these findings to human, it is crucial to discover compounds with similar activities. Herein, we report the identification of GABA as an inducer of α-to-β-like cell conversion *in vivo*. This conversion induces α-cell replacement mechanisms through the mobilization of duct-lining precursor cells that adopt an α-cell identity prior to being converted into β-like cells, solely upon sustained GABA exposure. Importantly, these neo-generated β-like cells are functional and can repeatedly reverse chemically-induced diabetes *in vivo*. Similarly, the treatment of transplanted human islets with GABA results in a loss of α-cells and a concomitant increase in β-like cell counts, suggestive of α-to-β-like cell conversion processes also in humans. This newly discovered GABA-induced α-cell-mediated β-like cell neogenesis could therefore represent an unprecedented hope towards improved therapies for diabetes.

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Environmental Influences on Endocrine Systems

S21.1

Lifestyle and environmental factors in metabolic diseases; endocrine disruptors: new diabetogens?

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France.

The prevalence of metabolic syndrome, obesity and type 2 diabetes has dramatically increased worldwide during the last few decades and exceeds World Health Organisation's predictions. It is not possible anymore to explain this real pandemic only by genetic predisposition and/or by classical lifestyle changes such as sedentary lifestyle or energy-dense diet. There is increasing experimental and epidemiological evidence suggesting that exposure to environmental factors such as noxy foods, dysbiosis or endocrine disrupting chemicals (EDCs) may also contribute to the prevalence of DT2. EDCs are natural or synthetic chemical compounds, present in the everyday domestic environment, interfering with hormonal regulation systems critical for energy homeostasis. Many are present in the food chain and after absorption are sequestred in adipose tissue. They may represent after low-doses exposure during sensitive windows or via chronic exposure to cumulative doses, one aspect of the genetic/environment interface, involved in the pathophysiology of DT2. In humans, some epidemiologic reports suggested a strong link between exposure to some persistent EDCs (pesticides, polychorinated biphenyls, bisphenol A, phthalates, dioxins, polycyclic aromatic hydrocarbons) and DT2, especially after acute and accidental releases of EDCs (Seveso plant explosion, Vietnam war veterans). Other cross-sectional studies around the world reported suggestive to strong association between diabetes and obesity and EDCs exposure, especially for persistent organic pollutants, which should be considered as insulin-resistance risk factors. In rodents, exposure to bisphenol A is responsible for modifications of insulin synthesis and secretion in pancreatic beta cells but also for modifications of insulin signaling in liver, skeletal muscle and adipose tissue, which both lead to insulin-resistanc. *In vivo* and *in vitro* experimental studies have shown that EDCs may act through nuclear receptors (ERs, AhR, PPARγ, ERRγ) involved in metabolic control and are able to induce in specific windows of exposure (fetal, perinatal, pre-pubertal periods) epigenetic changes (DNA methylation, histone modifications, miRNA dysregulation) programming later obesity, insulin resistance, and/or β cell failure. It is still necessary to better understand the involved molecular mechanisms, to develop additional human prospective, longitudinal case/control epidemiological studies, and to identify early biomarkers of exposure, in order to improve assessment of chronic exposure to mixture of EEDs in order to determine the real implication of EEDs in DT2 highly susceptible patients.

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S21.2

Evidence on reproductive disorders through endocrine disruption in-utero

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Finland.

Differentiation of male reproductive system is guided by testicular hormones and growth factors secreted during fetal development under gonadotropin control. Disruption of testicular hormone production or action leads to gonadal dysgenesis and maldevelopment of external genitalia. Cryptorchidism and hypospadias are the most common birth defects in boys, and both conditions can arise as a consequence of anti-androgenic disturbance during development. Both of them are also associated with poor semen quality and testicular cancer, suggestion similar pathogenetic pathways. Animal experiments show robust evidence that inhibition of androgen synthesis or action causes abnormalities in testicular and genital development. Chemicals with different mechanisms of action towards declined androgen activity work in an additive fashion. Therefore even small amounts of anti-androgens can add a critical dose to the total anti-androgenic load. While this is well documented in experimental animals, there is limited evidence on human harm. This is due to challenges in epidemiology to demonstrate causal relationships, albeit there are many examples of associations of chemical exposures with reproductive disorders.

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S21.3

Euthyroid: towards a euthyroid Europe

Henry Volzke
Germany.

Despite the fact that iodine deficiency (ID) can easily be prevented by iodine fortification of table salt, industrial salt and cattle food, Europe belongs to the worst regions in terms of access to iodized salt and is seriously iodine deficient, resulting in the perpetuation of the single most important, preventable cause of brain damage. Up to an estimated 360 million European citizens are exposed to ID, which is not only due to variable iodine provision, it is also rooted in significant heterogeneity of prevention and monitoring activities, leading to inappropriate interventions, health inequalities and increased disease burden with substantial impact on health-care costs. A major concern remains the large number of pregnant women exposed to ID, which results in a measurable decrease in cognitive potential of their children. The effects of ID in total cause significant, preventable costs in health-care systems of affected regions. More than 30 countries contribute to the EUthyroid consortium, which is funded by the EC Horizon2020 programme. The overall aims of EUthyroid are to evaluate IDD prevention programmes in European countries, to initiate capacity building for integrated activities in Europe. Coordinated measures at national and EU level are a long-term goal, which will be worked towards by targeted communication activities of project results. EUthyroid has established a meta-platform for collaborative data collection and use. National and regional registry data are collected to gain an overview over prevalent and incident thyroid diseases and treatments in European nations. In parallel, EUthyroid improves the data quality of ID monitoring studies by providing infrastructures for training and standardization of interviews, laboratory measurements and thyroid ultrasound. All data will be used to provide a European map of iodine status and subclinical disorders and to relate the iodine status of populations to thyroid-related outcomes for the evaluation of ID prevention programmes. In addition, thyroglobulin, a novel and promising biomarker for the iodine status will be evaluated using biomaterials collected in ID monitoring studies and three mother-child cohorts from regions with different iodine status. The latter cohorts will investigate the important association between the iodine status in pregnant women and the neurocognitive function in their children. Combining findings from all studies, health-economic analyses will be conducted to investigate benefits and harms as well as cost-effectiveness of IDD prevention. Potential barriers against harmonized IDD prevention and monitoring programmes will be explored by collecting information from national and European ministries.

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Rare Bone Diseases (*Endorsed by the European Journal of Endocrinology*)

S22.1

Approach for clinicians

Maria-Luisa Brandi
Italy.

Rare skeletal metabolic diseases comprise a group of diseases commonly associated with severe clinical consequences. In recent years, the description of the clinical phenotypes and radiographic features of several genetic bone disorders was paralleled by the discovery of key molecular pathways involved in the regulation of bone and mineral metabolism. Including this information in the description and classification of rare skeletal diseases may improve the recognition and management of affected patients. In a recent effort to recognize the rare skeletal diseases based on their metabolic pathogenesis 116 OMIM phenotypes with 86 affected genes related to bone and mineral homeostasis were recognized. The diseases were divided into four major groups, namely, disorders due to altered osteoclast, osteoblast, or osteocyte activity; disorders due to altered bone matrix proteins; disorders due to altered bone microenvironmental regulators; and disorders due to deranged calciotropic hormonal activity. This publication provides the first comprehensive taxonomy of rare metabolic skeletal diseases based on deranged metabolic activity. This classification will help in the development of common and shared diagnostic and therapeutic pathways for these patients and also in the creation of international registries of rare skeletal diseases, the first step for the development of genetic tests based on next generation sequencing and for performing large intervention trials to assess efficacy of orphan drugs. For their metabolic nature, the interest of endocrinologists towards this disorders is very high. The clinical management of these diseases from a metabolic point of view will be illustrated during the presentation.

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S22.2

Osteogenesis imperfecta & Ehlers-Danlos Syndrome

Anna Maria Formenti
Italy.

Abstract unavailable.

S22.3

Fibrous dysplasia of bone/McCune-Albright syndrome

Roland Chapurlat
France.

Fibrous dysplasia of bone/McCune-Albright syndrome (FD/MAS) is due to a somatic activating GNAS mutation. Patients may be asymptomatic in monostotic forms, which represent two thirds of cases. In those forms, the diagnosis is often incidental. But these monostotic FD may also be revealed by bone pain, bone deformity or fracture. The diagnosis is generally made in childhood or in young adults. Polyostotic FD is often more severe, with a higher incidence of fragility fracture. It is also commonly associated with renal phosphate wasting. About 5% of patients with FD also suffer from endocrine complications, including precocious peripheral puberty, growth hormone excess and hyperthyroidism. These endocrine conditions have to be treated as early as possible. For example, the precocious puberty generally responds well to an aromatase inhibitor, letrozole. Bisphosphonates have been used to treat bone pain and reduce bone turnover for more than two decades with satisfactory outcomes in most patients. This treatment can often be tapered after 2–3 years. Preventive surgery is often advised in children to avoid fracture and deformity of lower limbs. This kind of approach is also warranted in adults. A multidisciplinary management is necessary, involving specialists of bone diseases, endocrinologists, orthopedic surgeons, and sometimes cranio-facial surgeons along with neurosurgeons, both in children and adults. New therapies e.g., denosumab and tocilizumab are currently being studied to improve bone pain in those patients who do not adequately respond to bisphosphonates. An international collaboration is currently developing a framework that would be applicable around the world to improve the care of this rare disease, in particular to avoid delays in treatment.

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Endo Oncology: Prolactin, GH and Metabolic Hormones in Oncology Pathogenesis (*Endorsed by Endocrine Connections*)

S23.1

Prolactin regulation of prostate stem cells: potential implications in prostate cancer

Vincent Goffin
France.

Prostate stem cells have been proposed to participate in prostate cancer initiation. Furthermore, based on their androgen-independence, they are suspected to trigger prostate cancer recurrence when the tumor is no longer responsive to anti-androgens. Therefore better understanding the regulation of this particular cell pool may have important therapeutic relevance. In the human prostate, expression of prolactin (PRL) and activation of its major downstream signaling effector Stat5, have been correlated to prostate cancer progression and relapse. To understand these effects, we use the probasin (Pb)-PRL transgenic mouse model which involves prostate-specific expression of PRL. Pb-PRL mice recapitulate many pre-neoplastic features of the human prostate including focal areas of epithelial dysplasia, prostate intra-epithelial neoplasia and moderate inflammation ('reactive stroma'), together with hypertrophy and ductal dilatation of all prostate lobes. Using various cell lineage-specific markers coupled to immunohistochemistry and cell sorting (FACS), we showed some years ago that the p63+ basal/stem cell compartment (which contains 'tumor-initiating' cells) was highly enriched in Pb-PRL prostate tumors (Rouet et al, PNAS 2010). Subsequent studies revealed enrichment of another cell population that we discovered and named 'LSCmed' based on its FACS profile (Sackmann Sala et al, Am. J. Pathol 2014). LSCmed are luminal progenitors that exhibit stem-like properties *in vitro* (prostasphere assay, gland formation in transplantation assays) and importantly, resistance to androgen deprivation *in vivo*. Transcriptomic profiling showed that LSCmed is a distinct cell entity that differs from the well-known basal and luminal cell populations and that can be identified using a specific gene expression signature. LSCmed are rare in the normal prostate and their amplification in Pb-PRL prostate tumors more likely results from paracrine signals downstream of PRLR/Stat5 signaling than from a direct PRL effect. Strikingly LSCmed represent the major cell component of aggressive, castration-resistant prostate tumors driven by Pten loss, both before and after castration. This is particularly relevant since loss of PTEN is frequently observed in the human prostate oncogenome. In summary, LSCmed represent a newly-identified prostatic cell population that is a strong candidate for mediating cell resistance to androgen-deprivation therapy. Ongoing studies aim to elucidate the mechanisms that that regulate these luminal progenitors and to identify LSCmed(-like) cells in the human prostate.

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S23.2

Is GH a cancer growth factor?

Shlomo Melmed
USA.

Acromegaly is associated with increased soft tissue neoplasms, while GH deficient patients are protected from cancer development. Both environmental and age-related signals lead to cellular senescence and cell cycle dysregulation. We have shown that DNA damage-induced cellular senescence increases GH by inducing p53. GH, in turn, suppresses tumor suppressor proteins in both pituitary and nonpituitary cells.These observations led us to propose that intracellular epithelial GH in the mucosal microenvironment may enable neoplastic growth. Mechanisms underlying pro-neoplastic GH actions include: knockdown or suppressing either *GH* or *GHR* mRNA induces p53; GH suppresses p53 by inhibiting PTEN,a p53 acetylator, which protects p53 from ubiquitination, and up-regulates TRIM29, which also destabilizes p53. Thus, p53 ubiquitination and altered acetylation underlie suppression of p53 mediated by GH. GH also induces mTOR, EMT transcription factors and enhanced cell motility. *In vivo* epithelial p53 is markedly induced in GH-deficient $Prop1^{-/-}$, and in GH receptor deficient $GHR^{-/-}$ mice, and in mutant GH receptor (Laron syndrome) fibroblasts. In nutlin-treated mice with DNA damage, GH is induced in colon epithelial cells. Doubly mutant $Prop1^{-/-}$ (GH-deficient) and $Apc^{min+/-}$ (develop intestinal tumors) mice exhibit high colon p53 and markedly decreased intestinal tumor number and size compared to single mutant APC min+/− mice.GHR blockade induced by pegvisomant treatment of acromegaly patients leads to increased colon mucosal p53 and its transcriptional target p21. Overexpressing intracellular GH, or re-introducing WT GHR to mutant human fibroblasts, suppresses p53 thereby evading cellular senescence.

Conclusions
We hypothesize that GH leads to a pro-neoplastic environment and that high intracellular GH is a component of the field change enabling colon mucosal proliferation. GH-mediated senescence evasion may explain why GH deficiency is protective for cancer.

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S23.3

Is reducing insulin-resistance relevant to prevent cancer?

Michael Pollak
Canada.

Abstract unavailable.

Obesity: Pharmacological Solutions

S24.1

MSH analogs

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Germany.

The leptin-melanocortin signaling pathway plays a pivotal role in the regulation of body weight within the hypothalamus. Leptin, secreted by the adipose tissue, activates the leptin receptor at the arcuate nucleus, which in turn leads to the production of proopiomelanocortin (POMC) derived peptides as melanocyte stimulating hormone (MSH). MSH activates the melanocortin 4 receptor (MC4R), regulating thereby satiety and energy expenditure. Mutations within this pathway are leading to severe early onset obesity based on severe hyperphagia. After the discovery of MSH, different approaches have been made to generate MC4R agonists. Unfortunately, most of the studies were not successful either due to ineffectiveness of the drug to reduce body-weight or due to severe side-effects as e.g. increased blood pressure. However, recently the development of new MC4R agonists as setmelanotide (RM-493), which is leading to severe weight loss in POMC deficient patients, has open new perspectives for the treatment of monogenic obesity forms. Future studies will elucidate whether this new compounds will be of advantage and a new treatment option for obesity in these rare diseases.

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S24.2

The future drugs to come

Gema Frühbeck
Spain.

A complex interaction between environmental and genetic/epigenetic factors is driving the escalating obesity and diabetes epidemics together with a multitude of associated comorbidities. In the past decades the role of gastrointestinal signals in energy homeostasis and glucose control has made tangible progress mainly due to the findings derived from bariatric/metabolic surgery. In particular, incretin-based approaches in relation with glucagon-like peptide 1 and amylin have fostered the emergence of new treatment avenues. Interestingly, one of the most challenging obstacles in obesity treatment is maintaining a lower body weight after weight loss. It can be argued that weight loss and its maintenance may be uncoupled

biological processes that require different pharmacological approaches. Thus, the reduction in metabolic rate triggered by a high calorie-restriction-induced weight loss, contributes to powerful counter-regulatory 'homeostatic' mechanisms leading to weight regain. Therefore, innovative strategies aimed at effectively minimizing these compensatory adaptations with combinations of drugs (combos) using different mechanisms of action may prove useful. Consequently, targeting of food hedonics in combination with the archetypical anorectic and thermogenic pathways will probably provide unparalleled pharmacological efficacy to combat obesity and prevent weight regain. Glucagon has reemerged in weight loss polypharmacy relevantly complementing thermogenic agents. Fibroblast growth factors (FGFs) are undoubtedly among a plethora of newly identified metabolic macromolecules. Evidence that brown adipose tissue exists in adult humans and is activated after cold exposure has opened the interest in the potential browning of adipose tissue and the quantitative contribution of BAT induction/activation towards energy expenditure in obesity. Novel insights that facilitate the design of refined polypharmacy that relevantly targets food hedonics at the same time as stimulates energy expenditure without severe off-target effects that are currently frequently linked to behavioral pharmacology are being pursued.

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S24.3

US experience update

Mike Lean
UK.

Abstract unavailable.

HPA Axis Regulation During a Woman's Life: Impact on Metabolic Outcomes

S25.1

HPA axis regulation during a woman's life: impact on metabolic outcomes

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Serbia.

Aging in both men and women is linked with a decline in diurnal variations in cortisol secretion. Cortisol secretion is increased during circadian nadir and possibly in total through the day. Reduced suppressibility of cortisol after dexamethasone (DEX) administration and increased ACTH secretion with aging are well documented. It appears that aging associates with the decrease in cortisol negative feedback efficacy on HPA axis due to underexpression of mineralocorticoid receptors (MRs) and imbalance of MRs to glucocorticoid receptors (GRs) in hippocampus (HC). Chronically elevated glucocorticoids (GCs) in mice, but not in the other species, lead to neuronal cell loss in the HC. In contrast to these results, an age-related decline in peripheral cortisol values from 30 to 60 years of age within the obese subjects has been observed. This may be explained by emotional eating which reduce HPA axis activity by CRF suppression. No such correlation was found in healthy individuals with normal body-mass-index (BMI). It seems that 'healthy' aging does not lead to enhanced HPA axis activity and peripheral cortisol levels rather decline with aging. Parental regulation of hippocampal GR expression as well as the priming effect of high GC concentrations on the future responses to stressors imprint life history through epigenetic changes within HC. Additionally, men and women tend to react differently with stress–both psychologically and biologically. Clinical significance of reduced adrenal androgen production (DHEA and DHEAS) with aging is not well established. Aldosterone secretion appears to be slightly reduced in elderly whereas sympathetic tone vary from organ to organ. Altogether aging associated changes in HPA activity only in a part depends on genetic background. Individual differences in stress reactivity might be important risk factor for gender-specific health problems in men and women.

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S25.2

HPA axis, insulin resistance and adipocytokines in the fetal-maternal unit

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Greece.

'Stress' is defined as a state of disharmony or threatened homeostasis. Pregnancy is a transient period of relative hypercortisolism. Chronic or acute stressors influence maternal and fetal Hypothalamus-Pituitary-Adrenal Axes (HPA) during pregnancy. Insulin sensitivity is a feature of normal pregnancy, possibly reflecting an adaptive phenomenon aiming at diverting maternal glucose towards fetal needs. We investigated the effect of maternal stress into maternal insulin sensitivity during pregnancy by employing state-trait anxiety inventory (STAI) trait and state questionnaires for stress assessment and we found that in normal pregnant women, enhanced long-term stress is associated with decreased insulin sensitivity. Both long- and short- term stress are associated with enhanced maternal HPA axis and increased placental CRH secretion. Furthermore the decrease in insulin sensitivity during pregnancy is paralleled by the progressive increase of maternal adipose tissue deposition. Throughout pregnancy maternal adipose tissue is metabolically active, producing adipocytokines involved in the process of insulin resistance. Visfatin concentrations in the 1st trimester positively predict insulin sensitivity during the 2nd trimester. Body fat mass during 1st trimester of pregnancy is negatively associated with insulin sensitivity during the 2nd trimester and should be kept under control. Furthermore, first trimester maternal BMI and serum visfatin seem to be strongly associated with fetal insulin secretion and final birth weight, respectively, suggesting a role of early-pregnancy maternal adipose tissue in the pregnancy metabolic environment. Interestingly, during pregnancy, maternal GLP1 might be involved in mechanisms that compensate for the pregnancy-related increase in glycemia and insulin resistance, suggesting a role of this peptide in maternal metabolism and weight and fetal growth. In conclusion, both maternal adipose tissue and stress-induced HPA activation influence directly and/or indirectly the development of insulin resistance during pregnancy.

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S25.3

11β-hydroxysteroid dehydrogenase activity, androgen excess, and metabolic outcomes in woman

Jeremy Tomlinson
UK.

Steroid hormones have potent metabolic effects. Glucocorticoid excess is characterized by central adiposity, insulin resistance, type 2 diabetes and increased cardiovascular risk. Whilst endogenous glucocorticoid excess is rare, local tissue-specific availability of glucocorticoid is controlled by a series of enzymes that are, at a pre-receptor level, able to regulate cortisol's ability to bind and activate the glucocorticoid receptor. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts inactive cortisone to active cortisol, and therefore amplifies local glucocorticoid action. It is highly expressed in key metabolic target tissues including liver, fat and muscle and is dysregulated in metabolic disease including polycystic ovarian syndrome. It has been a target for therapeutic intervention and selective 11β-HSD1 inhibitors provide modest metabolic improvements in patients with type 2 diabetes. In parallel, the A-ring reductases, (5α- and 5β-reductase), inactivate glucocorticoids, but importantly, the isoforms of 5α-reductase convert testosterone to the more potent androgen, dihydrotestosterone. 5α-reductase activity is increased in patients with PCOS and may contribute significantly to the androgen excess observed in these patients and fuel their adverse metabolic phenotype. In addition, adipose tissue is able to generate androgens through the activity of 17β-hydroxysteroid dehydrogenase type 5 (AKR1C3), and activity and expression are increased in patients with obesity and PCOS. *In vitro* data suggest that AKR1C3 may drive lipid accumulation locally within adipocytes through enhanced androgen generation. In conclusion, pre-receptor steroid hormone metabolism has a powerful role to play in the regulation of metabolic phenotype in patients with PCOS and offers significant potential as a target for therapeutic intervention.

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Tissue Specific Defects in Thyroid Hormone Action

S26.1

Mouse models to study tissue specific hypothyroidism

Heike Heuer
Germany.

Thyroid hormone (TH) actions and metabolism are intracellular events that require the transport of TH across the plasma membrane in target cells. Consequently, impaired uptake of TH can lead to tissue- specific TH deprivation independent of the TH concentrations in the circulation. A prominent example for such a scenario represents the Allan-Herndon-Dudley syndrome (AHDS). This syndrome is caused by inactivating mutations in the X-linked Slc16a2 gene encoding the monocarboxylate transporter MCT8, a highly specific TH transporter widely expressed in CNS and peripheral tissues. Patients with inactive MCT8 display severe neurological symptoms and signs of brain hypothyroidism despite highly elevated serum T3 concentrations. Likewise, Mct8 ko mice exhibit abnormal TH serum values together with complex tissue-specific changes in the TH status ranging from hypothyroidism (brain, pituitary) to hyperthyroidism (liver, kidney, skeletal muscle). In order to define the tissue-specific function of Mct8 we recently started to generate mouse mutants that lack Mct8 in defined cell types only. In my presentation, I will report on our studies demonstrating pronounced cell-specific alterations in the TH status upon deletion of Mct8 at the blood-brain barrier (BBB), in hypothalamic tanycytes as well as in thyrocytes while absence of Mct8 in forebrain neurons or hepatocytes did not compromise proper tissue-specific TH action. Overall, our data clearly underscore the importance of Mct8 and other TH transporters in mediating TH transport thereby influencing tissue-specific TH homeostasis.

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S26.2

Syndromes of decreased sensitivity to thyroid hormone

Nadia Schoenmakers
UK.

Disorders of thyroid hormone action are classified broadly, to encompass conditions with defective cellular uptake, metabolism or nuclear action of thyroid hormones. Genomic thyroid hormone action is mediated via receptor subtypes (TRalpha, TRbeta) with differing tissue distributions. TRbeta-mediated Resistance to Thyroid Hormone (RTH) is characterised by elevated thyroid hormones, raised metabolic rate and cardiac hyperthyroidism but hepatic resistance (dyslipidaemia, steatosis). In contrast, TRalpha1-mediated RTH patients exhibit growth retardation, skeletal dysplasia and constipation together with reduced metabolic rate and cardiac hypothyroidism, with near-normal thyroid hormone levels. The contrasting phenotypes of TRalpha1 and beta- mediated RTH exemplify the differing importance of receptor subtypes in tissues, providing a rational basis for receptor-specific drug development. Mutations in *SECISBP2* and *TRU-TCA1-1* cause a multisystem disorder of defective selenoprotein synthesis, with features attributable both to tissue-specific selenoprotein deficiencies (e.g. male infertility, muscular dystrophy) and raised cellular reactive oxygen species due to lack of antioxidant selenoenzymes (e.g. photosensitivity, increased adipose mass and function). Additionally, patients have a characteristic biochemical signature resulting from impaired conversion of T4 to T3 via selenium-containing deiodinases. This presentation will describe clinical features of these conditions, which increase our understanding of thyroid hormone action and inform potential future therapeutic developments.

DOI: 10.1530/endoabs.49.S26.2

S26.3

Restoring TH action in patients with transporter defects: the triac trial

Stefan Groeneweg
The Netherlands.

Mutations in the thyroid hormone (TH) transporter MCT8 result in the Allan–Herndon–Dudley syndrome (AHDS), which is characterized by severe intellectual and motor disability and high serum T3 levels inducing thyrotoxicity in peripheral organs. At present, no effective treatment is available. Preclinical studies suggest that the T3 analogue Triac is a promising candidate to i) normalize serum T3 levels and thus alleviate the thyrotoxicosis and ii) restore TH signaling in the brain.

Methods

We conduct a world-wide prospective interventional trial in which about 45 AHDS patients receive 1 year Triac treatment. The primary end-point is the reduction of serum T3 levels, and secondary end-points include normalization of heart rate (HR), improvement of body weight (BW) and serum parameters that reflect TH action in peripheral tissues. Neuro(psycho)logical functioning is assessed before and after 1 year of Triac treatment.

Results

Currently, 41 patients (age: 1–66 years) have been enrolled (median (IQR) follow-up time: 8 (3–12) months) of whom 18 have completed 1 year of follow-up. Triac treatment effectively suppressed serum TSH levels (2.3 (1.6–3.9) to 0.9 (0.2–1.9) mU/l; $P<0.001$), resulting in a strong reduction of T3 levels (5.0 (3.9–6.5) to 1.7 (1.4–2.2) nmol/l; $P<0.001$). Importantly, BMI, serum HDL cholesterol, creatinine and CK levels significantly increased, whereas basal heart rate and serum SHBG levels significantly decreased.

Discussion

Triac treatment effectively normalizes serum T3 levels. This interim analysis suggests that Triac treatment has beneficial effects on the peripheral phenotype of AHDS, which will be further substantiated upon completion of the follow-up period by the other participants.

DOI: 10.1530/endoabs.49.S26.3

Vitamin D Beyond Bone (*Endorsed by Endocrine Connections*)

S27.1

Heart & Vessels

Klaus Witte
UK.

Vitamin D is a recognised important factor in bone health but in recent years is receiving much attention for its role in multiple other systems. The enthusiasm with which it is embraced as an elixir vitae especially in cancer, cardiovascular disease and neurodegenerative diseases is overwhelming and matched only by the skepticism from other quarters, since solid evidence is largely lacking. I will review the pleiotropic effects of vitamin D and how they may be of relevance to the specific syndrome represented by chronic heart failure and the evidence generated to date by, amongst others, the VINDICATE program at Leeds.

DOI: 10.1530/endoabs.49.S27.1

S27.2

Fertility

Elisabeth Lerchbaum
Austria.

Accumulating evidence from animal and human studies suggests that vitamin D is involved in many functions of the reproductive system in both genders. In women, vitamin D status has been associated with *in vitro* fertilization (IVF) outcome, features of polycystic ovarian syndrome (PCOS), endometriosis, and sex hormone steroidogenesis. In detail, cross-sectional data suggest a regulatory role of vitamin D in PCOS-related aspects such as ovulatory dysfunction, insulin resistance as well as hyperandrogenism. Moreover, results from randomized controlled trials (RCTs) suggest that vitamin D supplementation may be beneficial for follicular development and menstrual cycle regulation in PCOS women. Although several data converge towards a beneficial effect of vitamin D supplementation in metabolic disturbances in women with PCOS, this remains to be demonstrated in high-quality RCTs. Regarding assisted reproductive techniques, recent studies suggest that vitamin D supplementation might be beneficial for couples undergoing IVF. In men, vitamin D status has been associated with semen quality and sperm count, motility and morphology as well as with androgen levels in both fertile and infertile men. Further, there is evidence for a favourable effect of vitamin D supplementation on semen quality, fertility outcomes as well as on testosterone concentrations. In summary, vitamin D deficiency may be a risk factor for adverse fertility outcomes, there is, however, insufficient evidence to establish causality. High quality RCTs are needed to further evaluate the effects of vitamin D supplementation on fertility and sex hormone steroidogenesis in women as well as in men.

DOI: 10.1530/endoabs.49.S27.2

S27.3

Muscles

Roger Bouillon
Belgium.

The vitamin D endocrine system (D-endo) is essential for calcium and bone homeostasis. The vitamin D receptor, VDR, is ubiquitously expressed and about 3% of the mouse or human genome is regulated by D-endo. VDR knock-out mice show impaired striated muscle maturation and selective VDR deficiency in heart muscle cause cardiomyopathy. Muscle weakness may be severe in patients with severe chronic renal failure combined with vitamin D deficiency or in subjects with congenital CYP27B1 deficiency. Muscle strength and function may be impaired in elderly vitamin D deficient elderly subjects and result in increased risks of falls. The final proof of causality is hotly debated but meta-analyses of supplementation studies suggest a modest reduction in falls in elderly subjects with severe vitamin D deficiency. All cells of the immune system express VDR. A large number of immune-related genes are coherently controlled by $1,25(OH)_2D$. The native immune system is stimulated by $1,25(OH)_2D$. A low vitamin D status is associated with an increased risk for all types of infections. Human intervention studies however are equivocal. The acquired immune system is suppressed by D-endo. In animal models vitamin D deficiency leads to increased sensitivity to autoimmune diseases such as inflammatory bowel disease or autoimmune diabetes after exposure to predisposing factors. In man, epidemiological studies confirm such associations, but intervention studies till now fail to show preventive effects. The antiproliferative effect of 1,25(OH)2D on cancer cells has been confirmed in most cells with inhibition of the cell cycle. VDR deficient mice are more prone to cancer when exposed to predisposing factors. The association between a low vitamin D status and colon cancer is fairly consistent in several meta-analyses. A few RCTs however have so far not confirmed beneficial effects on caner. In conclusion, serum 25OHD levels above 20 ng/ml may convey some global health benefits beyond bone but ongoing studies will allow confirming or correcting this conclusion.

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Sleep, Love and Reproduction (*Endorsed by Endocrine Connections*)

S28.1

Candidate mechanisms underlying the association between poor sleep and obesity

Christian Benedict
Sweden.

An increasing proportion of people living in our 24/7 culture complain about insomnia symptoms, i.e., they experience problems to fall and/or stay asleep. As demonstrated by epidemiological studies, chronic sleep loss is correlated with weight gain. To investigate whether sleep loss would alter energy metabolism in favour of weight gain, my lab therefore performed a series of sleep loss experiments in metabolically healthy normal-weight subjects. These studies demonstrated that acute sleep loss alters circulating levels of appetite-modulatory metabolites (e.g. higher levels of the hunger-promoting hormone ghrelin), impairs the ability to control food impulses, and increases metabolic efficiency. In the setting of chronically insufficient sleep, such behavioral and metabolic effects may predispose normal-weight individuals to gain weight.

DOI: 10.1530/endoabs.49.S28.1

S28.2

Oxytocin: from biology to love

Susana Guerreiro
Portugal.

Oxytocin was discovered by Henry Dale in 1906 and synthesized in the early 50's by Vincent du Vigneaud and coworkers. It is secreted by axonal terminals in the neurohypophysis emanating from the neurosecretory neurons of the supraoptic and paraventricular nuclei of the hypothalamus. This hormone similarly to others is secreted in a pulsatile way and, classically, in relation to labor (uterine contractility), lactation and to the maternal behaviour. After the initial identification of its role in labor induction and lactation it became clear that Oxytocin plays other very important roles in human life namely in the creation of bonds which gave this hormone the title of social hormone. First it became clear that it was responsible for the strong bonds between mother and child but in the recent years it was investigated in relation to other types of pair bonding, the development of monogamous relations, and even the relation between different species like between humans and dogs. It's role in sexual orgasm was also recognized. Its secretion can be influenced by a hug or a simple conversation when feelings of trust are present. Indeed, Oxytocin could be responsible for social behaviour as it facilitates the development of trust and empathy between individuals, strengthening relationships. This neuropeptide seems to facilitate security in human relations thus being supportive of positive social interactions. For all of these discoveries it became known as the love hormone. However other roles have also been attributed to Oxytocin: decreasing levels of stress, fear and pain, and also a sort of selective influence on memory (allowing the individual to keep some memories while eliminating others). The therapeutically potential of oxytocin has already started to be studied in diseases like autism spectrum disorder, schizophrenia and depression. Lab tools like measurements of oxytocin in plasma, brain imaging (f-MRI/PET) and genetic/epigenetic assays bring new opportunities to explore the oxytocin pathway and will continue to help us to understand how to live a healthy life in a love ambience.

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S28.3

Kisspeptin and neurokinin B – novel reproductive hormones with therapeutic potential

Waljit Dhillo
UK.

Kisspeptin and neurokinin B are 2 novel key hypothalamic hormones which are vital in normal reproductive function. Inactivating mutations for the gene or the receptor for either of these peptides will cause a failure of puberty due to hypogonadtotrophic hypogondaism. In this talk I will present evidence to suggest that kisspeptin is important in sexual and emotional processing in humans (1). In addition I will present evidence which suggests that NK3R (the receptor for NKB in humans) is important as a mediator of menopausal flushing and this has potentially practice changing therapeutic potential (2).

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Novel Predictors of Diabetes

S29.1

Novel predictors of type 1 diabetes

Mikae Knip
Finland.

Islet autoantibodies are strong predictors of type 1 diabetes (T1D), as positivity for multiple, i.e.is two or more, autoantibodies is associated with a risk of around 70% of progression to clinical disease over the next 10 years. Autoantibodies do not, however, predict when T1D will present clinically. We have assessed the utility of signs of dysglycemia for the prediction of the time of disease manifestation and observed that an increase in HbA1c of 10% over 3–12 months provides a 50% likelihood of disease presentation within 1.1 year after the observed increase. When the HbA1c value was 5.9% (41 mmol/mol) in two consecutive samples, the median time to diagnosis was 0.9 years. The median time to diagnosis after the detection of impaired glucose tolerance on OGTT was 0.7 years. After the detection of an increased random plasma glucose ($\geq$7.8 mmol/l) the median time to diagnosis was 1.0 years. The omics technologies have raised the issue, whether there is a possibility to identify high risk individuals before the appearance of the first autoantibodies. We have looked at markers generated by transcriptomics. We observed that genes and pathways related to innate immunity functions, such as the type 1 interferon (IFN) response, were active, and IFN response factors were identified as central mediators of the IFN-related transcriptional changes. In a proteomics study we found that when including the total observation time from birth to diagnosis we were able to classify the participants into disease progressors and non-progressors

with a success rate of 91%. The classifica-tion was based on the combination of the relative levels of APOC4 (decreased) and afamin (AFAM, increased). Lipidomics and metabolomics analyses showed that individuals who developed T1D had reduced serum levels of succinic acid and phosphatidylcholine (PC) at birth, reduced levels of triglycerides and antioxidant ether phospholipids throughout the follow up, and increased levels of proinflammatory lysoPCs several months before seroconversion to autoantibody positivity. The appearance of insulin and glutamic acid decarboxylase autoantibodies was preceded by diminished ketoleucine and elevated glutamic acid. Another study focusing on the lipidome/metabolome in cord blood revealed that those children, who progressed quickly to clinical T1D, were characterized by a distinct cord blood lipidomic profile that includes reduced major choline containing phospholipids, including sphingomyelins and phosphatidylcholines. Risk children, who progress to clinical T1D are characterized by a decreased microbial diversity, an increased abundance of potentially pathogenic bacteria and a reduced functional gene content in their intestinal microbiome. These changes, can however, not be seen before seroconversion to autoantibody positivity. To summarize, metabolic markers help in the estimation of time to diagnosis in prediabetic individuals. The potential predictive markers generated by omics technologies have to be validated.

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S29.2

Clinical and genetic indicators for diabetes prediction

Valeriya Lyssenko
Denmark.

Worldwide diabetes epidemic leads to exponential increase in incidence and prevalence of associated co-morbidities and mortality. During the last 10 years we have devoted to investigate how clinical and genetic biomarkers can be used to facilitate prediction of these life-threatening hazards. Accumulating evidence from our large prospective studies indicate that decline in insulin secretion adjusted for the degree of insulin sensitivity is the key factor contributing to overt type 2 diabetes. Furthermore, genetic data indicate that risk alleles in genetic loci for type 2 diabetes influenced changes in pancreatic beta-cell function over time, while having no effect on changes in body mass index. Presently, genetic information has insufficient power to predict common type 2 diabetes. However, our follow-up studies on variants in *TCF7L2, MTNR1B, GIPR, GRB10* genes unravelled multiple and pleiotropic mechanisms of genetic loci which significantly contributed to our understanding of pathogenesis of type 2 diabetes including effects on insular-incretin axis (GIP/GLP-1 and glucagon) and hepatic glucose production in the liver. We and others have also reported α-hydroxybutyrate, linoleoyl glycerophosphocholine, and copeptin as novel biomarkers to be associated with increased risk of type 2 diabetes. However, these new biomarkers require a systematic evaluation and validation across different studies and populations before their actual diagnostic and prognostic value is confirmed.

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S29.3

Novel predictors of diabetes – NAFLD, diabetes and CVD

Enzo Bonora
Italy.

Abstract unavailable.

Moving Away from Old-fashioned Steroidogenesis: What Are the Clinical Implications?

S30.1

Clinical relevance of alternative synthesis of androgens

Hans Hofland
The Netherlands.

Recent years have seen many exciting developments in the field of steroidogenesis. These include improved diagnostics through mass spectrometry, novel clinical relevance attributed to steroids previously deemed irrelevant and successful implementation of new anti-cancer treatments. Prostate cancer is a prime example of the latter with the recent confirmation that castration-resistant disease is still androgen-dependent and susceptible to hormonal manipulation with next generation steroidogenic enzyme inhibitors and anti-androgens. In advanced stages of prostate cancer hormonal treatment leads to complex and incompletely understood changes in circulating steroid hormones levels. CYP17 inhibitors like abiraterone acetate lead to accumulation of mineralocorticoid precursors and progesterone metabolites. This ensues a steroid flux into the alternative pathway to 5α-dihydrotestosterone (DHT) with intermediates such as allopregnanolone and androstanediol. Our data in parental and abiraterone-resistant prostate cancer cells show a functional block at the level of CYP17 in prostate cancer cells, preventing *de novo* steroid synthesis and local activation of CYP17 precursors. However, accumulation of other steroid hormones intratumorally could affect nuclear receptor activation. Concurrently, interaction with supplemented glucocorticoids leads to a complex interaction between wild type, mutant and splice variants of nuclear receptors and DNA regulatory elements. Further research into pre-receptor regulation of steroid hormones combined with innovative genome-wide receptor-DNA binding analyses will pave the way towards comprehensive understanding of their effects. In turn, this could secure efficient targeting of the detrimental sequelae of steroid hormones in prostate cancer and other endocrine diseases.

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S30.2

Clinical relevance of steroid precursors in adrenocortical tumors

Vasileios Chortis

Adrenal incidentalomas represent an increasingly common diagnostic problem facing clinical Endocrinologists. Swift and accurate differentiation of benign from malignant disease is essential, but the diagnostic performance of current imaging modalities is sub-optimal and often leads to ill-advised management decisions. Urinary steroid profiling by modern mass spectrometry-based techniques can provide a comprehensive profile of steroidogenesis, quantifying both precursor molecules and end products. Adrenocortical carcinomas display a premature pattern of steroidogenesis, dominated by precursor hormone synthesis, which can be captured in the urinary profile. Emerging evidence highlights the unique diagnostic opportunities presented by this feature. The combination of high-sensitivity biochemical analysis and computational data processing is expected to transform the management of adrenal tumours, from the diagnostics of adrenal incidentalomas to the post-operative surveillance of adrenocortical carcinomas.

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S30.3

Glucocorticoid production in primary aldosteronism – from mechanisms to clinical implications

Felix Beuschlein
Germany.

Adrenal aldosterone excess is the most common cause of secondary hypertension and is associated with increased cardiovascular morbidity and mortality. However, adverse metabolic risk in primary aldosteronism extends beyond hypertension, with increased rates of insulin resistance, type 2 diabetes, and osteoporosis, which cannot be easily explained by aldosterone excess but would rather be associated with oversecretion of glucocorticoids. Over the last years, exome sequencing has provided new insights into the genetic set-up of adrenal adenomas highlighting the concept of calcium dependent signalling being the main driver for aldosterone secretion while the cAMP/PKA pathway can be considered of particular importance for cortisol production. In rare examples somatic mutations in genes involved in cAMP signalling could be identified. However, in the majority of cases the contribution of glucocorticoid oversecretion in patients with primary aldosteronism has remained uncertain. Recently, we have performed mass spectrometry-based steroid metabolome profiling in 24-h urines from consecutively recruited patients with primary aldosteronism. Comparisons were made with healthy controls, patients with endocrine inactive adrenal adenoma, and patients with mild subclinical and clinically overt adrenal cortisol excess. Based on these measurements, patients with primary aldosteronism had significantly increased cortisol and total glucocorticoid metabolite excretion, only exceeded by glucocorticoid output in patients with clinically overt adrenal Cushing syndrome. Several surrogate parameters of metabolic risk correlated

significantly with glucocorticoid but not mineralocorticoid output. We analysed the expression of cortisol-producing CYP11B1 and aldosterone-producing CYP11B2 enzymes in adrenal adenoma tissue from patients with primary aldosteronism, employing immunohistochemistry with digital image analysis. Intra-tumoral expression of CYP11B1 correlated significantly with glucocorticoid excretion, whereas CYP11B2 expression correlated with aldosterone output. Unilateral adrenalectomy for adenoma removal resolved both mineralocorticoid and glucocorticoid excess. Postoperative evidence of adrenal insufficiency was found in roughly one third of tested patients. These data show that glucocorticoid co-secretion is a prevalent feature in primary aldosteronism and significantly contributes to associated metabolic risk. Mineralocorticoid receptor antagonist therapy alone may not be sufficient to counteract adverse metabolic risk in medically treated patients with primary aldosteronism.

DOI: 10.1530/endoabs.49.S30.3

Guided Session 1

GS1.1

New international clinical practice guidelines for the care of girls and women with turner syndrome

Claus H Gravholt
Denmark.

Turner syndrome (TS) affects 25–50 per 100 000 females and can involve multiple organs through all stages of life, necessitating a multidisciplinary approach to care. Previous guidelines have highlighted this, but numerous important advances have been noted since their publication. These advances cover all specialty fields involved in the care of girls and women with TS. This new international guideline is based on an international effort that started with exploratory meetings in 2014 in both Europe and the USA, and culminated with a Consensus Meeting held in Cincinnati, Ohio, USA in July 2016. Prior to this meeting, five groups each addressed important areas in TS care: i) diagnostic and genetic issues, ii) growth and development during childhood and adolescence, iii) congenital and acquired cardiovascular disease, iv) transition and adult care, and 5) other comorbidities and neurocognitive issues. These groups produced proposals for the new guidelines. Additionally, four pertinent questions were submitted for formal GRADE (Grading of Recommendations, Assessment, Development and Evaluation) evaluation with a separate systematic review of the literature. These four questions related to the efficacy and most optimal treatment of short stature, infertility, hypertension, and hormonal replacement therapy. These guidelines were initiated and developed by the European Society of Endocrinology (ESE) in Europe, and by the Pediatric Endocrine Society (PES) in USA, with important contributions from the European Society of Human Reproduction and Embryology (ESHRE), the Endocrine Society (ES), the European Society for Cardiology (ESC), the American Heart Association (AHA), and the European Society for Pediatric Endocrinology (ESPE). Several delegates from other societies also participated. Advocacy groups appointed representatives who participated in pre-meeting discussions and in the consensus meeting. Here, we will present the most important new advances in the care of Turner syndrome.

DOI: 10.1530/endoabs.49.GS1.1

GS1.2

Growth and puberty induction

Theo Sas
The Netherlands.

In July 2016, an International Turner Syndrome Meeting was organized in Cincinnati, Ohio, USA. Today, an updated document concerning the Clinical Practice Guidelines for the Care of Girls and Women with Turner Syndrome is finalized. This document gives the summary of the evidence and expert opinions about several aspects of the treatment and follow-up of individuals with Turner syndrome. It will be published soon. In this presentation, the main conclusions and recommendations about growth and induction of puberty will be reported and discussed.

DOI: 10.1530/endoabs.49.GS1.2

GS1.3

Adult aspects of turner syndrome

Janielle Alfen-van der Velden

In this session, the adult aspects of Turner syndrome are addressed following the new Clinical Practice Guidelines for Turner syndrome. The presentation includes both theoretical backgrounds and practical recommendations. Fertility preservation is discussed and the results of our GRADE evaluation according to the outcome of oocyte donation is presented. New insights in health surveillance for co-morbidities are highlighted. Practical tools for transition from pediatric to adult care are provided. In addition, a toolbox for neuropsychological and psychological assessment of women with Turner syndrome is presented and possible options for intervention are discussed.

DOI: 10.1530/endoabs.49.GS1.3

GS1.4

Cardiovascular health issues in turner syndrome

Philippe Backeljauw

Individuals with Turner syndrome (TS) have an increased risk for congenital and acquired cardiovascular disease (23–50%). This results in increased morbidity and mortality throughout the TS lifespan. There is an increased prevalence of bicuspid aortic valve malformation, coarctatio of the aorta, elongation of the transverse aortic arch, and partial anomalous venous return. In addition, TS females may develop aortopathy that may result in clinically significant aortic dilatation, which occasionally leads to dissection or rupture. Other cardiovascular conditions such as hypertension, coronary heart disease, and cerebrovascular disease (stroke) further reduce the lifespan of TS individuals. Because of this high prevalence of cardiovascular disease, any care provider should have some familiarity with the non-invasive cardiac imaging techniques required for diagnosis and management. Imaging modalities include transthoracic echocardiography and cardiac magnetic resonance imaging. Echocardiography is useful in the diagnosis of a bicuspid aortic valve and other congenital heart diseases, and can be used for surveillance of aortic dilatation. Some abnormalities, such as elongation of the transverse aortic arch and partially anomalous pulmonary venous return, are not as readily ascertained by ultrasound however, and cardiac magnetic resonance imaging is now commonly used as a screening and surveillance tool, especially in adult TS patients. The newly developed clinical care guidelines for girls and women with TS include very specific recommendations on which aortic dimensions may warrant consideration for close monitoring and possible operative intervention. They also provide guidance in decision-making regarding participation in various sports disciplines, and greatly clarify when more frequent cardiovascular health monitoring may be beneficial. It is important that both pediatric and adult endocrinologists, as well as reproductive endocrinologists, are familiar with the updated recommendations for cardiovascular health management in TS, in order to coordinate care with the cardiologists and to facilitate over health maintenance of girls and women with TS.

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GS1.5

Abstract unavailable.

GS1.6

Abstract unavailable.

Guided Session 2

GS2.1

Aggressive pituitary tumours
Olaf Dekkers
The Netherlands.

Abstract unavailable.

GS2.2

Aggressive pituitary tumours
Ann Mc Cormack
Australia.

Abstract unavailable.

GS2.3

Aggressive pituitary tumours
Vera Popovic
Slovakia.

Abstract unavailable.

GS2.4

Aggressive pituitary tumours
Stephen Petersen
Denmark.

Abstract unavailable.

GS2.5

Aggressive pituitary tumours
Anthony Heaney
USA.

Abstract unavailable.

GS2.6

Aggressive pituitary tumours
Jacqueline Trouillas
France.

Abstract unavailable.

New Scientific Approaches

NSA1

Identifying molecular signatures for cancer patient stratification via metabolomics and integrative bioinformatics

Hector Keun
UK.

Altered metabolism in tumor cells is required for rapid proliferation but also can influence other phenotypes that affect clinical outcomes such as metastasis and sensitivity to chemotherapy. Integration of metabolome and transcriptome data for the NCI-60 panel of cancer cells lines allowed us to identify ecto-5′-nucleotidase (NT5E or CD73) and miRNA-22 as a major determinants of metabolic phenotypes in cancer cells. NT5E expression and associated metabolome variations were also correlated with sensitivity to several chemotherapeutics including platinum-based treatment. We observed that tumor NT5E levels were prognostic for outcomes in ovarian cancer and were elevated after treatment with platinum, supporting the translational relevance of our findings. The cancer-associated and cardioprotective miR-22 was shown to repress fatty acid synthesis and elongation in tumour cells by targeting ATP citrate lyase and fatty acid elongase 6, as well as impairing mitochondrial one-carbon metabolism by suppression of methylene tetrahydrofolate dehydrogenase/cyclohydrolase (MTHFD2). Importantly, a beneficial effect of miR-22 on clinical outcomes in breast cancer was shown to depend on the expression levels of the identified target genes, demonstrating the relevance of miRNA/mRNA interactions to disease progression *in vivo*. These studies illustrate one route towards patient stratification based the rational combination of different types of molecular biomarkers for metabolic processes.

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NSA2

Exosome profiling: potential in cancer diagnosis and stratification

Juan Falcon-Perez
Spain.

In the last decade, cell-secreted extracellular vesicles (EVs) have been isolated from most of the fluids of the body. There are many different types of EVs that include different subpopulations of exosomes, microvesicles and apoptotic bodies, all of them varying in size, composition and intracellular origin. Many laboratories around the world have shown that its composition of lipids, proteins, messenger and micro RNAs is cell-type specific, and subject to changes in pathological scenarios, consequently these vesicles are being actively studied as a source to identify disease biomarkers. Metabolic syndrome is a clinical condition affecting up to 25% of all adults worldwide. It influences many cellular systems including adipose tissue, macrophages and hepatocytes compromising most of the time the hepatic function that is essential for homeostasis of the organism. Apart of metabolic syndrome, liver injury ranging from mild infection to life-threatening liver failure constitute by itself a serious worldwide health issue. Consequently, a major goal in liver pathology is the identification of molecular markers for its early detection, i.e. before clinical manifestations are produced. In this context, by applying metabolomics, proteomics and transcriptomics technologies as well as specific biochemical tools, our group is studying the physiological role of extracellular vesicles in the hepatic function in normal and pathological conditions to identify novel low-invasive markers for liver injury. During last years, our group has demonstrated that hepatocytes are able to secrete exosomes-like vesicles enriched in metabolic enzymes. Now, we are currently achieving a thorough qualitative and quantitative analysis by proteomics, transcriptomics and metabolomics of extracellular vesicles secreted by hepatocytes obtained from experimental models of drug-induced liver injury and metabolic syndrome. Our work provides a repertoire of low invasive candidate markers to evaluate hepatic function in a low invasive manner. Furthermore, our results also support a physiological role of hepatic exosomes in different patho-physiological processes.

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NSA3

Genomic approaches on epigenetics

Salvatore Oliviero
Italy.

Abstract unavailable.

NSA4

CRISPR/cas9 cas9-generated mouse models of resistance to thyroid hormone due to THRA mutations

Frederic Flamant
France.

Resistance to thyroid hormone due to THRA mutations (RTHα) is a recently discovered genetic disease with high variability in its clinical presentation. This variability may result from the fact that patients bear different types of mutations, which may impact in different ways the functionality of thyroid hormone receptor α1 (TRα1). Our aim was to understand the relationship between specific THRA mutations and symptoms, using mouse models. CRISPR/Cas9 genome editing was used to generate five new models of RTHα, the human genetic disease caused by mutations in THRA. Like human patients, the mutant mice displayed a hypothyroid-like phenotype, with altered post-natal development. Phenotype severity varied over a broad range between models, mainly depending on the ability of the mutant receptor to interact with the NcoR transcription corepressor in the presence of thyroid hormone. These data illustrate the outstanding possibilities offered by CRISPR/Cas9 genome editing which allows to rapidly produce mouse models of human genetic disease, and even to model individual sporadic cases of the disease.

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NSA5.1

Methodical tools for the structural elucidation of G-protein coupled receptors

Patrick Scheerer
Germany.

In my short methodological talk, I will present why we need a detailed structural description of membrane proteins such as the TSH receptors (TSHR) of the endocrine system and how can we succeed to get three-dimensional structures. The talk includes a methodical toolbox of protein-production or -stabilization and advanced structural biology techniques like protein X-ray crystallography and cryo-electron microscopy for selected examples.

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NSA5.2

Small molecule agonists and antagonists as potential new therapeutics targeting the TSH receptor

Susanne Neumann
USA.

Thyroid-stimulating hormone (TSH, thyrotropin) is an activator of the TSH receptor (TSHR) in the hypothalamic-pituitary-thyroid axis leading to biosynthesis and secretion of thyroid hormones. We have developed an orally available small molecule, allosteric TSHR agonist, E2, for follow up diagnosis of patients with thyroid cancer. This ligand could replace recombinant human TSH (rhTSH, Thyrogen) which is currently used in the clinic. In a mouse model, oral administration of E2 is as efficacious as intraperitoneal injections of rhTSH. Therefore, E2 represents a next step in the pre-clinical development of an oral drug to stimulate radioiodine uptake and/or serum thyroglobulin levels in patients with thyroid cancer. Graves' disease (GD) is caused by persistent, unregulated stimulation of thyroid cells by thyroid-stimulating antibodies (TSAbs) that activate the TSHR. We identified the first small molecule TSHR antagonist (ANTAG3) which inhibits TSH- and TSAb-stimulated signaling. ANTAG3 is selective for TSHR because it does not inhibit activation of LH or FSH receptors, the receptors with the highest homology to TSHR within the seven transmembrane domain in which ANTAG3 binds, and it inhibits TSHR activation in the thyroid gland of mice *in vivo*. These findings suggested that ANTAG3 could be able to inhibit TSHR signaling in extra-thyroidal tissues that express TSHRs including orbital fibroblasts, which play a role in the pathogenesis of Graves' ophthalmopathy (GO), a disease of the eye that is associated with GD. None of the treatment regimens for GD and GO used today are directed at the pathogenesis of these diseases. In an ideal case the same drug would treat Graves' hyperthyroidism and GO. ANTAG3, directly acting at the TSHR, reduced TSH- and TSAb-stimulated hyaluronan (HA) production, a major component of GO, by Graves' orbital fibroblasts. Crosstalk between the TSHR and the insulin-like growth factor 1 (IGF-1) receptor (IGF-1R) initiated by activation of TSHR may play a prominent role in the development GO. We have

shown that TSHR activation alone is sufficient to stimulate HA secretion, through both IGF-1R-dependent and -independent pathways. ANTAG3 inhibited both IGF-1R-dependent and -independent pathways at all doses of the monoclonal stimulating antibody M22; whereas IGF-1R antagonist linsitinib (a small molecule kinase inhibitor) and 1H7 (inhibitory antibody) lost efficacy at high M22 doses. We propose that combination therapy targeting TSHR and IGF-1R may be an effective treatment strategy, especially for GO. We suggest that small molecule TSHR antagonists are leads for the development of orally active drugs to treat patients with Graves' hyperthyroidism and GO.

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NSA6

Mitochondrial epigenetics in obesity and its co-diseases

Ana Belén Crujeiras

The biological regulatory system through which the organism responds to environmental pressures is mediated by epigenetic modifications of the genome without altering the DNA sequence. Among the epigenetic processes, DNA methylation is perhaps the best understood epigenetic adaption and most common DNA modification. This mechanism plays an important role in regulating the gene expression of many biological processes and has wide-ranging effects on health. Aberrant epigenetic regulation has been described in many human diseases. Concretely, there is growing body of evidence that shows a relevant role of epigenetic marks with obesity and its co-disease susceptibility. However, while nuclear DNA methylation is a well stablished feature, very little attention has been devoted to mitochondrial epigenetics. Obesity is often associated with a state of mild chronic inflammation characterized by an abnormal production of proinflammatory and prooxidant mediators. This proinflammatory condition has been linked to a mitochondrial dysfuncion. In fact, an energy restriction therapy devised to lose weight induces an increase in the intracellular ATP content and mitochondrial-related gene expression, concomitantly with a decrease oxidative stress and inflammatory markers. Mitochondrial dysfunction and the increment of mitochondrial Reactive Oxygen Species (ROS) production are important benchmarks of the aging and metabolic disturbances development. Therefore, the mitochondrial dysfunction might be critically involved in the pathogenesis of obesity. However, the molecular mechanisms leading to mitochondrial dysfunction in metabolic diseases are still unknown. In this context, mitochondrial epigenetics is a novel mechanism to understand the pathobiology of diseases with a mitochondrial dysfunction involvement. Epigenetic regulation of mtDNA has received increasing attention in the last years due to its implication in clinically relevant disease. Variations in mtDNA methylation were associated with exposure to pollutants and Nonalcoholic fatty liver disease (NAFLD) and were proposed to have a role in mitochondrial gene expression regulation. mtDNA methylation was reported to be induced by hyperglycaemia in retinal endothelial cells and to negatively regulate mitochondrial gene expression. Moreover, mitochondrial epigenetic can modulate nuclear DNA and nuclear DNA epigenetic may affect mtDNA. Hence, abnormal mtDNA methylation is attracting increasing attention as potential biomarker and might have therapeutic potential for metabolic diseases management.

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Debates

Is There a Role for Medical Therapy for Non- Functioning Pituitary Adenomas?

D1.1

Is there a role for medical therapy for non- functioning pituitary adenomas? - FOR

Yona Greenman
Israel.

In this debate I will make an overview of outcomes of NFPA patients with post-operative remnants, who were treated conservatively after surgery. In view of the high rates of tumor progression with consequent need for repeated surgery and radiation therapy, we propose the use of dopamine agonists in these patients. Recent data showing that preventive treatment with dopamine agonists significantly reduces the rate of tumor progression and the need for radiation therapy or additional surgical interventions will be reviewed.

DOI: 10.1530/endoabs.49.D1.1

D1.2

Is there a role for medical therapy for non- functioning pituitary adenomas? - AGAINST

Stylianos Tsagarakis
Greece.

Non-functioning pituitary adenomas (NFPA) are the second most common variant of pituitary tumors. They are presented by compression symptoms, hypopituitarism and in rec as incidental findings during brain imaging. When symptomatic, primary therapy for NFPAs is surgery most commonly by the trans-sphenoidal (TSS) approach. Medical therapy is not generally recommended in this setting, particularly when immediate decompression of the optic chiasm is needed. Despite the debulking efficacy of TSS, in many occasions only partial tumor resection is achieved. Recurrence rates are high in partially resected tumors. Although less frequently, even completely resected tumors may also recur. Therefore, there is a need for post-surgical surveillance and intervention in order to prevent recurrence. The current practice in most centers is to follow-up the pituitary lesion by MRI-imaging and offer additional therapy, usually in the form of radiotherapy (RT), in case of recurrence. RT, either conventional or stereotactic, is effective in controlling further tumor growth but its use is compromised by significant side effects. Based on findings that many NFPAs demonstrate expression of dopamine and somatostatin receptors, medical therapy with dopamine agonists (DA) and somatostatin analogues (SSA) have been used after surgery in order to prevent recurrence. So far, DAs have been more widely tested showing some promise in several small-scale case series. In a recent larger study, introduction of DA immediately after surgery led to a lower number of recurrences compared to a control group that did not receive DA therapy. However, since not all patients will recur, such a strategy exposes a substantial number of patients to unnecessary long-term DA therapy. Unfortunately there are no robust predictors for tumor recurrence. In fact, the best predictor of tumor growth is growth itself. However, DA therapy was less effective when introduced later in patients that already demonstrated a tendency for tumor regrowth. Surprisingly the beneficial effect of DA therapy does not correlate with dopamine receptor expression. This finding raises concerns about the pathophysiological background of the observed DA benefit. Moreover, there are no solid data on hard end points e.g. prevention of visual fields defects and avoidance of second surgery. Although early initiation of treatment may be preferable, dosage and duration of treatment are largely empirical. The need for higher doses and long treatment periods raises some safety concerns. Definitely a well-designed randomized control trial will resolve many of these issues. However, the lack of industrial interest and the long time-length required to obtain valid data, limits the feasibility of such a perspective. To summarize, the promise of most medications is limited by imprecisions regarding the final outcome and uncertainties on dosing and duration of preventive therapy. So far, effective medications have rendered prolactinomas and acromegaly well manageable disorders. For NFPAs such a possibility still remains elusive.

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Incidentally Discovered Nonfunctioning Pancreatic NETs: Surgery or Not? (*Endorsed by the European Journal of Endocrinology*)

D2.1

Incidentally discovered nonfunctioning pancreatic NETs: Surgery or not? - FOR

Ulrich Knigge
Denmark.

Pancreatic incidentalomas are defined as asymptomatic pancreatic lesions, discovered incidentally by imaging for an unrelated indication. A significant proportion of these tumors may be malignant or have a malignant potential. As the use of improved cross sectional imaging increases incidentalomas are becoming more common. In the ENETS guidelines it is proposed that selected patients with incidentally found sporadic, asymptomatic, non-functioning (NF) pancreatic neuroendocrine neoplasms (pNEN) less than 2 cm in size may be followed with repeated imaging instead of resected. However, this conclusion is based on limited data as only few and retrospective studies with a heterogeneous design have investigated the safety of active surveillance. Only few patients had histological or cytological diagnosis and the Ki67 proliferation index, which is the most powerful prognostic marker in NF pNEN, was only determined in 10% of the patients. Up to 20% (in a single study 50%) of the patients had significant tumor growth although regional lymph node metastases developed in few patients. In a recent study, 38% of pNEN <2 cm displayed malignant features. Hence, it cannot be predicted which patients will progress during observation. Accordingly, active surveillance is a doubtful approach and resection should be offered patients with small NF pNEN, if not contraindicated by age, severe co-morbidity and poor performance status. Surgical procedures for small NF pNEN are safe when performed in high-volume centers. In contrast, in MEN-1 patients NF pNEN $\leq$ 2 cm are generally indolent tumors with low malignant features and surgical treatment is rarely indicated.

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D2.2

Incidentally discovered nonfunctioning pancreatic NETs: Surgery or not? - AGAINST

Reza Kiamanesh
France.

Abstract Unavailable.

Drug Holiday in Osteoporosis (*Endorsed by the European Journal of Endocrinology*)

D3.1

Drug holiday in osteoporosis - FOR

Bente Langdahl
Denmark.

Abstract Unavailable.

D3.2

Drug holiday in osteoporosis - AGAINST

Dennis Black
USA.

Abstract Unavailable.

Is Cardiovascular Risk Increased in Women with PCOS?

D4.1

Is cardiovascular risk increased in women with PCOS? - FOR

Harpal Randeva
UK.

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder amongst women of reproductive age and is associated with various cardiometabolic perturbations, in addition to chronic anovulation and factors related to androgen excess. Indeed androgen excess has been associated with increased cardiovascular risk in women; serum testosterone correlates with indices of subclinical atherosclerosis and cardiovascular disease (CVD). Moreover, women with PCOS, as compared with age- and body mass index-matched women without the syndrome, appear to have a higher risk of insulin resistance, hyperinsulinemia, glucose intolerance, dyslipidemia, and an increased prothrombotic state, possibly resulting in a higher rate of type 2 diabetes mellitus, fatty liver disease, subclinical atherosclerosis, vascular dysfunction, and potentially cardiovascular disease and mortality. Obesity, an independent risk factor for CVD, is also more prevalent in PCOS women as compared to age-matched controls, and is aggravated by androgen excess and has an detrimental android pattern of distribution. Further alterations in PCOS include an increased prevalence of sleep apnoea, as well as various changes in the secretion and/or function of adipokines and adipose tissue-derived pro-inflammatory factors, all of them with direct or indirect influences on the complex signaling network that regulates metabolism, insulin sensitivity, and energy homeostasis. The literature is full of conflicting data and this is partly due to the definition(s) used to identify women with PCOS and also the phenotypic variability of PCOS, which in itself generates significant influence on the cardiometabolic risks.

DOI: 10.1530/endoabs.49.D4.1

D4.2

Is cardiovascular risk increased in women with PCOS? – AGAINST

Enrico Carmina
Italy.

Young women with PCOS presents a severe risk of developing type II diabetes, cardiovascular diseases, chronic liver disease and endometrial cancer. However, in term of events, there is proven evidence only for type II diabetes and for endometrial cancer. In particular, it is still unclear whether CV events are increased in women with PCOS. Completely different data have been published and the quality of many studies is relatively low. Some recent evidence suggests a larger number of cardiovascular events (4 fold) in young population with PCOS. However, studies at this age present an inherent difficulty linked to the low number of CV events in young population. In addition, these data are based on hospitalized population and this approach may have some biases because it may exclude the less affected population. In our large follow up of unselected PCOS patients, no increase of CV events was noted. In aged PCOS patients the data are also contrasting with some studies showing a slight increase of CV diseases and others reporting normal prevalence of CV events. Large follow up studies are missing and are urgently needed to solve this important issue. However, it is clear that the number of events in aged women, who had PCOS during their reproductive age, is much lower than that expected on the basis of risk calculation during young adult age. The mechanisms of the discrepancy between CV risk and late events in PCOS are unclear but a progressive normalization of CV risk during late reproductive age may have a main role.

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Should We Still Ablate all Patients Undergoing Total Thyroidectomy for Thyroid Cancer?

D5.1

Should we still ablate all patients undergoing total thyroidectomy for thyroid cancer? - FOR

Markus Luster
Germany.

Abstract Unavailable.

D5.2

Should we still ablate all patients undergoing total thyroidectomy for thyroid cancer? - AGAINST

Sophie Leboulleux
France.

Regarding the debate about whether we should still ablate all patients undergoing total thyroidectomy, the answer is no. Most thyroid cancer patients have an excellent prognosis with a normal life expectancy and among them most of them have a low risk of recurrence. The absence of ablation in patients with thyroid cancer of 1 centimeter or less (pT1a) is already widely applied, so, we are used not to ablate all thyroid cancer patients treated with total thyroidectomy. The question, indeed, is whether the group of patients not undergoing systemic ablation can be extended beyond pT1aN0/x patients. The selection of patients to be spared from ablation can indeed be based on pathology examination, on tumour size, on lymph node involvement and since some of these patients are now recognized as low risk patients. The selection can also be based on postoperative thyroglobulin level because of its excellent negative predictive, whether measured after TSH stimulation or measured under levothyroxine treatment with ultrasensitive method, and on neck ultrasonography. However, prospective randomized trials are needed in order to answer this question of ablation. This will allow reinforcing the strength of recommendation that can be done.

DOI: 10.1530/endoabs.49.D5.2

Is It Time for Initial Combination in Type 2 Diabetes?

D6.1

Is it time for initial combination in type 2 diabetes? - FOR

Stefano Del Prato
Italy.

Abstract Unavailable.

D6.2

Is it time for initial combination in type 2 diabetes? - AGAINST

Didac Mauricio
Spain.

Type 2 diabetes mellitus is a heterogeneous disease with multiple pathophysiological pathways contributing to hyperglycemia, and also resulting in a variable clinical picture. Thus, individualization of hypoglycemic therapy is a mainstay of current clinical guidelines. Several factors should be considered for a given treatment choice. These include the characteristics related to a given medication (efficacy, hypoglycemia, effect on weight, other safety issues, the mechanism of action), and other factors, like costs related to each treatment, convenience for the patient, etc. Initial combination therapy may be considered as a suitable choice for some patients/circumstances. However, the evidence favoring this combinatory initial option has not been clearly established. Different issues concerning the convenience of using either initial combination therapy vs sequential addition of hypoglycemic drugs will be addressed during the discussion. The following aspects will be dealt with: long term efficacy of combination therapy vs sequential titration/addition of hypoglycemic agents; durability; overall cost and cost-effectiveness; safety issues, including hypoglycemia and weight changes; advantages/disadvantages in terms of treatment adherence; effects on patient-oriented outcomes, including long-term morbidity and mortality; effect on clinical inertia; what is the best combination of hypoglycemic agents; individualization vs combination for every patient. To conclude, the question about the implementation of initial combination therapy as a strategy in usual clinical practice is still open.

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Meet The Expert Sessions

MTE1

How to manage diabetes in the elderly?

Leocadio Rodriguez-Manas
Spain.

The prevalence of diabetes and glucose intolerance is close to 50% in people older than 65. At the same time, near 50% of people with type 2 diabetes are $\geq$ 65 years old. But being these figures relevant enough to raise a special consideration about how to manage diabetes in this population, there are other reasons supporting the need of that a special consideration. These other needs are not quantitative but qualitative ones, making older people with diabetes a particular group of patents with different characteristics, different aims and, as a consequence, different management compared to adult non-older patients with type 2 patient and, of course, younger patients with both type 1 and type 2 diabetes. These differences range from differences in the pathophysiology of diabetes, that although stemming from insulin resistance have a different origin of this insulin resistance, to the mechanisms underlying the development of vascular and other complications of diabetes, the impact of the disease in the several classical target organs (in people older than 80 diabetes does not increase the risk of blindness), the clinical manifestations of the disease, the diagnostic approach or the general management of the patient. Among all of those, and some others, differences, perhaps the most relevant is the focus on function. While in younger populations, the focus is usually centered in preventing or treating vascular disease (both micro- and macroangiopathy) and other complications of diabetes, when people is older the main focus is to avoid, delay or, if possible, reverse functional (both physical and cognitive) impairment. It is quite clear that diabetes increases less significantly the risk of death in this population, reaching relative risks as low as 1.2 in people older than 80 years. old. However, diabetes is one of the chronic diseases increasing the risk of mobility disability, dependency for instrumental or basic activities of daily living, falls and cognitive impairment/dementia in more than twice. In addition, the role of functional status in conditioning the prognosis (both functional and vital, plus other outcomes like hospitalization) is increasingly higher as patient is getting older, substituting the classical role of the comorbidities (both those related and those non-related to diabetes). Finally, the functional impact of the disease is also the main factor explaining the costs of the disease, reaching figures of 78% of the costs. As a consequence, the management of diabetes in older people should be based in functional status as the main factor in the decision-making process, but also as the main therapeutic target. This change in the focus is crucial to get the best benefits when facing older people with diabetes.

DOI: 10.1530/endoabs.49.MTE1

MTE2

Diagnosis and management of GH deficiency - from childhood to adulthood

Jens Jorgensen
Denmark.

Pituitary dwarfism has been known for many decades, originally as a component of organic panhypopituitarism. GH for clinical use was purified by Maurice Raben from human cadaveric pituitaries and tested for the first time and with success in 1957 in a patient with childhood onset disease. Moreover, pivotal short term studies on the metabolic effects were performed in both healthy and hypopituitary adults. The concomitant introduction of imunnoassays for GH led to the introduction of GH stim tests and recognition of isolated and idiopathic GHD. But the scarcity of GH for clinical use was a major limitation until the 1980s when biosynthetic GH became available. This opened the possibility of novel indications including GHD in adults (GHDA). The two first placebo-controlled studies in 1989 reported positive effects in both childhood- and adult-onset GHDA in terms of body composition and exercise capacity. This has since been corroborated in numerous trials, and it is also documented that discontinuation of GH in the transition from child to adulthood is unfavorable. Finally, there is indirect evidence to suggest that GH replacement in adults may reduce mortality and does not associate with increased cancer risk. Still, GH therapy in adults is by no means a fountain of youth, and there is no evidence to suggest that it is of any meaningful use in either normal or frail aging. This MTE will discuss this exiting journey from a personal point of view.

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MTE3

Hormone-secreting adrenal tumours in pregnancy

Catherine Williamson
UK.

Hormone-secreting adrenal tumours are rare occurrences in women or reproductive age. The commonest is phaeochromocytoma, followed by primary aldosteronism and Cushing's syndrome. The shared maternal phenotypic feature of these tumours in marked hypertension. They may be difficult to diagnose as many of the clinical features are mimicked by pregnancy, e.g. flushing, weight gain, palpitations. Furthermore hypertensive disease occurs in approximately 5% of pregnant women. However, there are specific clinical features associated with each tumour type that aid diagnosis; the hypertension in phaeochromocytoma may be paroxysmal; primary aldosteronism is often accompanied by hypokalaemia and the striae in Cushing's syndrome are usually more purple and marked than in normal pregnancy. It is important to know the normal ranges for the specific endocrine tests used to diagnose each hormone-producing tumour, and once a diagnosis has been made a multidisciplinary team should be involved with clinical management. This should include endocrinologists with an understanding of gestational disease, obstetricians, specialist anaesthetists, midwives and neonatologists. Individualised decisions should be made with regard to treatment with surgery or drugs. All hormone-secreting adrenal tumours are associated with increased rates of adverse pregnancy outcome, including preterm labour and stillbirth. This talk will summarise current knowledge about the management of these rare, and potentially life-threatening tumours in pregnant women and will consider the merits of prospective population cohorts to improve our understanding of the optimal management strategies to improve maternal and offspring outcomes.

DOI: 10.1530/endoabs.49.MTE3

MTE4

Treatment of congenital hypothyroidism

Heiko Krude
Germany.

Treatment for congenital hypothyroidism (CH), based on thyroid extracts, was introduced more than 100 years ago and resulted in a compelling improvement of impaired growth, obesity, depression and severe delay of motor development. However, severe mental retardation remained despite treatment. It was only after the implementation of neonatal screening for CH in 1970s that intellectual outcomes improved to an average normal IQ. However, whether complete normalization of cognitive outcome is possible remains controversial, since some studies have found significant gaps compared to control populations including healthy siblings. Furthermore, there is some evidence that quality of life (QoL) scores are lower compared to the general population. To further improve the outcome, higher starting doses of more than 10 μg/kg and commencement of treatment within the first two weeks of life were recommended. The most recent outcome study from New Zealand, reporting patients treated according to a regimen consistent with these recommendations, documented IQ at age 10 years that was no longer different from sibling control subjects. Nevertheless treatment with higher starting doses has raised concerns regarding adverse effects of supraphysiological T4 levels, with studies in rodents and patients with neonatal hyperthyroidism suggesting abnormal CNS development. In addition, it has been repeatedly shown that the recommended high LT4 dose of $>$10 μg/kg results in fT4 levels in newborns and infants with CH that exceed the reference ranges in this age group. However, after decades of neonatal screening and recent confusion about an "unfavourable" outcome with a high dose LT4 treatment, we now provide strong evidence –based on a recent IQoutcome study- that the present recommendations of a high initial dose above 10 μg/kg is necessary, efficient and safe to achieve optimal cognitive development in all CH patients including those who are severely affected.

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MTE5

Modern spectrum of bone turnover markers – are they clinically useful?

Richard Eastell
UK.

Bone turnover markers reflect the work of the osteoblast and the osteoclast. They can be measured in blood or urine and allow for an inexpensive and non-invasive way to study bone metabolism. They have been evaluated for their use in

predicting risk of fracture, accelerated bone loss or the presence of secondary osteoporosis, but for all these uses they are not yet established. They are useful in monitoring the response to treatment of osteoporosis, especially with drugs such as oral bisphosphonates. One study focused on the clinical utility of modern spectrum of bone turnover markers for monitoring oral bisphosphonate therapy (alendronate, ibandronate, risedronate) in women with postmenopausal osteoporosis. The study concluded that two approaches could be used to identify response, namely a change beyond the least significant change or a change to below the mean value of bone turnover in healthy young women (1). This approach identified about 90% of women from the study as responding by 12 weeks on treatment. The International Osteoporosis Foundation and European Calcified Tissue Society proposed that a bone marker measurement made after 12 weeks was a good way to identify patients who are not adhering to therapy, as non-adherence is the commonest reason for non-response (2). The meet-the-expert session will examine the evidence for the use of bone turnover markers in treatment monitoring and give case examples of this approach in practice.

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DOI: 10.1530/endoabs.49.MTE5

MTE6

How best to utilise technology in diabetes?

Hans DeVries
The Netherlands.

More and more devices are becoming available for people with diabetes. Should you advise your patients to use a pedometer? How can insulin pumps be of help? An insulin pump is the best way to accommodate the changing insulin needs over the 24 hours of the day and gives one the opportunity to temporarily stop insulin administration in case of unanticipated exercise, which is impossible when using injection therapy. Trials have mainly been done in Type 1 diabetes, but a recent trial also shows beneficial effects in a selected group of people with Type 2 diabetes. The evidence for Continuous Glucose Monitors Continuous has recently been brought to higher level, both for insulin pump and injection therapy users. Both a lower HbA1c and less severe hypoglycemia have now convincingly been shown in people with Type 1 diabetes. The role of continuous glucose monitoring in diabetic pregnancy on the other hand is unclear. The newest kid on the block is Flash Glucose Monitoring, for which the evidence is mixed and scarce, but it does herald the end of finger pricks. And how are we going to implement the holy grail of diabetes technology, the artificial pancreas or closed loop? A first generation closed loop is now on the market in the US, EU to follow early 2018. What can it do and what not? Together we will cover a number of the above questions in an interactive way.

DOI: 10.1530/endoabs.49.MTE6

MTE7

When and which treatment to use in Graves disease?

Tomasz Bednarczuk
Poland.

Graves' disease (GD) is a heterogeneous autoimmune disorder affecting, with varying degrees of severity, the thyroid, eyes and skin. GD is the most common cause of hyperthyroidism. The incidence peaks between 30 and 50 years of age, but people may be affected at any age. Hyperthyroidism is caused by autoantibodies stimulating the TSH receptor on thyroid cells. The severity of thyrotoxicosis in GD is variable and the response to anti-thyroid drugs is difficult to predict. Graves' orbitopathy (GO) is the most common and serious extrathyroidal manifestation of GD, significantly impairing the quality of life of affected patients. Clinically apparent orbitopathy occurs in 25%–50% of patients. Pretibial myxedema and acropachy are much less common, occurring in less than 2% of patients. The reasons for this variation in the clinical presentation of GD are largely unclear. There are three treatment options for Graves' hyperthyroidism: (1) blocking of hormone synthesis by antithyroid drugs (ATD), (2) destruction of the thyroid by radioactive iodine (RAI) and (3) partial or total surgical ablation of the thyroid. Additionally, patients can take β blockers for symptomatic relief. Although all three options are effective, no treatment is ideal and thus indicated in all patients with GD. Selection of therapy depends on multiple considerations, including: patient's age, severity of thyrotoxicosis, presence of goiter, orbitopathy, pregnancy, comorbidities. The treatment selection must also take into account the patient's preference. Before deciding on a treatment plan, the treating physician and patient should discuss each of the treatment options, including the logistics, local availability, advantages, disadvantages, potential side effects and costs.

DOI: 10.1530/endoabs.49.MTE7

MTE8

How best to manage neuroendocrine tumours? - Towards a new algorithm

Alicja Hubalewska-Dydejczyk
Poland.

During the last couple of years an essential increase of newly diagnosed NENs has been observed, however it should be underlined that many cases represent new challenges for the medical staff. Development of personalized approach to NEN patients on the basis of knowledge rapidly coming from genetic/molecular research, improvement of biochemical/imaging diagnostic methods and availability of more efficient therapeutic options, means that existing guidelines are still being changed. However, the questions: 'what of the future hold for NEN?' and 'how will future achievements influence the new algorithm?' remain open. In the majority of patients the overall prognosis depends on the grade (G) and stage (TNM) of the tumour. Recently proposed classification of NENs divides additionally G3 NENs into NET G3a and G3b neuroendocrine cancers. Ki-67 is currently the main prognostic index which drives the management of all NENs, nevertheless it should be stressed that very often patient outcomes are difficult to foresee and the lack of response to therapeutic treatment regiments remains unpredictable so the identification of other prognostic factors would be of great help and it would make diagnostic and therapeutic decisions more appropriate. At present chromogranin A, urinary 5-HIAA and tumour specific hormones in secreting NENs are widely used as biomarkers. One should bear in mind that surgery is the only possible curative method in NENs however, half of the patients have metastases at presentation and unknown primary focus can also be challenging. Therefore, the development of fast and accurate imaging procedures (endoscopies, USG, CT/MRI and the implementation of the different radiolabelled compounds targeting various membrane/intracellular receptors/metabolic pathways (PET/SPECT-CT/MRI) is necessary. Antiproliferative therapy with SSA, TKI, PRRT and cytotoxic therapy should be given rather as sequential monotherapy than a combination one. Based on clinical cases of patients with NENs in different locations and at a different stage of the disease the different diagnostic/therapeutic options will be discussed during the Meeting.

DOI: 10.1530/endoabs.49.MTE8

MTE9

Sarcopenia – why should we care?

Franz Jakob

Abstract Unavailable.

MTE10

Contraception in women with obesity, metabolic syndrome and diabetes

Phillippe Bouchard
France.

Abstract Unavailable.

MTE11

Drug induced osteoporosis

Gherardo Mazziotti
Italy.

Abstract Unavailable.

MTE12

A modern approach for treatment PCOS

Hector Escobar-Morreale
Spain.

Abstract Unavailable.

MTE13

What can new insulins provide for management of diabetes?

Jean François Gautier
France.

The major abnormality in type 1 diabetes is insulin deficiency. Type 2 diabetes is also characterized by an insulin secretory defect so that many patients are on insulin therapy. Methods of replacing insulin have improved throughout the decades, but there are still limiting factors that prevent the achievement of a better HbA1c levels such as hypoglycaemic events and glycaemic variability, weight gain and fatty liver. Additionally, most patients wish to do less insulin injections and less blood glucose self-monitoring! New insulins and newer delivery systems are being developed that can improve some of the limitations of current insulins or make the delivery of insulins more acceptable for some patients. Extending the duration of action of basal insulins (glargine U300, Insulin degludec, PEGylated insulin Lispro) may have advantages in reducing risk of hypoglycemia (and especially nocturnal hypoglycemia) and weight gain. PEGylated insulin Lispro is no more in development for safety reasons (high triglycerides and liver enzymes) and there is still no head-to-head comparison between glargine 300 U/ml and degludec. Shortening the peak of fast-acting insulins in order to mimic the physiological first phase insulin secretion (bioD-090, rHuPH20, Ultra-fast-acting insulin aspart, BioChaperone lyspro) may also have advantages. However, peer-reviewed evidence to date remains scarce. Biosimilars are developed to minimize insulin cost but do not bring something new for the patients. Combination of new long acting insulins with a short acting insulin or with a GLP-1 analogue are available in some countries. These combinations reduce the number of injections. Different delivery systems may make insulin more acceptable to patients. Whether these innovations permit a better glycemic control will be discussed. Lastly, we will see whether 'smart' insulin, that is glucose-responsive insulin, the Holy Grail promise, will be available in the next future.

DOI: 10.1530/endoabs.49.MTE13

MTE14

Thyroid carcinoma: complicated cases

Valeriano Leite
Portugal.

Thyroid neoplasias show a wide range of biological behaviours from indolent to highly aggressive, invasive and metastatic cancers. The great majority of thyroid carcinomas are successfully treated with surgery, radioactive iodine and TSH suppressive therapy. However, a subset of tumors can behave aggressively, with distant metastasis and/or local invasion. These patients have a poor prognosis and a shorter survival, remaining a challenging task in treatment options. Cytotoxic chemotherapy has only limited effect, without clear evidence that benefit outweighs risk of toxicity. Radiotherapy is an option for surgically unresectable neck recurrences and for bone and brain metastases. Recently, interest rose on tyrosine kinase inhibitors (TKI) and, currently, there are several TKIs that have been approved for advanced thyroid cancers either from follicular or parafollicular origin. A judicious use of different treatment modalities in advanced thyroid carcinoma may improve patients' outcome and prolong survival. Illustrative cases of some advanced thyroid cancer patients will be presented and discussed in this MTE session.

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MTE15

Gaucher disease: interdisciplinary management

Milan Patakov
Serbia.

Gaucher disease (GD) is a rare, genetic, autosomal recessive lysosomal storage disease with multi-system manifestations caused by a deficiency of the lysosomal enzyme glucocerebrosidase, which leads to an accumulation of its substrate glucosylceramide (glucocerebroside) in macrophages of various tissues with an inflammatory response and a release of cytokines. In general population its incidence is approximately 1/40 000 to 1/60 000, rising to 1/800 in Ashkenazi Jews. Clinical features comprise cytopenias, splenomegaly, hepatomegaly, and bone lesions. Non-neuronopathic type-1 Gaucher disease, which affects the majority of patients (90% in Europe and USA), is characterized by visceral effects, whereas neuronopathic types 2 and 3 are dominantly associated with neurological impairment. The diagnosis of GD can be confirmed by the deficient acid glucocerebrosidase activity in peripheral blood leukocytes. Patients with type 1 GD, and even carriers of one gene mutation have predisposition to develop Parkinson's disease, and there is increased risk of some neoplasia in GD patients. Disease-specific treatment of type 1 GD consists of intravenous enzyme replacement therapy (ERT) with one of the available enzymes (imiglucerase, velaglucerase, or taliglucerase) or oraly administered substrate reduction therapy (SRT) with inhibitors of glucosylceramide biosynthesis (miglustat or eliglustat). Currently there is no treatment for type 2 disease which is lethal early in the life.

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MTE16

New treatment approaches in dyslipidemia

Luis Masana

The introduction of PCSK9 inhibitors has changed the paradigm of dyslipidemia treatment. These monoclonal antibodies produce an incremental LDL reduction of about 60% add-on current therapy. Achieving LDL concentrations below 40 mg/dl is usual. The recent publication on the effect of very low LDL concentrations on atherosclerotic plaque burden (Glagov study) and on cardiovascular outcomes (Fourier and Spire) show the impact of this therapy in cardiovascular prevention. In the other hand these treatments seem to be pretty safe. Ebbinhouse study has demonstrated no impact on neurocognitive function. Price of therapy is the main limiting factors and several scientific societies have issued recommendation for use. The aim of this meeting is discussing about the new approaches of dyslipidemia therapy.

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MTNE1

A paediatric perspective of endocrine late complications following childhood cancer

Tanya Urquhart
UK.

Dramatic improvements in cancer survival over the past four decades means that greater than 80% of children diagnosed with cancer can expect to survive for more than five years. For some cancers, such as acute lymphoblastic leukaemia and Hodgkin's disease, cure rates exceed 90%. Currently, there are over 26000 young adults living in the UK, 600 000 across France, Italy, Switzerland, Netherlands and the Nordic countries and 363 000 in the US, who are survivors of childhood cancer (CCS). A late effect (LE) is the term used to describe any physical, psychological or social consequence of the disease itself or the disease treatment. The consequence of cytotoxic effects on maturing tissues may only become apparent many years following completion of treatment and with subsequent development, hence the term LE. Treatment for childhood cancer

usually involves chemotherapy, radiotherapy (including radiosurgery) and surgery. These treatments can occur in isolation or in any combination, and can affect almost any system in the body. The most common effect of these treatments is on growth, endocrine function, fertility, neuropsychology and the cardiac systems. Two-thirds of childhood cancer survivors will experience at least one LE and the endocrine system is commonly involved. Another third of patients will develop two or more LE which may be severe or life threatening. Therefore this session will explore the endocrinopathies associated with the treatment for cancer in childhood using case studies to provide examples from practice. Knowledge of oncology and endocrinology are paramount for nurse specialists working with this patient cohort to ensure accurate education for young people about their past treatment and its implications for their future health. Transition will also be considered as these young people grow, develop and require continuing care from adult healthcare professionals.

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MTNE2

Providing nursing care for the adult patient with endocrine late effects of cancer treatment

Cecilia Follin
Sweden.

Survival rates of childhood cancer have improved markedly and today more than 80% of those diagnosed with a pediatric malignancy will become 5-year survivors. Nevertheless, survivors exposed to cranial radiotherapy (CRT) are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications and cardiovascular morbidity. Deficiencies of one or more anterior pituitary hormones have been described following therapeutic CRT for primary brain tumours, nasopharyngeal tumours, and following prophylactic CRT for childhood acute lymphoblastic leukemia (ALL). Studies have consistently shown a strong correlation between the total radiation dose and the development of pituitary deficits. Further, age at treatment and also time since treatment has strong implications on pituitary hormone deficiencies. Studies have shown that childhood cancer survivors (CCS) need information regarding psychosocial support and social advocacy. Thus, the challenge is to guide the survivors through the potential late complications and offer care designed to meet their specific needs in order to optimise their quality of life. Information about late complications is essential in order to achieve an independent life and to engage in healthy behaviour, such as regular physical activity. Thus, having a holistic approach, tailored to their specific needs is crucial for their future well-being and quality of life.

DOI: 10.1530/endoabs.49.MTNE2

MTBS1

Unravelling the role of transient receptor potential channels in endocrine regulation and metabolism

Thomas Gudermann
Germany.

Abstract Unavailable.

MTBS2

Regulation and dysregulation of appetite and satiety

Patricia Iozzo
Italy.

The modulation of appetite, satiation and food intake stems from the interplay of central mechanisms of homeostasis, hedonism and cognitive control, receiving and integrating information on energy balance and feeding status of the body from peripheral organs, including dietary and gut-related signals. Obesity is a phenotype, likely resulting from the dysregulation of one or more of the above mechanisms. Different mechanisms may prevail in different people, though leading to a similar phenotype. The recognition of such diversity would offer opportunities for personalized treatment. This lecture will present data from a study conducted in well characterized overweight women, undergoing brain imaging of glucose metabolism to detect cerebral reactions to sensory food stimuli. The study suggests that women with food addictive behavior have a specific pattern of activation, which implicates cognitive control and diet-related factors (hormones, substrates, and possibly microbiota) in their food seeking behavior. This hypothesis is supported by the characterization of feeding behavior and brain and brown adipose tissue (BAT) metabolism in mice models of neurodegenerative disease and/or high-fat feeding, also in combination with intranasal insulin therapy. In order to better define the sequence of events linking brain function and feeding behavior, studies in the offspring of obese mothers are addressed, since maternal obesity represents a preventable condition, in which the factors above are affected since early life in the offspring. Results in humans, and animal models will be presented. Cumulatively, our studies suggest that a hypermetabolic brain, deriving from metabolic disturbances or high-fat dietary exposure may be an early detrimental factor, and a hypometabolic brain reflecting neuronal loss may enhance food intake, but also BAT browning. Substrates, hormones and gut microbes can promote a vicious cycle.

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MTBS3

MicroRNAs and the regulation of glucose and lipid metabolism

Markus Stoffel
Switzerland.

Abstract Unavailable.

Nurse Sessions

N1.1

Clinical practice overlap and seamless care – diagnosis and management of hypothyroidism in patients with diabetes mellitus

Elena Shelestova

Today diabetes (DM) is one of the largest global health emergencies. Each year a large number people live with this condition. Currently there are more than 422 mln people with DM worldwide. DM is one of the major public health problems in Georgia. Number of people with DM is on the rise, though no exact statistical data for Georgia exist. Diabetes Atlas (International Diabetes Federation, 2015) gives diabetes prevalence for Georgia of 7.9%, though these data are extrapolated from other countries. On the other hand, hypothyroidism (HOT) is believed to be a common health issue worldwide. The prevalence of HOT in the developed world is about 4–5%, and the prevalence of subclinical HOT is about 4–15%. Both HOT and subclinical HOT are thought to be risk factors for T2DM development. In our patients approximately 30% of women and 15% of men have both conditions. Prevalence of both conditions increases with the age of the patients (age 35–74 years, prevalence range 7–5%).

Materials and methods

Herein, 2 clinical cases (coexisting T2DM and HOT) are discussed. Both patients (pt) were diagnosed and are managed at the National Centre for Diabetes Research. Case #1 – pt. E.G., 49 years old, female. T2DM since 2008, HOT – since 2015. Pt. was treated with oral hypoglycaemic agents (OHAs) – SU and Metformin (Met), in 2017 pt. was transferred to DPP-4 and Met. DM control is satisfactory. In 2015 pt addressed the Centre with typical signs and symptoms – weight gain, dyspeptic symptoms, cognitive impairment, constipation. Ultrasound examination was performed and thyroid hormones (TSH, F_4, anti-TPO) were tested. L-thyroxine therapy was initiated (50 mg, then elevated to 100 mg). Since treatment initiation pt. condition is satisfactory, clinical and laboratory tests have improved. Pt is control every 3 months. Prescribed treatment is continued, Case # – pt. K.N., 65 years old, female, HOT and goiter with thyroid nodules (no biopsy performed) were diagnosed in 2010. Treatment with L-thyroxine was initiated. No follow-up was carried out though the drug (50 mg) was used regularly. In 2017 pt. came to our Centre for the 1-st time. Ultrasound of the thyroid gland and hormone tests was performed that revealed thyroid nodules (TSH was within the *n* range). Nodule biopsy was carried out, colloid goiter was diagnosed. Pt had following DM risk factors – family history of DM, obesity, arterial hypertension, HOT. Thus, she was screened for DM. HbA1c was 7.0% indicating to T2DM. Met. (500 mg) was initiate. Treatment with L-thyroxine at selected dose is continued. Diet and physical activity recommendations were selected individually. At present both pts are regularly followed-up (every 3 months). Doses and treatment are adjusted based on the results achieved.

Conclusion

Combination of the conditions is globally widely spread, it needs serious attention, knowledge and experience to manage. Proper management permits pts to live long and productive life and avoid complications caused by the conditions.

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N1.2

Clinical practice overlap and seamless care – links between hypogonadism, the metabolic syndrome and type 2 diabetes

Andrew Dwyer
Switzerland.

There is a bi-directional relationship between hypogonadism and type 2 diabetes and the metabolic syndrome (T2DM/MetS). Studies show that up to 50% of men with MetS/T2DM have testosterone deficiency. Moreover, both hypogonadism and MetS confer increased health risk for morbidity and mortality. Men with MetS are twice as likely to develop cardiovascular disease and have a fivefold higher risk for developing T2DM. Notably, the inverse relationship between testosterone and MetS is consistently observed across racial and ethnic groups. Therefore, in the setting of ever increasing obesity rates, the relationship between the reproductive endocrine axis and metabolism warrants renewed attention. Using a case-based approach, this presentation will provide an overview of the pathophysiologic basis for the relationship between hypogonadism and MetS/T2DM. Male patients may be trapped in the vicious cycle of hypogonadism-obesity-insulin resistance. We will review an evidence-based approach to the patient including the appropriate evaluation and treatment based on existing guidelines and recommendations. This presentation will have a particular focus on the role of the endocrine nurse in managing patients who present with this confluence of endocrine disorders. Current challenges in the field will be highlighted and we will touch on some yet unanswered questions as well as envisioned future directions. At the conclusion of this session participants will be able to:

- describe the interrelationship between hypogonadism and MetS/T2DM
- identify those patients who warrant screening for androgen deficiency
- recognize barriers to providing integrated care for these patients
- examine how their nursing care for these patients may be improved

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N1.3

Clinical practice overlap and seamless care – challenges in the management of patients with Cushing's syndrome and diabetes

Mies Kerstens
The Netherlands.

This lecture focuses on, a patient with Cushing's syndrome cased by bilateral adrenal hyperplasia. After adrenal surgery, there are major challenges in the care for this patient, that will be addressed: challenges in medical treatment (cortisol withdrawal and change of medication in hypertension en diabetes mellitus) as well as challenges in coaching (misconceptions in diabetes mellitus treatment, fears, educational needs with respect to hypercortisolisme and hypocortisolisme, withdrawal complains).

DOI: 10.1530/endoabs.49.N1.3

N1.4

Clinical practice overlap and seamless care – at risk of two endocrine emergencies: the patient with type 1 diabetes and Addison's disease

Sofia Sjöberg
Sweden.

Patients diagnosed with Addison's disease and diabetes mellitus type1, has a rare combination of two autoimmune conditions. Two diagnosis that requires a great deal of self-care. Patients have a potential risk to induce endocrine emergencies such as diabetic hypoglycemia, adrenal crisis and diabetic ketoacidosis. The lack of lifesaving hormones can put the patient in potential life threatening situations. I'll share my experience in meeting these patients. Brief physiology how the lack of hormones affects the glucose metabolism and what aid the patient need to handle the two disorders in daily life.

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N2.1

Nurses professional development and networking session – obstructive sleep apnea and comorbidities in patients with pituitary adenomas

Christine Yedinak
USA.

Short sleep duration and insomnia have been linked to higher risk of cardiovascular disease and CVD related mortality. Likewise, obstructive sleep apnea has been shown to confer a higher cardiovascular risk and is reported to be associated with 52-70% of acute myocardial infarctions and strokes. Hypertension (HTN), diabetes (DM), weight gain, sleepiness, fatigue and depression have all been correlated with obstructive sleep apnea (OSA). Patients with pituitary adenomas (PA), particularly those with Cushing's disease and acromegaly, often present with reported sleep dysfunction, fatigue and metabolic risk factors, diabetes, hypertension and cardiovascular disease and depression. The prevalence of sleep apnea in patients with pituitary hypersecretion at diagnosis has not been clearly quantified in patients as it may not be recognized and may go undiagnosed at the time of presentation. Additionally, the correlation with diabetes and other cardiovascular risk factors is not clear in these disorders. There is little data regarding the impact of treatment and disease remission on both OSA and persistent risk factors. The aim of this presentation is to explore the prevalence and correlation between sleep disturbance (SD), depression, BMI, HTN, diabetes

Mellitus (DM), pituitary deficiencies (PD), tumor size, diagnosis and risk of OSA for patients with PA pre and post treatment remission. Data from one institution will be presented.

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N2.2

Nurses professional development and networking session – utilising the competence framework to develop the role of endocrine nurses in adrenal insufficiency

Janina Kirchner
Germany.

The competence of endocrine nurse in the treatment of adrenal insufficiency (AI) is defined by the competence framework. Here is distinguished into Competent, proficient and expert. In these points, the nurse's knowledge is presented and gives a good overview of already acquired knowledge and things to be learned. With the acquired knowledge the endocrine nurse is intended to treat, train and support patients with AI as far as possible. Due to differences in the health systems of the countries in Europe, not all approaches are possible. Here the example of Germany is shown how patients with AI are provided with a national training program and the competence framework is also applied.

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N2.3

Nurses professional development and networking session – hybrid training of nurses in/for the endocrinology; train the trainer with help of e-learning modules

Johan Beun
The Netherlands.

Adrenal insufficiency is a rare adrenal disorder that can be made more complicated by an adrenal crisis even to a life-threatening situation. An adrenal crisis occurs when the body has a shortage of the hormone cortisol. If the patient does not receive the correct treatment an adrenal crisis can be fatal. This can be avoided by correctly and carefully following the 'stress instructions' (also known as 'sick day rules'). A significant percentage of patients have insufficient knowledge of these stress instructions or are not able to put them into practice themselves. In addition, it has become evident that the stress instructions vary between the different hospitals. For that reason, AdrenalNET has drawn up uniform stress instructions. These form part of the Quality of Care Standard for Adrenal Disorders, which sets out quality criteria (as applicable in the Netherlands) for the care of patients with adrenal insufficiency. One important quality criterion for the proper care of patients with adrenal insufficiency is that the hospital must have a nurse who has successfully completed this training course.
Objective
The objective of this training course is to offer nurses the essential theoretical and practical knowledge that they need if they are to provide adrenal patients with optimum care and instruct them how to apply the stress instructions for themselves. Indirectly, this will also help to promote the principle of co-management when patients with adrenal insufficiency find themselves in stressful situations. We are, in fact, training the trainers first via e-learning modules (4×) later one day at the university incl. a test at the end.

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N2.4

Nurses professional development and networking session – developing a European position statement for endocrine nurses providing care for patients with adrenal insufficiency

Sofia Llahana
UK.

Abstract unavailable.

N3.1

Update on diet and lifestyle throughout lifespan to improve health – prevalance and treatment of vitamin D deficieny in children

Pauline Musson
UK.

A number of factors have been associated with the apparent increase in children with vitamin D deficiency (VDD) in developed countries: increased awareness, increased migration, children living with chronic illness or disabilities, effects of medication (e.g. glucocorticoids, anticonvulsants), use of sunscreen, changes in lifestyles and a rise in childhood obesity. The clinical features of VDD vary with age and degree of deficiency and importantly, calcium deficiency is now recognized as a key factor in symptomatic VDD. At presentation, children may be asymptomatic or, have musculoskeletal pain; and in severe cases hypocalcaemic seizures, rickets and life threatening cardiomyopathy may occur. Evaluation of children should include careful assessment of dietary intake, previous medical history, medication review (including use of complementary alternative medicines), growth and puberty, and systemic enquiry of symptoms suggestive of malabsorption. Biochemical investigations are merited in symptomatic cases and there are important rare diagnoses that should be considered when interpreting results. There are a variety of treatment regimens for VDD. Typically treatment is with cholecalciferol, administered in daily, weekly, monthly or 12 weekly doses. Oral doses are considered as effective as intramuscular injections in children with normal intestinal absorption. Potential side effects from treatment should be communicated to the family and are rare. Calcium supplements should be considered in those with inadequate dietary intake. The family should be made aware of the reasons for intervening, the differences between treatment versus supplement doses of vitamin D, and how to optimize diet and adverse lifestyle factors. Some licensed products are not palatable for children and achieving adherence can be challenging. Poor medicine adherence may be further aggravated by confusion regarding the doses required and inconsistent information given to families by health care professionals. I will review the contemporary multidisciplinary approach to the child presenting with vitamin D deficiency with illustrative clinical cases.

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N3.2

Update on diet and lifestyle throughout lifespan to improve health – sexual hormones and bone, a close link throughout lifespan

Georgios Papadakis
Switzerland.

Bone health is increasingly recognized as a crucial factor for quality of life. Osteoporosis, defined as bone impairment leading to an increased risk of fracture, is an important source of morbidity and even mortality in later life. Both male and female achieve the peak bone mass at around the age of 25 years. This peak is significantly lower in case of puberty and/or growth disorders, thus increasing the risk of osteoporosis later in life.
Discussion
Our Reproductive Division of Endocrinology in Lausanne University Hospital specializes in Congenital Hypogonadotropic Hypogonadism (CHH), a disorder characterized by absent puberty and infertility due to complete or partial deficiency of GnRH, the hypothalamic hormone that initiates the reproductive cascade. When CHH is accompanied by anosmia, it is called Kallmann syndrome (KS). In our cohort of KS and CHH patients, there is an important decrease of bone density, which is more significant when the disease was diagnosed late in life, resulting in long periods without hormonal replacement. On the contrary, as our clinical cases illustrate, when diagnosis of these rare disorders is performed promptly and adequate treatment is followed, the patients maintain a near-normal bone density and avoid fractures later in life. In a different approach to the relation between bone and sexual hormones, using data from the OsteoLaus population-based study, a large cohort of post-menopausal women, we recently showed that menopausal hormone treatment (MHT) is associated with enhanced bone density and structure. Interestingly, the bone benefit seems to persist for at least 2 years after its withdrawal. These results corroborate other studies outlining that in young postmenopausal women aged 50 to 60 years old the ratio benefit/risk is clearly in favor of the benefits in terms of bone health, cardiovascular outcomes and even mortality. We should reconsider MHT for recently postmenopausal women with menopausal symptoms such as hot flushes and/or increased risk of fractures. In new unpublished data, we detected that MHT users have significantly lower visceral fat mass, an important element with potential bone and systemic implications.

Conclusion
Sexual hormone deficiency throughout lifespan severely impairs bone quantity and quality leading to bone fragility. Increased awareness of the link between bone and gonadal function is mandatory among endocrine physicians and nurses in order to promote early diagnosis and avoid lack of treatment. The risk of bone morbidity later in life can be an important argument to increase patient's adherence to therapy.

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N3.3

Update on diet and lifestyle throughout lifespan to improve health – osteoporosis and prevention of fractures: nurses can a play key role

Marsha Van Ooswaard
The Netherlands

Treatment of osteoporosis is all about prevention of fractures. It relies on a combination of approaches, including adjustments to the patient's diet and lifestyle, pharmacological therapy, and patient education. Changes to the patient's diet and lifestyle typically involve: optimizing calcium and vitamin D intake and exercise levels, cessation of smoking and reducing alcohol consumption. Pharmacological therapies used to treat osteoporosis by reducing the fracture risk include bisphosphonates or the RANK ligand inhibitor denosumab. Nurses have an important role in educating patients about fracture risk, the benefits of lifestyle modifications for maintaining bone health and the treatment options available, including side effects and the importance of adherence. In the current Dutch osteoporosis guidelines, it is recommended that hospitals appoint a specialised fracture nurse for the organisation and coordination of osteoporosis care. These specialised nurses provide care relating to case finding, risk evaluation, prevention, diagnosis, treatment and follow up. Each of these steps is essential and an insufficient implementation can result in suboptimal fracture prevention. Their main area of expertise is the recognition of risk factors. These risk factors can be related to the bone itself, a fall or the patient's lifestyle. Some of these factors can be influenced, some cannot. Patients need to have a good understanding of their diagnosis and fracture risk to make informed choices with regard to pharmacological treatment and/or lifestyle change.

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Oral Communications

Adrenal – Basic & Clinical

OC1.1

High resolution tissue mass spectrometry imaging: a new tool for identification of prognostic markers in adrenocortical carcinoma

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Adrenocortical carcinoma (ACC) is an orphan tumor entity the pathogenesis of which is poorly understood. In advanced tumour stages, prognosis is unfavorable, but biomarkers for early diagnosis are lacking. MALDI-Mass Spectrometry Imaging (MALDI-MSI) enables semi-quantitative detection of a broad spectrum of analytes including endogenous cell metabolites in tissue sections. MALDI-MSI was used as a discovery approach to analyse tissue specimens of 72 ACC patients in FFPE tissue arranged in tissue microarrays to identify pathways of pathophysiological relevance and histologic markers related to patient prognosis. We focused on steroid hormones and their metabolites which might also serve as tumour-derived blood biomarkers in the future. 3843 individual endogenous *m/z* species were obtained of which five were identified as known components of steroid hormone synthesis and metabolism. 2/5 steroid hormone metabolites showed differential abundance between ACC samples. Their low abundance in 5 and 6 of the 72 ACC samples was associated with poor overall survival in Kaplan-Meier analyses (Log rank $P = 0.0030$ and 0.0045, respectively). Based on the type of the steroid hormone modification present, mass spectra were screened for related *m/z* species. An unusual steroid hormone metabolite (M) was identified and validated by tandem mass spectrometry. After multivariable adjustment for age, tumor stage and sex by using the Cox proportional hazards model, presence of M was associated with poor overall survival (HR 4.54, 95%CI 1.56–13.22; $P = 0.0056$). By using immunohistochemistry we analysed protein expression of two related enzymes which was correlated with metabolites abundance. In conclusion, we demonstrated the utility of MALDI-MSI in detecting and identifying small molecule markers in FFPE tissue samples of ACC. A limited number of compounds related to steroidogenesis with strong prognostic value could be detected. One steroid hormone metabolite and related enzymes were of outstanding prognostic value. The potential of these metabolites as blood biomarkers remains to be investigated.

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OC1.2

EZH2: a master regulator of adrenal cortex homeostasis and zonation

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In adult mice the adrenal cortex is divided, in two distinct functional zones, outermost zona glomerulosa (ZG) and innermost zona fasciculata (ZF), encapsulated by a thin layer of mesenchymal cells (capsule). The adrenal cortex undergoes constant centripetal cell renewal, reliying on recruitment of progenitors located within an outer cortex niche. Progenitors initially differentiate as ZG cells and undergo lineage conversion to ZF as they move within the cortex. This relies on a subtle balance and trans-inhibition between WNT and PKA signalling pathways. Epigenetic histone modifiers are prototypical factors that play essential roles from embryonic development to carcinogenesis. We have recently shown that the histone methyl-transferase EZH2 is overexpressed in adrenal cortex carcinomas where is it associated with poor prognosis and tumour aggressiveness. In order to understand EZH2 function in adrenal physiology, we have developed a mouse model of EZH2 inactivation relying on a floxed allele of EZH2 and the Sf1:Cre driver (EZH2KO). Our analyses show adrenal hypoplasia and primary corticosterone insufficiency, associated with expansion of ZG at the expense of ZF and aberrant mixed ZG/ZF differentiation. Consistent with the role of PKA and WNT signalling in establishment and maintenance of zonation, WNT pathway is increased whereas PKA activity is decreased in EZH2KO adrenals. In addition to zonation defects, EZH2KO present abnormal accumulation of 'stress progenitors'. Recruitment of these particular progenitors is under control of WT1 and GATA4. Our *in vivo* ChIP and expression data show that these two transcription factors are direct targets of the inhibitory action of EZH2 in the adrenal. Altogether, these data suggest completely unanticipated functions of EZH2 in the control of stress progenitors homeostasis through WT1 and GATA4 and adrenal cortex zonation, which rely on a novel interaction between EZH2 and PKA signalling pathway.

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OC1.3

Steroid metabolomics for accurate and rapid diagnosis of inborn steroidogenic disorders

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Background
Urinary steroid metabolite profiling is an accurate reflection of adrenal and gonadal steroid output and metabolism in peripheral target cells of steroid action. Measurement of steroid metabolite excretion by gas chromatography-–mass spectrometry (GC–MS) is considered reference standard for biochemical diagnosis of steroidogenic disorders. However, performance of GC–MS analysis and interpretation of the resulting data requires significant expertise and age- and sex-specific reference ranges. Here we developed novel computational approaches for rapid interpretation of GC–MS data for diagnosis of inborn steroidogenic disorders
Methods
We analysed the urinary steroid metabolome by GC–MS in 829 healthy controls (302 neonates and infants, 167 children and 360 adults) and 118 untreated patients with genetically confirmed inborn disorders (21-hydroxylase deficiency, 17-hydroxylase deficiency, POR deficiency, 11β-hydroxylase deficiency, 3β-HSD2 deficiency, 17β-HSD3 deficiency, 5α-reductase type 2 deficiency, cytochrome b5 deficiency). We calculated age-related normative values for established metabolite ratios representing distinct enzymatic functions. We developed a novel interpretable machine learning technique, Angle Learning Vector Quantisation (ALVQ), which looks at all possible metabolite ratios, computationally reduces these to the most relevant for discrimination, and differentiates disease states by comparison to a representative prototype. The method runs independent of sex and age information, units of measurement and method of urine collection.
Results
Conventional biochemical ratios had 100% sensitivity but only very poor specificity. By contrast, ALVQ predicted 'affected urine' vs 'healthy urine' with 100% sensitivity and 97% specificity. For our three most prevalent conditions (PORD, SRD5A2 and CYP21A2), the specific condition was identified correctly in 96% of cases.
Conclusion
We developed a novel Steroid Metabolomics approach to automatically diagnose inborn steroidogenic disorders with very high sensitivity and specificity, superior to current methods, and with high potential for implementation in routine clinical care.

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OC1.4

The epidemiology of pheochromocytoma: increasing incidence and changing clinical presentation. A population-based retrospective study 1977–2015

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Pheochromocytoma is a rare disease but frequently poses a diagnostic dilemma due to the unspecific symptoms and its potentially life-threatening nature. There is a perception of an increase in the incidence of pheocromocytomas in recent years, but no data on time trends exist. We obtained data from The Danish National Registry of Patients, The Danish Registry of Causes of Death, and The National

Pathology Registry for all persons registered with pheochromocytoma in 1977–2015. Health records were reviewed to validate the diagnosis for all patients in the Northern and Central Regions of Denmark (population 1.75 million). Incidence rates were calculated using Poisson regression and time trends were analysed with year as a continuous explanatory variable. As incidence increased significantly in 2007–2015, we compared the clinical characteristics of patients diagnosed in this time interval with patients diagnosed in 1977–2006 in a secondary analysis using the Wilcoxon–Mann–Whitney test. We identified 183 confirmed cases of pheochromocytoma. A significant increasing trend ($P<0.001$) was observed in incidence rates from 2.06 (CI95% 1.68–2.49) per million person-years 1977–2006 to 4.65 (CI95% 3.72–5.82) 2007–2015. In 1977–2006 paroxysmal symptoms and secondary hypertension were the primary causes leading to the diagnosis (34 and 21%, respectively), while incidentalomas were the leading cause of diagnosis 2007–2015 (57%). Patients diagnosed 2007–2015 were older ($P<0.001$), less symptomatic ($P=0.003$) and had smaller tumours ($P=0.033$), compared to 1977–2006. No changes were observed in duration of symptoms or level of catecholamines. The incidence of pheochromocytoma has increased significantly in recent years, presumably due to increased use of imaging studies. It is unlikely that earlier diagnosis or lead-time bias accounts for the increasing incidence since patients are getting older. Therefore, these incidentaloma patients appear to represent a new group of pheochromocytomas not previously diagnosed. Whether surgical treatment provides a health benefit in this group remains unknown.

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OC1.5

Diagnostic accuracy of three confirmatory tests for primary aldosteronism: a prospective study and systematic review

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Background
Confirmatory tests, including saline infusion test (SIT), captopril challenge test (CCT) and fludrocortisone suppression test (FST) are commonly used for diagnosis of primary aldosteronism (PA). Each test has its advantages and disadvantages, but which one should be preferentially performed is controversial. We aimed to evaluate the diagnostic accuracy of three tests in a prospective study.
Methods
Five hundred and thirty-one hypertensive patients with high risk of PA were enrolled. Plasma aldosterone-renin ratio (ARR) was used for screening. Hypertensive patients tested positive at PA screening (ARR $\geq$ 3.7 ng/dl per μIU/ml), one in every three consecutive patient tested negative (ARR $<$ 3.7 ng/dl per μIU/ml) and patients who tested negative but PA was strongly suspected proceeded to three confirmatory tests. Area under receiver operator characteristics curve (AUC), sensitivity and specificity were calculated. A systematic review and meta-analysis of relevant studies were performed to place our results in context.
Findings
Finally, 132 patients diagnosed as PA and 104 diagnosed as essential hypertension completed three tests. AUC of CCT, SIT and FST were 0.97 (95% CI 0.95–0.99), 0.97 (0.95–0.99) and 0.98 (0.97–0.99), respectively, when post-test plasma aldosterone concentration (PAC) was used to confirm PA. But AUC of CCT significantly decreased to 0.76 (0.69–0.82) if PAC suppression ratio was used to confirm PA. When PAC cutoffs of SIT and FST was set at 8 ng/dl, and CCT at 11 ng/dl, the sensitivity were 87.9%, 93.2%, 92.4% and specificity were 93.3%, 90.4%, 90.4% respectively. No significant difference of synthetic AUC, pooled sensitivity or specificity between SIT and CCT was found in the meta-analysis. Only one study of FST fulfilling the criteria of the systematic review was included, reporting a sensitivity of 0.87 and a specificity of 0.95.
Interpretation
CCT, SIT and FST has comparable diagnostic accuracy. Based on their pros and cons, it is reasonable to recommend CCT as the first choice to confirm PA in clinical practice. When interpreting the results of CCT, PAC post-CCT is recommended.

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Diabetes Prediction and Complications

OC2.1

microRNA expression profile in plasma from patients with type 1 diabetes: a case–control study and bioinformatics analysis

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Context
Since the exact cause of type 1 diabetes mellitus (T1DM) remains unclear, the detection of novel biomarkers is necessary to complement the information obtained from the presence of autoantibodies together with genetic and environmental risk factors. MicroRNAs (miRNAs) are a class of small noncoding RNA molecules that negatively regulate gene expression. Changes in their expression were described in several pathological conditions, including autoimmune diseases. Circulating miRNAs are attractive biomarker candidates as they can be easily collected, are stable under different storage conditions and can be measured using specific assays.
Objective
To investigate a miRNA expression profile in plasma from patients with T1DM and nondiabetic controls and suggest their targets using bioinformatics analysis.
Design
Expressions of 48 miRNAs were investigated in the plasma from 33 T1DM patients and 26 age-and-gender-matched controls using Stem-loop RT-PreAmp Real-time PCR and TaqMan Low Density Array cards (Thermo Scientific Inc). Five dysregulated miRNAs were chosen for validation using RT-qPCR in an independent sample (27 T1DM patients and 14 age-and-gender-matched controls).
Results
Nine miRNAs were differentially expressed between controls and T1DM patients with <5 years of diagnosis: 1 miRNA was downregulated (has-miR-146a-5p) while 8 miRNAs were upregulated (hsa-miR-101-3p, hsa-miR-103a-3p, hsa-miR-1275, hsa-miR-146a-5p, hsa-miR-148b-3p, hsa-miR-155-5p, hsa-miR-200a-3p, hsa-miR-210-5p and hsa-miR-21-5p) in patients with <5 years of T1DM diagnosis compared to controls. In contrast, no differences were detected between controls and T1DM patients with >5 years of diagnosis. Bioinformatics analysis evidenced that hsa-miR-103a-3p, hsa-miR-146a-5p, hsa-miR-155-5p, hsa-miR-200a-3p and hsa-miR-210-3p participate in pathways associated with T1DM pathogenesis, such as apoptosis, insulin and immune system.
Conclusions
Our data demonstrate that 9 miRNAs are differentially expressed in T1DM patients in the first years of the diagnosis. Our study also provided novel information about biological pathways implicated in T1DM. Ongoing studies will further explore the role of these miRNAs as possible novel biomarkers for T1DM prediction.

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OC2.2

Effectiveness of complex therapy in patients with comorbidity of type 2 diabetes and essential hypertension depending on genetic polymorphism PPARγ2

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The aim
To evaluate effectiveness of complex therapy in patients with comorbidity of type 2 diabetes (DM2) and essential hypertension (EH) depending on genetic polymorphism peroxisome proliferator-activating receptor-γ2 (PPARγ2). Before and after 3 months of treatment we examined 145 patients with EH stage II, grade and DM2 moderate, subcompensated aged 45–60 years: group 1 (71 patients) received standart therapy (telmisartan, indapamide, metformin, gliclazide, atorvastatin, acetylsalicylic acid) and group 2 (74 patients) additionally received α-lipoic acid (α-LA). Both groups were matched for age, sex, EH stage and grade, the degree of compensation DM2. Methods: biochemical blood analysis, echocardiography evaluation of mitral diastolic blood flow and tissue Doppler spectral modes, reactive hyperemia, color Doppler mapping, enzyme immunoassay. We conducted genotyping of Pro12Ala polymorphism of PPARγ2.
Results
Patients with genotype Pro/Pro of PPARγ2 had significantly higher levels of total cholesterol, LDL, proinflammatory cytokines (TNF-α and IL-6), the values of intima-media thickness and significantly lower degree of endothelium-dependent vasodilatation as compared to genotype Pro12Ala/Ala12Ala. After standart therapy in patients with EH and concomitant DM2 (in all PPARγ2 genotypes) metabolic and hemodynamic parameters were improved. More pronounced dynamics was in patients with genotype Pro12Ala/Ala12Ala. Additional appointment of α-LA impacted more to vascular remodeling and levels of

proinflammatory cytokines as compared to standard therapy. Decrease HbA1c and triglyceride levels in patients with additional appointment of α-LA was significantly more pronounced as compared to standard therapy only in genotype Pro12Ala/Ala12Ala.
Conclusions
Effectiveness of complex therapy in comorbidity of DM2 and EH depends on PPARγ2 genotype. Dynamics of metabolic and hemodynamic parameters was more pronounced in additional appointment of α-LA, especially in genotype Pro12Ala/Ala12Ala.

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OC2.3

GLP-1 based multi-agonists-induced signaling includes profound TRP channel involvement in insulin secretion

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Promiscuous multi-agonists that simultaneously activate two or three key receptors (incretin- and/or glucagon receptor) were recently shown to improve glycemic control in mice. Here we investigated the underlying mechanisms of multi-agonists to enhance insulin secretion in murine islets and human pancreatic β-cells. These mixed agonists display a greater potency in cAMP signaling as compared to the native incretins. However, pharmacological blockade of cAMP signaling only partially inhibited the increases in insulin secretion. Therefore, additional mechanisms independent from Gs signaling-coupled Ca^{2+} influx appear to mediate insulin secretion. Here, we showed multi-agonists evoked significant increases in Ca^{2+} influx through activation of both voltage-dependent Ca^{2+} channels (VDCCs) and transient receptor potential channels (TRPs). These responses were more rapid and larger after multi-agonist stimulation than those after mono-agonists. Pharmacological blockade of TRP channels suppressed Ca^{2+} transients induced by multi-agonists to a greater degree than exposure to VDCC blocker. TRP blockers also blunted cAMP accumulation and abolished increases in whole-cell currents that are evoked with multi-agonists. These observations argue for a direct TRP channel activation by ligand-engaged incretin receptors. Collectively, direct activation of adenylyl cyclase through GPCR/channel constellations and concomitant rapid Ca^{2+} influx likely contribute to the increases in insulin secretion induced by multi-agonists.

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OC2.4

Effect of alive probiotic on insulin resistance in type 2 diabetes patients: randomized clinical trial

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Background
Probiotics have beneficial effect on obesity related disorders in animal models. Despite a large number of animal data, randomized placebo-controlled trials (RCT) concluded that probiotics have a moderate effect on glycemic control-related parameters. However, effect of probiotics on insulin resistance are inconsistent.
Aim
In a double-blind single center RCT, effect of alive multistrain probiotic vs placebo on insulin resistance in type 2 diabetes patient were assessed.
Methods
A total of 53 patients met the criteria for inclusion. They were randomly assigned to receive multiprobiotic 'Symbiter' (concentrated biomass of 14 probiotic bacteria genera Bifidobacterium, Lactobacillus, Lactococcus, Propionibacterium) or placebo for 8-weeks administered as a sachet formulation in double-blind treatment. The primary main outcome was the change HOMA-IR (homeostasis model assessment-estimated insulin resistance) which calculated using Matthews *et al.*'s equation. Secondary outcomes were the changes in glycemic control-related parameters, anthropomorphic variables and cytokines (TNF-α, IL-1β, IL-6, IL-8, INF-γ) levels. ANCOVA was used to assess the difference between groups.
Results
Supplementation with alive multiprobiotic for 8 weeks was associated with significant reduction of HOMA-IR from 6.85 ± 0.76 to 5.13 ± 0.49 ($P = 0.047$), but remained static in the placebo group (7.24 ± 0.74 to 7.95 ± 1.01; $P = 0.573$). With respect to our secondary outcomes, HbA1c insignificant decreased by 0.09% ($P = 0.383$) and 0.24% ($P = 0.068$) respectively in placebo and probiotics groups. However, in probiotic responders ($n = 22$, patient with decrease in HOMA-IR) after supplementation a significant reduction in HbA1c by 0.39% ($P = 0.022$) as compared to non-responders was observed. In addition, from markers of chronic systemic inflammatory state only TNF-α (15.8%, $P < 0.001$), and IL-1β (14.4%, $P = 0.001$) and IL-6 (22.1%, $P = 0.027$) changes significantly after treatment with probiotics.
Conclusion
Probiotic therapies modestly improved insulin resistance in patients with type 2 diabetes. Modulation of the gut microbiota represents a new treatment for diabetes and should be tested in larger studies.

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OC2.5

Urinary peptidomics for the detection of diabetic kidney disease

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Background
Diabetic kidney disease (DKD) is the main cause of end-stage renal disease It is defined by glomerular filtration rate (GFR) impairment and/or presence of increased urinary albumin excretion (UAE). However, these parameters are nonspecific and somewhat delayed manifestations of renal damage. Thus, earlier DKD new biomarkers are strongly warranted.
Objective
To investigate the urinary peptidomics profile of type 2 diabetes mellitus (DM) patients with different stages of DKD.
Methods
Casual urine samples were collected from 66 type 2 DM patients matched by age, gender and time of diabetes duration. Urine natural occurring peptides were purified by ultrafiltration under denaturing conditions and analyzed by LC–MS/MS. UAE was assessed by immunoturbidimetry and GFR was estimated by CKD-EPI equation. Kruskall–wallis, Mann–Whitney and $\chi 2$ tests were performed when appropriate; Perseus software was used to perform hierarchical clustering of significantly up- and down-regulated proteins.
Results
Type 2 DM patients (mean age $= -61.5 \pm 9.7$ years; males $= 47.1\%$) were stratified by the levels of albuminuria (normal ($n = 27$), moderately increased (MI, $n = 18$) and severely increased (SI, $n = 21$)). A total of 116 urinary proteins were detected by LC/-MS/MS. A distinct proteomic profile was identified in patients with SI albuminuria, represented by 11 proteins. When GFR values were analyzed, we observed that 13 urinary proteins differed significantly in the 9 patients with GFR < 60 ml/min per 1.73 m^2 when compared to 57 patients with GFR ≥ 60 ml/min per 1.73 m^2. Among the most remarkably different urinary protein profile, alpha-1 type I collagen was around 10% less expressed in SI patients, while alpha-1 antitrypsin, plasma protease C1 inhibitor and apolipoprotein-1 were ~twofold increased in these patients.
Conclusions
LC–MS/MS analysis revealed that at least 11 urinary proteins were differentially expressed in type 2 DM patients according to DKD severity. This study confirms the previously described findings in other populations and also detected novel proteins commonly altered in patients with GFR impairment and increased albuminuria.

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Receptors & Signalling

OC3.1

Epigenetic regulation of aldosterone synthase gene, CYP11B2 by potassium

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Purpose
We found the hypomethylation status of CYP11B2 gene in the aldosterone-producing adenomas compared with normal adrenal glands or non-functioning adrenal adenomas and reported that the methylation of promoter region of this gene influenced the mRNA expression in the adrenal cells. Angiotensin II or potassium regulates CYP11B2 gene expression in the adrenal cells. In order to clarify the acute effect of potassium on the methylation status of CYP11B2 gene, Human adrenal cells rats were treated with potassium and the methylation status of CYP11B2 gene in the adrenal cells was examined.
Methods
H295R cells were treated with potassium for 28 days. The gene expression of CYP11B2 was measured by real time quantitative PCR in the adrenal cells. ChiP assay and methylation activity were measured. Isolated DNAs from adrenal cells were treated with bisulfite and amplified using primers specific for the human CYP11B2 promoter regions.
Results
CYP11B2 mRNA levels were increased from 4th day to 7th day by the treatment with potassium. The methylation ratio was decreased from 4th day. The expression of CREB1 and NR4A1 were increased from 4th day. The methylation activity was increased from 7th day. The chromatin accessibility was increased from 4th day to 7th day
Conclusions
Aldosterone biosynthesis may be reversibly regulated by the epigenetic mechanism.

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OC3.2

Elucidating the role of Liver X receptors (LXRs) in the testis using lipid systems biology

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Introduction
The importance of the liver-X receptors (LXRs) in the maintenance of cholesterol homeostasis within the testis has yet to be fully characterised. By 7 months of age, Lxrα/β double knockout male mouse (Lxrα/β DKO) develops sterility with aberrations in testosterone production and lipid homeostasis. However, the underlying testicular LXR-regulated pathways are not well understood.
Aim
The aim of this study was to further understand the importance of LXRs in the testis by investigating disruption of candidate genes and networks of cellular lipids and steroid metabolites in Lxrα/β DKO mice.
Methods
We used RNA-seq and quantitative mass spectrometry to study whole testicular tissues from 6-month old Lxrα/β DKO mice alongside age-matched littermate controls. cDNA libraries were prepared followed by sequencing using NextSeq-500. Lipid extracts from mouse testis were prepared for LC-MS analysis using SONAR acquisition, based on an m/z isolation range of the quadrupole. Results were analysed using LipidMaps and Progenesis QI for normalized quantitation.
Results
Histological assessment of testicular tissues from Lxrα/β DKO mice confirmed abnormal seminiferous tubules, germ-cell loss and lipid deposition. Quantitative lipidomic analysis confirmed statistically significant differences in 53 lipid species including triglycerides and cholesterol esters (notably 20:4 cholesteryl ester) in the Lxrα/β DKO mice. Sphingolipid species (e.g. ceramide t18:0/20:0) were also altered. The retrieved curated targets were mapped onto KEGG pathway analysis, identifying key changes in steroid hormone biosynthesis and sphingomyelin metabolism. RNA-seq analysis revealed 1161 differentially expressed genes (log2 fold change in gene expression of -3.49 to $+2.17$, $P<0.01$) in Lxrα/β DKO. Androgen biosynthesis genes (Cyp17a1, Hsd3β2, Hsd17β3), triglyceride synthesis (Acsl, Acot7) as well as genes involved in sphingolipid metabolism were altered correlating with lipidomic data.
Discussion
Our integrative approach using lipidomic analysis with mRNA transcript studies provides novel data, implicating LXRs in pathways such as sphingolipid metabolism, critical for successful spermatogenesis.

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OC3.3

AKR1C3-mediated adipose androgen generation drives lipotoxicity in polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is prevalent metabolic disorder in women, associated with androgen excess and insulin resistance. These two major features are closely correlated, but the direction of causality remains unclear. Aldoketoreductase type 1C3 (AKR1C3) converts the androgen precursor androstenendione to testosterone (T), and is highly expressed in subcutaneous (SC) adipose tissue. We hypothesised that adipose tissue represents an important site linking androgen activation and metabolic dysfunction in PCOS. We undertook metabolic phenotyping in 10 PCOS women and 10 age- and BMI-matched controls. Participants underwent an oral challenge with the androgen precursor DHEA, alongside adipose tissue microdialysis, with measurement of metabolic markers and adipose androgens in microdialysate fluid. Non-targeted serum metabolome analysis was performed before and after androgen exposure. SC adipose tissue biopsies were collected for RNA-sequencing. Complementary *in vitro* experiments in primary SC adipocytes and a preadipocyte cell line were performed to examine the effects of insulin and androgens on AKR1C3 expression and de novo lipogenesis, respectively. PCOS women had higher adipose T ($P<0.0006$) and dihydrotestosterone (DHT, $P=0.01$) than controls as measured by liquid chromatography-tandem mass spectrometry. Non-targeted serum metabolomics and adipose microdialysis revealed pro-lipogenic effects of androgens at baseline and after DHEA in PCOS. AKR1C3 mRNA expression was increased in PCOS SC adipose tissue ($P=0.04$). Transcriptional profiling revealed dysregulation of mitochondrial and inflammatory pathways in PCOS SC adipose tissue. *In vitro* studies showed that insulin upregulates adipose AKR1C3 expression and activity, and androgens enhance adipose de novo lipogenesis. Pharmacological inhibition of AKR1C3 decreased adipose tissue androgen generation and androgen-mediated de novo lipogenesis. Complementary *in vivo* and *in vitro* studies highlight that AKR1C3-mediated intra-adipose androgen activation drives lipotoxicity and adverse metabolic risk in PCOS, fuelling a vicious circle of androgen generation and insulin resistance. Selective inhibition of AKR1C3 holds promise as a novel therapeutic approach in PCOS.

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OC3.4

Treatment with thyroid hormone metabolite 3,5-T2 alters cholesterol and sex steroid metabolism in mouse liver

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Recent findings revealed 3,5-diiodo-L-thyronine (3,5-T2) as a metabolically active iodothyronine affecting hepatic energy and lipid metabolism. Therefore, 3,5-T2 has been proposed as a potential hypolipidemic agent for treatment of obesity and its hepatic aftermath. So far only limited data exists relating to the effects of 3,5-T2 on metabolism in euthyroid mammals maintained on high-fat

diet from the day of weaning onwards. Therefore, we performed a study in which 20-week old diet-induced obese male mice in comparison to lean animals received either 3,5-T2 (2.5 µg/g body weight) or saline over a four-week period. To identify new target genes and signaling mechanisms of 3,5-T2 which are distinct from established hepatic T3 action we performed microarray-based transcriptome analyses of liver tissue. The transcriptome as well as qPCR data demonstrated higher hepatic expression of genes involved in cholesterol biosynthesis (e.g. Sqle 4.8-fold, Cyp51 2.8-fold, Hsd17b7 1.8-fold) and bile acid formation (Cyp7a1 2.0-fold, Cyp39a1 2.9-fold) in obese but not in lean mice treated with 3,5-T2. In contrast to the elevation of hepatic cholesterol biosynthesis, serum cholesterol concentration was reduced by up to 57% with 3,5-T2 administration. In addition, 3,5-T2 modulated expression of genes important for sex steroid biosynthesis and inactivation (e.g. Cyp17a1 3.5-fold, Hsd17b6 -7.8-fold). GC MS/MS analysis of the hepatic sex steroid hormone profile indicated higher progesterone and androstenedione content in livers of obese mice treated with 3,5-T2, whereas no such changes were observed in 3,5-T2-treated lean mice. These results suggest a diet-dependent role of 3,5-T2 in modulating local cholesterol as well as sex steroid biosynthesis and androgen homeostasis in mouse liver. Such actions of thyroid hormone metabolites have not been reported elsewhere up to date and might help to explain liver-targeting effects of T3-receptor beta-selective ligands.

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OC3.5

Accurate staging of non-alcoholic fatty liver disease through analysis of the urinary steroid metabolome

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is associated with dysregulated glucocorticoid metabolism. Advanced stages of NAFLD are associated with adverse outcome and current strategies to stage disease severity are still reliant upon liver biopsy. We have previously described changes to enzymatic pathways that regulate cortisol bioavailability; 11β-hydroxysteroid dehydrogenase type-1 (11β-HSD1) regenerates cortisol from inactive cortisone, and A-ring reductases, 5α- and 5β-reductase (5αR/5βR), inactivate cortisol to tetrahydrocortisol metabolites (THF/5αTHF). Changes to these pathways are apparent across the NAFLD spectrum (simple steatosis, steatohepatitis (NASH), fibrosis and cirrhosis). Here we have further validated these observations in a large cohort of patients with NAFLD and compared these to healthy controls and to patients with alcoholic cirrhosis.

Methods

Using gas chromatography / mass spectrometry, we analysed steroid metabolites in spot urine samples (corrected for creatinine) in patients with biopsy proven NASH ($n=65$), NAFLD cirrhosis ($n=51$), alcoholic cirrhosis (n=48) and in healthy controls ($n=58$). Additionally, we used machine learning-based analysis to investigate changes across 32 steroid metabolites.

Results

Cortisol regeneration (11β-HSD1 activity: THF+5αTHF/THE ratio), was significantly increased in NAFLD cirrhosis ($P=0.0004$), and alcoholic cirrhosis ($P<0.0001$), compared to controls. Cortisol inactivation (A-ring reductase activity: THF/5αTHF ratio) was significantly reduced in NAFLD cirrhosis compared to controls ($P=0.0004$), but not between controls and alcoholic cirrhosis ($P>0.99$) nor NASH ($P=0.332$). Machine learning-based analysis by generalised matrix-learning vector quantisation (GMLVQ) achieved excellent separation of control and NASH groups (AUC-ROC=0.87). Furthermore, there was near perfect separation of controls from NAFLD cirrhosis (AUC-ROC=0.99) and controls from alcoholic cirrhosis (AUC-ROC=0.98).

Conclusion

This data is consistent with our previous findings that identified differentially regulated steroid metabolic pathways across the spectrum of NAFLD. Furthermore, unbiased GMLVQ analysis of the urinary steroid metabolome appears robust in differentiating healthy controls from cirrhosis and warrants further exploration as a novel non-invasive biomarker tool to assess the severity of NAFLD.

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Thyroid Disease 1

OC4.1

Hypothyroidism in pregnancy is associated with twin pregnancies and with adverse obstetric outcome: Analysis of 142,277 deliveries data from a single center

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Introduction

Many studies have examined maternal and fetal complication rates in treated and untreated overt and subclinical hypothyroidism. Maternal hypothyroidism may adversely affect the development of the fetal pituitary–thyroid axis. It has also been reported to be closely related to adverse pregnancy outcome.

Aim

To study the prevalence and outcome of hypothyroidism in pregnancy during the last decade in a high volume obstetric center in Jerusalem.

Methods

A retrospective study of the obstetric database between August 2005 and December 2015 in Shaare Zedek Medical Center, Jerusalem.

Results

During the study period there were 142,277 deliveries of singleton or twin pregnancies (1.9% twin deliveries). The medical files of 4042 (2.8%) deliveries (group A) included a diagnosis of maternal hypothyroidism. Women giving birth with the diagnosis of hypothyroidism were older (31.1±6 years 28.8±5.6 y. $P<0.0001$). Gestational diabetes was more prevalent (7.3% vs 3.3%, $P<0.0001$) in group A as were hypertensive disorders (3.7% vs 2.3%, $P<0.0001$). Higher rate of assisted reproduction techniques were used in group A (8.5% vs 3.7%, $P<0.0001$). Although not previously reported, the incidence of twin pregnancies was higher in group A (3.8% vs 1.8% $P<0.0001$) and this association remained significant in a multivariate analysis with IVF as a co-variate (OR 1.43 95%CI[1.20–1.71], $P<0.001$). Obstetric complications including preterm deliveries (7.8% vs 5.2%, $P>0.0001$), cesarean sections (20.6% vs 11.4%, $P>0.0001$), any obstetric hemorrhage and prolonged hospitalization were more frequent in group A. The incidence of adverse neonatal outcome including low birth weight (7.3% vs 5.4%, $P>0.0001$) and NICU admission (5.1% vs 3.6%, $P>0.0001$) was higher in group A but there was no difference in fetal macrosomia and apgar scores.

Conclusions

In this large database, hypothyroidism is associated with adverse obstetric outcome. This is the first study to describe a higher incidence of hypothyroidism in twin pregnancies. TSH screening should be considered in twin pregnancies.

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OC4.2

Inducible thyrocyte-specific Gs alpha-deficient mice as a novel model for hypothyroidism

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The thyroid gland produces thyroid hormones, which are essential regulators of growth, development and metabolism of the body and is mainly regulated by the thyroid stimulating hormone (TSH)/TSH receptor (TSHR) interplay. The TSHR couples to all four G protein families *in vitro* but only for the Gs and Gq signaling cascade a role has been identified in vivo. To gain further insights into the complex signaling networks mediated by G proteins in the thyroid, we generated

a thyrocyte-specific tamoxifen-inducible Gs deficient mouse line (iTGsKO). Mice were injected with tamoxifen at P28 and phenotypic characterization was carried out by performing thyroid function tests at different ages. iTGsKO mice showed hypothyroidism at P56, four weeks after induction with tamoxifen. Furthermore, a decrease in thyroid weight and an increased pituitary weight support the conclusion of hypothyroidism in these mice. Morphometric analysis of the thyroid histology of iTGsKO mice with an age of 6 months (P168) showed that the thyrocyte layers between adjacent follicles and the follicle areas were significantly reduced when compared with controls. Interestingly, despite of an identical thyroid hormone status we observed a clear sex difference. In iTGsKO males, the body weight was significantly decreased at P70 when compared with control males but no weight difference was seen in females over the investigated time period of 6 months (P168). The lower body weight in iTGsKO males was associated with reduced fat mass. In summary, we show that iTGsKO mice are a useful tool for understanding the role of G-protein signaling in the thyroid as well as investigating the metabolic consequences in hypothyroidism.

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OC4.3

A novel variant in the SERPINA7 gene causing partial TBG deficiency in a women and two male siblings: molecular and protein structural analysis

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Background
Thyroxine-binding globulin (TBG) is the major human thyroid hormone transport protein. It is encoded by the SERPINA7 gene, located on the long arm of the X chromosome (Xq22.2). Inherited TBG abnormalities result in complete (TBG-CD) or partial (TBG-PD) TBG deficiency. We performed a comprehensive molecular analysis of the SERPINA7 gene in a Brazilian family with TBG-PD.
Methods
Genomic DNA was extracted from the female proband, her father, dizygotic twin sister and two brothers, and the coding region of the SERPINA7 gene was sequenced. The proband's X-chromosome inactivation pattern was evaluated by methylation analysis using the human androgen receptor (AR) gene, located next to SERPINA7 (Xq11.2). Structural analysis of the Serpin protein family was performed using PFSTATS, and was also used to map equivalent positions in all human homologs. Molecular modeling was done as described by Feyfant et al.
Results and Discussion
A novel missense mutation in the SERPINA7 gene (p.R35W; c.163C>T) was found in heterozygosity in the proband and in hemizygosity in her brothers. They presented low serum levels of total T4, total T3 and TBG, compatible with TBG-PD. The proband expressed an X-chromosome inactivation ratio of 20:80. The substitution of an arginine by a tryptophan is predicted to disrupt the protein surface and main electrostatic interactions. The conservation and correlation patterns showed that tryptophans are extremely rare (0.1%) in this position, and there is no significant ($P<10\text{-}10$) pairwise.
Conclusion
We report a new variant of the SERPINA7 gene associated with TBG-PD in three siblings. The proband's X-chromosome inactivation pattern may have accounted for the rare phenotypic expression in a heterozygous woman. The hydrophobic nature of the mutant is predicted to create an apolar patch at the protein surface, which would be significantly exposed to the solvent, and result in protein aggregation and/or misfolding with consequent thyroxin transport defect.

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OC4.4

The TSH receptor reaches the trans-Golgi network to induce PKA activation and trigger gene transcription

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Whereas G-protein coupled receptors (GPCRs) have long been believed to signal via cyclic AMP (cAMP) exclusively at the cell surface, our group has shown that GPCRs also stimulate cAMP production from the cell interior once internalized together with their ligands. This phenomenon, which we originally described for the thyroid stimulating hormone receptor (TSHR) in thyroid follicles, has now also been shown for several other GPCRs. However, the involved subcellular compartment(s) and the mechanisms linking signalling by internalized GPCRs to downstream biological effects are largely unknown. The aim of this study was to follow the trafficking of internalized TSHRs and involved signalling proteins in living primary thyroid cells by highly inclined thin illumination (HILO) microscopy as well as to monitor cAMP production and protein kinase A (PKA) activation by real-time fluorescence resonance energy transfer (FRET) microscopy. Importantly, using a biosensor nanobody that is specific for the active Gs-protein, we were able to directly demonstrate that the internalized TSHR activates an endogenous pool of Gs-protein located on membranes of the Trans Golgi Network (TGN). Direct monitoring of PKA activation with a Golgi-localized FRET sensor (AKAR2) showed a delayed PKA activation (approx. 10 min) after TSH stimulation, which is compatible with the time required for TSH/TSHR complexes to reach the Golgi/TGN. Moreover, our results also indicate that Gs-protein mediated signalling by internalized receptors at the TGN and the resulting PKA activation at a critical position near the nucleus are required for the efficient induction of CREB phosphorylation and gene transcription. These findings provide a mechanism to explain the biological relevance of GPCR signalling at intracellular sites, which might help explaining the pathogenesis of endocrine disorders such as Graves' disease and might pave the way to innovative pharmacological therapies.

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OC4.5

Levothyroxine replacement therapy: once treatment is started, should it last indefinitely?

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Background
Levothyroxine (LT4) is one of the most prescribed drugs worldwide. Once started, about 90% of patients continue LT4 treatment long-term.
Aim of the study
To evaluate the necessity of long-term thyroxine supplementation and to determine the prognostic factors that could identify which patients may discontinue LT4 treatment.
Design and methods
LT4 replacement therapy was paused for at least six weeks in all patients consecutively visiting our department, excluding those who have a definite need for L-thyroxine use (replacement after total thyroidectomy), those on thyroid-altering medication, women wishing to conceive and those who gave birth last year. 231 individuals were assessed (84% females), aged 48 years (SD = 16.5), who were categorized into the following categories: a) unknown reason for thyroxine supplementation ($n=62$), b) presence of thyroid nodules ($n=90$), normal TSH before thyroxine administration ($n=44$), over 10 years' use ($n=10$), therapy initiated post-pregnancy ($n=20$). Thyroid function was evaluated before and after the thyroxine pause. A value of TSH $\geq$4.5 IU/ml post treatment discontinuation was considered as 'relapse' and LT4 was reinstituted in those individuals. The potential prognostic factors analyzed were family history of thyroid dysfunction, sex, age, dose per BMI and dose per kg, thyroid volume, thyroid ultrasound characteristics, positivity of thyroid autoantibodies, basal TSH values and reason for the initial treatment indication.
Results
25.54% (83% females) of the studied subjects relapsed. Of the above-described factors, only diffuse inhomogeneous echogenicity was tentatively identified as the only predictive factor for relapse (71% vs 57%, *P*:001). The age (47.27 $\pm$ 15.45 vs 48.17 $\pm$ 16.98 years, *P*:0.72), the positivity of TPOAb (69%% vs 54%, *P*:0.064) and basal TSH values (1.51 $\pm$ 0.96 ΩΣ. 1.57 $\pm$ 0.84, *P*:0,81) did not differ significantly among the two groups.
Conclusions
One out of four individuals evaluated required thyroxine treatment. The need for a patient-centered approach regarding L-thyroxine supplementation and for a thorough review of patient history was evident.

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Cardiovascular Endocrinology

OC5.1

Polarized epithelial cells release exosomes loaded with miRNAs capable of interacting with HSD11B2 and MR genes

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Arterial hypertension is a major health problem affecting 1.13 billion people worldwide, of which 10% could be due to endocrine pathologies related to the mineralocorticoid receptor (MR) (i.e. primary aldosteronism, 11β-hydroxysteroid dehydrogenase type 2 enzyme (HSD11B2) deficiency). The MR pathway is expressed mainly in placenta, kidney and colon epithelial cells. Current research highlights potential epigenetic regulatory mechanisms for the MR pathway. Here, specific miRNAs are being studied as epigenetic regulators, either present in cells or exosomes (nanovesicles of 40–150 nm diameter) carrying miRNA, RNA, lipids and proteins. Those miRNAs could dynamically influence the onset and progression of the mineralocorticoid arterial hypertension (AH).

Aim

To isolate exosomes from polarized epithelial cells and to identify in their cargo miRNAs affecting HSD11B2 and MR gene expression.

Methods

The bioinformatic tool mirWalk2.0 was used to determine miRNAs capable to interact with HSD11B2 and MR RNAs. The cell line derived from colon epithelia (Caco-2) cells was cultured and polarized in Transwells. MR pathway genes and miRNAs targeting the MR and HDS11B2 were measured by qPCR. Exosomes from apical and basolateral culture medium were isolated at 24 h of incubation in basal conditions, quantified with NanoSight-NS300 and their specific miRNA content was determined.

Results

We identified bioinformatically that miRNA 135b, 644a and miRNA 488, 1205 could interact with the MR and HSD11B2, respectively. Caco-2 cells polarize after 21 days of culture (trans-epithelial resistance (TEER): 114.18 cm^2), expressing polarization genes (SLC11A2, SLGT1, ALPI), genes associated to MR pathway (NR3C2, HSD11B2, SCNN1A, SLC12A2, SGK1, ATP1A1) and pre-miRNAs (135b, 644a, 488, 1205). We identified that Caco-2 release $21\times109\pm0.69\times109$ (apical) and $4.1\times109\pm0.0029\times109$ (basolateral) extracellular vesicles per ml of which a 36.8 and 38.5% are exosomes with a modal range in 124–125 nm diameter respectively. Preliminary results show expression of miRNA 135b, 644a, 488 and 1205 in apical and basolateral exosomes.

Conclusion

Caco-2 cells release five-times more exosomes in the apical than basolateral side, both carrying miRNAs that could interact HSD11B2 and MR gene.

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OC5.2

Association of PPAR gamma gene expression with dietary intake of fat and oil among non-diabetic subjects

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Background and Objective

Several animal studies showed the expression of peroxisome proliferator activated receptor-gamma (PPAR gamma) in adipocytes among rats fed with high-fat diet was higher than those fed with normal diet. However, there are no human studies to support this. The objective of the present study was to investigate the association between the PPAR gamma expression in adipose tissue and intake of hydrogenated and non-hydrogenated vegetable oils and butter.

Materials and methods

Visceral and subcutaneous adipose tissues were obtained from 97 non-diabetic subjects (41 non-obese, 18 obese, and 38 morbid obese), who underwent open abdominal surgery with minimal impact on dietary intake. Intake of hydrogenated and non-hydrogenated vegetable oils and butter was collected using a valid and reliable food frequency questionnaire. The gene expressions of PPAR-gamma in visceral and subcutaneous adipose tissue were assessed by Real-Time PCR.

Findings

After adjustment for total energy intake and age, visceral adipose tissue PPAR-gamma gene expression was correlated with total fat and oil intake ($\beta=-0.531$, $P=0.014$) in total population. Among non-obese subjects, visceral adipose tissue PPAR-gamma gene expression was correlated with non-hydrogenated oil ($\beta=0.621$, $P=0.017$). PPAR-gamma gene expression in subcutaneous adipose tissue was correlated with non-hydrogenated oil ($\beta=0.481$, $P=0.026$) among obese subjects. Moreover, among morbid obese subjects we found significant correlations between visceral adipose tissue PPAR-gamma expression and total fat and oil intake ($\beta=0.417$, $P=0.020$).

Conclusions

Expression of adipose tissue PPAR-gamma mRNA negatively correlates with total fat and oil intake mostly in visceral fat. In addition, non-hydrogenated oil positively correlates with PPAR-gamma expression.

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OC5.3

Cardio metabolic assessment of lamin A/C mutation carriers according to R482 or Non-R482 mutation

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Background

Lamin A/C mutations show heterogeneous phenotypes expanding from cardiopathies to lipodystrophies. LMNA-related heart disease has recently been shown to be associated with a high incidence of phenotypic progression and adverse arrhythmic and non-arrhythmic events. Anticipatory planning to prevent sudden death has been recommended in a multicentric cardiologic recruitment. Nevertheless the specific cardiac prognosis of R482-LMNA mutated patients, the hot-spot for partial lipodystrophic syndromes, has not been well studied.

Objectives

To compare the cardio-metabolic complications of R482-LMNA mutated patients, and carriers of other LMNA mutations.

Methods

This retrospective study included 29 R482-LMNA mutated patients and 29 carriers of another lamin A/C mutation (non-R482 group) followed at a single university hospital for a median of 5.5 years. The cardiac and metabolic phenotypes were compared between the two groups.

Results

The non-R482 carriers showed more electrocardiographic anomalies and wore more cardiac devices than the R482-carriers ($P<0.001$). The ultrasound cardiac examinations of non-R482 patients showed a higher frequency of left auricular dilatations ($P<0.05$) and a lower mean left ventricular ejection fraction ($P<0.01$) than in R482-carriers. A family history of medical devices ($P<0.001$) or sudden death ($P<0.01$) was more frequent in non-R482 than in R482-carriers. The prevalence of diabetes ($P<0.01$) and hypertriglyceridemia ($P<0.05$) and coronaropathy was higher in R482 than in non-R482 carriers. The R482 carriers had a lower leptin ($P<0.01$) and BMI ($P<0.05$) level than the non-R482.

Conclusion
The non-R482 presented more arrhythmias than the R482-carriers, who were twice more often diabetic with more coronaropathies. The frequency of diabetes reached, however 40% in non-R482 mutations. The follow-up of laminopathies should be adjusted to the genotype. Arrythmias, especially associated to diabetes or medical device family history should lead to LMNA genetic testing.

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OC5.4

Food history characterization of Portuguese centenarians, nutritional biomarkers and cardiovascular risk: case control study

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Introduction
Eating habits may contribute to longevity. Consumption of red meat, source of saturated fatty acids and cholesterol may be associated with increased risks of diabetes, cardiovascular disease (CVD), and mortality risk.
Methods
We studied 521 subjects, both genders, 253 centenarians (CENT) (100.26 ± 1.98 age) and 268 controls (67.51 ± 3.25 age), both low (LCR) and high cardiovascular risk (HCR), calculated based on QRISK®2-2016. Anthropometric and body composition analysis were evaluated by bioimpedance. The abdominal obesity (cm), BMI (kg/m^2) and the cut-off for fat mass (FM) by gender, defined according WHO. Sarcopenia defined by muscle-mass index cut-off $\leq$ 16.7 kg/m^2. Statistical methods were chi-square test, ANOVA and binary logistic regression.
Results
There were differences in the distribution of food frequency history between centenarians and controls concerning food groups except oilseeds. The daily intake of red meat, adjusted for age and gender, was a protective factor for sarcopenia (OR = 0.25, CI 95% = 0.096–0.670, P = 0.006), but contributes for FM excess (OR = 4.946, CI 95% = 1.471–16.626, P = 0.01), overweight and obesity (OR = 4.804, CI 95% = 1.666–13.851, P = 0.004). Only 2% of the centenarians reported this eating habit unlike the 64.3% of the HCR group. The frequency history of red meat intake was associated with higher cardiovascular risk (χ2 = 239,807; df = 8, P < 0.0001), as well as canned food intake (χ2 = 225.321; df = 8, P < 0.0001). Basal metabolism (Kcal) was lower in centenarians and higher in HCR group (CENT = 1176.78 ± 201.98; LCR = 1356.54 ± 170.65; HCR = 1561.33 ± 267.85; P < 0.0001), in the same way as BMI (CENT = 21,06 ± 3.68; LCR = 28.49 ± 4.69; HCR = 29.56 ± 5.26; P < 0.0001), waist circumference (CENT = 85.29 ± 10.83; LCR = 96.02 ± 11.71; HCR = 104.50 ± 11.84; P < 0.0001) and hip-waist ratio (CENT = 0.88 ± 0.07; LCR = 0.92 ± 0.08; HCR = 1.01 ± 0.08; P < 0.0001).
Conclusions
Centenarians have different food history than the control population. Frequent consumption of red meat may contribute to obesity and increased cardiovascular risk, since the hemic iron of red meat may catalyze oxidations leading to disease processes. The low frequency of this consumption, observed in centenarians, although associated with sarcopenia, may be one of the keys to longevity.

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OC5.5

Sex dimorphism of renal corticosteroid signaling during development and long term consequence on blood pressure

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Sex differences have been demonstrated in various biological processes such as arterial blood pressure. However, the potential sex dimorphism of the renin-angiotensin-aldosterone system and, by extension, the mineralocorticoid receptor (MR) signaling pathway, major regulators of blood pressure, has only been poorly studied, notably in the kidney. Basal systolic blood pressure (SBP) and heart rate (HR) were measured in adult male and female mice. Renal gene expression studies of major players of MR signaling were performed at different developmental stages in male and female mice using RT-qPCR, and were compared to that of the same genes in the lung, another mineralocorticoid epithelial target tissue. The potential role of sex hormones in the regulation of these genes was also investigated in differentiated KC3AC1 renal cells. Additionally, renal expression of the 11βHSD2 protein, a regulator of mineralocorticoid specificity, was measured by immunoblotting and its activity was indirectly assessed in the plasma using LC-MSMS method. SBP (91.7 ± 1.1 vs 99.2 ± 1.0 mmHg, P < 0.0001) and HR (662 ± 3 vs 687 ± 4 bpm, P < 0.0001) were significantly lower in females compared to males. This was accompanied by a sex and tissue-specific expression of MR signaling pathway from fetal stage (E18) to adulthood, most notably for GR (Nr3c1) and Gilz renal mRNA expression which was twofold-lower in adult females mice compared to males (P < 0.01). Moreover, 11βHSD2 mRNA and protein expression was found significantly increased in females (P < 0.05), with a statistically different ratio of corticosterone/dehydrocorticosterone between both sexes (P = 0.012). Finally, the implication of sex hormones in this sex-specific expression profile was confirmed in vitro, most notably for Gilz mRNA expression. We demonstrate a tissue-specific, sex-dependent and developmentally-regulated pattern of expression of MR signaling that could have important implications in physiology and pathology, particularly in the development of essential hypertension in men.

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Diabetes therapy and complications

OC6.1

A passe-PAR2 for β-cell regeneration and protection

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Cell and tissue damage, particularly to pancreatic β-cells, is an essential characteristic of diabetes mellitus, triggered by autoimmune destruction of β-cells in type-1 (T1D) and by obesity associated factors or insulin resistance in type 2. Thus, stimulating β-cell regeneration has long been a most important goal of diabetes research. Recently, we have shown that pancreatic injury consisting of acinar cell inflammation and β-cell destruction led to islet cell transdifferentiation. In this work, we report that the molecular mechanism for this process requires the activation of the protease-activated receptor-2 (PAR2), a G-protein-coupled receptor. PAR2 modulation was sufficient to induce islet cell transdifferentiation in the β-cells ablated animals as PAR2 Knock out mice and mice injected with PAR2 pharmacological activator showed that it was necessary and sufficient for the induction of islet cell transdifferentiation in the settings of β-cell ablation. PAR2 expression was modified in an islet cell type-specific manner in murine and human T1D. In addition to transdifferentiation, PAR2 regulated β-cell apoptosis in caerulein-mediated pancreatitis, demonstrating that PAR2 was required for β-cell survival and protection during inflammation.

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OC6.2

Insulin-mimetic effects of short-term Rapamycin in type 1 diabetic patients prior islet transplantation

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It has been suggested that the selective m-TOR inhibitor, Rapamycin, has been improved the success pancreatic islet allotransplantation (ITx) in type 1 diabetic patients (T1DM). Forty-one ITx were studied. Thirteen T1DM in poor glycemic control underwent a 45-days Rapamycin before ITx followed by standard Edmonton Protocol (EP, group 1, Milan), and they were compared to 28 T1DM patients undergoing EP (group 2, Miami). Outcome measures were daily insulin requirement (DIR), HbA1c, C-peptide and the SUITO index of beta-cell function before and 1 year after ITx. Four patients from group 1 underwent euglycemic-hyperinsulinemic clamp with 6,6-d2-glucose infusion before and after ITx. We found a significant reduction in DIR after Rapamycin pre-treatment (-8 ± 6 U/day, mean $\pm$ S.D., $P < 0.001$). Nine patients from group 1 fulfilled follow-up. One year after ITx, DIR significantly decreased (-37 ± 15 U/day, $P < 0.001$) and six patients became insulin independent. We observed greater DIR reduction in group 1 as compared to group 2 at 1-year follow-up (-37 ± 15 vs -19 ± 13 U/day, $P = 0.005$), which remained significant after adjusting for gender, age, glucose and baseline HbA1c (beta coefficient of multivariate regression analysis $\pm$ S.E. 18.2 ± 5.9, $P = 0.006$). In patients from group 1, HbA1c significantly decreased 1 year after ITx ($-2.1 \pm 1.4\%$, $P = 0.002$), while C-peptide ($+1.5 \pm 0.9$, $P = 0.002$), and SUITO index increased ($+57.4 \pm 39.7$, $P = 0.016$). We did not observe differences in change between group 1 and 2 as far as HbA1c, C-peptide and SUITO index are concerned before and after ITx. Hepatic glucose production during the insulin clamp decreased after Rapamycin pre-treatment (-1.1 ± 1.1 mg/kg per min, $P = 0.04$) and after ITx (-1.6 ± 0.6 mg/kg per min, $P = 0.015$), while no changes in peripheral glucose disposal were observed during Rapamycin treatment. In conclusion, Rapamycin contributes to improve metabolic control also enhancing hepatic insulin sensitivity after ITx. Rapamycin pre-treatment may improve ITx success rate by reduction of pre-transplant DIR and increase of hepatic insulin sensitivity.

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OC6.3

Alterations in DNA methylation from peripheral blood cells in humans threated with metformin

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Metformin is a biguanide class agent widely used as a first-line treatment for type 2 diabetes, however the detailed mode of action and exact pharmacodynamics has not been clarified. Moreover there is no studies in humans displaying the effect of metformin on DNA methylation. We therefore performed a clinical study involving twelve healthy nondiabetic individuals who were subjected to the 1 week of metformin ($2\times$ 850 mg/day) treatment. Peripheral blood for DNA isolation was drawn at three time points during metformin treatment: i) right before metformin treatment, ii) 10 hours after the first metformin dose and iii) after a week-long metformin administration. DNA methylation was estimated using genome-wide Illumina Infinium HumanMethylation450 BeadChip (Illumina), which allows interrogation of 485 512 CpG dinucleotides. Analysis global methylation data displayed predominance of demethylated CpGs over the methylated as the result of metformin treatment. In order to identify differentially methylated gene promoter regions we filtered all CpGs located in 2000 pb proximity of the transcription start site and having median methylation change across all samples larger than 3% with Bonferroni corrected P values. This stringent approach resulted total in 35 genes with differentially methylated CpG regions near the promoters. Five genes, considered most likely biologically relevant to have impact in diabetes were those involved in processing of energy molecules, differentiation and formation of adipocytes and exhibiting GTF-ase activities. Eighteen regions included genes with known specific functions that are not directly linkable to influencing diabetic phenotype. Finally 12 genes where either pseudogenes or had unknown function. In conclusion this is the first study that shows influence of metformin in altering DNA methylation in humans and identified markers may prove to be valuable biomarkers for the understanding of the molecular basis of metformin action and may lead to the identification of new drug targets.

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OC6.4

Copeptin and its association to cardiovascular dysfunction in type 2 diabetes

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Background
We aim to test whether plasma copeptin (copeptin), the C-terminal fragment of vasopressin, has predictive value of cardiovascular events in patients with type 2 diabetes without previous cardiovascular disease who were treated in primary care.
Methods
We measured copeptin in 697 patients who participated in the epidemiological study CARDIPP (Cardiovascular Risk Factors in Patients with Diabetes – a Prospective Study in Primary Care; ClinicalTrials.gov identifier NCT01049737) and who did not have previously known myocardial infarction or stroke. The outcome variable was a composite endpoint consisting of cardiovascular mortality, hospitalization for myocardial infarction and hospitalization for stroke.
Results
During a median follow-up time of almost 7 years, the unadjusted HR per each increment of Copeptin by 1 pmol/l was 3.5 (95% CI 1.7–7.1, $P < 0.001$) for the primary endpoint. Following adjustments for age, sex, HbA1c, arterial stiffness (PWW) as well as atherosclerosis plaque the adjusted hazard ratio was 2.4 (95% CI 1.1–5.2, $P = 0.03$).
Conclusions
In primary preventive patients with type 2 diabetes treated in primary care, copeptin predicted a composite outcome of incident cardiovascular events independently of age, sex, HbA1c, arterial stiffness as well as atherosclerosis plaque.

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OC6.5

Activation of the Renin-Angiotensin II-Aldosterone-System leads to increases in extracellular protein disulfide isomerase: role in insulin resistance

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Insulin resistance and type II diabetes (T2D) are associated with activation of the Renin-Angiotensin-Aldosterone-System (RAAS) in part via regulation of its principal effector molecule, Angiotensin II (AngII). Endothelial cell activation leads to, among other factors, increased

extracellular protein disulfide isomerase (PDI), a multifunctional protein that is critical to thrombus formation and regulation of reactive oxygen species. However, the effects of RAAS on PDI are unknown. We studied the *in vitro* effects of AngII on EA.hy926 human endothelial cells and measured PDI activity. Our results show that AngII (10 nM), dose- and time-dependently, increased PDI activity ($P<0.05$, $n=6$); an event that was blocked by pre-incubation with 0.5 μM losartan, an AngII Type I receptor antagonist (ARB). Western blot analyses showed increased PDI following AngII that was likewise reduced by losartan. In normal in Sprague–Dawley rats, we studied the *in vivo* effects of exogenous AngII infusion and observed significant increases in plasma PDI levels ($P<0.05$, $n>5$) that were blunted by ARB treatment. We then studied the obese Otsuka Long Evans Tokushima Fatty (OLETF) ($n=6$/group) rats, a model of naturally increased AngII and RAAS-mediated insulin resistance and hypertension. Our results show that OLETF rats had increased insulin resistance and greater circulating PDI activity than lean control rats ($P<0.05$) and was reduced by ARB treatment to baseline levels ($P<0.05$). To assess the clinical relevance of our findings, we measured circulating PDI in subjects with and without T2D. PDI activity correlated with measures of insulin resistance in our cohort (HOMA2-IR, Spearman $P=0.496$, $P<0.001$, $n=134$) and was significantly greater in T2D patients than healthy controls ($P<0.01$, $n=56$ vs 78, respectively). Our data in human and animal models suggest that RAAS activation represents a novel mechanism for PDI secretion. Thus we posit that PDI may contribute to the deleterious effects of RAAS-mediated vascular disease.

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Cardiovascular endocrinology

OC7.1

Estrogens enhance gonadectomy-induced adrenocortical tumor progression in mice

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Prepubertally gonadectomized (GDX) wild-type DBA/2J mice develop adrenocortical neoplasms presenting with small spindle-shaped non steroidogenic A-cells and large lipid-laden, steroidogenic and mitotically active B-cells. Neoplastic B-cells overexpress estrogen receptor α (ERα, Ers1) and β (ERβ, Ers2), aromatase (CYP19a1) and produce sex-steroids, resembling gonadal rest tissue. To test the role of estrogen-ER system in adrenocortical tumor progression, GDX 12 months-old DBA/2J females were treated with selective estrogen receptor modulator tamoxifen (TMX, 0.4 mg/kg/24 h) and aromatase inhibitor letrozole (LET, 2 mg/kg/24 h) for 21 days. Both TMX and LET treatments significantly reduced the adrenal weights, with stronger effect of the latter. Both treatments decreased the expression of proliferation marker MKI67 and induced apoptosis predominantly in the tumorous B-cells. TMX and LET treatments decreased plasma estradiol (E2) levels significantly decreasing sensitivity of the negative feedback on luteinizing hormone (LH) secretion. Gene expression profiling showed that TMX and LET downregulated gonadal-like markers Ers2, LH receptor (Lhcgr) and transcription factor Gata4, but upregulated a negative regulator of steroidogenesis Nr0b1. Additionally, LET significantly decreased expression of Esr1, Cyp19a1 and Cyp17a1. Control GDX mouse uteri displayed endometrial hyperplasia without cellular atypia. TMX- and LET-treated mice uteri were significantly smaller and showed cystically dilated endometrial glands and signs of mild chronic inflammation. In summary, we showed that adrenal estrogens promote progression of GDX-induced adrenocortical tumors. Our findings also support the rationale for TMX- and LET-based therapeutic strategies in treating ERs-positive/estrogen responsive adrenocortical carcinomas in human.

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OC7.2

Targeted molecular markers derived from genomic classification for adrenocortical cancer prognostication

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Background

Adrenocortical cancer (ACC) is an aggressive tumour with heterogeneous prognosis. Recently integrated genomics reported distinct genomic alterations: transcriptome "C1A" (high expression of proliferation/cell cycle-related genes) vs "C1B", "CIMP" (CpG islands hypermethylation) vs "non-CIMP", chromosome alterations "Noisy" (numerous and anarchic alterations) vs "Chromosomal" (extended patterns of loss of heterozygosity) and "Quiet" (limited alterations), and recurrent somatic mutations in 20 genes. These alterations converge into a single three-groups classification, correlating with outcome. The aim was to develop and validate targeted molecular markers reflecting these genomic groups.

Patients and methods

Two hundred and forty five ACC were included from 21 ENSAT (European network for the Study of Adrenal Tumors) centers. Tumor RNA was assessed by RT-qPCR for BUB1B-PINK1 expression ($n=135$). Tumor DNA was studied by SNP array for chromosomal alterations ($n=238$), targeted NGS for mutations of 20 driver genes ($n=251$), and MS-MLPA for CpG islands methylation of four genes -PAX5, GSTP1, PYCARD, PAX6- ($n=221$).

Results

Gene expression levels identified "C1A", "C1B" and "undetermined" ACC in 50, 38 and 12% of cases respectively. Methylation assay identified "CIMP" and "non CIMP" ACC in 44 and 56% of cases respectively. Chromosomal alteration profiles identified "chromosomal", "noisy" and "quiet" ACC in 55, 32 and 13% of cases respectively. Recurrent mutations or deletions were found in ZNFR3, CDKN2A, TP53 and CTNNB1 in 21, 17, 15 and 11% of cases respectively, in agreement with previous exome studies. All molecular statuses were available for 107 tumors. 87/107 (81%) concordantly recapitulated the 3 main ACC subgroups previously identified by genomic classifications: 37 were "C1A/CIMP", 18 were "C1A/non-CIMP", and 32 were "C1B/non-CIMP". Death events occurred in 34/37, 7/18 and 1/32 patients respectively (Fisher exact $P<10–15$).

Conclusion

Targeted molecular measures can recapitulate the genomic classification of ACC, giving original and useful prognostication information for patient management.

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OC7.3

High Total 68Ga-DOTATATE-Avid Tumor Volume (TV) is associated with low progression-free survival and high disease-specific mortality rate in patients with neuroendocrine tumors

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Background
Patients with neuroendocrine tumors (NETs) have divergent survival, even when having the same site of primary tumor, and tumor stage and grade. 68Gallium (68Ga)-DOTATATE positron emission tomography (PET)/computed tomography (CT) is a sensitive imaging modality for detecting NETs. The purpose of this study was to determine whether 68Ga-DOTATATE PET/CT imaging has any prognostic utility in patients with NETs.
Methods
One hundred and eighty-four patients with NETs were enrolled in a prospective study of 68Ga-DOTATATE PET/CT imaging and comprehensive biochemical analysis. Total 68Ga-DOTATATE-Avid Tumor Volume (68Ga-DOTATATE TV) was measured in all participants. The primary outcome measures were progression-free survival (PFS) and disease-specific mortality (DSM). PFS and DSM rates were compared according to 68Ga-DOTATATE TV quartiles of the current cohort. Then, specific 68Ga-DOTATATE TV cut-offs were set using a receiver operating characteristic (ROC) curve analysis, and the risks for DSM and PFS were validated with Kaplan-Meyer and Cox regression analyses.
Results
Patients were followed for a median of 18 months (range 4–35 months). 68Ga-DOTATATE TV quartiles had inverse correlation with PFS ($P=0.001$) and survival rates ($P=0.002$). Using cut-offs derived from ROC curve analysis, 68Ga-DOTATATE TV $\geq$7.0 was associated with a lower PFS (HR = 2.0, $P=0.03$), and 68Ga-DOTATATE TV $\geq$35.8 ml was associated with increased (HR = 10.7) disease-specific mortality in multivariate analysis ($P=0.03$), as well as in subgroup analysis of patients with pancreatic NETs.
Conclusions
We show for the first time the prognostic utility of 68Ga-DOTATATE TV in a large cohort of patients with NETs, enabling clinicians to determine the need for intervention using this non-invasive tool.

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OC7.4

A novel insight into the anticancer mechanism of metformin in Pancreatic Neuroendocrine Tumor cells

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Metformin (1.1-dimethylbiguanide hydrochloride), a widely used antidiabetic drug, has been reported to display potent anticancer properties in various types of cancers, including neuroendocrine tumors. Recently, a potential synergistic activity between metformin and octreotide (SSA) in Pancreatic Neuroendocrine Tumors (P-NETs) has been proposed. AIP (aryl hydrocarbon receptor-interacting protein) acts as tumor suppressor gene in neuroendocrine tumors at pituitary level and it is up-regulated by SSA. We investigated the effects of metformin on P-NETs cell proliferation, apoptosis and colony formation, the potential synergistic effect between metformin and octreotide and the possible role of AIP pathway in mediating these effects. We found that in QGP-1 cells metformin significantly inhibited cell proliferation ($-37\pm2\%$ $P<0.001$ vs basal at 10 mM). We showed no additive effect between Metformin and Octreotide on P-NETs cell proliferation. Moreover, metformin incubation reduced colony formation, cells amount after 7 days ($-66\pm6\%$ $P<0.001$ vs basal) and it promoted apoptosis ($+150\pm8\%$ $P<0.05$ vs basal). As expected, octreotide induced AIP up-regulation ($+60\pm11\%$ $P<0.05$ vs basal), and surprisingly, AIP expression levels were also increased by metformin ($+90\pm13\%$ $P<0.05$ vs basal). In addition, AIP silencing abolished the antiproliferative and proapoptotic effects of metformin, confirming its involvement in mediating metformin effects. Interestingly, metformin decreased HSP70 expression, increased Zac1 and AhR expression levels. These effects were totally abolished in QGP-1 cells lacking AIP. In conclusion, metformin acts as anticancer agent in P-NET cells, its activity is mediated by AIP and its interacting proteins, HSP70, AHR and Zac1. These findings provide a novel insight into the antitumorigenic mechanism of metformin.

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OC7.5

Regulation of steroid receptor signalling by tumor suppressor INPP4B

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Androgen receptor (AR) signaling is the main driver for prostate cancer progression and androgen ablation is the treatment of choice for tumors that spread beyond the prostate. Efficient at first, androgen ablation fails due in part to altered cell signaling and expression of AR spice variants. Cell signaling in prostate cancer is regulated by dual specificity phosphatases and tumor suppressors INPP4B and PTEN that are lost with prostate cancer progression. Loss of PTEN destabilizes AR and alters AR transcriptional output. We investigated how loss of INPP4B affects AR signaling. We have previously shown that AR induces expression of INPP4B in prostate cancer. Intriguingly, AR splice variant AR-V7, which also contributes to ADT resistance, was unable to induce INPP4B expression. We performed microarray analysis of changes in gene expression caused by INPP4B knockdown. Gene expression clustering and GSEA analysis revealed that the INPP4B loss significantly altered AR transcriptional activity. Using immunofluorescent labeling with 3D rendering we determined that INPP4B localizes to cellular and endoplasmic membranes. We and others have shown that INPP4B suppresses PI3K/Akt and PKC pathways. We show that INPP4B specifically inhibits PKCζ and βII in multiple prostate cancer cells. The analysis of PI3K, Akt and PKC specific inhibitors, LY294002, AZD5363, and BIM-I, showed that Akt and PKC signaling did contribute to the changes in AR signaling. We investigated INPP4B functions in prostates of Inpp4b$^{-/-}$ mice. AR expression in mouse prostate was not affected by the loss of INPP4B. Remarkably, expression of several direct AR target genes like Msmb, Apof, and Nkx3.1 was significantly reduced in Inpp4b$^{-/-}$ prostates. We compared Akt and PKC signaling in the anterior (AP), dorsal/lateral (DLP) and ventral (VP) prostate lobes of the wild-type and Inpp4b$^{-/-}$ mice. Loss of INPP4B increased Akt signaling in DLP and VP and PKC ζ and β II pathways in AP and DLP. We determined that levels of PTEN protein were unchanged in Inpp4b$^{-/-}$ mouse prostates suggesting that Akt signaling was elevated exclusively due to Inpp4b loss. Taken together, full length AR, but not AR-V7 induce INPP4B expression. INPP4B reciprocally modulates AR transcriptional activity without altering AR protein level in both normal prostate and prostate cancer cells and suppresses Akt and PKCζ and β II signaling and the suppression is required for optimal AR transcriptional activity.

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Neuroendocrinology

OC8.1

Elucidating the molecular mechanisms underlying AIP dependent tumorigenesis

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Pituitary adenomas (PAs) are benign neoplasms that comprise 10–20% of all intracranial tumors. Mutations in the aryl hydrocarbon receptor interacting protein (AIP) have been identified to cause a small subset of hereditary PAs. To study the mechanisms of tumor formation in patients with AIP-mutated PAs we conducted a miRNA array analysis comparing AIP-mutated PAs with AIP-wild type PAs. We found a novel and specific set of miRNAs differentially expressed between the two groups of PAs. We selected several candidate miRNAs and validated them in the patient tissues. To characterize the candidate miRNAs *in vitro* and clarify their role in AIP dependent tumorigenesis we performed

functional studies using mouse embryonic fibroblasts (MEFs) derived from Aip knockout (AIP-KO) mice and a rat somatotroph tumor cell line (GH3). In the AIP-KO MEFs we saw that transfection of mutant AIP altered the expression of two of the candidate miRNAs according to the changes observed in the miRNA array. Additionally, cell viability and cell migration were increased after transfection of mutant AIP. Since deregulation of cAMP levels is a common feature of PAs we also checked cAMP levels upon transfection of mutant AIP. We could observe that mutant AIP increased cAMP levels in AIP-KO MEFs. Overexpression of the candidate miRNAs in GH3 cells increased cell migration and cAMP levels while apoptosis was decreased. To further clarify the role of the selected miRNAs in tumor development we identified their predicted targets and focused on those involved in cAMP signalling. We plan to validate the role of these predicted targets in PAs in the future. In conclusion, we identified novel miRNAs in AIP-mutated PAs and were able to show that these miRNAs promote a tumor-like behaviour in several functional assays in AIP-KO MEFs and GH3 somatotroph cells.

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OC8.2

Knocking down/out the prokineticin pathway during zebrafish development results in the GnRH neurons axons misguiding

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Studies conducted using knockout mouse model revealed that defects of PROKR2 affect the correct ontogeny of GnRH neurons and, by consequence, neuroendocrine control of reproduction. Nevertheless its exact role during these processes and in the pathogenesis of congenital hypogonadotropic hypogonadism (CHH) remains elusive due to the phenotypic differences observed between mouse and human. Zebrafish (ZF) has emerged in the last ten years as a reliable model organism for studying the GnRH neuronal development and the neuroendocrinology of reproduction. Previous results obtained in our lab identified two well-conserved loci in the ZF genome, on chr1 and chr13, respectively named prokr1a and prokr1b. Whole mount *in situ* hybridization (WISH) and qRT-PCR experiments conducted at different developmental stages of ZF revealed distinct patterns of expression for prok-receptors suggesting prokr1b as the potential candidate involved in the GnRH-secreting neurons migration process from olfactory placode to their final hypothalamic destination. To verify these indications and better elucidate the function of both prokineticins receptors we recently conducted knockdown experiments using morpholino oligonucleotides sequences. Our results display an alteration of the GnRH fibers network architecture at 48 hours post fertilization (hpf) after downregulation of prokr1b that appeared misguided and reduced in numbers especially at level of pallium commissure and optic chiasm. Moreover, we also generated in ZF the prokr1b knockout model and our preliminary data are confirming the knockdown model observations. On the contrary, the downregulation of prokr1a does not affect GnRH fibers architecture. Taken together these results confirm the role of prokr1b during GnRH neurons migration establishing it as the ZF orthologous of human PROKR2. A deeper characterization of ZF prokr1b KO model could provide new information regarding the early establishment of the forebrain GnRH system, the factors controlling this complex developmental event, and its functional significance.

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OC8.3

RNA sequencing and RT-qPCR identify different gene expression profiles in fast- vs. slow-growing non-functioning pituitary adenomas

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Background
Non-functioning pituitary adenomas (NFPAs) necessitate prolonged clinical, biochemical and radiological observation, constituting a significant burden in terms of medical resources and societal costs. Reliable biomarkers associated with aggressiveness and recurrence of NFPAs are lacking. As the growth of tumor remnants is highly variable, molecular markers that can predict growth potential and tumor behavior are necessary.
Aim
To identify target genes in fast- and slow- growing NFPAs estimated by postoperative initial tumor volume doubling time (TVDT), and to find reliable biomarkers predicting the growth potential of the remnant tumor, focusing on the specific role of epithelial-mesenchymal transition (EMT) process.
Material and methods
RNA sequencing was performed in gonadotroph NFPAs with short TVDT (median <30.05 months, fast group, $n=4$) and long TVDT (median >30.05 months, slow group, $n=4$). Data was analyzed by tophat2 and cufflinks/cummeRbund pipeline. Furthermore, genes ($n=40$) were selected based on significance, fold of change and pathway analysis for validation with RT-qPCR in a larger cohort of gonadotroph NFPAs ($n=20$, 13 male).
Results
RNA sequencing identified 350 genes significantly differentially expressed, between the two groups (285 genes up- and 65 down- regulated in the fast group, P adjusted <0.05). Of the 40 genes chosen for further validation by RT-qPCR, 11 showed significant correlations with TVDT ($-0.669 \leq R \geq -0.466$, $P<0.05$). These were six genes involved in EMT (PCDH18, SPAG9, SKIL, MTDH, HOOK1 and CNOT6L), and also UNC5D, EMCN, MYO1B, GPM6A and PRKACB.
Conclusions
Fast- and slow- growing NFPAs show different gene expression profiles. Genes known as related to EMT have higher expression in fast-growing tumors, suggesting a pathogenic role in tumor growth. The identified genes and their products could represent useful markers for predicting tumor aggressiveness and recurrence, and may be potential targets for drug therapy.

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OC8.4

Cerebrovascular stroke incidence in GH-treated adults: experience from KIMS (Pfizer International Metabolic Database)

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Background and aim
Patients with GH deficiency (GHD) have increased risk of cerebrovascular events. The aim of this study was to evaluate the rate and factors associated with the occurrence of stroke, a major cause of death and disability, in adults with GHD.
Patients and methods
Data from 15,188 GHD patients treated with GH replacement therapy (GHRT) enrolled in KIMS were analyzed. Stroke incidence rates were compared to rates from the Oxford Vascular Study (Lancet_2004; 363:1925–33) by standardized incidence ratios (SIRs). Age at first radiotherapy (RT) corrected for attained age and sex, was analyzed with Poisson regression.
Results
Causes of GHD comprised pituitary adenoma 42.9%, craniopharyngioma 10.8% and idiopathic GHD 15.6%. Mean age at KIMS entry was 43.7 (range 17–75) years. Mean GH dose was 0.42 mg/day and number of patient treatment-years was 81,086. Mean age at first radiotherapy (RT) was 34.5 (range 3–72) yrs. First-ever stroke was reported in 155/7667 (M) and 123/7521 (F) patients. The crude incidence was 377 (M) and 308 (F) per 100,000 patient- years and overall SIR was 2.51 (95% CI: 2.22–2.82). SIR ranged between causes of GHD from 1.02 (0.41–2.1) in patients with Idiopathic GHD and unexposed to RT to 19.3 (11.6–30.1) in patients with GHD secondary to a malignant cranial tumor. RT was reported in 3866 patients and 146 reported a stroke (SIR: 3.96; 3.35–4.66). Rates were increased in all ages at first exposure ($P<0.01$), especially in younger patients

(RR = 2.2 (1.05–4.63) for <18 vs ≥18 years of age). Among 11,322 patients who did not receive RT, 132 cases were reported, SIR 1.78 (1.49–2.11).
Conclusion
GHD patients have a significantly increased rate of strokes with considerable variability between causes of GHD. Rates were positively associated with RT in all studied ages, with younger patients at first RT showing a higher risk.

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OC8.5

Ephrin-B2 is required for pituitary development

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The pituitary progenitors are responsible for generating a fully functional endocrine organ during embryonic development. They also preserve potency, to maintain the homoeostasis in the adult pituitary, being able to respond to endocrine challenges, such as pregnancy or obesity. But the main players of this complex process remain elusive. Eph-Ephrins have been implicated in an increasing number of physiological functions such as axon-guidance, eye field segregation from neural plate, tissue boundary formation, cell migration, angiogenesis and more recently stem cell maintenance and differentiation in the colon and mammary gland. However, the EprhinB:EphB signalling pathway in hypothalamic-pituitary function is not known. Using a transgenic line that expresses GFP under the EphrinB2 (Efnb2) genetic locus we observed that cells expressing Efnb2 are localised in the pituitary progenitor of the anterior pituitary. We found Efnb2 co-expressed with known PPSCs markers Sox2/Sox9 during embryogenesis and this expression continues in adulthood, suggesting a role in adult pituitary homoeostasis. Conditional genetic removal of Efnb2 in the undifferentiated precursor using a Cre-pituitary line, results in significant pituitary abnormalities, comprising multiple bifurcations hyperplasia of the anterior pituitary gland. These data suggest for the first time, that Efnb2 is a critical regulator of pituitary development and could have an effect on hypothalamic-pituitary body endocrine regulations. Interestingly a proportion of Efnb2 Knock-out animals exhibit features of congenital hypopituitarism, such as dwarfism and eye abnormalities suggesting that, in this physiological context, Efnb2 could be a candidate gene for rare unknown conditions such Septo-Optic Dysplasia.

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Thyroid Disease 2

OC9.1

Thyroid function and metabolic syndrome: results from the population-based LifeLines Cohort study

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Background
The metabolic syndrome (MetS) is a combination of unfavourable health factors including abdominal obesity, dyslipidaemia, hypertension and impaired fasting glucose. Several small-scale studies have reported a relationship between thyroid function and some MetS components or suggested that serum FT3 levels within the normal range were independently associated with insulin resistance. We assessed how thyroid function relates to the prevalence of MetS in a large population-based study.
Methods
Data of 26,719 western European participants aged 18-80 years from the Dutch LifeLines Cohort study, all with normal TSH, FT4 and FT3 levels (electrochemiluminescent immunoassay, Roche Modular E170 Analyzer), were available. MetS was defined with the revised NCEP ATP III criteria. We calculated prevalence of all MetS components according to FT4 and FT3 quartiles.
Results
At similar TSH levels and age (mean 45 yrs), men had significantly higher levels of FT4, FT3, blood pressure (BP), heart rate, total and LDL-cholesterol, triglycerides (TG), and creatinine, but lower HDL-cholesterol compared to women (all $P<0.001$). In total, 9.1% of women and 10.2% of men were treated with BP-lowering agents. In men, lower FT4 levels were associated with higher prevalence of all MetS components. The lowest FT4 quartile was associated with the highest prevalence of elevated BP (60%), elevated glucose (22.7%), waist circumference (33.4%) and TG (30.2%), low HDL-cholesterol (26.5%), and MetS (27.7%). In women, the lowest FT4 quartile was only associated with elevated TG (11.2%), waist circumference (47.4%), and MetS (13.8%). In contrast, higher FT3 levels were associated only with low HDL-cholesterol in both sexes, and with a higher percentage of participants with ≥3 MetS components (21.6% in men, 12.4% in women).
Conclusions
Levels of FT4, but not FT3, were inversely associated with all components of the metabolic syndrome in men, and with elevated TG, waist, and overall MetS in women.

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OC9.2

Effect of restoration of euthyroidism in patients with hypothyroidism on cold induced thermogenesis

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Background
Thyroid hormones have been shown to be necessary for proper function of brown adipose tissue (BAT) and cold induced thermogenesis (CIT) in rodent models. In humans hyperthyroidism has been demonstrated to activate BAT and increase thermogenesis. However, the data on CIT in humans in the hypothyroid vs. the euthyroid state are limited and conflicting.
Methods
This was a prospective observational study. We recruited 40 patients presenting to a University hospital out-patient endocrine clinic with subclinical or overt hypothyroidism, and in whom thyroid hormone replacement was planned. Currently, 24 patients completed the study. Thermogenesis was measured by indirect calorimetry during warm conditions and after a mild cold stimulus of 90 min, both during the hypothyroid state and after at least 3 months of sufficient thyroid hormone replacement. CIT was determined as the difference between resting energy expenditure (REE) during cold (REEcold) and warm (REEwarm) conditions. Additionally, skin temperature was measured using wireless probes in one-minute intervals in the supraclavicular region adjacent to the major human BAT depot. The primary endpoint was CIT in the hypothyroid vs euthyroid state. Data were analysed by non-parametric tests and are given as mean ± S.D.
Results
CIT increased from 73(±103) kcal/d during the hypothyroid state (CIThypo) to 160 (±143) kcal/d in the euthyroid state (CITeu), $P=0.0007$. REEwarm was 1324 (±120) kcal/d during hypothyroidism and rose slightly to 1395(±140) kcal/d, $P=0.0137$. REEcold rose profoundly from 1396(±157) kcal/d to 1555(±178) kcal/d, $P=0.0001$. While the inter-individual variability of CIT was large, the correlation between CIThypo and CITeu was moderate, $r=0.657$, $P=0.001$. The change in supraclavicular skin temperature during cold exposure correlated with CIT in the euthyroid ($r=0.389$, $P=0.067$), but not in the hypothyroid state ($r=0.041$, $P=0.853$).
Conclusion
Cold induced thermogenesis is blunted in hypothyroid patients and increases markedly after restoration of euthyroidism. The difference in CIT is larger than the difference in resting energy expenditure during warm conditions.

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OC9.3

How much of the genetic predisposition to Hashimoto's thyroiditis can be explained by genes commonly associated with the disease?

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Background
Hashimoto's thyroiditis (HT) is a common autoimmune disorder of the thyroid (AITD) which affects about 1–2% of the European population. The disease often

clusters in families, which is why many attempts have been undertaken to find the genetic background that would underly the predisposition to HT. In contrast to another AITD - Graves' disease, results of genetic analyses have been ambiguous and have failed to find a major genetic locus that would be essential for HT development.

Aim

To assess the joined impact of disease loci associated in the literature with HT predisposition.

Methods

One hundred and forty seven HT fully-symptomatic patients and 147 healthy controls (matched for age, gender, incomes, education, marital status and place of descent), unrelated to each other, were genotyped for 40 polymorphisms (Illumina GoldenGate, custom panel), which were located in genes most often tested in literature for association with AITD, or typed out by genome-wide association studies. All polymorphisms were confirmed to be in Hardy-Weinberg equilibrium in the control group ($P > 0.05$). Variations in the HLA-DRB1 gene were analyzed by Sanger sequencing. A genetic model for HT predisposition was obtained with use of stepwise logistic regression. Biostatistical analyses were performed with the programs Statistica v12, Plink v1.9, and GCTA v1.02.

Results

The model which best explained the predisposition to HT contained seven polymorphisms in the genes PTPN22, IFIH1, CTLA4, RGS6, TNMD, NOX1, and the promoter region of FAM155A. The model was able to classify correctly 67% of all cases, similarly for both groups. Such a model explained only 5.12% of the between-group variance. This value is in agreement with a model published lately for another autoimmune disorder.

Discussion

Our data confirm that there seem to be no genes that are per se crucial for HT development. Future analyses on HT predisposition should focus on the joined influence of many polymorphisms in different genetic regions.

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OC9.4

Thyroid dysfunction during the use of PD-1/PD-L1 blockade predicts its therapeutic response in the patients with advanced non-small cell lung cancer

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Background

PD-1/PD-L1 blockade is one of the promising drugs in the treatment of advanced non-small cell lung cancer (NSCLC). and predicting drug effect is important due to unique pattern of response. Immune-related adverse event (IRAE) might be associated with favorable clinical outcome. Thyroiditis is the most common IRAE which can be easily detected with the measurement of thyroid hormone levels. However, the relationship between thyroid dysfunction during the use of PD-1/PD-L1 blockade and its therapeutic response has not been well demonstrated in advanced NSCLC patients.

Methods

A total 53 patients with stage IV NSCLC treated with PD-1/PD-L1 blockade were enrolled. Patients were categorized into thyroid dysfunction and euthyroid group. Overall survival (OS) and progression free survival (PFS) of two groups were compared. Hazard ratio (HR) adjusting patients, tumor, and drug factors were analyzed using Cox proportional hazard model. Response rate (RR) and durable RR were assessed according to thyroid dysfunction and its severity.

Results

OS (mean 148.5 ± 82.6 vs 82.0 ± 65.1, log-rank $P = 0.003$) and PFS (143.2 ± 88.2 vs 68.0 ± 50.0, log-rank $P = 0.001$) were significantly longer in the thyroid dysfunction group. After adjustment for age, sex, smoking status, tumor stage, and drug type, adjusted HR (95% CI) for overall death and progression disease were 0.08 (0.01–0.65) and 0.29 (0.12–0.69) compared with euthyroid group. RR (36.0 vs 10.7%, $P = 0.028$) and durable RR (28.0 vs 0%, $P = 0.003$) were more frequent in the thyroid dysfunction group. Severity of thyroid dysfunction was also associated with RR (P for trend $= 0.018$) and durable RR (P for trend $= 0.001$).

Conclusions

Thyroid dysfunction during the use of PD-1/PD-L1 blockade and its severity predict its favorable disease outcome in NSCLC patients. Therefore, regular measurement of thyroid hormone levels during the use of PD-1/PD-L1 blockade could be the good biomarker of immune monitoring.

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OC9.5

Selenium supplementation in the management of thyroid autoimmunity during pregnancy: results of the 'Serena Study' a randomized, double-blind, placebo-controlled trial

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Autoimmune thyroiditis and related complications represent a growing concern during pregnancy. Selenium is frequently present in nutraceuticals recommended for thyroiditis and pregnancy, given its advocated role in immunity, fertility and thyroid function. However, most evidences come from non-controlled studies.

Materials and Methods

We designed a multicenter, randomized, double-blind, placebo-controlled trial (Serena Study: NCT01465867) to evaluate the effects of L-selenomethionine (Se) supplementation on antibodies title in euthyroid women with positive anti-thyroid antibodies that are pregnant or undergoing *in-vitro* fertilization. Secondary outcomes included: implantation rates, pregnancy rate, delivery, obstetrical, fetal and neonatal complications. Ten endocrinology and gynecology Italian referral centers participated. The study was promoted and supported by EnGioI Club (Italian Young Endocrinology).

Results

56 women were randomly assigned to placebo (PLB) or Se 83 mcg/die. Thyroid hormones, TgAb, TPOAb, selenium concentration were measured during pregnancy and after labor (months 3° to 6°). All analysis were centralized. Of the enrolled women, 45 (80.3%) were pregnant and 11 (19.6%) embryo transferred. A significant reduction of TgAb was observed in Se-treated women after labor: treatment effect $d = 108.67$ (95%CI: -1.3, 218.6; $P = 0.03$). The change in antibodies was paralleled by a significant increase in selenium serum concentration measured already at 36 ± 2 weeks: (PLB: -11 ± 23.76, Se: $+30.5 \pm 17.63$; treatment effect $d = 35.57$ 95% CI:14.9, 62.3; $P = 0.004$) and confirmed after labor: treatment effect $d = 17.56$ (95% CI: 3.9, 31.2; $P = 0.014$). Post-labor rebound in antibodies' title of PLB treated, as compared to Se-treated women was paralleled by a trend toward TSH rise (PLB: $+3.96 \pm 12.56$ vs Se: $+1.69 \pm 6.00$). Safety analysis showed no discontinuation in the Se-treated subjects. Two miscarriage occurred in PLB vs 0 in Se-treated. No differences were found in fetal and maternal complications. The pregnancy rate after embryo transfer was 3/5 (60%) in Se-treated vs 1/6 (16.6%) in PLB.

Conclusion

SERENA Study demonstrated a beneficial effect on the title of TgAb with a safety profile. Larger studies are needed to confirm the trends observed on post-partum thyroiditis recurrence and hypothyroidism, miscarriage and pregnancy rate in *in vitro*-fertilization.

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Bone & Calcium Homeostasis

OC10.1

Treatment of 711 patients with hypoparathyroidism: a retrospective study in 3 German endocrine centres

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Care of patients (pts.) with hypoparathyroidism (HypoPT) is a challenge, because pts. are usually not treated with the absent hormone, but with several forms of vitamine D. We retrospectively evaluated the data of pts. with HypoPT in three endocrine centres in Germany.

Methods

Records of 711 pts. with HypoPT (Centre 1 (C1): $n=381$, C2: $n=253$, C3: $n=77$) were reviewed (female: 592, male: 119). The following data under treatment (time range 2–199 months) were evaluated: medication, Calcium (Ca) – values, tingling sensations (paresthesia), and cramps.

Results

Of these 711 pts. 29 had idiopathic HypoPT, 10 HypoPT after parathyroidectomy, 669 after thyroid operation (Tx): subtotal Tx: 471, HemiTx: 12, totalTx: 186 pts. Age of pts. at first visit (V1): 49.85 years (mean), time between Tx and V1: 76.85 months (mean, range 0–733 months). Mean values of Ca (mmol/l), PO4 (mg/dl) in serum, Ca in urine (Ca U; mmol/24 h); % of patients with paresthesia (par.) and cramps under different therapies (mean daily dose in brackets) as follows:

Medication	Ca	PO4	Ca U	par. %	cramps %
Calcium (1462 mg/d)	2.08	1.49	1.67	90	63
Vitamine D (11,442 U/d), Ca (1245)	2.12	1.46	2.88	51	43
1-Alphacalcidol (2.41 ug/d), Ca (1321)	2.19	1.26	2.65	32	26
1-Alphac.(1.26), Vit.D (15,949),Ca (1005)	2.19	1.44	2.65	38	38
Calcitriol (0.64 ug/d), Ca (1354)	2.19	1.43	2.52	57	35
Calcitr.(0.60), Vit.D (9845), Ca (1133)	2.18	1.34	3.27	48	31
Tachysterin (0.73 mg/d)	2.29	1.35	2.52	36	34
Tachysterin (0.77), Ca (1292)	2.22	1.43	2.75	67	48

Conclusion

As expected monotherapy with high doses of calcium was not sufficient. The combination of 1-Alphacalcidol and Calcium was the best regimen for treating HypoPT and improving complaints. Further correlations between different treatment regimen and parameters of renal and bone metabolism will be calculated.

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OC10.2

Evaluation of bone quality, measured by trabecular bone score (TBS) in patients with primary hyperparathyroidism (PHH) with and without surgery

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Evaluation of bone quality represents a challenge since the analysis by bone mineral density (BMD), provides useful but incomplete information. New tools are arising, and amog them, TBS is emerging as a new surrogate marker of bone texture and microarchitecture which may be useful to potentially evaluate the risk of bone fracture and can be obtained from already existing BMD scans. Retrospective study of 23 patients with PHH. Clinical, analytical and BMD data were collected form clinical records. TBS was calculated by reevaluating the already existing BMD images. Patients were classified into two different groups according to their treatment: 1) 13 patients who underwent surgery, in whom TBS was evaluated before surgery (B-S) and one year after surgery (A-S), and 2) 10 patients who received standard medical treatment, in whom TBS was evaluated with a time-lapse of 1 year. Basal age, body mass index (BMI), serum calcium, vitamin 25-OH-D levels and *T*-Scores were not significantly different between the two groups. Only PTH levels (82 vs 110 pg/ml, $P=0.04$) presented differences. We observed a significant improvement of TBS one year after surgery in the first group ($1.244\pm$ 0.11 vs 1.311 ± 0.1 $P=0.08$). A subtle deterioration on TBS was observed one year after standard treatment in the second group ($1{,}249\pm0.06$ vs 1.223 ± 0.07 $P=0.124$). Overall, surgical patients experienced a TBS increase 5.8% whilst a decrease of -2.04% was observed in the second group ($P=0.02$). In the multivariate correlation analysis, the percentage of variance in TBS was negatively correlated with the level of PTH and calcium at the moment of the second BMD (0.04 and 0.03 respectively). Bone microarchitecture, measured by TBS, improves after surgery in patients with PHH and has shown to be sensitive to changes developed during only one year time-lapse in bone. This parameter is a promising tool in the evaluation of bone status in PHH.

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OC10.3

High prevalence of radiological vertebral fractures in patients with differentiated thyroid carcinoma undergoing L-thyroxine TSH-suppressive therapy

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Thyroid hormones play a central role in the regulation of bone turnover and thyrotoxicosis is an established cause of secondary osteoporosis. Increased prevalence of reduced bone mineral density (BMD) has been reported even in patients with subclinical thyrotoxicosis such as those with differentiated thyroid carcinoma undergoing long-term L-thyroxine (L-T4) TSH-suppressive therapy. Morphometric vertebral fractures (VFs) are an early and clinically crucial marker of bone fragility but they have never been investigated so far in this setting. In this cross-sectional study, we evaluated the VF prevalence (DXA quantitative morphometry) and BMD (DXA Hologic 4500 W, at lumbar spine, total hip and femoral neck) in 53 consecutive patients with differentiated thyroid carcinoma (two males, 51 females; median age 61 years, range: 42–82; 45 with papillary carcinoma and eight with follicular carcinoma; median duration of therapy 5 years, range: 1–45) and 75 control subjects (72 females and three males; median age 62 years, range: 42–83) with normal thyroid function attending an outpatient bone clinic. VFs were significantly more prevalent in patients with thyroid carcinoma as compared to the control subjects (30.2 vs 9.3%; $P=0.002$) without significant ($P=0.21$) differences in BMD at either skeletal sites. BMD was not significantly different between fractured and non-fractured TSH suppressed patients at either skeletal site. Prevalence of VFs was not significantly ($P=0.29$) different among patients with normal BMD (11.1%), osteopenia (39.1%) and osteoporosis (28.6%). In patients under TSH-suppressive therapy, VFs were significantly associated with age (OR 1.1, C.I.95% 1.01–1.12; $P=0.03$) but not with duration of L-T4 therapy (OR 1.03; C.I.95% 0.96–1.11; $P=0.34$). This is the first study showing high prevalence of VFs in patients with thyroid carcinoma undergoing L-T4 TSH-suppressive therapy likely due to an impairment in bone quality. Vertebral morphometry should be performed at baseline and during follow-up of TSH-suppressed patients to assess their skeletal health.

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OC10.4

The effect of denosumab or bisphosphonates in women with severe postmenopausal osteoporosis after completion of teriparatide treatment

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The ideal antiresorptive agent to preserve or further increase bone mineral density (BMD) following teriparatide treatment is not known. We aimed to compare BMD changes after one year of therapy with denosumab or bisphosphonates in osteoporotic patients who had completed treatment with teriparatide. We retrospectively analyzed 140 women (age 74 years, 26 years from menopause, BMI 27 kg/m^2 on average) with severe postmenopausal osteoporosis who had been treated between 2006 and 2014 with teriparatide for 18–24 months at our outpatient clinic. After stopping teriparatide, they continued with a bisphosphonate (alendronate, risedronate, ibandronate or zoledronic acid) or with denosumab in standard doses per physician's and/or patient's preference. All patients were prescribed with vitamin D3 1000 IU daily and were instructed to ingest 1200 mg of calcium daily. BMD was measured at lumbar spine (LS), total hip (TH) and femoral neck (FN) by DXA when teriparatide was stopped and after 12 months of further treatment. The data were analyzed using multiple linear regression to adjust the comparison between groups for age, BMD, 25-hydroxyvitamin D, serum urate, procollagen type 1 N-terminal propeptide (P1NP) at baseline and BMD gain on teriparatide. Seventy patients continued treatment with a bisphosphonate and 70 received denosumab. The results indicate a lower BMD increase (especially at LS) in patients on bisphosphonates when compared to denosumab; a lower BMD increase at FN and LS in patients who had a larger BMD increase on teriparatide (i.e. regression to the mean); a lower BMD increase at FN and a higher BMD increase at LS in patients with higher baseline P1NP; and a higher BMD increase at FN in patients with higher baseline serum urate. Twelve months after stopping teriparatide, sequential osteoporosis treatment with denosumab yields higher additional BMD gain as compared to a bisphosphonate. The effect is more pronounced at LS.

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OC10.5

Gα11-Phe220Ser loss-of-function mutation causes familial hypocalciuric hypercalcemia type-2 (FHH2) by disrupting a hydrophobic cluster critical for G-protein signaling

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Mutations of the calcium-sensing receptor (CaSR), G-protein alpha-11 subunit (Gα11), and adaptor protein-2 sigma subunit (AP2σ) resulting in a loss-of-function, cause familial hypocalciuric hypercalcemia types 1-3 (FHH1-3), respectively. We investigated a family with FHH (four affected and two unaffected members) for CaSR, Gα11 and AP2σ mutations, and identified a heterozygous Gα11 missense mutation, Phe220Ser, which is predicted to disrupt a cluster of hydrophobic residues that are important for G-protein/G-protein coupled receptor interactions. Gα11, which acts downstream of the CaSR, activates phospholipase C (PLC) leading to two predominant signal outputs: intracellular calcium (Ca2+i) release; and activation of the extracellular-signal regulated kinase (ERK) mitogen-activated protein kinase (MAPK) pathway. We assessed the effects of the Gα11 mutation on signalling by expressing Gα11-wild-type Phe220, and three Gα11-mutants: Ser220, detected in the FHH2 kindred; and engineered mutants, Ala220 (a hydrophobic residue); and, Glu220 (a non-hydrophobic residue), in HEK293 cells stably expressing CaSR. Ca2+i responses to extracellular calcium (Ca2+e) were assessed using a Fluo-4 fluorescent assay and an NFAT-response element-containing luciferase reporter that measures Ca2+i–induced gene expression; and MAPK responses assessed using a phospho-ERK (pERK) AlphaScreen assay and a serum-response element (SRE)-containing luciferase reporter that measures ERK-induced gene expression. Mutation of Phe220 to the non-hydrophobic Ser220 and Glu220 residues, but not the hydrophobic residue, Ala220, significantly impaired Gα11 signalling via PLC-Ca2+i and ERK/MAPK pathways. Thus, Ser220 and Glu220, when compared to wild-type (Phe220) and Ala220 led to: a rightward shift of the dose-response curves of Ca2+i responses to Ca2+e with increased mean half-maximal concentration (EC50) values; reductions in NFAT reporter responses; impaired pERK responses; and reductions in SRE reporter activity. Thus, we have identified a novel Gα11 mutation, Phe220Ser, causing FHH2, and have demonstrated the importance of the hydrophobic Phe220 residue, which forms part of a cluster, for G-protein signaling via PLC-Ca2+i and ERK/MAPK pathways.

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Obesity

OC11.1

Role of Extracellular vesicles in the crosstalk between adipocytes and pancreatic beta-cells

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Obesity is characterized by insulin resistance and pancreatic β-cell dysfunction; moreover, secretion of adipokines from adipocytes may affect metabolic functions in several tissues, including pancreatic β-cells. Extracellular vesicles (EVs), released by cells as exosomes or shedding vesicles, play a key role in cell-to-cell communication, modifying the phenotype and function of recipient cells by delivering proteins, RNAs and microRNAs. The crosstalk between adipocytes and β-cells in the regulation of glucose and lipid metabolism is still unclear. We hypothesized that EVs derived from adipocytes are able to influence the survival and function of β-cells in pathophysiological conditions. In this study, the role of EVs released by murine 3T3-L1 adipocytes was evaluated on cell viability and proliferation, apoptosis and function of rat INS-1E β-cells and human pancreatic islets. INS-1E β-cells and human pancreatic islets were treated for 24 and 72 hours, respectively, with EVs in either presence or absence of CKs or palmitic acid and high glucose (P/G). Our results show that EVs derived from untreated adipocytes promote cell survival and proliferation, inhibit apoptosis in β-cells and pancreatic islets treated with CKs and P/G, and stimulate glucose-induced insulin secretion. Conversely, EVs derived from adipocytes treated with CKs enhanced the detrimental effects of CKs and P/G. These results suggest a functional crosstalk between adipose tissue and β-cells/pancreatic islets. Furthermore, the protective effects of EVs derived from adipocytes on survival and function of β-cells exposed to stress, such as inflammatory CKs or glucolipotoxicity, suggest possible therapeutic implications in pathological conditions like diabetes and obesity.

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OC11.2

Three year prospective study in morbidly obese patients between longitudinal gastrectomy and gastric bypass based on a composite outcome combining weight loss efficacy and surgery related complications (PHRC SLEEVE K060213 / IDRCB2007-A00373-50)

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Since its first description in 2000, Longitudinal Gastrectomy (LG) has become the first surgical procedure in the treatment of morbid obesity in the world, exceeding in numbers Gastric Bypass (GB). GB is considered to have better results regarding long-term weight loss and improvement in co-morbidities. We aimed to demonstrate that LG is non inferior to GB for a composite end point that included more than 50% excess weight loss from the baseline and surgery related complications after a mean follow-up of 36 months. This is a prospective study in

morbidly obese patients that tested a two hypotheses composite outcome: the first hypothesis was that after 36 months LG was non-inferior to GB regarding EWL (the predefined margin of non-inferiority was ±15%), and the second hypothesis was the presence of significant difference in post-operative morbidity and mortality. From February 2008 to March 2015 we included 277 patients (91 GB vs 186 LG). The mean age was 41.1 years, 19.2% had a previous bariatric operation, 85.9% were women and the average pre-intervention BMI was 45.3 kg/m^2. At baseline there were no significant differences between the GB and LG for age, sex and BMI. The % of patients with EWL > 50% was at 18 months for 82.1% (GB) vs 84.5% (LG), and 79.1 vs. 79.5% respectively at 36 months. The estimated difference in EWL was [−10.5% to 9.8%], confirming the non-inferiority of LG compared to BP. Finally there was a significant less morbidity and mortality for the LG group (GB vs LG, 12.1 vs. 4.8%, one death for LG, $P=0.01$). This is the first prospective study demonstrating that LG is not inferior to GB for an estimated 10% difference in EWL but with less surgical complications. These results reinforce the choice of LG as surgical procedure for obesity.

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OC11.3

Interleukin-1 antagonism decreases cortisol levels in obese individuals

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Background
Increased cortisol levels in obesity may contribute to the associated metabolic syndrome. In obesity, the activated innate immune system leads to increased interleukin (IL)-1β, which is known to stimulate the release of adrenocorticotropin hormone (ACTH). We therefore hypothesised that in obesity IL-1 antagonism would result in downregulation of the hypothalamo-pituitary-adrenal (HPA) axis, leading to decreased cortisol levels.
Methods
In this prospective intervention study we included 73 patients with obesity (BMI >30 kg/m^2) and at least one additional feature of the metabolic syndrome. The primary endpoint was change in morning cortisol from baseline to after the administration of the IL-1 receptor antagonist (anakinra/Kineret®, total dose 3×100 mg). Secondary endpoints were effects on salivary cortisol and ACTH.
Results
Median morning serum cortisol levels (nmol/l) decreased significantly after IL-1-antagonism (from baseline 452 to 423, absolute difference −38.7, 95%CI −64 to −13.4, $P=0.0019$). Similar effects were found for salivary cortisol levels (−2.8, 95%CI −4.4 to −1.3, $P=0.0007$), ACTH levels (−2.2, 95%CI −4.2 to −0.1, $P=0.038$), systolic blood pressure (−5.2, 95%CI −8.5 to −1.8, $P=0.0006$) and heart rate (−2.9, 95%CI −4.7 to −1.0, $P=0.0029$).
Conclusion
IL-1 antagonism in obese individuals with features of the metabolic syndrome leads to a decrease in serum cortisol, salivary cortisol and ACTH-levels along with a reduction in systolic blood pressure and heart rate. IL-1 antagonism could thus be a novel treatment option to improve cortisol levels and associated comorbidities in obesity.

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OC11.4

Comparing effects of weight loss by liraglutide with intensive lifestyle modification on hepatic steatosis, inflammation and stiffness, and insulin resistance in obese Asians with non-alcoholic fatty liver disease (NAFLD)

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Background and Aims
Non-alcoholic fatty liver disease (NAFLD), a leading cause of cirrhosis and liver cancer, is increasing worldwide due to rising obesity rates, particularly in Asia. Weight loss induced with diet and exercise decreases hepatic steatosis and inflammation, but requires greater efforts to sustain compared to medication. We therefore aimed to compare the effects of liraglutide, a glucagon-like peptide-1 agonist which induces weight loss, on hepatic steatosis and inflammation in obese Asian adults with NAFLD with intensive lifestyle modification.
Methods
22 abdominally obese Asian (mean BMI 33.6±3.9 kg/m^2, mean waist circumference WC 108.5±10.6 cm) non-diabetic normotensive adults with NAFLD, as diagnosed by a hepatologist based on elevated serum alanine transaminase (ALT) and aspartate transaminase (AST) levels and liver fat fraction >5% using magnetic resonance imaging (MRI) in the absence of other causes of hepatic steatosis and transaminitis, were randomized to supervised dieting (restriction by 400 kcal/day) plus moderate-intensity exercise (200 minutes/week) to induce ≥5% weight loss (DE group, $n=11$) or liraglutide 3 mg daily (LI group, $n=11$) for 26 weeks. Insulin resistance was estimated by homeostasis model assessment (HOMA-IR) and liver shear stiffness with MRI elastography.
Results
At 26 weeks, both DE and LI groups had significant ($P<0.01$) and similar reductions in weight (−3.1±2.9 vs −3.6±2.4 kg), WC (−4.4±3.2 vs −5.7±3.9 cm), liver fat (−9.5±13.8 vs −7.7±7.3%), liver stiffness (−0.22±0.20 vs −0.32±0.25 kPa), ALT (−42±34 vs −43±39 U/l), AST (−21±16 vs −26±25 U/l) and HOMA-IR (−2.87±2.67 vs −3.12±2.40).
Conclusion
Once-daily liraglutide is as effective as intensive lifestyle modification for decreasing hepatic steatosis, inflammation and stiffness in obese Asian adults with NAFLD.

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OC11.5

Differentiating constitutional thinness from anorexia nervosa in DSM 5 era

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Introduction
Constitutional thinness (CT) is an underweight state characterized by normal menstruations and no change in feeding behaviour. Thinness is the only resemblance between Anorexia Nervosa (AN) and CT. Removal of amenorrhea in the new DSM 5 definition of AN might lead to misdiagnosis between these two populations. The objective of this study was to compare CT, AN and Control subjects in terms of biological, anthropometric, and psychological markers in order to better distinguish AN from CT subjects.
Patients and method
This retrospective study conducted from 2000 to 2015 included three groups of young women: fifty-six CT, forty restrictive-type AN and fifty-four control subjects were included in the study. Basal evaluation was made in all groups with any intervention. Body composition, nutritional markers, pituitary hormones, bone markers and psychological scores were evaluated in three groups. For every markers, a receiver Operator Characteristics (ROC) curve was calculated to evaluate the accuracy of differentiation between AN and CT groups.
Results
For the majority of the studied parameters, CT subjects were similar to controls but dramatically different from AN subjects. According to ROC data, while psychological scores were unsuccessful to differentiate AN from CT, except for DEBQ Restrained Eating item, free-T3 and Leptin were strong tools for AN and CT distinction as they displayed high sensitivities and specificities with low P values (<0.0001).
Conclusions
Taking AN and CT distinction as a major objective, the exclusive use of psychological criteria is not sufficient and should be completed by at least a free T3 determination, which is a cheap and an accessible laboratory testing for general practitioners. The final goal is to avoid social stigmatization and excessive useless therapies for CT women.

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Pituitary Clinical

OC12.1

T2-Weighted signal intensity of functional pituitary adenomas: correlation with clinicopathological findings and response to treatment

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Purpose
Somatotrophinomas have been shown to demonstrate T2-weighted signal intensity (WSI) on MRI that is correlated with clinicopathological findings and response to treatment. Therefore, we aimed to investigate these correlations in functional pituitary adenomas, including prolactinoma and corticotrophinoma.
Material and Methods
Patients with somatotrophinoma ($n=87$), prolactinoma ($n=78$) and corticotrophinoma ($n=33$) were involved in this study. The initial T2-WSI findings (grouped into hypo-, iso- and hyperintense) were compared with hormon levels, tumor diameter, granulation patterns and treatment response.
Results
While most of somatotrophinomas were hypointense, most of prolactinomas and corticotrophinomas were hyperintense. Tumor diameter was significantly larger in hyperintense somatotrophinomas than in hypointense group ($P=0.007$), but the tumor diameter in the isointense group did not show any difference when compared to the others. IGF-1% ULN (upper limit of normal) was higher in hypointense somatotrophinomas than the other two groups ($P=0.02$). Sparsely granulation pattern in hyperintense somatotrophinomas and densely granulation pattern in hypointense somatotrophinomas are more frequent ($P=0.035$), whereas the granulation pattern distribution in isointense group did not differ from the other two groups. The hormonal response to somatostatin analogs (SSA) treatment (percentage of IGF-1 reduction) was higher in the hypointense group than in the other two groups ($P=0.04$). The tumor diameter was smaller in the hyperintense prolactinomas than in the other groups ($P=0.039$), but the basal PRL levels were not different between the groups. The response to dopamine agonist (DA) treatment of iso- and hyperintense prolactinomas is much better than the hypointense group ($P<0.001$). Tumor diameter was larger in hyperintense corticotrophinomas than the other two groups ($P=0.012$), but there was no difference between the baseline cortisol and ACTH levels of the groups. Sparsely granulation pattern was higher in hyperintense corticotrophinomas and densely granulation patern in hypointense corticotrophinomas ($P=0.029$), whereas granulation pattern distribution in isointense group was not different from the other two groups. There was no difference between the groups in terms of remissions and recurrences.
Conclusion
Hyperintense somatotrophinomas support literature knowledge with increased tumor diameter, sparsely granulation pattern and less responsiveness to SSA treatment. The response to DA treatment of iso- and hyperintense prolactinomas is much better, but there was no difference between the groups in terms of remissions and recurrences in corticortophinomas. Our results in prolactinomas and corticotrophinomas should be supported by further studies.

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OC12.2

Use of temozolomide in a large cohort of patients with aggressive pituitary tumours and pituitary carcinomas: Results from a European Society of Endocrinology (ESE) survey

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Objective
To collect clinical and treatment outcome data in a large patient cohort, and specifically to report experience with temozolomide (TMZ).
Design
Cohort study based on an electronic survey open for participation to ESE members Dec 2015-Nov 2016.
Results
Reports on 167 patients, 40 pituitary carcinomas, and 127 aggressive pituitary tumours were obtained. Median age at diagnosis was 43 (range 4–79) years. 59% of tumours were clinically functioning at presentation, and the most frequent were corticotroph tumours. TMZ was the first line chemotherapy in 157 patients. At the end of TMZ treatment (mean 9.92 cycles) radiological evaluation showed complete response in 6%, partial response in 31%, stable disease in 33% and progressive disease in 30%. Progression occurred more often in pituitary carcinomas (40%) than in aggressive adenomas (26%), $P=0.05$. Clinically silent tumours showed less regression compared with secreting tumours, 17 vs 45%, $P=0.01$ (overall χ^2 test). Median follow-up after TMZ treatment was 21 months. Of patients with complete response, partial response and stable disease 22, 34 and 40% respectively showed progression during further follow-up. Twenty five patients received a second course of TMZ, 3 had a partial response. Overall mortality was 33%, and highest in patients with progression after TMZ treatment (54%).
Conclusion
TMZ was accompanied by tumour regression in 37% of patients, documenting its value in the management of these aggressive tumours. The high recurrence rate following TMZ cessation highlights the need to identify additional effective therapies.

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OC12.3

Recombinant Growth Hormone added to physical therapy in GH-deficient adults with complete (ASIA A) Spine Injury (EudraCT 2011-005377-23)

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Introduction
Although *in-vitro* models suggest GH-induced differentiation, migration and survival of astrocytes and oligodendrocytes, no studies had been published in-vivo. We want to evaluate the efficacy and safety of GH associated with physical therapy compared to placebo in patients with complete spine injury (SI) and associated GH deficiency (GHD).
Methods
Eighteen Patients with complete SI were screened for GHD (glucagon test). 12 severe (GH < 3 ng/ml) or partial (< 10 ng/ml) GHD were randomized in a double-blind placebo-controlled study. Motor and sensory ASIA scale, SCIM-III (spinal cord injury independence measure), Ashworth (spasticity), Neuropathic Pain Scale and Quantitative Sensory tests were assessed. Patients received subcutaneous injections of placebo or GH (Nutropin®) 6 days/week IGF1-adjusted, in addition to intensive physical therapy 2 h/day, for 6 months. Both groups were similar according to age, sex, BMI, waist circumference.
Results
Significant ($P=0.05$) improvement was observed in SCIM-III score at 3 months: 55.6 (14.4 s.d.) vs 74 (2.8 s.d.) and 6 months: 55.4 (14.2 s.d.) vs 73.5 (2.1 s.d.), comparing GH-treated group with placebo. A significant improvement in the electrical perception threshold from the 1st up to the 5th metamera below the SI site was observed on both sides after 6 months of treatment in the GH, but not in the placebo group. These differences were observed intra-individually ($P=0.04$ Friedman's test) and between groups (5th left level ($P=0.023$) and 5th right level ($P=0.031$), mixed linear model). No correlations with IGF1 were observed. No GH-related adverse events were reported.
Conclusions
Not studied so far, GHD seems very prevalent in SI. This is the first trial with complete SI and concomitant GHD. GH added to intense physical rehabilitation improved functional parameters (SCIM) and changes in sensory quantification up to 5 levels below SI. Larger studies should be performed to confirm a GH beneficial effect on sensitive pathways in SI.

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OC12.4

Subclinical cardiovascular system dysfunction in the patients with Cushing's disease

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Background
Hypercortisolism in Cushing's disease (CD) is associated with high cardiovascular risk. Hemodynamic disturbances, especially excessive vasoconstriction and elevated blood pressure (BP), may contribute to accelerated myocardial remodeling. Early identification of subclinical left ventricular (LV) dysfunction may be crucial for optimizing treatment and reducing mortality in patients with CD.
Purpose
The aim of this study was to assess the hemodynamic function of cardiovascular system in three groups of patients: 1/ with CD (CD), 2/ with essential arterial hypertension (AH) and healthy volunteers (HV).
Methods
In 171 subjects (CD – 22, AH – 114, HV – 35), without any symptoms of heart failure, the echocardiographic assessment of LV systolic and diastolic function and non-invasive hemodynamic assessment by impedance cardiography (ICG) were performed. Statistical comparison included separate analysis for women and men.
Results
CD revealed good BP control (82% below 140/90 mmHg). However, in comparison to AH and HV they presented: 1) significantly lower LV contractility expressed by global longitudinal strain (GLS: −17.7% vs −19.2 vs −20.0; $P=0.004$); 2) higher prevalence of LV diastolic function (45.0% vs 14.2% vs 0.0%; $P<0.00001$); 3) lower impedance indices of LV performance: stroke index (SI: 39.8 vs 52.2 vs 49.9 ml/m^2; $P<0.00001$) cardiac index (CI: 2.86 vs 3.54 vs 3.27 l/min/m^2; $P<0.0001$) and 4) higher afterload: systemic vascular resistance index (SVRI: 2560 vs 1901 vs 1907 dyn*s*m^2/cm^5; $P<0.0001$). Men with CD distinguished with lower CI ($P<0.00001$) and SVRI ($P<0.0001$), as though worse LV diastolic function (e': $P=0.0002$; GLS: $P=0.052$). In women hypercortisolism was more related to impaired LV systolic function (GLS: $P=0.010$; e': NS).
Conclusions
Cushing's disease, even with well-controlled BP, is associated with LV systolic and diastolic dysfunction and pronounced vasoconstriction which individual presentation depends on sex. These hemodynamic alterations can be detected by modern non-invasive diagnostic tools and became potential therapeutic objectives.

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OC12.5

Effects of pegvisomant and somatostatin receptor ligands on risk of vertebral fractures in patients with Acromegaly

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Acromegalic osteopathy is an emerging complication of chronic GH excess characterized by increase in bone turnover, deterioration in bone microarchitecture and high risk of vertebral fractures (VFs). Medical therapies may exert direct effects on peripheral targets leading to improvement of clinical outcomes regardless of biochemical control of acromegaly. In this longitudinal study, we compared the effects pegvisomant (PegV) and somatostatin receptor ligands (SRLs) on VF risk in 80 acromegaly patients (47 females, 33 males; mean age 53 years, range 24–86 years) who were prospectively evaluated by quantitative vertebral x-ray morphometric approach. During the 30 month study period, 39 patients (48.8%) were treated with PegV, 33 (41.2%) with SRLs and 8 (10%) showed a controlled disease after neurosurgery. At follow-up, 23 patients (28.8%) experienced incident VFs which were significantly correlated with persistently active disease (OR .49, C.I.95% 1.75–17.22; $P=0.003$) and preexisting VFs (OR 2.79, C.I. 95%1.03–7.61; $P=004$). By contrast, no significant differences in incident VFs were found between patients receiving PegV and those treated with SRLs alone, either when disease was persistently active (58.3% vs 60.0; $P=0.94$) or when disease was controlled by treatment (20.0 vs 27.0%; $P=0.67$). In conclusion, this longitudinal study showed that PegV and SRLs had comparable effects on VF risk in acromegaly. Biochemical control as well as early diagnosis of the disease are the main endpoints for fracture prevention in acromegaly.

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Reproduction & Endocrine Disruption

OC13.1

Abstract withdrawn.

OC13.2

Thyroid peroxidase antibodies do not predict outcome in 900 women with recurrent pregnancy loss

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Introduction
Thyroid autoimmunity has been associated with pregnancy loss. A possible mechanism is an overactive maternal immune system leading to rejection of the fetal allograft. In women with recurrent pregnancy losses (RPL), we investigated the association of thyroid peroxidase antibodies (TPOAbs) with number of losses and outcome of first pregnancy after referral.
Methods
Prospective study of women with RPL (≥ 3) followed at the RPL Unit, Copenhagen University Hospital, from 2011 to 2016. Upon first visit, all women were screened for TSH (Roche Modular E170 electrochemiluminescense immunoassays) and TPOAbs (automated Kryptor immunoflourescent assay). TPOAb-positivity >60 kU/l. We performed test for trends by chi-square or independent *t*-tests as appropriate, and adjusted regression analyses with covariates: maternal age, TSH (logtransformed), number of losses, immunotherapy, thyroxine replacement therapy. The National Data Protection Agency approved the project.
Results
We included 5219 pregnancies (76.6% spontaneous) in 900 women; 119 (13.2%) women were TPOAb-positive. TPOAb-positivity was neither associated with number of losses ($P=0.87$, aOR 0.004 (-0.3-0.3), $P=0.98$), nor number of pregnancies ($P=0.62$, aOR 1.02 (0.92-1-11) $P=0.76$). Among TPOAb-positive women, TPOAb-concentration was not associated with number of losses (B = 0.75 (-0.12-0.27), $P=0.45$). In women with a registered first pregnancy after referral, TPOAb-positivity (72 of 557 (12.9%)) was not associated with live birth rate (54.4 vs 60.6%, $P=0.35$, aOR 0.78 (0.42-1.43) $P=0.38$). However, live birth rate was significantly associated with total number of losses (aOR 0.53 (0.45-0.61) $P=0.000$). TSH-levels were positively associated with TPOAb-positivity ($P=0.00$), but not with any investigated outcome. Immunoglobulin therapy or thyroxine replacement did not alter results.
Conclusion
In a large cohort of women with RPL, we found no association between TPOAbs and pregnancy outcome. TSH-levels were significantly increased in TPOAb-positive women and screening according to guidelines should be performed. However, if RPL is caused by an immunological reaction, thyroid autoimmunity does not seem to be a sensitive marker hereof.

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OC13.3

Sertoli cell expressed hydroxysteroid (17beta) dehydrogenase 1 is required for male fertility

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Hydroxysteroid (17beta) dehydrogenase 1 (Hsd17b1) is a steroidogenic enzyme catalyzing the conversion of estrone (E1) to estradiol (E2), and androstenedione (A-dione) to testosterone (T). We have shown that the deletion of Hsd17b1 gene in mice resulted in the failure of ovarian estrogen production and subfertility. In this study, we clarified the role of Hsd17b1 in male reproduction. The data revealed that in mice Hsd17b1 mRNA is highly expressed in the Sertoli cells at the fetal age. The Sertoli cell function is critical for normal spermatogenesis, and their action is dependent on the pituitary gonadotropins and testosterone. The breeding tests revealed that the Hsd17b1 knockout male mice (HSD17B1KO) were infertile. Because the Hsd17b1 is part of the steroid synthesis machinery, we analyzed the *in vivo* biomarkers for androgen action, while no changes were observed in fetal masculinization or in onset of puberty. Furthermore, the weights of androgen-dependent tissues in HSD17B1KO were neither affected. Also, the serum gonadotropin levels and the steroid concentrations in the testis, were close to normal in the HSD17B1KO males, with minor changes in the E1/E2 and A-dione/T ratios. Interestingly, several steroidogenic genes, Hsd17b3, Star, Cyp11a1 and Hsd3b1, were significantly upregulated in HSD17B1KO testes, suggesting a functional compensation due to the lack of Hsd17b1 activity. Although no marked changes were observed in the hormonal environment, histological analysis of HSD17B1KO testis revealed defects in the organization of differentiating germ cells in the seminiferous epithelium, and major defects in the haploid germ cell differentiation, particularly in the head shaping of elongating spermatids. Consequently, the epididymal sperm count was dramatically reduced in the HSD17B1KO males, and the remaining spermatozoa were morphologically abnormal. These results revealed a novel role for Hsd17b1 in the control of spermatogenesis and male fertility, and suggest that Hsd17b1 is required for a proper function of Sertoli cells.

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OC13.4

Diabetes mellitus: a new cause of male infertility

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Introduction
Diabetes mellitus (DM) may cause male infertility acting with pre-testicular, testicular and post-testicular mechanism.
Aim
To evaluate the presence of male infertility and the mechanisms of sperm damage in diabetic patients in childbearing age.
Patients and methods
Thirty-four patients with DM1, 55 with DM2 and 100 healthy fertile men (controls) were enrolled. Diabetic patients were further divided into three groups based on their glycometabolic status and illness duration. Conventional and biofunctional sperm parameters were evaluated by standard semen analysis and flow cytometry. This latter included sperm DNA fragmentation, vitality, early and late apoptosis, chromatin condensation, mitochondrial membrane potential (MMP), leukocyte subpopulations, lipid peroxidation (PL) and sperm mitochondrial superoxide. In addition, all patients and controls underwent testicular ultrasound sca and serum LH and testosterone measurements.
Results
Diabetic patients had lower sperm concentration, progressive motility and morphology vs controls ($P<0.05$). The ejaculate volume is significantly lower in patients with DM1 vs controls ($P<0.05$). Leukocyte concentrations were higher in patients with DM2 ($P<0.05$), showing a statistically significant reduction in the percentage of T helper cells and an increase of the suppressor T lymphocytes compared to controls ($P<0.05$). The analysis of the biofunctional sperm parameters showed worsening MMP in diabetic patients ($P<0.05$). Patients with DM2 showed a significant decrease in the degree of sperm vitality and increased spermatozoa in late apoptosis vs Controls and of the DNA fragmentation compared to the other two groups ($P<0.05$). Moreover, patients with DM1 had a lower progressive motility when the disease duration was >10 years vs the other two groups, and lower MMP after 5 years of disease ($P<0.05$). The degree of PL was higher in DM2 patients compared to the other two groups ($P<0.05$), while the concentrations of mitochondrial superoxide were greater in DM2 patients compared to DM1 and control group ($P<0.05$). The ultrasound data showed that the diameter of the epididymal head and tail after ejaculation were greater in patients with DM1 long term than those of short duration compared to controls ($P<0.05$). Testosterone levels were lower in DM2 patients vs controls ($P<0.05$).
Conclusion
Patients with DM1 have low ejaculate volume for an altered epididymal emptying and a mitochondrial damage that anticipates the later decline of sperm motility. DM2 is instead characterized by an inflammatory condition with increased leukocyte and oxidative stress and elevated levels of sperm DNA fragmentation and decreased sperm vitality.

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OC13.5

Urinary cadmium excretion is associated with increased synthesis of cortico- and sex steroids in a family-based Swiss population study

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Background
Cadmium (Cd) is considered as a human carcinogen. A potential intermediate mechanism could be hormone-related by disturbing steroidogenesis in gonads and adrenal glands. We tested whether urinary Cd excretion, as a marker of long-term exposure, is associated with the urinary steroid profile in the general adult population.
Methods and Findings
The Swiss Kidney Project on Genes in Hypertension (SKIPOGH) is a multicentric family-based population study with a response rate of 25.6%. We measured 24-h urinary excretions of Cd and steroid hormone metabolites by gas chromatography and mass spectrometry in 1000 participants (473 men, 527 women), with separate day and night collections. Mixed linear models were used to analyse the associations of each steroid metabolite with Cd excretion.
Cd and testosterone excretions were positively associated in men (β[SE, *P*]: 1.378[0.242, <0.00001] and 1.440[0.333, 0.00002] for day and night, respectively), but not in women (0.333[0.257, 0.2] and 0.674[0.361, 0.06]). There was a strong positive association of the urinary excretion of Cd and cortisol (0.475[0.157, 0.0025] and 0.877[0.194, 0.00001], for day and 0.875[0.253, 0.00053] and 1.183[0.277, 0.00002] for night, respectively). Cd excretion was not associated with the excretion of tetrahydroaldosterone, the major metabolite of aldosterone, but with other mineralocorticoid metabolites ($P<0.01$ in men and women). Further adjustment revealed an independent effect between the synthesis of sex hormones and corticosteroids and an interdependent effect of Cd on gluco- and mineralcorticoid synthesis.
Conclusions
Our findings provide evidence for a global stimulating effect of low-dose Cd exposure on sex and corticosteroid synthesis in the general adult population. Further studies are needed to explore the health consequences of chronic low-dose exposure to Cd on selected diseases such as steroid-sensitive cancers or metabolic disorders.

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Thyroid Cancer

OC14.1

Anti-Mullerian hormone (AMH) in pre-menopausal females after ablative radioiodine (RAI) treatment for differentiated thyroid cancer (DTC): single-center study

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Background
It is generally reported that female fertility is not affected by high-dose RAI treatment. AMH has been considered a reliable and accurate index of ovarian reserve. There are few data on AMH values in thyroid diseases. Recently, in DTC women who had undergone RAI ablation treatment, Acibucu *et al*. (2016) reported low AMH levels without significant impairment of fertility.
Aim
The aim of this single-center study was to evaluate AMH levels in association with the characteristics of spontaneous menstrual cycles and the levels of pituitary–gonadal hormones in our cohort of pre-menopausal women with a history of low-risk DTC.
Subjects
From a group of 68 women, 39 who were not on oral contraceptive therapy were enrolled. All hormone evaluations were performed on chemiluminescence assays. AMH, FSH, 17B-estradiol (E2) were assayed on day 2 and PRL and progesterone (P) levels on day 21–24 of the same menstrual cycle. Twenty-seven women (aged 40 ± 6 years) were studied 7 ± 4 years after primary DTC treatment, which included at least one RAI treatment (median activity 80 mCi). As a control group, 12 female DTC patients (aged 40 ± 8 years) who had undergone only thyroidectomy were used.
Results
All women were free from DTC. Pregnancy (study group 62%; control group 50%) and abortion rates (17 and 33%) were similar. TSH and f-T4 were similar in both groups. Hyperprolactinemia was found only in one patient, while FSH >30 mU/l was found in 2 (1 study, 1 control). Regular (28 ± 2 days) menses were reported in 33% of both groups. A high incidence of polymenorrhea was reported in the study group (33%), while a high incidence of oligomenorrhea was noted in the control group (50%). Ovulatory cycles ($P>4$ ng/ml) were noted in 72 and 60% of study and control women, respectively. AMH levels were found to be negatively correlated with age ($P=0.002$), but not with E2, FSH, TSH or f-T4 levels. AMH levels were 2.0 ± 0.4 ng/ml and 2.3 ± 1.5 ng/ml in the study and control groups, respectively.
Limitations
These data are preliminary, as data collection is still ongoing.
Conclusions
AMH should replace FSH in the evaluation of gonadal reserve in pre-menopausal DTC women. At present, age is the only predictor of AMH levels. About one out of two women with a history of DTC suffers from menstrual dysregulation, but infertility must be considered a low risk.

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OC14.2

Suppression of heme oxygenase-1 inhibits growth and invasion of thyroid cancer

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Oxidative stress generated in the process of iodide metabolism and thyroid hormone synthesis may play a role in thyroid tumorigenesis and progression of thyroid cancer. The transcription factor Nrf2 is the most important regulator of antioxidant responses. It has been shown that Nrf2 expression is upregulated in papillary thyroid cancer. In response to oxidative stress, nuclear Nrf2 activates antioxidant-responsive elements and induces the expression of stress-responsive genes, including heme oxygenase-1 (HO-1). Previously we have demonstrated that HO-1 overexpression was associated with advanced tumor stage in thyroid cancer. Therefore, we hypothesize that HO-1 may represent a potential target for cancer therapy. HO-1 inhibitors have been clinically used in patients with hyperbilirubinemia and hereditary porphyria. In the present study, thyroid cancer cells were treated with two different classes of HO-1 inhibitors: metalloporphyrin and imidazole–dioxolane compound. We found that treatment with HO-1 inhibitors suppressed cell growth, colony formation, cell migration, and invasion of thyroid cancer cells in a dose-dependent manner. Cell cycle analysis by flow cytometry revealed that growth arrest in the G0/G1 phase. However, there was no synergistic effect of HO-1 inhibitors in combination with doxorubicin or sorafenib. Our results suggest a modest susceptibility of thyroid cancer cells to HO-1 inhibitors. Nonetheless, HO-1 inhibition may not act as a sensitizer to chemotherapy in thyroid cancer.

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OC14.3

TERT, BRAF and NRAS in the molecular profile of metastatic thyroid cancer: differences between primary and distant disease

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Context
Little is known about the frequency of key mutations in thyroid cancer metastases and its relationship with the primary tumor genotype.
Objectives
To evaluate the frequency of TERT promoter (TERTp), BRAF and NRAS mutations in metastatic thyroid carcinomas, analyzing primary thyroid tumors, lymph node metastases (LNM) and distant metastases.
Material and Methods
Mutation analysis was performed in 437 tissue samples from 204 patients, mainly with papillary thyroid carcinomas (PTC) ($n=180$), including 196 LNM and 56 distant metastases. All the distant metastases included corresponded to radio-iodine-refractory metastatic tissue.
Results
We found the following mutation frequency in primary thyroid tumors, LNM and distant metastases, respectively: TERTp- 15.9, 10.8, and 52.4%; BRAF (PTC-only)- 44.6, 41.7, and 23.8%; NRAS- 1.7, 1.3, and 11.9%. In the subgroup of patients with PTC, the TERTp mutation frequency in primary tumors, LNM and distant metastases was 12.9, 10.5, and 52.4%, respectively. There was a significant concordance between the primary tumor genotype and the corresponding LNM, in particular for BRAF-mutated PTC. The overall concordance between primary tumors and respective distant metastases was low. In the group of patients with PTC, we found a high frequency of TERTp mutations and a low frequency of BRAF mutations in distant metastases, in comparison to the paired primary tumors.
Conclusions
The frequency of BRAF, NRAS and TERTp mutations is similar in primary tumors and matched LNM, whereas distant metastases show an enrichment in TERTp mutations and a decrease in BRAF mutations. TERTp mutations seem to play an important role in distant metastases.

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OC14.4

Inverse relation between thyroid cancer incidence and threshold for thyroid surgery: a national population-based retrospective study

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Background
In Belgium, lower thyroid cancer incidence – most pronounced for microcancers (T1a) – is present in the North compared to the South. This variation is paralleled by differences in clinical practice: in the North less thyroid surgery is performed, more surgery is preceded by fine needle aspiration (FNA), and more patients with a final cancer diagnosis (2004–2006) underwent a presurgical FNA or a lymph node dissection (LND) at fist surgery.
Aim
To study 1/ the evolution in the use of FNA and LND, and 2/ the weight of T1a non-thyrotoxic thyroid glands in a recent thyroid cancer cohort.
Methodology
Population-based retrospective study, using data from the Belgian Cancer Registry (including case-by-case study of pathology protocols) and Belgian Healthcare Insurance database for differentiated thyroid cancer (DTC) cases diagnosed between 2009 and 2011 ($n=2659$).
Results
Linkage of both databases resulted in 2557 DTC cases (96%). In the North a higher proportion of DTC cases underwent FNA before surgery: 62.3%[95%CI 58.3;66.3] compared to 33.6%[95%CI 29.3;39.9] in the South ($P<0.0001$), confirming geographical differences. A positive trend for FNA was observed in the period 2004–2012, at national and regional level, especially in the South. The execution of LND during first thyroid surgery was proportionally higher in the North (24.3%[95%CI 20.6;28.0]) compared to the South (15.3%[95%CI 12.0;18.7], $P<0.0001$), without temporal trend. Finally, in the subgroup of T1a DTC cases – considered to be mainly incidental findings – the mean thyroid weight was 57.7 ± 52.1 g in the North, compared to 37.99 ± 29.1 g in the South ($P<0.0001$).
Conclusion
In the present cohort, more FNA precedes thyroid cancer diagnosis, according to international guidelines. However, geographical differences clearly persist. A lower thyroid weight is present in DTC T1a in the South. These findings support the alignment of a higher thyroid cancer incidence with a lower threshold for thyroid surgery in case of nodular disease, strongly suggesting overdiagnosis.

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OC14.5

Dose aggressive variants of papillary thyroid carcinoma have worse clinical outcome than classical papillary carcinoma?

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Background
Unlike excellent prognosis of classical papillary thyroid carcinoma (cPTC), certain pathological subtypes of aggressive variants of PTC (AV-PTC) are considered to have poor clinical outcome. However, the evidence of unfavorable outcome of AV-PTC is not clear because previous studies did not control other confounding factors contributed to clinical outcomes.
Methods
This retrospective cohort study initially included 4339 patients with cPTC and 121 patients with AV-PTC including tall cell, columnar, hobnail, solid and diffuse sclerosing variants. Dynamic risk stratification (DRS) and recurrence free survival (RFS) between the two groups were compared after two-to-one individual risk factor matching by age, sex, tumor size, and initial surgical extent.
Outcome
AV-PTC was associated with larger tumor size ($P<0.001$) and higher rates of cervical lymph node (LN) metastasis ($P<0.001$) compared to cPTC. A total of 121 patients with AV-PTC and 242 patients with cPTC were evaluated after individual risk factor matching. There were no significant differences in the tumor size and cervical LN metastasis between the two groups after mating. When we compared the proportion of patients according to the DRS, there was no significant difference between patients with cPTC and those with AV-PTC ($P=0.14$). There was also no significant difference in RFS (hazard ratio [HR] 1.93, 95% confidence interval [CI] 0.68-5.47, $P=0.23$) between the two groups. In subgroup analysis including patients with tall cell, columnar, and hobnail variants of PTC, there were no significant differences in DRS ($P=0.68$) and RFS (HR 2.04, 95% CI 0.56-7.41, $P=0.29$) compared with matched patients with cPTC.
Conclusion
The clinical outcome of patients with AV-PTC was not different with those with cPTC when their other clinicopathological risk factors were similar. Therapeutic and follow-up strategies for PTC might not need to be modified according to presence of AV-PTCs.

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Guided Posters

Adrenal 1

GP1

PRKACA mutations in adrenal Cushing can alter substrate specificity

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Previously, we identified seven mutations in the main catalytic subunit of protein kinase A (PKA Cα) to be responsible for cortisol-secreting adrenocortical adenomas (CPAs): L206R, L199_C200_insW, S213R_L212_K214insIILR, C200_GlyinsV, W197R, del244-248+E249Q, E32V. Here we performed a functional characterization of these mutants. Specifically, we evaluated the association between PKA regulatory and catalytic subunits using co-immunoprecipitation and PKA activity using a kemptide assay and a western blot analysis. Our results show that four mutations (L206R, L199_C200_insW, W197R, del244-248+E249Q) cause increased basal PKA activity. Interestingly, the measured activity varied considerably among mutants depending on the assay used, suggesting changes in substrate specificity. Binding to RIα and RIIβ subunits was lost for three and two mutants respectively. One mutant (E32V) showed no differences with the wild type. The S213R_L212_K214insIILR mutant was associated with a loss of PKA activity, but showed a strong accumulation in the nucleus. The C200_G201insV mutant was associated with a loss of activity in the kemptide assay but showed normal behavior in the western blot and nuclear translocation. For all mutants we performed an in silico analysis to predict the effect of the mutation on substrate specificity. The analysis suggested changes in substrate specificity for five mutants. Based on this, we performed phosphoproteomic experiments, which directly compare the phosphorylation of a large number of PKA substrates. The results directly demonstrated altered substrate specificity for three mutants (L206R, del244-248+E249Q, C200_G201insV). Taken together, these findings suggest that the PKA Cα mutations found in CPAs alter substrate specificity and that interference with the formation of a stable PKA holoenzyme is probably just one of the mechanisms through which these mutations affect PKA signaling, ultimately leading to increased cortisol production and cell proliferation. The results of the phosphoproteomics analysis might lead to the identification of new PKA targets involved in the pathogenesis of CPAs.

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GP2

Contribution of retinoic acid receptor signalling to adrenal cortex morphology and functional zonation through modulation of WNT/β-catenin pathway

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Recurrent somatic mutations in *KCNJ5, CACNA1D, ATP1A1* and *ATP2B3* have been identified in aldosterone producing adenoma (APA). Although the role of these mutations in regulating aldosterone biosynthesis has been clearly established, the mechanisms involved in proliferation and APA formation still remain to be elucidated. The aim of our study was to identify pathways involved in adrenal cortex nodulation and APA formation.

Transcriptomic analysis from 123 APA and 11 control adrenal and correlations of gene expression with genetic, morphological and functional characteristics of the tumors allowed us to identify retinoic acid receptor (RAR) signalling as a central molecular network involved in APA formation independently of the mutation status. Treatment of H295R cells with all-trans retinoic acid and 9-cis retinoic acid reduced cell viability in a time and dose dependent manner. This effect was due to decreased cell proliferation and increased cell apoptosis. In contrast to the effects observed in vitro, 9-cis retinoic acid did not modify tumor progression in a mouse xenograft model.

Investigation of the adrenal phenotype of rar$\alpha^{-/-}$ mice demonstrated that in young (12 weeks) and old (52 weeks) rar$\alpha^{-/-}$ mice the characteristic cellular arrangement of the adrenal cortex was replaced by an enlarged zona glomerulosa and a disorganized zona fasciculata. This is also associated to dilatation and disorganisation of vessels and increased capsule thickness. Furthermore, young rar$\alpha^{-/-}$ mice displayed lower plasma aldosterone concentration and decreased expression of steroidogenic enzymes. Interestingly, this was associated with the inhibition of WNT/β-catenin pathway.

Our results suggest that RAR signaling contributes to normal adrenal morphology and functional zonation through modulation of WNT/β-catenin pathway and that its disruption could contribute to abnormal cell proliferation in the adrenal cortex, creating a propitious environment for the emergence of specific driver mutations in APA.

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GP3

Exosomal hsa-miR-483-5p and hsa-miR-101 are potential minimally invasive biomarkers of adrenocortical carcinoma

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Background

Extracellular vesicles (exosomes, microvesicles) shed from tumor cells containing microRNAs can be exploited as markers of malignancy. The preoperative diagnosis of adrenocortical malignancy is difficult and microRNAs have proved useful in the diagnosis of many tumors, including adrenocortical cancer (ACC), but there have no studies to date on extracellular vesicle associated microRNAs in ACC.

Aim

To evaluate the diagnostic potential of extracellular vesicle-associated (exosomal) microRNAs in human adrenocortical tumors.

Methods

The isolation of extracellular vesicles (EV) was performed either by differential centrifugation/ultracentrifugation or by applying Total Exosome Isolation Kit. EV preparations were also assessed by transmission electron microscopy and flow cytometry. 6 adrenocortical adenomas (ACA) and 6 histologically verified ACC samples were profiled by Taqman Human Microarray A-cards in the discovery cohort. The significantly differentially expressed microRNAs were validated in 13 ACAs and 12 ACCs by targeted quantitative real-time PCR.

Results

Significant overexpression of EV-associated hsa-miR-101 and hsa-miR-483-5p was measured in ACC vs ACA samples in the microRNA profiling. We could confirm the overexpression of these microRNAs in the validation cohort, too. dCThsa-miR-483-5p normalized to cel-mir-39 showed the highest area under curve (AUC) value (0.96), with 91.67 sensitivity and 92.33 specificity.

Conclusions

Extracellular vesicle-associated (exosomal) hsa-miR-483-5p might be a promising minimally invasive biomarker in the preoperative diagnosis of ACC.

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GP4

Androgen receptor signalling is essential for regression of the adrenal x-zone and regulation of the adrenal cortex in the male mouse

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Introduction
Androgens have long been known to play an important role in health and wellbeing. A range of clinical disorders in males and females can arise due to disruption to production and action of androgens. Androgen receptor (AR) is widely expressed throughout the adrenal cortex, yet the wider role for androgen signalling in the adrenal remains underexplored due to the lack of suitable animal models.
Methods
An adrenal-specific androgen receptor knockout mouse model was created by targeting GFP-Cre-GC to the mouse *Cyp11a1* locus to drive Cre Recombinase expression in steroidogenic cells. Males were then mated to C57BL/6 female homozygous $AR^{fl/fl}$ mice. C57BL/6 mice were also used to investigate normal adrenal function. Tissue was analysed through qRT-PCR and statistical analysis by one way ANOVA. Immunohistochemistry was used to determine changes in protein localisation.
Results
Results highlight that androgens signalling through AR is essential for the regression of the foetal 'X-zone' during puberty in male mice. Loss of androgens (through castration) or AR results in significant morphological differences in the adrenal cortex and X-Zone cells. However, interestingly, loss of androgens or AR impact cortex structure, gene expression and protein localisation differently.
Conclusions
We show that androgen signalling through AR is essential for removal of X-zone cells during puberty. We also demonstrate that androgens can act independently of AR to modulate cortex function. Additionally, the loss of androgen signalling results in a decrease in apoptotic cells, suggesting the adrenal has become more resistant to cell death. Improper removal of cortical cells and loss of apoptosis could have serious implications for adrenal function and disease progression. The impacts of this are undergoing further investigation.

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GP5

Protein Kinase A signaling saves regulatory subunit IIβ from PRKACA mutation-mediated degradation

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Protein Kinase A (PKA) consists of two catalytic and two regulatory subunits with several isoforms (Cα,β,γ, RIα,IIα,Iβ,IIβ). In 30–40% of cortisol-producing adrenocortical adenomas (CPA) heterozygous activating somatic mutations in the catalytic subunit α (Cα) of PKA have been found. Previous reports found strikingly reduced levels of RIIβ in CPA compared to other adrenocortical tumors. Here, we investigated the correlation between Cα mutational status, RIIβ expression levels and the underlying regulation mechanisms in CPA and the adrenal cell line NCI-H295R. RIIβ expression was strongly reduced in Cα-mutated CPAs, especially in tumors harboring the frequent L206R mutation (34 Cα-WT and 23 Cα-mutated CPA) by both immunohistochemistry (mean expression: 1.5 ± 0.7 vs 0.4 ± 0.5, $P<0.05$) and WB. Similar results were observed for RIα (1.8 ± 0.9 vs 2.6 ± 0.6, $P<0.05$) but not for the other regulatory subunits. Notably, mRNA expression of all subunits was unchanged in Cα-WT compared to Cα-mutated CPA. In NCI-H295R cells co-transfected with RIIβ and Cα-WT or different Cα mutants, only the L206R mutation led to a full degradation of RIIβ and this degradation could not be abolished by proteasome and lysosome inhibition but, surprisingly, by stimulating PKA signaling. Same co-transfections with RIα did not lead to its degradation. By performing RIIβ co-IP experiments in the presence of Cα-WT or Cα-L206R, followed by nanoLC-MS/MS analysis, we could identify possible novel RIIβ interaction partners mediating RIIβ stability in NCI-H295R cells. In conclusion, our data demonstrate that mutations in PKA Cα lead to post-transcriptional downregulation of the main regulatory subunit in CPA. In NCI-H295R cells, transfection with the L206R mutant led to full degradation of RIIβ, which could not be rescued by different degradation mechanisms, suggesting another mechanism that can be abrogated by stimulating PKA signaling. LC-MS/MS revealed putative RIIβ interaction partners affecting its stability in the presence of Cα L206R only after stimulation of PKA signaling.

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GP6

Involvement of ARMC5 in proliferation and cell cycle control of human cell cultures from adrenal nodules of primary macronodular adrenocortical hyperplasia (PMAH)

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Background
The mechanisms causing hypercortisolism in primary macronodular adrenocortical hyperplasia (PMAH) are not fully clarified. The participation of ectopic receptors and autocrine/paracrine regulation of intra-adrenal ACTH in hyperplastic tissue have been considered. Additionally, germline *ARMC5* mutations have been described as main cause of PMAH. So far, the functional study that analyzed the role of ARMC5 used the adrenocortical carcinoma cell line, H295R. Therefore, we propose a more suitable model in cell cultures obtained from nodules of PMAH.
Aim
To investigate the role of ARMC5 related to PMAH.
Methods
Cell cultures obtained from nodules of 13 unrelated patients with PMAH *ARMC5* mutated or not were analyzed for: i) Morphological and functional characterization; ii) *ARMC5* sequencing; iii) ARMC5 silencing through shRNA in non-mutated PMAH cells for steroidogenic and proliferative functional studies; iv) ARMC5 overexpression through transient transfection in mutated PMAH cells and viability analyses.
Results
i) The cell cultures demonstrating presence of steroidogenic cells, ectopic/aberrant receptors and functional intra-adrenal ACTH. ii) *ARMC5* mutations were located mostly in exons 1, 2 and 3, responsible for protein-protein interactions of ARM repeat family; *ARMC5* germline mutations identified in seven samples were associated or not to somatic mutations or LOH. In six samples, ARMC5 mutation was not identified; iii) ARMC5 silencing in non-mutated PMAH cell cultures decreased *StAR, CYP17A1*, *CYP11A1*, *NR5A1* and *MC2R,* increased *CCNE1* mRNA expression and its proliferative capacity, but without interference in cell viability. iv) ARMC5 overexpression induced apoptosis and necrosis after 8h in PMAH mutated cell cultures, decreasing cell viability.
Conclusions
We confirm the role of ARMC5 as a pro-apoptotic protein and its importance in the steroidogenesis related to PMAH, as previously described in H295R cells. We also report for the first time the involvement of ARMC5 in proliferation control and cell cycle regulation of PMAH cell cultures, which needs to be further explored.

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GP7

Identification of a new glucocorticoid receptor mutation underscores the substantial prevalence of genetic *NR3C1* alterations in adrenal hyperplasia: the French National Research Program MUTA-GR

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Primary generalized glucocorticoid resistance is characterized by glucocorticoid excess without any Cushing syndrome. Patients exhibit variable clinical presentation including arterial hypertension, hirsutism or adrenal hyperplasia. Although glucocorticoid resistance has been associated with glucocorticoid receptor (GR) mutations (encoded by *NR3C1* gene), only 23 mutations have been reported so far. We have conducted a French National Research Program, referred to as MUTA-GR that aims at determining the prevalence of *NR3C1* genetic alterations in patients with adrenal masses associating by glucocorticoid resistance. In this context, we have recently identified a novel GR stop mutation in a 43-year-old man presenting with glucocorticoid resistance, bilateral adrenal hyperplasia and biological hypercortisolism (1.5 to 3-fold increased in 24 h urinary free cortisol, negative response to dexamethasone suppression test and normal plasma ACTH concentrations). Alteration of GR signaling is currently validated by transient transfection assays, binding studies, subcellular trafficking, Chromatin Imunoprecipitation experiments, stability investigation, three-dimensional modeling and gene expression studies.

More than 120 patients have been enrolled and five original GR heterozygous mutations (two missense and three false sense including R469X, R477S, Y478C, L672P) were discovered. Each original mutation impaired a different step of GR intracellular signaling. Ex vivo experiments performed on patients' fibroblasts demonstrated that some mutations (R469X, R477S) led to an haploinsufficiency phenotype with a decreased response in glucocorticoid-dependent target gene expression (*FKBP5, SGK1*).

Interestingly, all mutated patients present with metabolic disorders (high BMI, metabolic syndrome, …), supporting the essential role played by glucocorticoid signaling in adipocyte physiology that we are currently exploring. Altogether, GR mutations are not such an uncommon event given that 5% of our patients carried *NR3C1* alterations. Collectively, GR defects are not a rare cause of glucocorticoid resistance, an incidence initially minimized. We propose that genetic screening of the *NR3C1* gene should be conducted in patients with adrenal incidentalomas and subclinical hypercorticism.

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GP8

Clinical and translational relevance of circulating miR483 in adrenocortical cancer

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Adrenocortical cancer (ACC) is a rare aggressive malignancy, with poor prognosis when metastaic at diagnosis. Recent ACC pan-genomics analysis contributed to redefine the risk groups on molecular bases, including tumor micro RNA (miR), which can be detectable not only in the primary lesion but also in the bloodstream.

We develop a quantitative real-time assay for the measurement of absolute levels in plasma samples of miR483 and its mature miR483-5p form. miR483/miR483-5p levels were evaluated in plasma samples of 27 patients with ACC before surgery and at follow up, and in an independent validation cohort of 21 metastatic ACC. Statistically significant difference in miR483-5p and miR483 levels of pre-surgery and post-surgery samples was found between low (stage 1/2) and high (stage 3/4) risk groups. Moreover the mean levels of both miRs were significantly higher in plasma of patients belonging to the high stage risk group compared to subjects with the benign form (ACA) and healthy subjects. ROC curves analysis of miR483–5p levels resulted in predicting the risk stage (accuracy 0.917 ± 0.084). The best ROC cut-off value for miR483-5p (0.221 ng/ml) significantly predicted overall and recurrence-free survival. miR483-5p was the only variable that significantly predicts recurrence, but not overall survival, in a multivariate Cox analysis (HR 16.2, 95%CV[1.39–188.6, $P < 0.026$]). In addition, miR483 and 483-5p levels significantly correlated with the number of circulating tumor cells in the same blood samples, independently of the timing of sampling. Analysis of an independent cohort of metastatic ACC ($n = 21$) revealed that miR483 negatively correlated with mitotane levels.

In conclusion, we demonstrated that miR483 and miR483-5p absolute plasma levels in ACC patients are powerful molecular markers that may help to follow patients after surgery and chemotherapy, and contribute to better classify and predict tumor evolution.

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GP9

Mortality is increased in patients with Cushing's disease in long-term remission: A nation-wide study

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Background

It is still undetermined whether patients with Cushing's disease (CD) in remission have an increased mortality. Most previous studies are limited by small numbers of patients and/or short follow-up time.

Objective

To study mortality in a nation-wide cohort of patients with CD during long-term follow-up.

Methods

Patients with ICD codes for Cushing's syndrome and/or CD, between 1987 and 2013, were identified in the Swedish National Patient Registry. Medical records of the patients were reviewed (clinical, biochemical, imaging and histopathological data) to verify the diagnosis, and to determine remission status. All other forms of Cushing's syndrome than CD were excluded from the study. Standardized mortality ratios (SMRs) with 95% confidence intervals were calculated using the Swedish general population as reference.

Results

Out of 1252 identified patients, 502 (387 women (77%)) had a confirmed CD diagnosis. Of these, 411 (82%) were in biochemical remission. The mean $\pm$ s.d. age at diagnosis was 46 ± 16 years. The median (interquartile range) follow-up time was 13 (6–23) years, resulting in 7165 patient-years of follow-up. Of the 502 patients, 364 (73%) had been treated with pituitary surgery, 129 (26%) with radiotherapy and 102 (20%) with bilateral adrenalectomy. The observed number of deaths was 133 vs 54 expected, resulting in an overall SMR of 2.46 (95% CI 2.06–2.91). SMR in patients not in remission ($n = 91$) was markedly increased, SMR 8.23 (95% CI 5.42–12.0). Mortality in patients in biochemical remission was lower ($P < 0.0001$), but increased compared to the general population, SMR 1.80 (95% CI 1.44–2.23).

Conclusion

This large nation-wide study demonstrates that patients with CD have an excess mortality, irrespective of remission status. The findings emphasize the importance of curative treatment as well as continued active surveillance after remission has been achieved.

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GP10

Expression of GATA transcription factors and their role in the aetiology of Testicular Adrenal Rest Tumours

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Background

Recently, GATA transcription factors have been linked to the development of Testicular Adrenal Rest Tumours (TART), benign adrenal-like testicular tumours that frequently occur in male patients with congenital adrenal hyperplasia (CAH). The objective of this study is to determine GATA expression in TART and other steroidogenic tissues, examining their discriminative potential and their possible role in the aetiology of TART.

Methods

GATA1-6 expression was determined in TART, Leydig cell tumour (LCT), adult testis, adult adrenal, foetal testis, and foetal adrenal tissues. In addition, GATA expression was measured in Hs181.tes cells after induction with dibutyryl cAMP (dbcAMP).

Results

In TART, testis-like *GATA4* gene expression, but higher compared to adult adrenal, was found. In contrast, *GATA3* and *GATA6* expression in TART is similar to adrenal, but higher compared to adult testis or LCT. *GATA3* and *GATA6* could discriminate between TART and testis (AUC of 0.982 and 0.920, respectively). ACTH is a potential stimulator of TART differentiation in CAH. Stimulation of the Hs181.tes cell line with 0.1 mM dbcAMP for 4 hours increased gene expression of both *GATA3* and *GATA6*.

Conclusion

Gene expression of GATA transcription factors in TART shows both testicular and adrenal characteristics. Additionally, *GATA3* and *GATA6* mRNA levels can help discriminate TART from LCT. Furthermore, we found that dbcAMP can induce GATA3 and GATA6 gene expression, which might indicate that ACTH can stimulate testis cells to become more adrenal like and eventually TART cells. To confirm this, we are pending on the results of stimulation experiments with dbcAMP or ACTH in ACTH-responsive H295RA cells.

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Adrenal 2

GP11

A country comparison of glucocorticoid replacement therapy in patients with primary and secondary adrenal insufficiency: data from the EU-AIR

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Introduction

The daily maintenance dose of conventional hydrocortisone currently recommended by international guidelines for the management of primary adrenal insufficiency (PAI) or secondary adrenal insufficiency (SAI) is 15−25 mg/day, in 2−3 divided doses. The aim of this analysis was to investigate inter-country differences in glucocorticoid replacement doses in patients with PAI and SAI.

Design

EU-AIR (ClinicalTrials.gov identifier: NCT01661387) with 20 contributing centres across Germany, the Netherlands, Sweden and the UK started enrolling patients with AI in August 2012. Baseline clinical and biochemical data from patients in the four countries were compared. 1798 patients (626 PAI, 1172 SAI) were included in the current analysis of data collated until November 2016. Patients with congenital adrenal hyperplasia or tertiary AI were excluded.

Results

No major differences between countries were seen in disease duration, BMI, blood pressure or blood lipids in patients with PAI and SAI. However, BMI was generally higher in patients with SAI than PAI. Most patients were treated with conventional hydrocortisone, with similar mean doses administered in Germany, the Netherlands, Sweden and the UK (PAI: 24.7±8.4 mg/day, 22.2±5.7 mg/day, 21.5±10.0 mg/day, 21.0±9.3 mg/day; SAI: 20.0±6.4 mg/day, 20.8±6.1 mg/day, 21.6±9.4 mg/day, 18.9±5.2 mg/day). Cortisone acetate was most commonly used in the Netherlands (PAI, 23%; SAI, 27%). No difference was observed in fludrocortisone dosing in patients with PAI between countries (0.1±0.07 mg/day, 0.1±0.04 mg/day, 0.1±0.05 mg/day, 0.1±0.12 mg/day). Patients with PAI treated with dual-release hydrocortisone (DRHC) were treated with lower doses in Germany 21.3±2.3 compared with those in Sweden 28.0±6.0 mg/day.

Conclusions

The maintenance doses of hydrocortisone observed in this study are in line with international guidelines in all four countries. The country difference in maintenance doses in DRHC is consistent with data showing that mean daily doses of hydrocortisone tend to be higher in Sweden than in other countries.

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GP12

Activation of the cAMP/PKA transduction system triggers abnormal expression of the serotonin signaling pathway in human adrenocortical cells

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In human adrenals, serotonin (5-HT), released by subcapsular mast cells, increases aldosterone secretion through activation of type 4 serotonin receptors (5-HT_4R) but only exerts a modest control on cortisol production. Interestingly, illicit synthesis of 5-HT in adrenocortical cells as well as overexpression of the 5-HT_4R and ectopic expression of the type 7 receptor (5-HT_7R) have been observed in bilateral macronodular adrenal hyperplasia responsible for hypercortisolism. In this study, we have investigated the expression of the key enzyme of 5-HT synthesis tryptophan hydroxylase (Tph) and 5-HT_4R, 5-HT_6R, 5-HT_7R in the adrenal samples removed from patients suffering from diseases associated with activation of the cAMP/PKA pathway in adrenocortical cells, such as primary pigmented nodular adrenocortical disease (PPNAD), Cushing's disease (CD), ectopic secretion of ACTH, and 21-hydroxylase deficiency (21-OHD), in comparison with normal adrenals. In PPNAD cells, we observed upregulation of Tph together with 5-HT_4R, 5-HT_6R and 5-HT_7R. Overexpression of the 5-HT signaling pathway appeared to be the consequence of the activation of PKA by *PRKAR1A* gene mutations which cause the disease. 5-HT strongly stimulated cortisol production and inhibition of Tph reduced corticosteroidogenesis in cultured PPNAD cells. High expression of Tph and 5-HTRs was also detected in adrenal tissues exposed to high plasma ACTH levels, including CD, 21-OHD and ectopic Cushing's syndrome. Our results indicate that activation of the cAMP/PKA pathway in adrenocortical cells resulting either from *PRKAR1A* mutations or activation of the MC2R by sustained increase in plasma ACTH levels induces an aberrant serotonergic stimulatory loop in zona fasciculata. They also suggest that the intraadrenal 5-HT signaling pathway may participate in the pathophysiology of PPNAD-associated and ACTH-dependent hypercortisolisms and could represent an adaptive mechanism to increase glucocorticoid synthesis in 21-hydroxylase deficiency.

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GP13

PRKARIA (Carney complex gene) is a major regulator of the tight link between cell cycle phases and steroidogenesis in the adrenocortical tumor cells H295R

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The cyclic AMP/PKA signalling cascade is involved in the pathogenesis of cortisol-secreting adrenocortical tumors (ACT). Defects in cell cycle checkpoints play a major role in oncogenesis. The PKA regulatory subunits *PRKARIA and PRKARIIb* are involved in cell survival and steroidogenesis in the adrenocortical carcinoma H295R cell line. We have previously shown that their inactivation enhances the accumulation of cells in the G2 phase and activates PKA and MAPkinases pathways.
This study investigates the correlation between the cell cycle phases and the adrenal steroid secretion, as well as their control by PKA.
Methods
Using pharmacologic drugs, H295R cells were synchronized at specific cell cycle check point (G1 phase), (S phase) and (G2 phase). The cell cycle distribution (Cytometry), the expression of cyclins, PKA subunits, cell signalling pathways, StAR and steroidogenic enzymes were analysed. The effect of PKA activation either by the different PKA subunits, or cAMP, PKA inactivation by H89 and PKI along the cell cycle synchronization were studied.
Results
Cells synchronized at G2 phase increased the expression of the steroidogenic enzymes and steroid secretion. Arresting H295R in G1 phase decreased the steroidogenic enzymes expression and cortisol secretion. PKA subunits distribution and PKA activity modulation were cell cycle dependent. PKA activation by *PRKARIA* inactivation counteracted specifically the decrease of steroidogenesis in cells arrested in G1 phase: StAR/luc reporter gene activity and cell progression in G2 phase were stimulated. *PRKARIIb* inactivation and *PRKACA* overexpression or cAMP increased the StAR/luc reporter gene activity, independently of the cell cycle check point arrest. The H89 and PKI differentially reduced StAR/luc reporter gene activity, and both reversed the cell cycle in the G2 arrested cells.
Conclusion
Inactivation of the Carney complex gene stimulates steroidogensis in the low steroidogenic G1 phase arrested cells. This study shows a link between the cell cycle check points and the regulation of steroidogenesis, in which the *PRKARIA* subunit is a key regulator of both cell cycle and steroidogenesis.

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GP14

Simultaneous assays of aldosterone and renin concentrations in just ten minutes could change the clinical assessment for the diagnosis of primary aldosteronism

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Measurement of plasma aldosterone and renin concentration, or activity, is useful for selecting antihypertensive agents as well as detecting hyperaldosteronism in hypertensive patients. However, it takes several days to get results when measured by radioimmunoassay and development of more rapid assays has been long expected. We have developed chemiluminescent enzyme immunoassays enabling the simultaneous measurement of both aldosterone and renin concentrations in ten-minutes by a fully automated assay using antibody-immobilized magnetic particles with quick aggregation and dispersion. We performed clinical validation of diagnostic ability of this newly developed assay-based screening of 125 patients with primary aldosteronism from 97 patients with essential hypertension. Results of this novel assay significantly correlated with the results of radioimmunoassay (aldosterone, active renin concentration and renin activity) and liquid chromatography-tandem mass spectrometry (aldosterone). The analytical sensitivity of this particularly novel active renin assay was 0.1 pg/ml, which was better than that of radioimmunoassay (2.0 pg/ml). Using Bland-Altman plots with the mass-spectrometry values, both bias and limits of agreement with 95% confidence interval of the automated aldosterone assay were smaller than those of the radioimmunoassay, indicating smaller systemic errors in the novel measurement. The ratio of aldosterone-over-renin concentrations of 11.2 (ng/dl per pg/ml) provided 80.8% sensitivity and 94.9% specificity as a cut-off for differentiating primary aldosteronism from essential hypertension. This novel measurement is expected to be a clinically reliable alternative for conventional radioimmunoassay and to provide better throughput and cost-effectiveness in diagnosis of hyperaldosteronism from larger numbers of hypertensive patients in clinical settings.

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GP15

Integrated genomic and phenomic analysis reveals key molecular pathways of aldosterone producing adenoma

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Primary aldosteronism is the most common form of secondary hypertension. Somatic mutations in *KCNJ5*, *ATP1A1*, *ATP2B3* and *CACNA1D* have been described in 50% of aldosterone producing adenomas (APA). To identify genetic alterations in new genes, we performed whole exome sequencing in 23 patients with APA negative for recurrent mutations in known driver genes. A low number of somatic variations were identified per patient, ranging from 1 to 22. No somatic variations were identified in two patients. Somatic mutations in *KCNJ5* and *CACNA1D* were identified in 12 APA. These mutations were not observed or were present at very low levels on previous Sanger sequencing, indicating tumor heterogeneity. Two patients harbored mutations in genes involved in the Wnt/β-catenin pathway, which represents, together with the membrane ion transporter activity, the two significantly overrepresented pathways in gene ontology analysis. Sequencing of *CTNNB1* in somatic DNA from 150 subjects with APA identified additional variants in 13 subjects, including 2 APA harboring also a *KCNJ5* mutation. Transcriptome data obtained from 123 APA and 11 control adrenals did not show differences on the expression levels of Wnt4, an activator of the Wnt/β-catenin pathway, and *LEF1* and Axin2, two β-catenin target genes, as a function of the mutation status. Hierarchical clustering of transcriptional profiles at a genome-wide scale was not associated to the APA mutation status, supporting a model whereby all recurrent mutations converge upon activation of calcium signaling and increased aldosterone production. In addition, β-catenin activation was observed by immunohistochemical analysis in two thirds of APA independently of *CTNNB1* mutations, suggesting the involvement of additional mechanisms promoting cell proliferation. Using transcriptome affinity-propagation-based analysis we identified 15 different clusters of APA. These clusters are not associated with demographic or clinical data, highlighting additional molecular pathways underlying APA development and identifying subgroups to be targeted for gene discovery.

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GP16

Cardiovascular features of autonomous cortisol secretion in patients with adrenal incidentalomas

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Background
Possible Autonomous Cortisol Secretion (pACS) is a condition found in 1–29% of patients with adrenal incidentalomas. The diagnosis of pACS has been variably associated with an increased risk of cardiovascular events and mortality. However, dedicated studies describing the morphologic and functional cardiac alterations in these patients are lacking.
Aim
To compare the cardiovascular features of patients with pACS to those with nonfunctioning (NF) adrenal masses.
Materials and methods
Fifty-eight patients with adrenal incidentaloma without the classic signs or symptoms of overt hypercortisolism were prospectively enrolled. Anthropometric, metabolic and hormonal parameters, adrenal magnetic resonance, echocardiography B-mode ultrasound and arterial stiffness calculated with oscillatory method were assessed in all patients. We diagnosed patient with pACS after 1-mg overnight dexamethasone suppression test (1 mg-DST), confirmed by traditional 48-h Liddle tests, if post-test serum cortisol felt between 51 and 138 nmol/l.
Results
Overall 30 patients had pACS and 28 NF adrenal masses. No differences in gender, smoke habits, hypertension, obesity and diabetes prevalence were observed between pACS and NF patients. Mean left ventricular (LV) mass index was increased in the pACS compared to the NF group (112.6 ± 29.2 vs 94.8 ± 31 g/m^2 $P=0.032$). We also detected a significantly higher prevalence of LV hypertrophy in PACS than NF group (35.7% vs 14.3% $P=0.007$). Furthermore, there was a negative correlation between the post-dexamethasone cortisol levels and ejection fraction ($r=-0.26$; $P=0.041$). The assessment of arterial stiffness showed a higher pulse wave velocity in pACS compared with the NF group (11.3 ± 1.4 vs 10.2 ± 0.6 m/s; $P=0.048$).
Conclusions
Autonomous Cortisol Secretion (pACS) can lead to early cardiac and vascular dysfunction even in apparently asymptomatic patients. These results underline the need for further studies, including second line cardiovascular assessment, to correctly define the management of pACS and allow early recognition of possible complications.

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GP17

Hypercortisolism is prevalent in newly diagnosed type 2 diabetes: a prospective study of 384 consecutive patients

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Background
Cross-sectional studies in small and selected populations indicate a relatively high prevalence of incipient and/or subclinical Cushing's syndrome (CS) in patients with type 2 diabetes (T2D), which could have therapeutic implications.
Aim
To estimate the prevalence of CS in a large, unselected cohort of recently diagnosed T2D patients.
Methods
A total of 384 consecutive out – patients with T2D diagnosed after 1 January 2009 were investigated by means of an overnight dexamethasone (1 mg) suppression test (DST). Patients who failed to suppress to ≤ 50 nmol/l after the DST were further examined with 48 h low dose dexamethasone suppression test (LDDST) and 24-h urinary free cortisol collection (UFC). Patients with elevated cortisol levels according to LDDST or UFC underwent ACTH measurements and imaging.
Results
85 (22%) patients had elevated cortisol after DST of whom 20 (5%) failed to suppress after LDDST and/or had elevated UFC. No significant difference in age, BMI, HbA1c, T-score, Total Body Fat or blood pressure were recorded between the two groups. Among the 20 patients with biochemical CS subsequent imaging with either pituitary MR or abdominal CT, according to suppressed ($n=10$) or unsuppressed ($n=10$) ACTH levels, revealed adrenal adenoma(s) in nine cases and a pituitary macroadenoma in one case.
Conclusion
i) The prevalence of hypercortisolism is high in T2D, also in unselected newly diagnosed patients, ii) Hypercortisolism was not associated with a persuasive phenotype, iii) The clinical implications remain uncertain but continued interest is justified, preferably in terms of randomized intervention trials.

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GP18

Effects of two mineralocorticoid receptor antagonists on the morphology of the adrenal cortex

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Arterial hypertension usually results from the deregulation and hyperactivity of the renin angiotensin-aldosterone system. One of the available therapeutic approaches for its treatment is the use of mineralocorticoid receptor (MR) antagonists, thus blocking aldosterone action.
The aim of this study was to characterize the effects of spironolactone and eplerenone, on the morphology of the adrenal gland of spontaneously hypertensive (SHR) and normotensive (Wistar-Kyoto) rats.
SHR ($n=18$) and Wistar-Kyoto ($n=18$) rats were exposed, for 1 month, to spironolactone (100 mg/kg per day, $n=6$), eplerenone (50 mg/kg per day, $n=6$) or not exposed to either drug ($n=6$) and at the end of this period their adrenal glands were collected and we evaluated the percentage of the stained area (%SA) of CyP11B1, CyP11B2, the adrenal inner zone antibody (IZAb), a proliferation marker (ki-67), β-catenin and finally the percentage of cellular area occupied by lipid droplets as well as the capsular width.
SHR Hypertensive rats presented higher area of lipid droplets in all layers of the adrenal cortex, an effect that was even further increased by the exposure to eplerenone, in the fasciculata and reticularis zones. In the normotensive rats it was only spironolactone that elicited this effect, being significant only in zona reticularis. Both drugs also increased Ki-67 expression in the hypertensive rats, but only eplerenone increased it on normotensive rats. Finally, spironolactone decreased the capsular size but only in the normotensive rats. No significant differences were found for the % SA of CyP11B1, CyP11B2, IZAb or β-catenin.
In conclusion, we have found that, morphologically the adrenal glands of normotensive and SHR only differed in number of lipid droplets. Exposure to the MR antagonists had significant consequences on the capsular size, lipidic depots and on the cellular proliferation of both normotensive and SHR adrenal glands.

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GP19

Plasma cortisol and aldosterone responses to insulin tolerance test and sodium depletion in women with non classic 21-hydroxylase deficiency caused by bi-allelic CYP21A2 mutations (NC-CAH)

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NC-CAH is diagnosed in pubertal/post-pubertal women because of androgen excess however, the risk of potential adrenal insufficiency is not known, and indication of systematic glucocorticoid replacement therapy is controversial.
Aim
To evaluate cortisol and aldosterone secretions in response to challenges tests.
Design
Prospective controlled clinical study in a tertiary referral center. 20 women with NC-CAH (serum stimulated 17-OHP >10 ng/ml/250 µg, Synacthen) comparatively to matched healthy women, were included if they had not receive glucocorticoid treatment >1 year and estrogen-based oral contraception stopped >3 months. Each participant underwent sequentially two tests separated by a 2 to 7-days: insulin tolerance gold standard test (ITT) and a sodium depletion test (oral 40 mg furosemide under low sodium diet) to stimulate both endogenous active renin (AR) and aldosterone. Steroid levels measured by LC-MSMS.
Results
NC-CAH had lower pic plasma cortisol concentrations during ITT than healthy women: 17.2 µg/dl (13.1–22.8) vs 21.2 µg/dl (17.1–33.5), $P=0.0002$. A peak plasma cortisol above 17.0 µg/dl was obtained in all controls but only in 60% NC-CAH women. NC-CAH had higher baseline ACTH and AR levels. 24-h after sodium depletion, mean plasma aldosterone levels were comparable between the two groups, but NC-CAH women had higher ($P=0.003$) stimulated AR levels than healthy women: 67 mUI/l (15–156) vs 39 mUI/l (6–87).
Conclusions
Forty percent women with NC-CAH have subnormal glucocorticoid adrenal function. Their aldosterone secretion was maintained normal by increased AR levels. Besides androgen excess therapy, clinical management of NC-CAH women should include assessment of their cortisol and aldosterone secretion; systematic chronic replacement therapy is still an open question, but transient glucocorticoid supplementation and rehydration during periods of stress should be considered.

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GP20

Which are the factors and causes of death in patients with adrenal insufficiency? Mortality data from EU-AIR

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Introduction
If untreated, adrenal insufficiency (AI) leads to premature death. Hospital record data suggest mortality associated with primary (PAI) and secondary AI (SAI) to be 2–3-fold higher than in the general population. Major causes of death include cardiovascular disease, Addisonian crises, brain tumours and infections; however, there is little further characterization of patients who died.
Design
We analysed real-world data from the European Adrenal Insufficiency Registry (EU-AIR; NCT01661387) with centres across Germany, the Netherlands, Sweden and the UK. Clinical and biochemical data at enrolment were compared for patients who had died and those alive for each AI subset. Patients with congenital adrenal hyperplasia or tertiary AI were excluded. 1798 patients were included (626 PAI, 1172 SAI) in the current analysis.
Results
To November 2016, 21 deaths had occurred (7 PAI, 14 SAI). Causes of death were cardiovascular ($n=8$), infection ($n=3$), unclear ($n=3$), Addisonian crisis ($n=1$), suicide ($n=2$), renal failure, drug-induced hepatitis, cachexia and brain tumour (each $n=1$). Patients who died were significantly older at enrolment than those alive (PAI, 63.4 ± 13.4 vs 50.0 ± 15.8 years, $P=0.0253$; SAI, 64.0 ± 16.6 vs 54.3 ± 16.2 years, $P=0.0250$). Interestingly, duration of AI was shorter in patients with PAI who died versus alive patients (6.5 ± 5.7 vs 16.3 ± 13.1 years, $P=0.0035$), whereas the reverse was true for SAI (20.4 ± 13.2 vs 13.7 ± 11.1 years, $P=0.0257$). There were no significant differences in sex, BMI, blood pressure, triglycerides, LDL-cholesterol, cholesterol or HbA1c between the deceased and alive cohorts. Patients who died were generally more likely to have hypertension (PAI, 85.7% vs 21.8%, $P=0.0007$; SAI, 71.4% vs 33.9%, $P=0.0076$) and diabetes mellitus (PAI, 57.1% vs 14.4%, $P=0.0112$; SAI, 28.6% vs 11.5%, ns) at study inclusion.
Conclusions
This is the first study providing detailed characteristics of AI patients who died. Hypertension and diabetes, as well as infectious diseases, appear to play a major role in mortality.

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Adrenal 3

GP21

Is diabetes mellitus associated with catecholamine-secreting tumours always a secondary diabetes?

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Introduction
Hyperglycaemia occurs frequently in catecholamine-secreting tumours due to insulin suppression or induced insulin resistance. These changes can be reversible postoperatory (postOp).
Objective
Our study aims to establish the impact of surgery in patients with catecholamine-secreting tumours upon glucose metabolism disorders, as well as the predictive factors for postOp diabetes-free patients.
Methods
We retrospectively analysed 72 patients (46 women-26 men), mean age 48 years (9–82), median body mass index 24.5 kg/m^2 (16–36.19), 66 with pheochromocytoma, 6 with paraganglioma, 3 malignant, 12 known with genetic syndromes. We evaluated their glycaemic status preoperatory (preOp), and for 64 of them postOp, with a median follow-up of 4.17 years. Glucose metabolism disorders were diagnosed according to World Health Organization criteria.
Results
We found preOp diabetes mellitus (DM) in 32 patients (44.44%). We identified significant glycaemic changes in older patients, with longer hypertensive period, higher frequency of metabolic syndrome, adrenal tumours rather than ectopic, and a higher level of ChromograninA ($P<0.05$). PostOp, 66.6% of patients were free of DM, 30% of them starting from week one postOp. We found significantly more cases of remnant DM in patients with longer duration of preOp DM ($P=0.0004$, 110-vs-10 months) and in those requiring insulin preOp ($P=0.005$). Patients with or without postOp DM did not differ in presence of metabolic syndrome (but all patients with remnant DM had metabolic syndrome), history of familial DM, tumour characteristics, clinical or laboratory findings.
Conclusions
Our study found that DM is associated frequently with catecholamine-secreting tumours and 2 thirds disappear postOp. Remnant DM suggests that DM associated with catecholamine-secreting tumours is not always a secondary DM. A longer duration of preOp DM and the fact that the glycaemic control is obtained with insulin upon tumour diagnosis are predictive factors for remnant DM.

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GP22

Epithelial to mesenchymal transition in adrenocortical tumours: focus on FGF-FGFR pathway and c-MET

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Ad Adrenocortical carcinoma (ACC) is an aggressive tumour and treatment remains unsatisfactory in advanced disease. Activation of epithelial to mesenchymal transition (EMT) is considered causative for metastatic spread in a variety of human cancers. Accordingly, new drugs were developed specifically targeting EMT with a focus on hepatocyte growth factor (HGF)/HGF receptor (c-MET) and fibroblast growth factor (FGF)/FGF receptor (FGFR) signalling.
We here asked whether EMT is relevant to ACC progression to evaluate the therapeutic potential of small molecule drugs targeting EMT.
Expression of FGFR family members and c-MET was analysed in 20 normal adrenal glands (NAG), 23 adrenocortical adenomas(ACA) and 27 ACC at mRNA and protein level. Expression of FGFR1-4 was quantified in FFPE tumour tissue using RNAscope mRNA *in situ* hybridization technique. c-MET mRNA was quantified by qRT-PCR. In a subset of 40 samples we quantified expression of 92 different genes involved in FGF-FGFR pathway signalling.
FGFR2 mRNA was lower in ACC compared to ACA (3.1 ± 2.1 vs 6.5 ± 2.3 mRNA copies/cell, $P=0.0005$) whereas FGFR1 (7.5 ± 5.3 vs 4.5 ± 2.9, $P=0.09$) and FGFR4 (5.1 ± 2.3 vs 2.6 ± 1.3, $P=0.002$) were higher in ACC. FGFR4 expression was higher in advanced vs localized ACC (6.2 ± 1.6 vs 3.9 ± 2.7, $P=0.03$). Pan-FGF-FGFR pathway qRT-PCR confirmed differential FGFR expression and revealed decreased expression of FGF7, FGF17 and mitogen associated protein kinases in tumours compared with NAG. In advanced ACC protein kinase c PRKCA was decreased but PRKCQ increased.
c-MET mRNA expression was significantly higher in ACC compared to ACA and NAG (0.03 ± 0.05 vs 0.01 ± 0.03 and 0.01 ± 0.02, respectively, $P=0.02$). Considering median expression as a cut-off, high c-MET expression in ACC was associated with decreased overall survival (HR = 8.8, $P=0.02$).
In conclusion, EMT appears to be relevant for adrenocortical tumourigenesis and progression. PRKCQ may be involved in EMT signalling in advanced ACC. EMT-related kinases such as c-MET and FGFR4 may be suitable treatment targets in advanced ACC.

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GP23

Clinical features and treatment outcomes in a group of SDHx-related pheochromocytoma/paraganglioma patients

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Introduction
Germline mutations in succinate dehydrogenase complex (SDHx) are a risk factor for developing Pheochromocytoma (Pheo) and/or Paragangliomas (PGL) (named together PPGL), being responsible for approximately 30% of cases. The precise genotype-phenotype correlations and best management strategies are still uncertain.
Objective
To characterize the clinical features and genotype-phenotype associations in a group of SDHx-mutated PPGL patients.
Methods
Retrospective analysis of all germline SDHx-mutated PPGL cases followed in a reference centre.
Results
Total PPGL patients with SDHx-mutation: 30 (16 female). SDHB-related: 18(60%); SDHD-related: 9(30%); SDHC-related: 3(10%). Mean age at diagnosis: $36,8\pm15,4$ years. Median follow-up: 94,8 months. Twenty nine patients had symptoms at diagnosis. Cathecholamine secretion was detected in 9(30%). Nine cases (30%) were malignant. Anatomical distribution: SDHB: 9 head and neck PGL (HNPGL), 5 Pheo and 5 thoraco-abdominal PGL (TAPGL) cases; SDHD: 9 HNPGL, 1 Pheo and 1 TAPGL cases. All SDHC were single non-metastatic HNPGL. Malignancy: SDHB = 44,4%; SDHD = 11,1%. Multiple PPGL: SDHB = 16,7%; SDHD = 55,6%. Family history of SDHx-related PPGL was present in 20%. Deletions in SDHB exon-1 were the most frequent genetic defect. Complete resection was achieved in 7(33,3%) and pre-surgery vascular embolization was performed in 10(47,6%) of HNPGL patients. Radiotherapy was used in 12(40%) patients (mainly unresectable HNPGL) achieving partial response/stabilization. 177Lu-DOTATOC or 131I-MIBG were used in 4. Overall, remission was observed in 33,3%, stable disease in 53% and progression in 13,3% of patients. Related morbidity was observed in 66,6% of patients, and one death occurred.
Conclusion
SDHC and SDHD patients are prone to develop single and multiple HNPGL, respectively, and SDHB patients carry increased risk of malignancy, as suggested in other studies. SDHB patients and HNPGL had the worse prognosis, the former related to malignancy, and the last to cranial nerve deficits, unresectable disease and multimodality interventions. Radiotherapy represented a good alternative in unresectable HNPGL.

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GP24

Increased exosomes in endogeneous Cushing syndrome

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Exosomes are nano-sized vesicles secreted by the cells in the exatracellular fluids representing a novel way of intracellular communication. Exosomes secreted from blood cells like monocytes and platetes have been reported to be checkpoints involved in haemostatic and thrombotic response. Glucocorticoids are inducing a profound alteration of blood cells homeostasis with atherothrombotic, bleeding and immune response alterations. Hereby we quantified for the first time circulating exosomes in overt Cushing syndrome (CS) patients.
Methods
Cross sectional study in CS patients and controls. Diagnosis of CS was performed following ECE and Endo guidelines. Blood samples from active, drug naive CS patients ($n=20$) and age and sex matched controls ($n=20$) were obtained after overnight fast. Peripheral blood cells, biochemical and hormonal parameters were analyzed using standard methods. Circulatory exosomes were quantified in plasma by a sandwich enzyme-linked-immuno-sorbent assay (ExoTEST) employing a monoclonal antihuman CD9 antibody. Further exosome phenotyping and analysis is ongoing.
Results
CS patients present as compared to controls a significant increased number of CD9 positive exosomes (2.35×10^{10} vs 7.74×10^{9}/100 µl; $P=0.005$**). Absolute monocytes (MN) number and 24 h urinary free cortisol (UFC) level correlates with the number of exosomes, respectively $P=0.022$* with r:0.391 for MN and $P=0.005$** with an r:0.467 for UFC.
Conclusion
Circulatory exosomes are increased in the hypercortisolemic state of Cushing syndrome.

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GP25

Tumor microenvironment increases migration/invasion of murine pheochromocytoma SDHB silenced spheroids

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Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors. About 30-40% of Pheo/PGLs are due to a germ-line mutation in one

of the 13 main susceptibility genes which include the genes encoding the four subunits of the succinate dehydrogenase (SDH - mitochondrial complex II). In PHEO/PGL due to SDHB mutations up to 80% of affected patients develop metastatic disease and no successful cure is at present available. To obtain an experimental model resembling the *in vivo* conditions of the SDHB-mutated PHEO, we used multicellular tumor spheroids (3D culture) of a murine cell line cultured alone or in co-culture with mouse primary fibroblasts, evaluating the effects of SDHB silencing and microenvironment on invasion and migration processes. The growth of spheroids is linear with clear edges. When the spheroids are treated with conditioned medium of cancer-associated fibroblasts (CAFs), we observe an evident detachment of clusters of viable cells in the surrounding space. SDHB silenced cells show a greater migratory capability than negative control (NC) cells. In particular, SDHB silenced cells invade the surrounding space moving collectively, unlike the NC spheroids where cells tend to move individually. This difference was even more evident when spheroids were co-cultured directly with mouse primary fibroblasts. Using electronic microscopy on spheroids, we observed that SDHB silenced cells show swollen mitochondria and, alterations of mitochondrial crests (similarly to mitochondria of patients with SDHB mutations) while SDHB mutated spheroids show borders that are more fraying than those of NC spheroids. In conclusion, SDHB silencing strongly increased the invasion/migration capabilities, and these changes are more evident in SDHB spheroids co-cultured directly with primary fibroblasts. Further studies on these mechanisms may suggest new therapeutic targets.

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GP26

Metformin reduces viability and proliferation of pheochromocytoma cells in vitro

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Background
Pheochromocytomas (PHEO) are rare neuroendocrine tumors derived from chromaffin cells of the adrenal medulla. Catecholamins' secretion is associated with a high risk of cardiovascular complications. Malignancy is rare, but still demands effective treatment. Metformin has been shown to have antiproliferative properties in several cancer cell lines, possibly related to its ability to inhibit cell proliferation pathways. Accordingly, we aimed to evaluate the effects of metformin in the survival and proliferation of PHEO cells.
Methods
Cell viability was evaluated by MTT and TRIPAN assays using the PC12-Adh PHEO cell line treated with metformin in increasing concentrations (0–30 mM). A lipid peroxidation assay and determination of O_2 consumption using a respirometer were performed to evaluate cellular stress. The effects of metformin on cell proliferation markers were analyzed by western blot.
Results and Discussion
Metformin at 20 mM induced an inhibition of 60% of cell viability after 48 h treatment, as compared to untreated controls, and increased cellular lipid peroxidation, while decreased O_2 consumption in PC12-Adh PHEO cells. Moreover, metformin treatment reduced the activation of proteins of the AMPK/PTEN/AKT/mTOR pathway, which suggests growth and cell proliferation impairment. We then performed a primary culture of a PHEO from a 10-year-old boy with VHL disease to test wheter metformin exerts its antiproliferative effects *ex vivo*. Our results suggest that metformin has a moderate inhibitory effect on the viability of PC12-Adh PHEO cells. This effect is associated with enhanced lipid peroxidation and decreased O_2 consumption by those cells, which are both suggestive of increased cellular stress. Moreover, metformin treatment induced a positive modulation of the AMPK/PTEN/AKT/mTOR signaling pathway. Altogether our results corroborate the hypothesis of an inhibitory effect of metformin on PHEO cellular proliferation *in vitro*.

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GP27

The role of in vivo metabolomics using H-MRS in SDH deficient disease

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Tumours caused by mutations in the SDH enzyme complex have a unique tumour metabolome due to a truncated citric acid cycle. The accumulation of the onco-metabolite succinate is believed to drive tumourigenesis. The aim was to investigate the role of MRI spectroscopy (H-MRS) to detect *in vivo* succinate elevations in suspected SDH deficient tumours including GIST, phaeochromocytoma/paraganglioma (PPGL) and pituitary adenomas (PA). Suitable patients were identified based on *SDH* germline status, clinical phenotype and or tumour SDHB immunonegativity. A minimum tumour size of 1.5 cm was applied. H-MRS was performed on a 3T MRI scanner and spectra with and without water suppression, was obtained. Succinate when detected, was visible on the spectra at a frequency of 2.4 ppm and a succinate to choline ratio of >0.1 was deemed confirmatory of succinate detection. H-MRS was performed on nine patients to date including four patients with GIST, 4 with PPGL and 1 with a PA. A succinate peak was detected in 7/9 patients and correlated with the immunohistochemistry (IH) and or germline status in all seven cases. H-MRS of a PA in a patient with a germline mutation in *SDHB* demonstrated no succinate peak and this correlated with the tumour SDHB immunopositivity. H-MRS successfully detected a succinate peak in a patient with a metastatic GIST and a somatic mutation in *SDHC*. This is the first study to investigate the use of in *vivo* metabolomics in SDH deficient GIST and pituitary adenomas and has proven efficacy as a non-invasive test for the identification of *in vivo* succinate peaks and detection of SDH deficient tumours. It may be particularly useful for the detection of somatic *SDH* mutations and to clarify the role of *SDH* mutations in newly identified phenotypes. Future application includes the use of *in vivo* succinate detection as a biomarker for therapeutic response.

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GP28

A PRKACB somatic mutation in a cortisol producing adenoma: a new example of protein kinase A activation leading to adrenal Cushing syndrome

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Introduction
Alterations of the cAMP signaling pathway are described in adrenal tumors causing Cushing syndrome, specifically mutations in the gene coding for the protein kinase A (PKA) catalytic subunit alpha (PRAKCA) in cortisol producing adenomas (CPA) with overt Cushing syndrome.
Materiel and Methods
Eight CPAs without PRKACA mutations were analyzed by whole exome sequencing. Direct sequencing of PRAKCB encoding for the catalytic subunit beta (Cβ) of the PKA was performed in 21 others. Interaction of WT or mutant Cβ with the PKA-regulatory subunits was studied by bioluminescence resonance energy transfer and surface plasmon resonance analysis. To study the PKA activity, phosphorylation of the synthetic PKA-substrat Kemptide was analyzed in cellulae in HEK293 cells transfected with a combination of RIα and Cβ and *in vitro* with purified proteins.
Results
A PRKACB somatic mutation p.S54L was found in one CPA, from a 41-year-old patient presenting with a severe form of Cushing syndrome. Direct sequencing of PRKACB did not show any other mutations in additional samples. Functional studies demonstrated loss of interaction between the mutant Cβ and the regulatory subunit type 1 (RIα, RIβ). After stimulation by cAMP or forskolin, dissociation of Cβ and RIα was faster and stronger with the mutant than with the WT Cβ. In addition, basal PKA activity was higher for the mutant catalytic than the wild-type while the maximal activity after stimulation was lower.
Conclusions
PRKACB is a new gene responsible for at least one CPA, mutated in the somatic state. This finding suggests that the Cβ subunit of the PKA, too, may have specific functions in the adrenal cortex. Particularly, the role of the residue Ser54 (as was previously suggested) may be very important for PKA function in the adrenal cortex.

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GP29

Familial case of SDHB mutation presenting as a macroprolactinoma

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Germline mutations in the succinate dehydrogenase subunit-B gene (SDHB) are well recognised for predisposing to head and neck paraganglioma, sympathetic paraganglioma, phaeochromocytoma and renal cell carcinoma. The co-existence with pituitary adenomas remains uncommon.

We report a 31-year-old female who presented at age 29 years old with 9 months of secondary amenorrhoea. Prolactin was 3000 mIU/l and a 1.7-cm macroprolactinoma revealed on MR pituitary. Taking prolactin-lowering therapy, she achieved normal menses and subsequent MRI imaging demonstrated reduction in the size of this macroprolactinoma. At age 30 years, she was found to have a paraganglioma in the aortic–pelvic region. On reflection, she had noticed anxiety, sweating, palpitations and extreme exercise intolerance for the 2 years preceding diagnosis, which resolved following surgical resection. She was screened for familial paragangliomas, which revealed she was a carrier of the SDHB mutation. Interval screening MRI neck to pelvis has since demonstrated no evidence of recurrent or new disease. Plasma metanephrines have subsequently remained normal.

Her father, aged 64 years old, was referred for genetic counselling and testing. He too is an SDHB mutation carrier. His plasma metanephrines are normal and MRI neck to pelvis has not revealed a paraganglioma or phaeochromocytoma. Both the index case and father will remain under lifelong specialist care in a Neuroendocrine Tumours Clinic. Family members have been advised to seek genetic counselling.

Although uncommon, increasing incidence of pituitary adenomas in carriers of SDH mutations are being reported. These pituitary adenomas tend to be larger with macroprolactinomas commoner than other pituitary adenomas. Screening programmes vary widely for carriers of SDH mutations and tend not to involve pituitary imaging. However, given the association with pituitary lesions, screening imaging might need to include the pituitary. At present, however, it is thought that this is likely to be a low-yield strategy.

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GP30

Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia with cyclical ectopic adrenocorticotrophic hormone secretion

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DIPNECH is pre-invasive precursor to carcinoid tumors and tmorlets, most of which present with pulmonary symptoms. We present a case of ectopic cyclical ACTH producing DIPNECH.

33-year lady presented with a short history of weight gain, abdominal striae, proximal myopathy and secondary amenorrhoea. She reported a previous episode with similar symptoms one year earlier which resolved spontaneously after a few weeks. Random cortisol 4000 nmol/l, ACTH 98 ng/l. LDDST failure to suppress cortisol levels. IPSS showed no central:peripheral ACTH gradient, representing ectopic ACTH source. CT chest showed multiple pulmonary nodules, a dominant RLL nodule larger since 2006. 68-Gallium DOTATATE PET/CT scan was normal. Metyrapone was commenced. One week later, Metyrapone was stopped due to low cortisol levels. Off Metyrapone, cortisol levels remained low with concomitant reduction of ACTH levels, indicating another spontaneous remission of Cushing's syndrome. Histology from an excision biopsy of the RLL nodule revealed tumourlets with a typical carcinoid appearance and a background of DIPNECH. Post-operatively, she was treated with hydrocortisone replacement for a couple of weeks. After a few months later symptoms of Cushing's recurred and repeat imaging of the chest has not shown any progression of the lung nodules. Repeat LDDST confirmed the biochemical excess of cortisol. She is currently awaiting bilateral adrenalectomy.

As per the literature review, DIPNECH is common in female. There is only one case presented with ACTH secretion. It is relatively a stable disease with only 26% of the patients deteriorates clinically and radiologically. Octreotide has not shown to improve the prognosis.

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GP31

Long-term treatment of acute ectopic ACTH syndrome with Etomidate

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Case description

A 25-year-old male was admitted to the Intensive Care Unit due to progressive muscle weakness, difficulty walking, weight loss, headache, chest discomfort, type 1 diabetes for few months. He was confused and irritated, with "moon" face, facial plethora, acne, and hyperpigmentation of the skin, few obscure red-bluish striae and significant wasting of proximal and distal muscles of lower limbs. Cortisol hypersecretion due to ectopic ACTH production was confirmed by plasma ACTH (> 1250 ng/l) and cortisol (1120–2145 nmol/l), 24-h urinary free cortisol (14 726 nmol/24 h), failure to supress cortisol on a high dose intravenous and 16 mg oral 2 days dexamethasone suppression tests. Severe hypercortisolemia resulted in critical fluid and electrolyte imbalance, deterioration in physical and mental state. Daily Etomidate infusion 20–60 mg for 14 days stabilized condition and later was used for treatment on alternate days in the dose of 20–40 mg for 10 months in day care clinic. Alternative treatment with Ketoconazole induced hepatic injury, Octreotide was ineffective, Metyrapone was not available. Following Etomidate infusions, plasma cortisol decreased to 280–560 nmol/l, potasium – 3.7–4.3 mmol/l with oral supplementation of KCl 3 g/day and Spironolactone 50 mg, glucose became normal without insulin. In 10 months Metyrapone became available and 1 g/day was used to achieve control. Patient refused from adrenalectomy.

Pituitary MRI, chest and abdomen CT, somatostatin receptor scintigraphy, bronchoscopy, esophagogastroduodenoscopy, colonoscopy revealed no potential source of ectopic ACTH production. Further assessment by whole body 18F-FDG PET-CT and 68Ga-DOTATOTE PET-CT scans, selective sinus petrosus inferior sampling and enteroscopy failed to detect the source of ACTH. Thorax CT and colonoscopy was performed three times, abdominal CT and pituitary MRI – twice during 16 months. Primary tumour was not detected.

Conclusion

Etomidate infusion could be used for long term treatment of ectopic ACTH syndrome when other options are ineffective or unavailable.

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GP32

Multiple pathologic fractures as the presenting manifestation of Cushing's syndrome in patients with vitamin D receptor FokI gene polymorphism

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Rare cases of Cushing's syndrome have been diagnosed only based upon bone manifestations. Fracture risk is related to individual susceptibility to glucocorticoids that is genetically determined by several factors, including VDR gene polymorphism.

We report three patients with VDR FokI gene polymorphism and multiple non-traumatic pathologic fractures as the presenting manifestation of Cushing's syndrome.

Case reports

The first case is a 55-year-old man who presented with pain in the right hip. CT scan revealed fracture in the right femur. Additionally bone scintigraphy revealed non-traumatic micro-fractures in ribs and pelvis.

The second case is a 44-year-old woman who presented with pain in the left hip. She reported weight gain (25 kg) in the last 6 years, depression, fatigue, and muscle weakness. MRI revealed fracture in the left hip, while bone scintigraphy showed multiple non-traumatic micro-fractures in ribs and right femur.

The third case is a 64-year-old woman presented with recurrent rib and low extremities fractures the last 10 years. She also suffered from depression and hypercholesterolemia.

Dual-energy X-ray absorptiometry (DXA) revealed severe osteoporosis in all patients. Additionally laboratory tests and imaging techniques confirmed the diagnosis of Cushing's syndrome due to an adrenal mass. Further investigation for FokI and Bsm polymorphism of VDR gene by polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) analysis showed that all patients had the ff genotype of the VDR FokI gene.
Discussion
VDR FokI gene polymorphism correlates significantly with an increased rate of bone loss in ff postmenopausal women. However data of its functional significance on glucorticoid-induced osteoporotic fractures is lacking so far. We report for the first time an association between the ff genotype and multiple non-traumatic fractures as the predominant manifestation of Cushing's syndrome. Our findings suggest that VDR FokI gene polymorphism may increase fracture risk in ff subjects with endogenous hypercortisolism.

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Bone & Calcium Homeostasis 1

GP33

"Hyperparanet": a multicenter Italian study on Primary Hyperparathyroidism

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The aim of the present study was to evaluate the phenotype of PHPT, the adherence to International Guidelines and the rate of surgical cure of PHPT in Italy. From January 2014–January 2016, we conducted a prospective, multicenter ($n=29$ endocrine tertiary referral centers) study on patients with PHPT, recording clinical and biochemical data, parathyroid imaging and therapy choice at baseline and at last follow-up. The study group included 604 patients with PHPT, with a mean age of 61 ± 14 yrs (F:M = 5:1). Most patients had sporadic PHPT ($n=566$ (93.7%), mean age 63 ± 13 yrs); the remaining 38 (6.3%, mean age 41 ± 17 yrs) were familial forms. Follow up data were available in 345 patients: 158 (45.8%) with symptomatic and 187 (54.2%) with asymptomatic PHPT. Eighty-six patients (54.4%) of the former group underwent PTx, mainly for symptomatic nephrolithiasis ($n=71$, 82.6%). One hundred twenty-one asymptomatic patients (64.7%) met at least one criterion for PTx according to the 2008 International guidelines for parathyroidectomy and 65 patients (53.7%) underwent surgery. Criteria for PTX were: serum calcium levels 1 mg above the upper normal limit ($n=37$, 56.9%), osteoporosis ($n=35$, 53.8%) and age <50 yrs ($n=14$, 21.5%). Surgery was not performed in the remaining patients ($n=56$, 46.3%) despite the presence of serum calcium levels 1 mg above the upper normal limit ($n=12$, 21.4%), osteoporosis ($n=44$, 78.6%) and age <50 yrs ($n=11$, 19.6%). Surgery was also performed in 16 of the 66 (25.7%) patients who did not meet the criteria for surgery. A total of 168 patients underwent PTX. The histological diagnosis was single adenoma in 89% of cases, hyperplasia in 9%, atypical adenoma in 1%, and carcinoma in 1%. The large majority ($n=158$, 94%) of patients were cured. Persistence of PHPT was observed in the remaining 10 patients, who were apparently sporadic. Patients followed without surgery showed a stable clinical and biochemical disease, after one year of follow-up. This is the first multicenter Italian study with the specific aim of evaluating PHPT phenotype and therapeutic approach. International guidelines recommendations for surgery were observed in half of cases, either for symptomatic or asymptomatic patients.

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GP34

Fat mass distribution and resistin are independent predictors of bone mass in postmenopausal, but not premenopausal women.

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Introduction
Body weight and lean mass (LM) are classic bone mass determinants. However, the association between total fat mass (FM), regional FM and bone remains controversial, especially as fat is a source of adipocytokines, with both positive and negative bone consequences.
Materials and methods
Anthropometric, bone mass (assessed by Dual X-Ray Absorptiometry; DXA) and body composition parameters (assessed by DXA) and also serum adipocytokine (leptin, adiponectin, resistin) levels were determined from 93 female volunteers (38 premenopausal and 55 postmenopausal women). Correlation analysis was performed in order to assess the association between body mass index (BMI), body composition parameters, adipocytokines and bone mass. Multivariable and hierarchical regression models were used to determine which of the above factors are independent predictors of bone mass.
Results
In correlation analysis, BMI, total LM, total FM and regional FM (trunk FM and lower limbs FM) were positively associated with bone mass in both groups. Correlations between adipocytokines and bone were found only in the postmenopausal group. In multivariable regression analysis, only LM remained an independent predictor of bone mass in premenopausal women, explaining 38.1% ($P<0.001$) of femoral neck, 24.5% ($P=0.002$) of total hip and 20% ($P=0.005$) of whole-body bone mineral density (BMD) variance; in postmenopausal women, LM, trunk-to-lower limbs FM ratio (together explaining 30.9% of the variance of total hip BMD, $P<0.001$) and resistin (adipokine known to regulate bone cell proliferation and bone turnover) remained independent positive predictors of bone mass. Hierarchical regression showed no additional effect of BMI or of total FM to that of total LM in predicting bone mass in both groups.
Conclusions
LM independently predicts bone mass in premenopause, while after menopause FM distribution becomes an important factor in regulating bone mass together with total LM and resistin. These parameters may find their place for fine tuning the evaluation of fracture risk.

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GP35

Aldosterone and parathyroid hormone – is there a connection?

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Introduction
Recent studies seem to support a bidirectional positive interaction between aldosterone and parathyroid hormone (PTH). Understanding the normal physiological relationship between renin-angiotensin-aldosterone system (RAAS) and PTH is of clinical interest because their inappropriate activity may negatively impact cardiovascular and skeletal health.
Objective
To evaluate the presence of an interaction between aldosterone and PTH in a cohort of patients assessed for suspicious hyperaldosteronism or hyperparathyroidism.
Material and Methods
We retrospectively evaluated consecutive patients followed in our Endocrinology Department between January 2014 and December 2016. We collected data about renin-angiotensin-aldosterone system and calcium metabolism from clinical and laboratorial records and selected patients whenever both data were available.

Results
We identified 97 patients evaluated for suspicious hyperaldosteronism or hyperparathyroidism. 51 patients were excluded due to insufficient data. From the 46 patients included, 8(17%) had confirmed primary hyperparathyroidism and one had confirmed primary hyperaldosteronism; 74% ($n=34$) were women, mean age of 60.0 ± 13.2 years and mean BMI of 27.8 ± 4.1 Kg/m^2. This group had a mean aldosterone level of 141.9 ± 74.6 pg/ml (reference range: 40–310), PTH level of 87.3 ± 48.0 pg/ml (reference range: 9–72), 25(OH) vitamin D level of 26.5 ± 10.2 ng/ml and plasma calcium level of 9.6 ± 1.1 mg/dl (reference range: 8.8–10.6). PTH and aldosterone levels presented a moderate correlation in our cohort (rho$=0.474$, $P<0.01$). After exclusion of the patients with confirmed disease, PTH and aldosterone levels presented a week correlation, though still statistically significant (rho$=0.377$, $P=0.021$).
Conclusion
Aldosterone levels were positively correlated to PTH levels in our sample. This interaction may be one of the mechanisms responsible for hypertension and increased cardiovascular risk in patients with hyperparathyroidism. On the other hand, hyperaldosteronism may indirectly impair calcium metabolism and bone health.

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GP36

Relationship between circulating microRNAs and bone mineral density in patients with active acromegaly

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Objective
Acromegaly (ACRO) is associated with abnormal bone remodeling and reduced volumetric bone mineral density (vBMD) at the lumbar spine and proximal femur. Circulating microRNAs (miRNAs) modulate the activity of osteoblasts and osteoclasts, and are currently being investigated as potential biomarkers of osteoporosis. The aims of our study were: 1) To identify differentially expressed miRNAs in the serum of five patients with active ACRO vs. healthy controls, and 2) To correlate selected miRNAs concentrations with altered bone parameters in 11 ACRO patients.
Patients and methods
Eleven patients with active ACRO (six females; mean age, 47.5 ± 6.7 years; BMI, 27.2 ± 3.8 kg/m^2) and 11 age-, gender-, and BMI-matched controls were recruited. Analysis of differential expression of miRs was performed in 5 of them (5 males; mean age, 44.3 ± 4.3; BMI, 26.2 ± 2.8). Areal BMD (aBMD) at lumbar spine and femur was assessed through dual energy X-ray- absorptiometry (DXA); vBMD was measured by quantitative computed tomography (QCT). Serum miRNA levels were assessed by qPCR. Osteocalcin (OC), type 1 amino-terminal propeptide (P1NP) and carboxy-terminal collagen crosslinks (CTx) were measured using electrochemiluminescent immunoassay.
Results
Expression of miR-885-5p, miR-99a-5p, and miR-29a-3p was significantly higher, while that of miR-7-1-3p and miR-335-3p was significantly lower in the ACRO patients. Both miR-885-5p and miR-7-1-3p were inversely associated with femoral aBMD ($r=-0.64$, $P=0.034$ and $r=-0.73$, $P=0.009$, respectively), and trocantheric vBMD ($r=-0.66$; $\rho=0.038$ and $\rho=0.67$; $P=0.023$) in ACRO but not in the controls. They were also positively associated with P1NP ($r=0.82$, $P=0.002$ and $r=0.79$, $P=0.004$, respectively) and CTx ($r=0.73$, $P=0.010$ and $r=0.68$, $P=0.019$) in ACRO. MiR-99a-5p was inversely associated with femoral aBMD ($r=-0.66$, $P=0.26$) and positively associated with P1NP ($r=0.83$; $P=0.001$) and CTx ($r=0.88$, $P<0.001$) in ACRO only. The relationship between femoral aBMD and miR-99a-5p remained significant after adjusting for age and IGF-SDS ($\beta=-0.52$, $P=0.012$).
Conclusions
Circulating miRNAs may be one of the mechanisms whereby BMD is impaired, mainly at the femoral level. Further larger studies are needed to confirm these preliminary data.

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GP37

Effects of BCR-ABL targeted tyrosine kinase inhibitors on the whole transcriptome pattern of cultured murine osteoblasts

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Breakpoint cluster region abelson fusion oncoprotein (BCR-ABL) targeted tyrosine kinase inhibitors (TKIs) are widely used in long-term medications of hematological malignancies. Numerous clinical observations confirmed that these drugs significantly modify the physiology of bone tissue as a side effect. Currently, there are numerous contradictory results regarding the complex effects of TKIs on bone metabolism, as well as there is no clear evidence to explain them, either in the level of basic or clinical research.
The aim of the present study was to analyze the whole transcriptome differences of cultured murine osteoblasts (MC3T3E1) after imatinib or nilotinib treatment using SOLiD next generation RNA sequencing technique. Based on the cell viability test, 1 μM drug concentration and 6-day incubation period had the greatest effects on the expression profile of osteoblastic cells.
The results showed only three common up-regulated genes in the TKI-treated groups with almost the same expression activity compared to the control one. Ingenuity Pathway Analysis was applied to reveal the cellular response for the two drugs. Six and five top canonical pathways were identified from the whole transcriptome sequencing data in case of imatinib and nilotinib, respectively. GABA receptor cascade was found among the markedly upregulated signaling pathways in both of the treated groups. During the bone remodeling process, this signal transduction network is deeply involved in bone cell proliferation, differentiation and development.
In conclusion, this was the first study to observe the complete mRNA pattern of osteoblasts after selective TKI administration. These preliminary transcriptional results indicate various mechanisms of action of the examined TKIs on osteoblast function that might be due to their different chemical profiles and non-kinase target spectrum. Therefore, further investigation is required to verify the detected expression changes of the reported genes as well as to validate the biologically significant targets.

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GP38

Decreased trabecular bone score but not bone mineral density in patients with acromegaly and concurrent hypogonadism: cross-sectional study with healthy controls

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Introduction
Acromegaly is associated with higher prevalence of vertebral fractures (VFx) and bone microarchitecture potentially play a role in fracture development. Trabecular bone score (TBS), a novel indicator of bone microstructure could provide additional information.
Objectives
Assessment of BMD, TBS and bone turnover markers (BTM) in acromegaly patients in comparison to healthy controls with regard to gender, hypogonadism and disease activity.
Patients and methods
A cross-sectional study of acromegaly patients with age-, gender- and BMI-matched healthy controls was conducted. Study group consisted from all acromegaly patients (regardless age, gender, disease duration or activity) which came for follow-up visit during period 6/2016 – 12/2016 and the control group consisted of healthy subjects. In all subjects a single measurements of all pituitary axis hormones levels, BTM, BMD of total hip (TH) and lumbar spine (LS) and TBS was performed. N-terminal type 1 procollagen (P1NP) - marker of bone formation and C-terminal telopeptide (CTx) –marker of bone resorption were analyzed.

Results
Thirty Seven acromegaly patients (12 males/25 females with mean age 56.7 years, mean BMI 29.8 kg/m^2) and 27 of control group subjects (seven males/20 females with mean age 59.5 years, mean BMI 30.9 kg/m^2) were included. TBS was significantly lower in patients in comparison to controls (1.16 vs 1.22; $P<0.05$), but no BMD and BTM difference was observed. Hypogonadal patients had lower TBS in comparison to patients without hypogonadism (TBS 1.13 vs 1.20; $P<0.05$) and no BMD difference. BTM were increased in hypogonadal patients (CTx 0.67 vs 0.38 ng/ml; P1NP 75.5 vs 47.5 ng/ml; both $P<0.05$). No difference in TBS, LS BMD and BTM with regard to gender was observed.
Conclusion
This study indicates that patients with acromegaly, especially those with hypogonadism, despite unchanged BMD, may have impaired trabecular bone microstructure, which can lead to increased prevalence of fractures.

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GP39

Association of changes in serum urate level and bone mineral density during treatment with teriparatide: a retrospective observational study

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Serum urate level has recently been associated with increased bone mineral density (BMD). Teriparatide, an osteoanabolic medication for osteoporosis, is associated with increased incidence of hyperuricemia. Hence, we hypothesized that changes in serum urate are associated with changes in BMD and procollagen type 1 N-terminal propeptide (P1NP) during treatment with teriparatide.
We collected data from 151 women (mean age 72 years, mean BMI 26.6 kg/m^2) with severe postmenopausal osteoporosis who had been treated with teriparatide for 2 years at our outpatient clinic. They were prescribed with vitamin D3 1000 IU daily and were instructed to ingest 1200 mg of calcium daily. BMD was measured at the three standard sites by DXA at baseline, after 12 and 24 months of treatment. Routine laboratory parameters (including serum urate), 25-hydroxyvitamin D and P1NP were measured at the same time-points. Estimated glomerular filtration rate (eGFR) was calculated. The associations were assessed using univariate correlations and multiple linear regression models (each fitted using casewise deletion of records with missing data as well as missing data imputation). Repeated-measures analysis of variance was used to verify the increase in serum urate level and stability of eGFR.
During the 2-year treatment with teriparatide, we observed no notable univariate association between change of serum urate level and change of BMD. When adjusting for basal eGFR, vitamin D sufficiency, previous bisphosphonate treatment, change of serum and of urinary calcium during the same period, we observed a weak positive association of serum urate level change with change of BMD at lumbar spine. Conversely, change of serum urate level tended to be weakly positively univariately associated with change of P1NP, but the association vanished when adjusting for the confounders listed above.
Our results may indicate that the effect of teriparatide on bone might be partly mediated by changes in serum urate level.

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GP40

Coexistence of primary hyperparathyroidism with papillary thyroid carcinoma: a case series

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Introduction
Primary hyperparathyroidism (PHPT) may rarely coexist with non-medullary thyroid carcinoma (NMTC). We report the clinical manifestation and management of nine cases of synchronous PH and NMTC.
Cases
Eight women and one man were included (mean age at diagnosis: 64 ± 6.6 years). In all cases, PH was the initial diagnosis, whereas NMTC was detected incidentally, after ultrasound assessment for PH. The histological diagnosis of NMTC was classical papillary thyroid carcinoma (PTC) in all cases, with follicular subtype in four cases. In one patient, medullary carcinoma was also detected and a diagnosis of multiple-endocrine neoplasia type 2B syndrome was set. In three cases (33.3%), NMTC was multifocal. Extrathyroidal extension was detected in one case, but without metastatic disease. In seven cases (78%), maximum NMTC diameter was <10 mm (mean diameter: 7.6 ± 4.4 mm). Thyroid autoimmunity was positive in two cases.
The histological diagnosis of PHPT was single parathyroid adenoma (mean diameter: 15.4 ± 19.3 mm, in six cases on the right side) in all cases. In one case, the adenoma was intrathyroidal. Nephrolithiasis was diagnosed in one case, hypercalciuria in two, whereas low bone mass in eight patients. Preoperative mean parathyroid hormone (PTH) and total calcium concentrations were 133.5 ± 43.9 and 11.3 ± 0.8 mg/dl (corrected calcium: 11 ± 0.78 mg/dl), respectively. Cardiovascular risk factors, such as arterial hypertension, dyslipidemia and/or hyperglycemia were diagnosed in six cases (66.7%).
PH and NMTC were successfully managed with parathyroidectomy and total thyroidectomy (mean post-operative PTH concentrations: 33.3 ± 24.7 pg/ml). No case developed post-operative hypocalcemia. Prophylactic central lymph node resection was performed in one patient. No recurrence of either PH or NMTC has been reported (mean follow-up time: 3.8 ± 5.1 years).
Conclusions
NMTC may rarely be incidentally detected in patients with PH. It is usually unifocal microcarcinoma of classical PTC subtype, without extrathyroidal extension. The pathogenetic mechanisms linking these two endocrine entities are currently unknown.

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GP41

Follow-up of patients with surgical hypoparathyroidism: unknown cause of renal function decline?

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Background
Hypoparathyroidism is a rare endocrine disease with low calcium and insufficient parathyroid hormone levels. In most cases it is caused by thyroid surgery. The objective of this retrospective cohort study was to evaluate if the typical therapy regimens of postsurgical hypoparathyroidism with calcitriol have a negative effect on renal function.
Methods
We performed a chart analysis of patients that were seen in a tertiary care hospital in Brussels, Belgium. A total of 101 patients were identified as patients with permanent post-surgical hypoparathyroidism, based on the hospital records of patients who underwent a total thyroidectomy between 1996 and 2016, while still being treated with calcitriol. Patients with pre-existing renal insufficiency and/or active malignancy were excluded. The cohort was predominantly female of Caucasian origin. Kidney function was evaluated before and after surgery (with a maximum follow-up of 12 years), using the CKD-EPI equation.
Results
A multivariate linear regression model was used to correlate kidney function decline with the duration of calcitriol therapy, while accounting for the mean calcium-phosphate product and age. We found a statistically significant ($P=0.027$) relation between the duration of calcitriol treatment and renal function decline at a rate of 1.06 ml/min/1.73 m^2 per year of calcitriol therapy.
Conclusions
Renal abnormalities are frequent finding in patients with hypoparathyroidism. Our study, although being retrospective, is the first one to demonstrate a relationship between the duration of calcitriol therapy and progressive renal insufficiency.

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GP42

Expression of hypoxia-inducible factor-1α in Calbindin-D_{9k} Knockout mice

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Introduction
Hypoxia-inducible factors (HIF) are the key transcription factor induced by hypoxic condition, which regulate expression of specific target genes including angiogenic factors, erythropoietin, glucose transporters, and glycolytic enzymes. Recently, many studies connected to intracellular calcium levels and regulation of HIF-1α protein level. Calbindin-D_{9k} is a cytosolic calcium-binding protein and compensate with other calcium transporter protein for maintenance of cellular calcium level. It is expressed in primarily duodenum for absorption of calcium and in kidney for resorption of calcium. The objective of this study is to investigate interaction between HIF-1α and calbindin-D_{9k}.
Materials and methods
8–10 weeks old C57BL/6 mice and calbindin-D_{9K} knockout mice were exposed to hypoxia (12±2% O2) for 3 weeks in closed polycarbonate chamber with nitrogen supply to remove the oxygen vs the normoxic groups. Calbindin-D_{9k}-transfected ACHN cells were cultured in normobaric hypoxia (1% O2), with match control in normoxic conditions. Expression of HIF-1α and glucose transporter 1 (GLUT1, a downstream gene of HIF-1α) were analyzed in mRNA or protein level.
Results
Protein level of HIF-1α was increased in calbindin-D_{9K} knockout mice compared with that of control in normoxic condition. However, increased protein level of HIF-1α of calbindin-D_{9k} knockout mice was reduced in hypoxic condition. mRNA levels of GLUT1 showed similar pattern with HIF-1α expression. In comparison to in vivo experiment, expression of HIF-1α and GLUT1 in mRNA and protein levels corresponded to that of Calbindin-D_{9k} knockout mice.
Conclusions
These results suggest that calbindin-D_{9k} can regulate expression of HIF-1α in protein level.

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Bone & Calcium Homeostasis 2

GP43

Chromosome 2q37 microdeletions in two cases of sporadic PHP-1B with broad GNAS imprinting defects

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Pseudohypoparathyroidism type 1B (PHP-1B) is a rare, familial or sporadic, imprinting disorder due to the epigenetic dysregulation of the GNAS locus, whose main product is the α subunit of the stimulatory G protein (Gsα). Sporadic PHP-1B cases (spor-PHP-1B) display broad methylation abnormalities at multiple GNAS DMRs, but the underlying molecular mechanism is still unknown.
Classically, PHP-1B patients show PTH and TSH resistance, but, in the past years, also physical features of Albright hereditary osteodystrophy (AHO) were described, suggesting the existence of an overlap among PHP subtypes. Moreover, mutations in *PRKAR1A* and *PDE4D* genes, and deletions of 2q37 were reported in small subsets of clinically diagnosed PHP patients with no detectable GNAS defects, highlighting the clinical overlap with diseases in differential diagnosis. Brachydactyly-mental retardation syndrome (BDMR), associated with 2q37 deletions, may present a spectrum of clinical features, including intellectual disabilities, developmental delays, behavioural abnormalities and skeletal abnormalities, among which brachydactyly type E.
In the present study, we screened our series of spor-PHP-1B pts with ($n=21$) or without AHO ($n=33$) for BDMR-associated deletions to find modifier genes possibly involved in the phenotypic heterogeneity observed in PHP-1B, and we detected 2 different deletions (ranging from ~2.83-Mb up to ~4.5-Mb) in 2 unrelated pts with AHO. Additional analysis confirmed rearrangements and allowed to roughly delineate the genetic defects extension.
Deletions overlapped with previously described rearrangements and included several genes already proposed as causative for BDMR. Interestingly, our mutated patients displayed molecular (GNAS loss of imprinting) and endocrine characteristics (overt PTH resistance) usually absent in BDMR, although so far only one BDMR patient with raised PTH levels was described (Power et al. 1997 J Med Genet). These preliminary results prompt us to confirm the causative role of found genetic variants, and to clarify their role in the pathogenesis of specific and unexpected clinical manifestations.

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GP44

Investigation of total and free 25OHD vitamin levels in patients with chronic renal failure on different dose of cholecalciferol

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The total 25-hydroxy-vitamin-D (t-25OHD) level reflects the vitamin-D supply, but it is also influenced by the levels of vitamin-D-binding-proteins (DBP) and albumin. The type of dialysis influences the levels of serum proteins. The 'free-hormone hypothesis' states that only the free molecules (f25OHD) can diffuse intracellular. Our aim was to evaluate the total, calculated (c-f25OHD) and direct measured (dm-f25OHD) 25OHD levels in patients with chronic renal disease on cholecalciferol.
Methods
100 patients [45 men; 55 women; 69±14 years: 40 on haemodialysis (HD), 26 chronic renal failure (CRF) both on 1000 IUD_3/day; 34 on peritoneal dialysis (PD) on 3000 IUD_3/day] were investigated. Their sera were analysed for DBP (Dako), albumin, Ca, PTHi, t-25OHD (Roche), dm-f25OHD (DIAsource).
Results
Albumin levels were significantly lower (PD:38±5 HD:40±5; CRF:43±3 g/l; $P<0{,}001$) and DBP concentrations higher (390±55 CRF:352±42; HD:323±61 mg/l; $P<0{,}001$) were in PD group. The t-25OHD and c-f25OHD were the lowest in PD (t-25OHD: 65±30; CRF:78±38; HD:79±45 nmol/l, c-f25OHD: 14±7; CRF:18±9; HD:20±11 pmol/l, $P<0.05$). There were no significant differences among dm-f25OHD levels (PD:16±5; CRF:16±6; HD:15±6 pmol/l). The highest incidence of suboptimal vitamin D supply was found in PD patients on the bases of t-25OHD (PD:65%; CRF:42%; HD:43%) and also in c-f25OHD levels. These incidences decreased significantly into 15%–23%, when dm-f25OHD was taken into consideration. Out of the three 25OHD fractions only dm-f25OHD levels gave the opportunity to prove significant relationship between PTHi/Ca and 25OHD level ($OR=3.8_{CI:1.024\text{-}14.4}$; $P=0.036$).
Conclusions
t-25OHD and c-f25OHD values underestimate the vitamin D supply particularly in PD patients. Patients on PD need much higher doses of cholecalciferol, without any differences from other two groups in dm-f25OHD levels either. Patients, who have higher dm-f25OHD level have 3.8 times higher chance for normal Ca/PTHi levels. In case of dm-f25OHD there was a significant relationship proven between 25OHD level and related biomarkers. The dm-f25OHD seems to be a reliable marker for estimation of vitaminD supply in patients with chronic renal disease.

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GP45

Methylation patterns at the novel DMR of GNAS (GNAS-AS2) in pseudohypoparathyroidism 1B (PHP1B or iPPSD3) subtypes

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PHP1B -iPPSD3 per the new proposed classification- is a rare disorder characterized in most patients by proximal tubular resistance to PTH resulting in hypocalcemia, hyperphosphatemia and elevated PTH. Loss-of-methylation (LOM) at the Differentially Methylated Region (DMR) at *GNAS* exon A/B occurs in all PHP1B patients, but methylation changes at other DMRs within GNAS

occur in some familial and most sporadic PHP1B cases. All patients with autosomal dominant PHP1B (AD-PHP1B) due to a maternal deletion that comprises the STX16 region (del*STX16*+) present with LOM restricted to the GNAS-A/B DMR, while sporadic cases (sporPHP1B) present with broad *GNAS* methylation defects, including LOM at a novel, recently identified DMR within the *GNAS* locus referred to as antisense DMR2 (GNAS-AS2).
Objectives and patients
Characterize the methylation pattern at the GNAS-AS2 DMR in AD-PHP1B del*STX16*+ ($n=9$) and del*STX16*- ($n=5$) patients; furthermore, sporPHP1B ($n=10$) and healthy controls ($n=10$) were investigated. *STX16* and *GNAS* deletions were excluded in the del*STX16*- patients by MLPA, genomic multiplex and quantitative PCR of the *GNAS* and *STX16* regions.
Results

1. The mean methylation index at the GNAS-AS2-DMR was significantly higher in delSTX16- patients (32±14%) than in controls (24±6%), del*STX16*+ (5±2%) and sporPHP1B patients (3+1%) ($P<0.0001$).
2. Bisulfite-treated DNA of PHP1B patients with del*STX16*- was PCR amplified across the GNAS-AS2-DMR and products were cloned into pcDNA3.1. First, we identified 2 CG-rich subdomains (SD1 and SD2) within the GNAS-AS2 DMR that are separated by 184 bp. Second, in del*STX16*- patients we observed a unique pattern of methylation including an gain of methylation at SD1 and a methylation pattern at SD2 similar to that of controls, whereas both del*STX16*+ and sporPHP1B patients displayed full LOM at SD1 and SD2.

Conclusion
We have further refined the GNAS-AS2-DMR and identified a subgroup of PHP1B patients with a specific pattern of methylation at the GNAS-AS2-DMR. Our findings reinforce the hypothesis that del*STX16*- patients carry a defect in an element that controls the methylation both at the GNAS-A/B DMR and at the GNAS-AS2 DMR.

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GP46

Vitamin D correction elevates apolipoprotein levels in a sex-specific manner

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Numerous studies have identified several extra-skeletal health outcomes to be associated with vitamin D deficiency, yet a definitive causal link is yet to be discovered. Our recent 3D LC-nESI-FTMS proteomic analysis among normal and overweight but apparently healthy adult Saudis identified apolipoproteins, a known independent cardiovascular risk factor, as one of the serological molecular signatures that modulate vitamin D levels. The present interventional study aims to compare and validate the identified apolipoproteins among vitamin D deficient subjects that have achieved full vitamin D status correction. 199 Saudi adults [89 males, mean age 42.0±10.4; BMI 28.6±4.4 kg/m^2; 110 females, mean age 39.1±12.0; BMI 30.7±5.3] (with vitamin D deficiency [25(OH)D <50 nmol/l] were recruited and given 50 000 IU cholecalciferol (VitaD50000®) weekly for 2 months, then twice a month for 2 months, followed by daily 1000 IU (VitaD1000®) until month 6. Blood samples were taken at baseline and after 6 months. Serum 25(OH)D was measured using electrochemiluminescence and apolipoproteins (AI, AII, B, CI, CII, CIII and E) using commercially available kits. In all subjects, serum 25(OH)D increased significantly from baseline and after 6 months (32.6±11.1 vs 63.4±16.4 nmol/l; $P<0.001$). In parallel, a significant increase in apolipoproteins B, CI, CII, CIII and E (P-values <0.05) after 6 months compared to baseline was observed. After stratification according to sex, only apolipoproteins CII and CIII were significantly increased in males (P-values <0.001), and only apolipoprotein CI was significantly increased in females ($P<0.001$), showing sexual dimorphism in the effects of vitamin D with regards to apolipoprotein levels. The rest of the apolipoproteins were not significantly different pre- and post-vitamin D correction. The present study partially explains the effects of vitamin D correction in the reduction of cardiovascular risk through significant modification of apolipoproteins, particularly the apolipoprotein C class. These effects differ according to sex.

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GP47

Recombinant human parathyroid hormone (rhPTH[1-84], parathyroid hormone rDNA) improves hypercalciuria in patients with hypoparathyroidism: 3-year analysis from RACE study

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Hypoparathyroidism (HPT) is characterised by hypocalcaemia and impaired renal phosphate excretion and calcium conservation. Oral calcium supplements and calcitriol can improve serum calcium levels but lack the physiologic effects of PTH on renal reabsorption of calcium. RACE is an ongoing open-label study evaluating the long-term safety of recombinant human parathyroid hormone 1-84 (rhPTH[1-84], parathyroid hormone rDNA) in adults with HPT (NCT01297309). In this interim analysis, we report the 3-year treatment effect with 25–100 µg/day rhPTH(1-84) on 24-h urinary calcium levels, with or without thiazide diuretics. All data are presented as mean (SD). The study cohort comprised 49 patients enrolled at 12 USA centres; 38 (78%) completed 36 months of rhPTH(1-84) treatment. Baseline demographics were as follows: 82% women, age 48 (9.8) years, HPT duration of 16 (12.5) years, 100% taking prescribed calcium supplements and calcitriol. In response to rhPTH(1-84), albumin-corrected serum calcium remained within the target range over the 3 years; 2.1 (0.17) mmol/l at baseline (i.e., start of rhPTH[1-84], $n=49$) and Month 36 ($n=36$). Treatment with rhPTH(1-84) also led to a reduction in urinary calcium, from baseline 8.9 (5.0) mmol/24 h to 6.5 (2.8) mmol/24 h ($n=35$; $P<0.05$). Urinary calcium excretion at Month 36 was similar for men compared with women, and in patients taking or not taking thiazide diuretics. Overall, 71% of rhPTH(1-84)−treated patients with baseline hypercalciuria had normal 24-h urinary calcium excretion at Month 36 ($n=12/17$). Treatment with rhPTH(1-84) improved calcium–phosphate product from baseline 3.4 (0.5) mmol^2/l^2 ($n=49$) to 2.9 (0.5) mmol^2/l^2 ($n=36$) ($P<0.0001$). eGFR was baseline 108.2 (36.4) ml/min ($n=41$) and 115.7 (47.3) ml/min ($n=36$) at Month 36 ($P<0.0772$). Over 3 years, rhPTH(1-84) maintained target levels of serum calcium and reduced urinary calcium to normal levels in HPT patients. More information is needed to understand the timing of the beneficial effect on urinary calcium excretion.

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GP48

Vitamin D levels after 4 weeks of very low calorie diet (VLCD)

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Introduction
Vitamin D is a liposoluble molecule which takes part in calcium–phosphorous homeostasis of the human body. Its optimum levels according to SEIOMM range between 30 and 75 ng/ml. Being liposoluble substances they require the presence of biliar salts for their absorption; 80% is absorbed in the yeyune and in a lesser extent in the duodene. The correct concentration of vitamin D is of key significance in obesity, particularly its visceral type. An excessive body weight is thought to represent a significant determinant of a reduced vitamin D concentration in serum. Due to its high metabolic activity, visceral adipose tissue promotes sequestration and alterations in turnover of the vitamin-resembling hormone. Care for elimination of the factors which promote deficiencies is particularly essential in obese persons in whom degree of adiposity correlates with reduced concentrations of this vitamin in blood. Given the

importance of this vitamin in the body we have analysed its levels in obese patients which were going to follow a VLCD (600 kcal) before undergoing bariatric surgery. The patients followed a VLCD during 4 weeks before the surgery. The values of vitamin D were analysed at two different moments: before beginning the diet and after the diet, 4 weeks later.
Method
We have designed a prospective observational study; 18 patients were analysed with IMC >35 kg/m^2 with associated comorbility or IMC >40 kg/m^2, between 18 and 60 years old, candidate for bariatric surgery with laparoscopic gastric by-pass. Vitamin D concentrations were monitored at two different moments: 1 month before surgery and at the moment of surgery, 4 weeks after the VLCD.
Objective
To establish whether there are statistically significant variations in the values of vitamin D before and after following a VLCD.
Results
We obtain an average level of vitamin 25 (OH) D of 16,31 ng/ml in the analytical evaluation 1 month before surgery and 21,32 ng/ml at the time of the surgery, which takes place at the end of the VLCD. Statistically significant differences are observed between the levels of vitamin 25 (OH) D 1 month before surgery and at the time of the chirurgical act.
Conclusions
According to the results, patients that follow a 4-week VLCD significantly improve the levels of vitamin 25 (OH)D in blood. Those levels do not reach a normal level after the diet, however it is evident the benefit of the recommended process, and it would be interesting to evaluate in the long term if such a tendency remains.

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GP49

Upper gastrointestinal symptoms, endoscopic and pathological features, and serum gastrin and chromogranin A levels in patients with primary hyperparathyroidism

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Introduction
Upper gastrointestinal (UGI) symptoms are frequently encountered in patients with primary hyperparathyroidism (PHPT). Some of these symptoms may improve after PHPT treatment, while hypercalcemic state may also cause permanent effects. We aimed to evaluate UGI symptoms, UGI endoscopic and pathologic features and determine the relationship between these features with serum chromogranin A (CgA) and gastrin in PHPT patients.
Methods
Seventy-one patients diagnosed with PHPT were included in the study after exclusion of patients who refused UGI endoscopy, had an UGI surgery or used drugs that affect serum chromogranin A or gastrin. Patients were questioned regarding UGI symptoms. Serum CgA and gastrin were measured. Endoscopy was performed and gastric biopsy specimens were taken to evaluate atrophic gastritis.
Results
There were 60 females and 11 males, and median age was 52 years. Mean serum CgA and gastrin levels were 134.10 ± 19.43 ng/ml (28-620) and 219.39 ± 48.6 pg/ml (14-2255), respectively. Dyspepsia, epigastric pain and weight loss were the most common symptoms and presented in 61, 51.7 and 46.6% of patients, respectively. *Endoscopy* was *normal* in 25(35.2%) patients. Erosive antral gastritis, atrophic gastritis, gastric ulcers, duedonal ulcers, reflux gastritis and nodular gastritis were present in 14 (19.7%), 12 (16.9%), 6 (8.5%), 5 (7%), 4 (5.6%) and 4 (5.6%) patients, respectively. Intestinal metaplasia, gastric atrophy, gastric neuroendocrine tumor and Helicobacter pylori infection were detected in 29.2, 20, 1.4 and 66.2% of patients, respectively. Serum CgA was similar in patients with and without atrophic gastritis, while serum gastrin was higher in patients with atrophic gastritis ($P=0.024$). Presence of intestinal metaplasia and Helicobacter pylori infection did not affect serum CgA and gastrin levels.
Conclusion
Dyspeptic symptoms are common in patients with PHPT. The frequencies of atrophic gastritis and peptic ulcers are increased. We think that patients with PHPT should be questioned for UGI symptoms and evaluated with UGI endoscopy when needed.

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GP50

Localisation of parathyroid adenomas using ^{11}C-methionine-PET/CT when conventional imaging methods are negative

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In primary hyperparathyroidism (pHPT) an exact localization of the pathological parathyroid gland(s) is essential before minimally invasive parathyroidectomy. We have previously shown in a small group of pHPT patients, that ^{11}C-methionine-PET/CT provides additional information if ^{123}I/^{99m} Tc-sestamibi (MIBI) scan remains negative. The aim of the present study was to evaluate the clinical value of ^{11}C-Met-PET/CT in a larger pHPT patient cohort.
Methods
Totally 89 patients with pHPT (66 females, 23 males, age 18-81 years) and negative or inconclusive localisation findings with ^{123}I/^{99m}Tc- MIBI-SPECT/CT (78,7%) or ^{99m}Tc-MIBI-SPECT/CT (21.3%) were studied with ^{11}C-Met-PET/CT. Most of the patients (87.6%) were surgical treatment naive and the rest of them (12.4%) were previously operated 1–2 times.
Results
^{11}C-Met-PET/CT revealed the pathologic parathyroid gland in 48 (60.8%) of the 79 surgically treated patients. Totally 26 patients (32.9%) had a negative ^{11}C-Met-PET/CT finding and 16 of them had further explorative surgery, whereas 10 of these Met-PET negative patients were not operated, but treated conservatively instead. In five cases (6.3%) Met-PET detected a false-positive finding, i.e. the pathological parathyroid gland was found in another location. On a per-lesion level PET results were 48 true positive (60.8%) and 21 false negative (26.6%). The lesion-based sensitivity was 75.4% (positive predictive value 94.6%) and specificity 40.0% (negative predictive value 10.5%). The diagnostic accuracy of ^{11}C-Met-PET/CT in this study was 73%. Based on the histological examinations 67 adenomas (84.8%) and six hyperplastic (7.6%) parathyroid glands were found. In five cases the finding was normal parathyroid tissue or unspecified. Ten patients (12.7%) had more than one pathological parathyroid glands. There were no parathyroid carcinomas detected in this study. Totally 79 patients had parathyroid surgery and 55 (69.6%) of them were biochemically cured, but in 16 patients (20.3%) pHPT persisted and in eight patients (10.1%) the postoperative status remained unknown.
Conclusion
^{11}C-methionine-PET/CT offers an additional noninvasive imaging method to localize hyperfunctiong parathyroid glands in a situation when conventional imaging methods ^{99m}Tc or ^{123}I/^{99m}Tc-sestamibi SPECT/CT fail or are equivocal.

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GP51

Calcium to phosphorous ratio (Ca/P) as helpful index to recognize primary hyperparathyroidism, but not primary hypoparathyroidism: a big-data approach

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Background
Primary hyperparathyroidism (HyperPT) and primary hypoparathyroidism (HypoPT) are often underdiagnosed. Several strategies have been investigated in the past in order to identify diagnostic parameters, although the diagnosis of both HyperPT and HypoPT remains challenging so far, especially in asymptomatic patients. Calcium (Ca) and phosphorus (P) are inversely related together, thus the Ca/P ratio could be an useful tool to define these conditions. Recently, we proposed for the first time a cut-off of 3.5 for Ca/P ratio for the diagnosis of HyperPT.
Aim
To evaluate the diagnostic value of the Ca/P ratio for HyperPT and HypoPT through a big-data approach.
Methodology
A retrospective, observational, case-control study on big-data was carried out. All examinations of parathyroid hormone (PTH), Ca and P performed at the laboratory of Modena Hospital from 2010 to 2016 were consecutively included. We considered only patients between 18 and 90 years of age. Laboratory ranges of normality for both PTH and Ca were used to divide records in HyperPT, HypoPT and controls.
Statistical analysis
The diagnostic accuracy of Ca/P ratio was investigated using receiver operator characteristics (ROC) curves in order to define cut-off points, which show higher sensitivity and specificity for the identification of affected patients.
Results
46 597 records were considered. 576 HyperPT (1.2%), 323 HypoPT (0.7%) and 45 698 controls (98.1%) were found. Ca/P ratio was significantly different among groups ($P<0.001$). In particular, Ca/P ratio was significantly higher in HyperPT than controls ($P<0.001$). For the diagnosis of HyperPT, the threshold of 3.17 for Ca/P ratio was obtained by means of the ROC curve analysis, with 85% of both sensitivity and specificity. HypoPT showed lower Ca/P ratio compared to controls ($P<0.001$), although no useful threshold for the diagnosis was found at ROC curve because of the low sensitivity.
Conclusions
We confirm the high sensitivity and specificity of Ca/P ratio for the diagnosis of HyperPT using the largest cohort of patients available so far in the literature. On the contrary, Ca/P ratio does not contribute to identify patients with HypoPT and further researches are needed to better describe this condition. In conclusion, Ca/P ratio is a simple and inexpensive diagnostic tool to recognize HyperPT.

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Cardiovascular & Lipid Endocrinology

GP52

Liraglutide prevents right ventricle hypertrophy by avoiding ACE1 & ACE2 reduction in an experimental model of idiopathic pulmonary fibrosis

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The Glucagon-like peptide-1 (GLP-1) receptor is expressed in the lung having a very important role in the modulation of the Angiotensin Converting Enzymes (ACEs). ACE1 cleaves angiotensin-I into angiotensin-II, which is converted by ACE2 to Ang(1-7). Ang(1-7) has vasodilating effects. The Idiopathic Pulmonary Fibrosis (IPF) is characterized by excessive extracellular matrix deposition disrupting the alveolar architecture and physiology. IPF develops by a sequence of inflammation multifocal process that leads to a fibrotic response. IPF presents pulmonary hypertension and right ventricle hypertrophy.
The aim of this study is to elucidate the effect of precocious treatment with LIR during the inflammatory phase of IPF in ACE1 & ACE2 in the late fibrotic phase in an experimental model of IPF.
IPF was induced in rats by a single intra-tracheal instillation of Bleomycin (BLM, 2.5 mg/kg) on day 0 (D0). From day −1 to day 6, animals were treated with Liraglutide (LIR, 100 μg/kg/12h subcutaneous). On D21 rats were sacrificed. Heart ventricles and lungs were isolated, weighted and frozen. Histology of lungs confirmed interstitial lung fibrosis in all BLM-treated rats.
The real time-PCR levels of ACE-1 & ACE-2 were lower in lungs of BLM-IPF than in controls (40% and 48% reduction, respectively). Right ventricle weight was markedly increased in BLM-IPF rats (+66%). The treatment with LIR at the beginning of the inflammatory phase completely restored the levels ACEs at the fibrotic phase (21D), and prevented the right ventricle hypertrophy.
In conclusion BLM instillation causes local injury with inflammation and alteration of lung vasculature with pulmonary hypertension reflected by right ventricle hypertrophy and related to a reduction in the expression levels of ACEs in the lung, especially ACE2. The precocious LIR treatment in the inflammatory phase prevented all these pathogenic alterations.

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GP53

Clinical, laboratory and cardiac parameters in overt primary hypothyroidism versus overt central hypothyroidism

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Background
Hypothyroidism affects cardiac function, leading to cardiomyopathy, pericarditis, lower left ventricular performance, etc. The present study investigates different parameters (clinical, hormonal, biochemical, echocardiographic) in overt primary hypothyroidism (OPHypo) and overt central hypothyroidism (OCHypo).
Material and methods
The study included 33 untreated patients with OCHypo (5 with empty sella, 3 with idiopathic hypopituitarism, 7 with Sheehan's syndrome, 18 with different types of pituitary macroadenomas, before or after surgery) and 67 cases with OPHypo, respectively with chronic autoimmune thyroiditis. Among the patients with OCHypo, 4 presented partial pituitary insufficiency (2 cases on gonadotropins and TSH secretion and 2 cases on growth hormone and TSH secretion), the rest of the cases showing global pituitary insufficiency. Patients with acromegaly and Cushing's disease were excluded.
Results
The clinical picture was more severe in OPHypo as in OCHypo (dominated by fatigue, edema, dry skin, neurological alterations). The values of serum thyroxin were significantly lower in OPHypo ($P<0.0001$). 40% of OPHypo patients presented pericarditis, as compared to OCHypo (2 cases, $P=0.0003$). No statistical differences were noted between the two groups, regarding heart rate, systolic and diastolic blood pressure values, isovolumic contraction time. Nonetheless, the isovolumic relaxation time was significantly higher in OPHypo group (91.8 ± 8.5 ms), as in OCHypo (80.2 ± 9.9 ms, $P<0.0001$). Coronary artery disease was more common in OPHypo group (21 cases, 31.3%), as compared to OCHypo (5 cases, 15.1%, $P=0.095$). Hyponatremia was recorded in 4 patients with OPHypo and in 3 cases with OCHypo ($P=0.68$). The values of serum total cholesterol, LDL-cholesterol, glycemia, creatin-kinase, transaminases, creatinine were significantly higher in OPHypo group, correlated to lower values of serum thyroxin. The incidence of anemia was similar in both groups (18 cases in OPHypo group, 6 cases in OCHypo group, $P=0.456$).
Conclusion
The metabolic and cardiac parameters were more profound altered in primary hypothyroidism, as compared to central hypothyroidism.

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GP54

Correlation between triglyceride glucose index (TyG) and coronary artery calcification in Korean adults

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Objective
Triglyceride glucose (TyG) index is considered a surrogate marker of insulin resistance, and insulin resistance is known risk factor of cardiovascular disease. Until now, few studies have investigated the relationship between TyG index and coronary artery calcification (CAC), thus we investigated the correlation between TyG index and CAC in healthy Korean Adults.
Methods
A total of 4,463 participants underwent cardiac computed tomography in health promotion center were enrolled. TyG index was calculates as ln[fasting triglycerides(mg/dl) X fasting glucose(mg/dl)/2]. Multi-detector CT was used to measure coronary artery calcium score (CACS) and CACS > 0 was defined as the presence of CAC.

Results
There were significant differences in cardiovascular parameters among the groups and the prevalence of CAC significantly increased with TyG index levels. In the logistic regression analysis after adjusted for multiple risk factors, the odds ratios (95% CI) for the prevalence of CAC were 1.0, 1.03 (0.72–1.45), 1.23 (0.85–1.74), 1.68 (1.15–2.44) for increasing TyG index level ($P<0.05$).
Conclusion
There was a significant association between TyG index and prevalence of CAC. TyG index, a simple measure reflecting insulin resistance, might be useful to the indicator of atherosclerosis. TyG index is even simple to calculate and seems a useful marker of atherosclerosis, and reflect cardiovascular risk.

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GP55

Both oral and vaginal combined hormonal contraceptives induce unbeneficial metabolic effects in women with PCOS: a randomized study

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Oral combined hormonal contraceptives (CHCs) have been suggested to induce more unbeneficial metabolic effects than vaginal CHCs. CHCs are used routinely to treat the clinical symptoms of polycystic ovary syndrome (PCOS), but there are no studies investigating whether the vaginal route is safer in women with known metabolic risks.
Twenty-five women with PCOS defined according to the Rotterdam criteria were randomized to use either oral contraceptive pills (desogestrel-ethinylestradiol) ($n=14$) or contraceptive vaginal rings (etonogestrel-ethinylestradiol) ($n=11$) continuously for 9 weeks. Blood samples were drawn and OGTT performed at baseline and at 9 weeks.
Serum levels of SHBG increased and consequently the free androgen index (FAI) decreased in both study groups from baseline to 9 weeks of treatment [oral: 3.2 (95% confidence interval, CI: 2.2; 4.3) to 0.7 (0.5; 1.0); vaginal: 3.8 (1.8; 5.8) to 0.6 (0.5; 0.8), $P\leq0.003$ in both groups]. Insulin sensitivity was reduced at 9 weeks according to the Matsuda index [oral: 2.5 (0.1; 4.8) to 0.2 (0.2; 0.3), $P=0.035$]; vaginal: 3.0 (0.4; 4.4) to 0.2 (0.1; 0.2), $P=0.366$]. Serum levels of triglycerides [oral 0.9 (0.7; 1.2) to 1.3 (0.8; 1.8) mmol/l, $P=0.132$; vaginal 0.8 (0.6; 1.0) to 1.3 (0.9; 1.7) mmol/l, $P=0.003$] hs-CRP ($P=0.034$) and the AUCglucose during the OGTT ($P=0.017$) rose significantly only in the vaginal group. The AUCinsulin (oral: $P=0.36$, vaginal: $P=0.16$) increased non-significantly from baseline to 9 weeks in both treatment groups. There were no differences in serum levels of glucose, insulin, hs-CRP, lipids or testosterone between the treatment groups at baseline or after 9 weeks.
Against our hypothesis, vaginal CHCs were not metabolically safer than oral CHCs. These results emphasize the importance of monitoring glucose metabolism during CHC use regardless of the route of administration, especially in PCOS women displaying typically risks of type 2 diabetes or cardiovascular diseases.

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GP56

PCSK9 in relation to coronary damage severity in patients with cardiovascular disease

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Proprotein convertase subtilisin/kexin type 9 (PCSK9), a circulating protein that promotes degradation of the low density lipoprotein (LDL) receptor, has been emerged as a novel therapeutic target for the dyslipidemia. It is well known that the pathogenesis of cardiovascular disease (CVD) involves lipid metabolism alteration, but the predictive value of circulating PCSK9 level concerning coronary disease severity is largely unknown. The main objective of this study is to determine whether circulating PCSK9 concentration is linked to coronary damage severity in patients with acute coronary syndrome (ACS). We studied 137 patients with ACS who underwent coronary angiography. The study population was divided into two groups depending on the presence of coronary artery lesion (lesion (+): $n=112$, lesion (−): $n=25$). Baseline characteristics and PCSK9 levels were measured and coronary lesions were evaluated using the SYNTAX scoring system. After adjustment for established CVD risk factors including age, body mass index (BMI), total cholesterol and low-density lipoprotein-cholesterol (LDL), ACS patients with coronary artery lesion have significantly higher PCSK9 levels than patients without lesion (178.26 ± 63.9 ng/ml vs. 223.0 ± 76.1 ng/ml, $P=0.026$). Spearman's correlations revealed that PCSK9 was positively associated with the number of involved coronary artery (Pearson coefficient, 0.034; $P=0.01$) and the global registry of acute coronary events (GRACE) risk score which is a risk prediction tool applicable for ACS patients (Pearson coefficient, 0.209; $P=0.015$). Furthermore, we found that plasma PCSK9 level was positively correlated with SYNTAX score (Spearman's $R=0.115$, $P=0.048$). In the present study, we show that Serum PCSK9 concentration is associated with angiographic severity of ACS and GRACE score after adjustments for established CVD risk factors. Further studies are needed to confirm this observation.

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GP57

Clinical significance and hormonal relationships of visceral adiposity index (VAI) in independently living old subjects

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Introduction
The Visceral Adiposity Index (VAI) has been proven to be an indicator of adipose distribution and function that indirectly expresses cardiometabolic risk, in particular in specific populations such as women with polycystic ovary syndrome, acromegaly or type 2 diabetes. Little information is known about its usefulness in the definition of cardiometabolic risk in ageing population.
Objective
To study VAI in relation to metabolic and hormonal data, frailty and mortality in non-institutionalized people more than 70 years old of the Mataró Ageing Study.
Methods/Design
289 participants (142 men/147 women) were included. Individuals were characterized by anthropometric variables, metabolic syndrome (MS) parameters by IDF and ATP-III as well as hormonal factors (TSH, free-T4, growth hormone, IGF-I, ghrelin, cortisol, dehidroepiandrosterone –DHEA-, DHEAs, testosterone, SHBG, estradiol, estrone, cortisol/DHEA and cortisol/DHEAs), grip strength, Barthel and assessment of cognitive impairment (MiniCognoscitive Examination -MCE- Spanish version) and frailty by Fried criteria. VAI was calculated according to Amato et al.
Results
The whole cohort showed a statistically significant association of the individual components the MS with VAI. In women but not in men, a lineal trend association was observed between the prevalence of diabetes and VAI categorized in quartiles. However, VAI showed no association in our sample population with the presence of cardio or cerebrovascular disease. The multiple regression analysis showed that ghrelin ($B=-0.240$, $P=0.005$) and SHBG ($B=-0.199$, $P=0.034$) were the only hormonal variables independently associated to VAI in women, while no associations were found in men. After a prospective follow-up of two years, those individuals with higher VAI at basal time point were associated to frailty condition at two years (media (SD): 2.47 (2.19) in frail vs 1.71 (0.97) in non-frail, $P=0.064$). No significant association was found between VAI and mortality 2 and 8 years follow-up.
Conclusions
VAI does not provide additional information to MS criteria in ageing individuals in relation to cardiovascular risk or mortality in our population. However, VAI was associated to frailty in the whole cohort, and in women, with diabetes and ghrelin.

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GP58

Circulating levels of miR24-1 cluster microRNAs are increased in primary aldosteronism

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Introduction
Measurement of microRNA (miRNA) in aldosterone-producing adenoma (APA) tissue from primary aldosteronism (PA) patients show levels of the miR24-1 cluster miRNAs (i.e. miRNAs 24-1, 27b and 23b) are significantly reduced relative to normal adrenal tissue. Our previous studies also show that miRNA-24 directly targets *CYP11B2* (aldosterone synthase) gene expression. Circulating miRNAs released into the bloodstream may be diagnostic biomarkers or signalling molecules. Here, we assessed whether circulating levels of miR24-1 cluster miRNAs differ significantly between PA patients and essential hypertensives, and whether they correlate with relevant phenotypic traits.
Methods
Patients with essential hypertension patients ($n=18$) were drawn from the British Genetics of Hypertension (BRIGHT) study and matched with 18 confirmed PA patients for age, gender and systolic blood pressure. Circulating miRNA was isolated from 200 μL EDTA plasma and analysed using quantitative realtime assays for miRNAs 24, 27b and 23b.
Results
PA patients had significantly increased circulating levels of miRNAs 24 ($P<0.05$) and 23b ($P<0.0001$) relative to primary hypertensive patients; there were also trends towards higher miRNA-27b but this was not significant. MiRNA-23b negatively correlated with diastolic pressure ($P<0.05$), left ventricular mass ($P<0.01$) and age ($P<0.05$). MiRNAs 27b and 23b positively correlated with BMI ($P<0.05$).
Conclusions
We have identified and validated increased circulating miR24-1 cluster miRNA levels in PA patients. These contrast with the significantly reduced levels of these miRNAs observed in APA tissue. Interestingly, miR-24 has been proposed to act as a feedback signal, repressing *CYP11B2* expression when aldosterone levels are high. Therefore, increased secretion of these miRNAs into the circulation may be the result of high aldosterone levels and be intended to suppress its release. Future studies will examine the role of these miRNAs in the aetiology and pathology of PA.

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GP59

Body composition and testosterone determined VO2max in 780 young men – results from the Odense Androgen Study

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Background
Cardiorespiratory fitness is a measure for physical activity and a prognostic health indicator. However, measurement of maximal oxygen consumption (VO2max) is not possible in clinical practice.
Aim
We hypothesized that body composition and testosterone levels could be used as possible determinants of VO2max in young men.
Participants and design
The Odense Androgen Study, a population-based, observational study including 780 men aged 20–30 years. VO2max (ml/min/kg 0.73) was indirectly measured by a mechanically braked cycle ergometer. Fat mass (%) and lean body mass (%) were assessed by whole-body DXA scans. Total testosterone levels (nmol/l) were measured (RIA using extraction and chromatography). SHBG levels (nmol/l) were determined by immunoluminometric assay. Bioavailable and free testosterone were calculated.
Results
Descriptive data of the subjects were BMI 24.4 kg/m^2 (22.4–26.6), waist 88 cm (82–94), percentage lean body mass 79.1% (75.6–82.5), percentage fat mass 17.2% (18.8–21.1), total testosterone 20.7 nmol/l (17.0–25.4), SHBG 27 nmol/l (21–34) and VO2max 160.3 ml/min/kg 0.73 (143.3–177.6) (median (interquartile range). In bivariate analysis, lean body mass (%) ($r=0.62$), SHBG ($r=0.26$), total testosterone ($r=0.24$), and free testosterone ($r=0.13$) were positively associated with VO2max, whereas fat mass (%) ($r=-0.63$) and waist ($r=-0.47$) were negatively associated with VO2max (all $P<0.001$). Fat mass (%) and lean body mass (%) were closely associated ($r=-0.998$, $P<0.001$). In multivariate regression analysis, models with VO2max as the dependent variable and lean body mass (%) or fat mass (%) as independent variables were the best predictors of VO2max (both models $R2=0.47$), whereas the models including testosterone (total, free or bioavailable testosterone) or SHBG as independent variables had lower R2 values ($R2=0.09$–0.13). All models were adjusted for age and smoking.
Conclusion
Body composition measures were the best predictors of VO2max in young men. VO2max was more closely associated with waist than testosterone or SHBG.

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GP60

Probiotics and nutraceuticals as a new frontier in obesity prevention and management

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Introduction
The beneficial interaction between the microbiota and humans is the way how bacteria contained within the gut 'talk' to the immune system. Into this landscape probiotics and nutraceuticals play a major role. The study **aims** to determine whether probiotics plus nutraceuticals such as smectite or omega-3 are superior to probiotic alone on the monosodium glutamate (MSG) induced obesity model in rats.
Methods
Totally 75 rats divided into five groups were included ($n=15$, in each). Rats of group I were intact. Newborns rats of groups II-V were injected with MSG. The III (Symbiter) group received 2.5 ml/kg of multiprobiotic "Symbiter" containing concentrated biomass of 14 probiotic bacteria genera. The IV (Symbiter-Omega) and V (Symbiter + Smectite) groups received combination of probiotic biomass supplemented with flax and wheat germ oil (250 mg of each, concentration of omega-3 fatty acids 1–5%) or smectite gel (250 mg) respectively. Anthropometric, biochemical parameters of lipid and carbohydrate metabolism, and level of proinflammatory cytokines (IL)-1β, IL-12Bp40, INF-γ) and anti-inflammatory cytokines (IL-4, IL-10, TGF-β) were measured.
Results
In all interventional groups significant reduction of total body and VAT weight as compared to MSG-obesity were observed. However, the lowest prevalence of obesity was noted for Symbiter-Omega (20% vs 33.3% as compared to other interventional groups). Moreover, supplementation of probiotics with omega-3 lead to more pronounced decreasing of HOMA-IR (2.31 ± 0.13 vs 4.02 ± 0.33, $P<0.001$) and elevation of adiponectin level (5.67 ± 0.39 vs 2.61 ± 0.27, $P<0.001$) as compared to obesity group. Both nutraceuticals combination with probiotic and probiotic alone equally attenuated inflammation that was confirmed by the decrease of the pro-inflammatory and the activation of anti-inflammatory system.
Conclusion
Probiotics and nutraceuticals led to a significantly lower prevalence of obesity, reduction of insulin resistance, total and VAT weight. Our study demonstrated that supplementation of probiotics with omega-3 may have most beneficial antiobesity properties.

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GP61

Constructing a long-acting leptin analogue

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Introduction
Leptin is a 16-kDa peptide hormone secreted by adipose tissue and acts as a sensor for energy stores. It feedsback at the hypothalamic arcuate nucleus to suppress appetite. Leptin treatment has been highly effective in suppressing appetite in the rare cases of leptin-deficient obesity and improving the metabolic profile in congenital generalised lipodystrophy. These patients require 2.5–10 mg once daily recombinant leptin treatment. We hypothesised that prolonged constant exposure to leptin with a long acting leptin may have a more potent metabolic action and appetite supression and therefore we designed a long acting leptin molecule.
Aim
To construct, express, purify and test for bioactivity a long acting leptin.
Methods
We have previously demonstrated that a fusion of growth hormone to growth hormone binding protein (GHBP) generated a long acting GH. In this project we utilise GHBP as a fusion partner with leptin the concept being that linking a fusion protein to the C-terminus will decrease clearance through reduced proteolysis and renal clearance. We further modified this molecule by introducing a W104A (Tryptophan-Alanine amino acid substitution) in the GHBP to prevent GHBP binding to GH in the circulation.
Results
GHBP(W104A)-leptin fusion was cloned in to a modified invitrogen pSecTag plasmid with the secretion sequence for leptin. This plasmid was transfected into CHO Flp-In cells by reagent-mediated transfection. Protein was expressed in CHO cells grown in roller bottles in the presence of valproic acid at a set temperature of 31 °C and purified by antibody affinity chromatography. *In vitro* bioactivity was assessed by luciferase expression induced by leptin. Approximately two times fold induction was achieved.
Conclusion
We have demonstrated it is possible to generate a fusion of leptin to GHBP and that this fusion retains bioactivity. Future studies will assess pharmacodynamic and pharmacokinetic properties of this molecule.

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Developmental & Protein Endocrinology

GP62

Effects of prenatal dexamethasone on fetal rat ovary

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Glucocorticoids affect the growth and maturation of fetal organ systems, but overexposure to exogenous glucocorticoids retard fetal growth and may alter developmental process in sensitive tissues. On the other hand, fetal ovary is not characterized by definitive follicular structure, but the clusters of germinative cells are predominant. Germ cells may be in meiotic prophase or with sign of degeneration.
The aim of this study was to determine whether prenatal exposure to dexamethasone (Dx) altered normal structure and development of ovary in 19 day old rat fetuses. Pregnant females in the experimental group received subcutaneous injections of 1.0, 0.5 and 0.5 mg Dx /kg body weight on days 16–18 of pregnancy. Control mothers were injected with the same amount of saline. On day 19 of pregnancy, the dams and their fetuses were sacrificed under ether anesthesia and the fetuses were referred to as 19-day-old fetuses. Fetal ovaries were prepared for further stereological examination.
The volume of the fetal ovary estimated using Cavalieri's principle was significantly reduced after exposure to Dx by 22% ($P<0.05$) in comparison with control ovary. Using a fractionator-physical disector method, a reduction in total number of germ cells in meiotic prophase by 43% ($P<0.05$) was observed, while total number of germ cells with sign of degeneration increased by 54% ($P<0.05$), when compared with control values.
Overexposure to dexamethasone during fetal development intensifies the process of degeneration of germ cells in the ovary, contributing thus the reduction of reproductive potential for the individual.

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GP63

Does the loss of RAD52 in PC contribute to resistance to antiandrogen therapy?

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Recent statistics indicate that prostate cancer (PC) is the most frequent cancer in men worldwide and is the leading cause of cancer death in men above 50 years of age. The Androgen receptor (AR), a member of the superfamily of nuclear hormone receptors, plays a well-established role in the development and progression of the disease. PC localized to the prostate is commonly treated with surgical removal of the gland and is often associated with a favorable outcome. However, metastatic PC requires more aggressive treatment modalities often consisting of gonadotropin releasing hormone (GnRH) agonists and/or an AR antagonist (ex: bicalutamide). Although initially successful in alleviating symptoms, the disease progresses to a castrate resistant state, where drugs targeting the AR axis have limited clinical utility. Several mechanisms were suggested to explain resistance to antiandrogen treatment including AR mutations, AR amplification and/or local production of androgens. Additionally, some studies also suggest that deregulation of AR cofactor expression may permit weak androgens or even antiandrogens to function as full AR agonists and fuel tumor growth, a mechanism that contributes to the castrate resistance phenotype. This puts into context our observation that RAD52, a protein involved in DNA repair machinery also functions as an AR cofactor whose deregulation affects PC response to antiandrogens. Herein, using PC cell models, we found that knockdown of RAD52 increases AR protein levels and enhances AR transcriptional activity in the presence of low levels of androgens. More importantly, we found that RAD52 knockdown converts the AR antagonist bicalutamide into a full agonist in cell reporter assays and on AR target genes; an activity associated with enhanced recruitment of AR to target gene promoters. Taken together, our results suggest that deregulation of RAD52 expression may mediate PC resistance to antiandrogen therapy.

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GP64

Thyroid hormone protects hepatocytes from HBx-induced carcinogenesis by enhancing mitochondrial turnover

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Infection by hepatitis B virus (HBV) accounts for 50∼80% of hepatocellular carcinoma (HCC) development worldwide, in which the HBV encoded X protein (HBx) plays critical role in the induction of carcinogenesis. Several studies have shown that thyroid hormone (TH) suppresses HCC development and protects hepatocytes from HBx induced damage, thus it is of interest to examine whether TH can protect hepatocytes from HBx-induced carcinogenesis. By treating HBx-transgenic mice with or without TH, we confirmed the protective effects of TH on HBx-induced hepatocarcinogenesis, which was achieved via reduction of ROS inflicted DNA damage. We further found that TH induced biogenesis of mitochondria (MITO) and autophagy of HBx-targeted mitochondria simultaneously, consequently leading to suppression of HBx-promoted ROS and carcinogenesis. Using microarray data analysis, this protective effect of TH was found to be mediated via activation of PTEN-induced kinase 1 (PINK1) in hepatocytes. PINK1, in turn, activated and recruited Parkin, an E3 ligase, to ubiquitinate MITO-associated HBx protein and trigger selective mitophagy. The pathological significance of the TH/PINK1 pathway in liver protection was confirmed by the concomitant decrease in expression of both TR and PINK1 in matched HCC tumor tissues and negatively correlated with aggressive progression of cancer and poor prognosis. Our data indicates that TH/PINK1/-Parkin pathway plays a critical role in protecting hepatocytes from HBx-induced carcinogenesis. Notably, several liver-targeting therapeutic derivatives of thyroid hormone facilitating prevention or therapy of steatosis have been identified. Furthermore, our proof-of-concept experiments suggest that application of T3 constitutes an effective novel therapeutic or preventive option for HCC. Thus, the

utilization of the agonists of TRs could be the meaningful strategy in liver relative diseases, ranging from simple hepatic steatosis to HCC.

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GP65

3-year safety and efficacy Update of the VERTICAL & VISTA trials of somavaratan (VRS-317), a long-acting rhGH, in children with Growth Hormone Deficiency (GHD)

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Requirement for daily rhGH injections is a treatment burden that can compromise adherence and efficacy in patients with GHD. Somavaratan is a novel long-acting rhGH fusion protein in clinical development for pediatric and adult GHD. In a multicenter, randomized Phase 1b/2a study, somavaratan significantly improved height velocity (HV) and IGF-I in pre-pubertal children with GHD. Preliminary efficacy and safety in subjects who have completed 3 years of somavaratan treatment are presented. Of 64 subjects randomized in the Phase 2a VERTICAL study to receive 5.0 mg/kg/month (weekly/twice-monthly/monthly dosing) for 6 months, 60 elected to continue treatment in the long-term safety study, VISTA. Initial IGF-I response supported a dose increase, and all subjects transitioned to somavaratan 3.5 mg/kg twice-monthly by the 2nd treatment year. Data cutoff was December 8, 2016. Of 48 subjects (24 males, 24 females), the mean ± SD age was 7.6 ± 2.4 years, and mean IGF-I SDS was −1.6 ± 0.8 at baseline. In Year 3, IGF-I SDS increased to 1.2 ± 1.7 at peak (3–5 days post-injection) and −0.3 ± 1.0 at trough (end of dosing cycle). Mean HV remained consistent during Years 1, 2, and 3, at 8.4 ± 2.0, 8.3 ± 1.6, and 7.8 ± 1.6 cm/year, and height (HT)-SDS continued to increase from −2.6 ± 0.6 at baseline to −2.1 ± 0.6, −1.6 ± 0.7, and −1.2 ± 0.8; delay in bone age (years) was −1.48 ± 0.81 at baseline, −1.34 ± 0.89 (Year 1, $n=48$), −1.09 ± 1.02 (Year 2, $n=47$), and −0.66 ± 0.82 (Year 3, $n=25$). Treatment-related AEs were generally transient and mild. Overall, IGF-I, HV, HT-SDS, and bone age showed continued improvement through 3 years of somavaratan treatment in pre-pubertal children with GHD. Dose increase to somavaratan 3.5 mg/kg twice-monthly resulted in consistent growth rates through 3 years of treatment, and overall Year 3 growth was consistent with daily rhGH from US registries. A Phase 3 study of somavaratan 3.5 mg/kg twice-monthly in treatment-naïve GHD children is ongoing.

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GP66

Achievement of a suitable basis of comparison in phase 2 and 3 clinical trials (VERTICAL/VISTA, and VELOCITY) comparing somavaratan vs daily rhGH for pediatric GH deficiency

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Efficacy of rhGH for treatment of pediatric GH deficiency (PGHD) may depend on several variables at treatment initiation (age, body weight, height velocity (HV), IGF-I SDS, skeletal maturation, GHmax), but may be compromised by poor adherence to required daily injections. Somavaratan is a novel, long-acting rhGH fusion protein that demonstrated clinically meaningful improvements in HV and IGF-I concentration in PGHD patients. Over 200 pre-pubertal GHD subjects have enrolled in somavaratan trials to date, including 137 in the Phase 3 noninferiority VELOCITY trial comparing somavaratan vs daily rhGH. In the randomized Phase 1b/2a VERTICAL study in pre-pubertal children with GHD, primary determinants of Year 1 HV included age at treatment initiation and GHD severity. To achieve a valid basis of comparison of efficacy outcomes across trials (VELOCITY, VERTICAL, VISTA (long-term safety)), distribution of clinical characteristics known to affect HV should be similar between treatment arms (somavaratan vs daily rhGH) and between trials. The same primary efficacy endpoint (HV) and similar eligibility criteria were used across trials. Stratification for Phase 3 randomization (somavaratan vs daily rhGH) was based on region, expected age, and expected baseline IGF-I SDS. In VELOCITY ($n=104$ somavaratan; $n=32$ daily rhGH), mean ± S.D. baseline ages were 7.07 ± 2.0 vs 7.03 ± 2.4 years, respectively, mean GHmax 5.77 ± 2.6 vs 5.87 ± 2.5 ng/ml, mean height-SDS −2.76 ± 0.7 vs −2.64 ± 0.7, mean IGF-I SDS -1.72 ± 0.7 vs −1.87 ± 0.9, and mean bone ages 5.28 ± 1.9 vs 5.29 ± 2.2 years. In VERTICAL (N = 64), mean age was 7.8 ± 2.4 years, mean height-SDS −2.6 ± 0.6, mean IGF-I SDS −1.7 ± 0.8, and mean bone age 6.4 ± 2.4 years. No clinically meaningful differences in baseline characteristics were noted between trials, or between VELOCITY treatment arms. Collectively, similar populations were achieved between trials by use of consistent eligibility and stratification procedures. This allowed balanced treatment arms for clinical characteristics that may influence the primary efficacy outcome, thereby achieving a valid basis of comparison between trial populations.

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GP67

Karyotype and mid-childhood gonadotropin concentrations in prediction of spontaneous puberty in Turner syndrome patients

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Gonadotropin levels in all Turner syndrome (TS) patients present a diphasic pattern: highest in early childhood, declining at 6–10 years of age, and then increasing again. Here, we have investigated whether karyotype or FSH&LH can be used as indicators of spontaneous puberty in TS. From a consecutive group of 139 TS girls treated at one clinical center (1996–2015) the clinical & biochemical data were finally analyzed in 110 TS patients (1268 visits). The study population was divided into two subsets based on karyotype (type A- 45X, 54%; type B- others excluding 45X/46XY). The mean diagnosis age and duration of follow-up were 10.7 ± 4.0 and 5.9 years, resp. The average number of visits was 10.4. Spontaneous puberty was confirmed in 48.2% and menarche in 20%, both less common in group A than B (31.1% and 9.8.% vs 69.4% and 32.6%, resp., $P<0.05$). The mean age of Tanner B2 and menarche in all girls were 13.7 ± 2.4 and 14.2 years, no difference between the groups (13.5 ± 2.5 and 13.2 ± 1.0 years (A) vs 13.8 ± 2.3 and 14.6 ± 1.7 years (B), $P>0.05$). The median FSH and LH values in all patients at the age of 6–10 were 8.16 and 0.35 IU/l resp., significantly lower comparing to younger (44.6 and 0.76 IU/l) and older (93.0 and 16.1 IU/l) age ($P<0.0001$). LH were similar in both groups, whereas in group B FSH values were significantly higher only in the older age. At the age of 6–10 FSH and LH levels ≥than 6.7 and 0.2 resp. decrease the chance of spontaneous menarche (33.3% vs 13.9% and 28.6% vs 11.8%). Conclusion: Nearly half of our TS patients showed spontaneous puberty symptoms and every fifth had spontaneous menarche with higher frequency in non-45,X girls. The diphasic pattern of FSH&LH was confirmed, however using their cut-off values one can predict the chance for spontaneous menarche.

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GP68

Assessment of reports of behaviour by patients and their parents in paediatric Cushing disease

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Context
Prior studies of children with endogenous Cushing syndrome (CS) have identified cognitive decline despite reversal of brain atrophy after remission as well as residual impairment of quality of life measures. Although parental observations support personality changes with CS, significant psychopathology has not been described. We investigated the feasibility of using paediatric Patient-reported

outcomes (PROMIS) using a computer interface to assess patient perception of burden of illness and correlation with parent proxy report using Child Health Questionnaire (CHQ).
Setting
Subjects were enrolled in a clinical protocol at the National Institutes of Health Clinical Center in Bethesda, MD, USA.
Method
We report 9 children (6F, 12±3.5 years) diagnosed with Cushing disease (CD). Prior to surgical treatment, subjects completed paediatric PROMIS measures and parents completed CHQ using an online secure website.
Results
PROMIS measures scores (mean±S.D.): anxiety (54±9), depression (55±11) anger (50±9), and emotional support (52±10) (higher scores indicate more of the concept being measured); CHQ total Psychosocial score (mean±S.D.) (43±10) (lower values are associated with a greater deficit in functioning). A significant correlation was found between Psychosocial summary score of CHQ and paediatric PROMIS measures of anxiety ($r=-70.5$; $P<0.03$) and depression ($r=-0.9$; $P<0.002$). No correlation was found between urinary free cortisol level or midnight serum cortisol and PROMIS measures.
Conclusion
Prior to treatment for CS, a significant correlation was found between children's endorsement of anxiety and depression symptoms and parental proxy report of psychosocial function. Our findings support that paediatric PROMIS measures represent feasible and potentially valuable instruments for future studies to assess behavioural symptoms in children diagnosed with CS prior to and after treatment.
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GP69

5β-reductase (AKR1D1) is a potent regulator of carbohydrate and lipid metabolism and inflammation in human liver
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Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic disease. 5β-reductase (AKR1D1) is highly expressed in human liver where it inactivates steroid hormones and catalyzes a fundamental step in bile acid synthesis. Steroid hormones, including glucocorticoids, as well as bile acids are established regulators of metabolic phenotype. We hypothesized that AKR1D1 plays a crucial regulatory role in hepatic metabolic homeostasis. Genetic manipulation of AKR1D1 (over-expression, siRNA knockdown) was performed in human liver HepG2 and Huh7 cells. Gene expression changes were confirmed by qPCR. Functional activity, assessed using gas chromatography mass spectrometry to measure cortisone clearance and tetrahydrocortisone generation was paralleled by the anticipated changes in glucocorticoid receptor activation measured by luciferase reporter assays. AKR1D1 knockdown in HepG2 cells increased glucose transporter mRNA expression and extracellular glucose concentrations in the cell media decreased (15.3±1.5 vs 12.1±0.9 μmol/mg, $P<0.05$) while intracellular glycogen levels were increased (18.9±0.3 vs 22.7±0.3 μg/ml, $P<0.05$). AKR1D1 knockdown increased Fatty Acid Synthase and Acetyl CoA Carboxylase 1 expression, the rate-limiting step in *de novo* lipogenesis, DNL) (0.52±0.06 vs 0.89±0.04, $P<0.01$), and increased intracellular triglyceride (54.3±12.7 vs 73.3±11.0 nmol/mg, $P<0.01$). Furthermore, 3-hydroxybutyrate levels in the cell media were reduced, indicative of impaired fatty acid oxidation (18.7±2.3 vs 11.4±2.7 nmol/mg, $P<0.01$). Mass spectrometry analysis of lipid composition demonstrated increased palmitic and palmitoleic acid production consistent with increased DNL and fatty acid saturation. In addition, bile acid composition was altered with a significant increase in chenodeoxycholic acid levels. Conversely, pharmacological manipulation of the bile acid receptors FXR and LXR using the FXR agonist GW4064 and LXR antagonist 22-S-Hydroxycholesterol rescued HepG2 cells from metabolic dysfunction by reducing the expression of lipogenic genes. Furthermore, AKR1D1 knockdown increased proinflammatory cytokine IL-1, IL-6 and IL-8 mRNA expression; changes were confirmed by elevated cell media IL-8 levels (4.68±0.70 vs 13.39±2.28 ng/ml, $P<0.05$), increased IκBα degradation and induced IRE-1α protein expression, indicative of inflammation and cellular ER stress. In conclusion, AKR1D1 activity regulates steroid hormone and bile availability, potently modulating hepatic carbohydrate and lipid metabolism in addition to an inflammatory phenotype suggesting a crucial role in the pathophysiology of NAFLD.
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GP70

The adverse effects of prescribed glucocorticoids are worsened by co-administration of 5α-reductase inhibitors
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Introduction
Glucocorticoids (GC) are prescribed to 2–3% of the population of the UK and USA. Their use is associated with a significant side effect profile that includes the development of central obesity, insulin resistance and type 2 diabetes. 5α-reductase (5αR) inhibitors (Finasteride and Dutasteride) are also commonly prescribed in the context of prostate disease, where they inhibit the conversion of testosterone to dihydrotestosterone. Additionally, they have a role to inactivate and clear GC. We have therefore hypothesised that 5αR inhibitors have the potential to exacerbate the adverse metabolic effects of GC.
Methods
We conducted a prospective, randomised, study in 19 healthy male volunteers (age; 45±8.5 years, BMI; 27.1±3.1 kg/m^2). Participants underwent detailed metabolic assessments including a 2-step hyperinsulinaemic euglycaemic clamp incorporating stable isotopes, adipose tissue microdialysis and biopsy. They were then randomised to receive either prednisolone (10 mg OD) or prednisolone (10 mg OD) and a 5αR inhibitor (finasteride 5 mg OD or dutasteride 0.5 mg OD) for 7 days, metabolic assessments were then repeated.
Results
We have previously shown that high dose parenteral GC administration decreases glucose utilization (M value; 3.1±0.4 vs 1.6±0.1 mg/kg per min, $P=0.001$) and 5αR inhibitors alone are without effect (M value; 3.5±0.4 vs 3.3±0.4 mg/kg per min, $P=0.42$). In this study, prednisolone only did not alter glucose utilization (M-value; 3.2±1.3 vs 2.8±1.6 mg/kg per min, $P=0.37$), however, co-administration of prednisolone and 5αR inhibitors significantly decreased it (M-value; 4.0±2.0 vs 2.6±1.3 mg/kg per min, $P=0.02$). Similarly, high dose GC, but not 5αR inhibitors alone, impair insulin-mediated suppression of circulating non-esterified fatty acids (NEFA). Prednisolone 10mg OD did not alter insulin-mediated suppression of NEFA (0.15±0.27 vs 0.13±0.13, $P=0.88$), however, co-administration with 5αR inhibitors impaired the ability of insulin to suppress NEFA (0.15±0.1 vs 0.29±0.18, $P=0.01$).
Conclusion
5αR inhibitors exacerbate the adverse metabolic effects of prescribed GCs. This has significant translational implications, not only with regards to the need to consider steroid dose reductions, but also the necessity for increased vigilance for the development of adverse effects.
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Diabetes & Complications 1

GP71

Carbohydrates metabolism and H. pylori: case-control study
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Introduction
H. pylori infection has been related with extragastric diseases such as type 2 diabetes.
Aim
to evaluate changes in carbohydrate metabolism induced by 75g oral glucose tolerance test (OGTT), before and after antibiotic eradication treatment in patients colonized by H. pylori compared to healthy controls.
Materials and methods
A prospective case-control study. Biochemical parameters, carbohydrate profile, ghrelin and GLP1 levels before and after antibiotic eradication treatment were analyzed.

Results
We studied 40 cases and 21 controls (60% and 57.1% women, respectively). Mean age: 46,95±2,02 vs 44,52±2,73 years, family history of digestive disorders: 70% vs 57.1% and clinical history of gastrointestinal disease: 57,5% vs 42.9%, respectively. After antibiotic treatment, significant improvements in HbA1c ($P=0,014$), glucose levels post OGTT at 60′ and 120′ ($P=0,018$ and $P=0,019$, respectively) and HDL Cholesterol ($P=0,021$) were observed. Significant changes in basal ghrelin levels ($P=0,05$) were found, but C peptide levels did not change. We observed differences between infected population by H. pylori and healthy people: lower post OGTT insulin levels at 30′ and 60′ ($P=0.042$ and $P=0.03$, respectively) in infected patients. Those differences disappeared after treating the infection. In cases and controls, we found significant positive correlations in carbohydrate metabolism, and significant negative correlations in controls between ghrelin with basal insulin and C peptide. No significant correlations respect to GLP1 were found. 90% of patients completed correctly the treatment, 31,6% needed ranitidine and 97,5% eradicated H. pylori after conventional antibiotic treatment.
Conclusion
1) H. pylori eradication improved carbohydrate metabolism. 2) Significant positive correlations in carbohydrate metabolism in cases and controls were found. 3) Negative correlations between ghrelin and pancreatic reserve were observed in cases. 4) Carbohydrate metabolism differences between healthy and infected people disappeared after eradication treatment. 5) More than 95% of patients achieved H. pylori eradication with conventional antibiotic treatment.
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GP72

Specific plasma amino acids alternations associated with metabolic syndrome
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Objectives
Amino acids (AA) plasma profile is associated with cardiometabolic diseases (CMD), predicts diabetes mellitus type 2 (DM2) and cardiovascular diseases (CVD) many years in advance. Metabolic syndrome (MS) defines the area of metabolic disturbances that precede DM2 and CVD development. The primary objective of the study was to examine the association between BCAA (branched chain amino acids), AAA (aromatic amino acids) profile and MS's phenotype and to evaluate its clinical utility for MS diagnosis.
Methods
263 healthy, professionally active men, with and without MS (MS+, $n=165$; MS−, $n=98$) were included into the study. Anthropometrical, biochemical and AA measurements were performed. AA were tested for the ability to discriminate subjects with MS and insulin resistance irrespectively. Based on logistic discrimination multivariate early MS diagnostic model was built and its discrimination properties were evaluated.
Results
2 functionally independent AA clusters were identified. BCAA and phenylalanine differed strongly between MS+ and MS- participants ($p=0.003$), appeared as significant indicator of MS+ individuals (AUC 0.66; 95%CI: 0.5757–0.7469) and correlated with cardiometabolic factors. No statistical significant differences in AAs concentrations between IR+ and IR− groups were noted and none of the AA group appeared as meaningful IR+ indicator. Proposed MS multivariate diagnostic model consisted of phenylalanine, insulin, leptin, adiponectin and had good discrimination properties – AUC 0,79; (95% CI: 0.7239–0.8646).
Conclusions
MS is associated with selective hiperaminoacydemia that could be a part of CMD pathogenesis. Present study suggests that AA disturbances do not derive directly from insulin sensitivity impairment nor obesity or muscle mass. AA utility for MS diagnosis needs further evaluation. The original outcome of the study became MS diagnostic model creation – MS screen test, with good discrimination properties and that could be validated in the next coming studies.
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GP73

Permanent neonatal diabetes in a 24 year old Spanish patient
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Introduction
Neonatal diabetes mellitus is a rare form of diabetes, diagnosed within the first six months of life. We report a case of a 24-year-old patient with permanent neonatal diabetes.
Case Report
The patient had no relevant family history. Her mother had no gestational diabetes. Personal history included: Normal birth weight, polycystic ovarian syndrome and ovarian teratomas. She was diagnosed of diabetes at 3 months of age, starting immediately with insulin treatment. Glucose control had always been optimal (HbA1c l $<6.7\%$). Acute diabetic complications included: symptomatic hypoglycemias every 3 days, usually after dinner and, less frequently nighttime hypoglycemias. No hyperglycemias that required in hospital management. No chronic metabolic complications. The patient came to our clinic to continue follow up. We completed her work up doing islet antibodies detection (anti GAD65, anti tyrosine phosphatase IA2, anti insulin and anti zinc transporter), and as expected the results were negative. Considering the age of the diagnosis, genetic testing for monogenic forms of diabetes was performed, discovering a heterozygous mutation c.323Ag (pY108C) in INS gene. Family genetic mutation are still pending.
Discussion
Neonatal diabetes mellitus have an incidence of 1 in 500000 live births. Most common genes are KLF 11, ABCC8 and less frequently INS gene (30%, 19% and 14% respectively). Depending on the severity of the mutations insulin bioactivity will be affected, ranging from a decreased biosynthesis to altered transcription. Clinical implications include transient requirement of insulin, later switching to sulfonylureas or even completely stopping hypoglycemic treatment; and permanent insulin treatment. In the latter, the risk of ketoacidosis also depends and the recessive or dominant inheritance.
Conclusions
Monogenic forms of diabetes are uncommon, however it is important to consider them in the differential diagnosis of particular cases. Genetic mutation study is important to assess future treatment options and the risk of ketoacidosis.
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GP74

Rescue study of trapped AVPR2 mutants with chemicals
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Diabetes insipidus (DI) is a disorder that characterized by producing large volume of urine for daily due to the problems at the arginine vasopressin (AVP-NPII), aquaporin 2 (AQP2) and arginine vasopressin receptor 2 (AVPR2) genes. These problems can be inherited or acquired. Among these genes, AVPR2 is a G protein coupled receptor and most of the inherited type of DI are caused by mutations in AVPR2 gene. Mutations can cause improper folding of the receptor protein and this situation causes to retention of the protein in cellular compartments such as endoplasmic reticulum (ER) or Golgi apparatus. For treatment strategies, researchers try to use chemicals to rescue of mutant proteins from the control mechanisms to make them at least functional. In this study, we aimed to do pre-research for the rescuing mutant receptors (R68W, V162A, T273M, R67_G69del/G107W, V88M, R106C, G12E). We performed functional characterization of these mutant receptors in our previous study and they were observed as trapped in the ER or Golgi apparatus. In the present study, COS-7 cells were transfected with mutant and wild type AVPR2s. 48 hours after the transfection, different concentrations of DMSO and glycerol were performed to the cells. 16–18 hours after the treatment of DMSO and glycerol, cell surface ELISA were performed to understand cell surface expression of the mutant proteins when they were treated with different concentrations of DMSO and glycerol. According to the ELISA results, mutant receptors showed different rescue profile compared to the wild type receptor. As a result, we can say that rescuing trapped mutant receptors from ER or Golgi apparatus control mechanisms using with chemicals could be a forward step for the treatment of DI. Receptors that have mutations which cause retention in ER or Golgi apparatus may be functional if they are rescued by chemicals. For further studies, instead of chemicals, pharmacochaperons could be use. We can conclude that, rescue

studies of mutated proteins by using chemicals or pharmacochaperons shed light to the treatment strategies of DI. This work was supported by The Scientific and Technological Research Council of Turkey (Project Numbers: 216S304 and 112S513).

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GP75

GLP-1 acutely regulates carbohydrate and lipid metabolic routes in the liver

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The Glucagon-like peptide-1 receptor is widely expressed in diverse tissues including the liver. GLP-1 contributes itself to the regulation of glucose homeostasis and has important effects in lipid metabolism even preventing liver steatosis induced by high fat diets.
The aim of this study was to analyse the short-term effects of liraglutide on key enzymes of the hepatic energy metabolism.
Thirty-six Sprague-Dawley young adult male rats were studied (weight range 350–400 g). Control rats were fed *ad libitum*, while the fast group (F) were deprived of food for 48 hours, and treated with liraglutide (100 µg/Kg/12 h; CT/LIR; F/LIR) or vehicle (CT/VEH; F/VEH) for 48 hours. Rat body weight was measured at 0, 24 and 48 hours. At 48 h, rats were sacrificed and liver samples were collected and stored at −80 °C until analysis. mRNA expression of G6P, PCK-1, DGAT-1, GPAT4, CPT1A and ACACA in the liver were assessed by real time PCR.
CT/LIR rats gained less body weight (−6.4 g/100 g, $P<0.0001$) than CT/VEH at 24 h and still less at 48 h (−2.9 g/100 g, $P<0.0001$). The expression levels of G6P and PCK-1, key enzymes in gluconeogenesis, decreases in rats treated with liraglutide by a 58% ($P<0.05$) and 75% ($P<0.01$) respectively. On the other hand, DGAT-1 and GPAT4 levels, involved in synthesis of triacylglycerol, were not modified by LIR. In addition, CPT1a and ACACA, enzymes implicated in the synthesis & metabolism of fatty acids, yielded no significant differences. Fasting just increased CPT1 levels (271% F/VEH vs CT/VEH, $P<0.01$), and LIR treatment reduced them (92% F/LIR, $P<0.01$ vs F/VEH).
In conclusion, Liraglutide modifies the metabolism of energy substrates in the liver reducing glucose production in normal feeding and CPT1a specially in fasting, limiting lipid access to mitochondria. These metabolic changes may underlie the prevention of liver steatosis attributed to GLP-1 analogues.

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GP76

Increased risk of diabetes and hyperglycaemia associated with treatment with statins, beta-blockers and diuretics: the PPP-Botnia study

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Background
Statin medication is commonly used in prevention of cardiovascular diseases. Pooled evidence shows that statin therapy is associated with increased risk of incident diabetes, but studies vary in results and there is no consensus of the diabetogenic mechanism of statins. Beta blockers and diuretics are commonly used antihypertensive agents that also have been shown to increase the risk of incident diabetes. Our objective was to examine the effects of statins, beta blockers and diuretics on glucose metabolism and the risk of incident diabetes.
Methods
5208 subjects from western Finland identified through the Population registry participated in the baseline PPP-Botnia Study, and 3,614 subjects participated in the follow-up study after a mean time of 6.7 years. Participants underwent oral glucose tolerance tests (OGTT) and gave information about their use of medication. Insulinogenic index (IGI) and corrected insulin response (CIR) were calculated from the glucose and insulin response during OGTT.
Results
After controlling for confounding factors, the group treated with statins during the entire follow-up had a, nominally significant, 79% (95% CI 1.16, 2.76 $P=0.008$) increased risk of developing incident diabetes, compared to the group without statins, and statin use was significantly associated with higher levels of fasting plasma glucose (FPG) and 2 hour plasma glucose (2hPG). Statin therapy was associated with a reduced CIR30, but not IGI30. Beta blocker therapy was associated with a nominally significant 63% increased risk of developing incident diabetes.
Conclusion
Statin treatment is associated with an increased risk of incident diabetes, higher levels of FPG and 2hPG, and reduced insulin secretion. Beta blocker therapy is associated with an increased risk of incident diabetes.

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GP77

Susceptibility to type 2 diabetes may be modulated by haplotypes in G6PC2, a target of positive selection

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Introduction
The endoplasmic reticulum enzyme glucose-6-phosphatase catalyzes the common terminal reaction in the gluconeogenic and glycogenolytic pathways and plays a central role in glucose homeostasis. In most mammals, different G6PC subunits are encoded by three paralogous genes (G6PC, G6PC2, and G6PC3). Mutations in G6PC and G6PC3 are responsible for human Mendelian diseases, whereas variants in G6PC2 are associated with fasting glucose (FG) levels.
Methods
We analyzed the evolutionary history of G6Pase genes in mammals. Results indicated that negative selection was the major force shaping diversity at these genes. Nonetheless, site-wise estimation of evolutionary rates at corresponding sites revealed weak correlations, suggesting that G6Pases have evolved different structural features over time. We also detected pervasive positive selection at mammalian G6PC2 genes. Most selected residues are located in the C-terminal protein region, where several human variants associated with FG levels also map. This region was thus re-sequenced in a cohort of ∼560 subjects from Saudi Arabia, 185 of whom suffering from type 2 diabetes (T2D).
Results
The frequency of rare missense and nonsense variants was not significantly different in T2D and controls. Association analysis with two common missense variants (V219L and S342C) revealed a weak but significant association for both SNPs when analyses where conditioned on rs560887, previously identified in a GWAS for FG. Two haplotypes were significantly associated with T2D with an opposite effect direction.
Conclusion
These results, although preliminary, suggest that distinct haplotypes at the G6PC2 locus modulate susceptibility to T2D.

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GP78

Contribution of genetic predisposition and lifestyle to gestational diabetes risk

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Aim
The aim of our study was to assess the contribution of genetic variation in some previously reported gestational diabetes mellitus (GDM) susceptibility loci and lifestyle parameters to GDM risk.

Methods
We performed a case-control study of 278 GDM cases and 179 controls who had filled up special questionnaires concerning their lifestyle habits during the oral glucose tolerance test (OGTT) on the 24–32 week of gestation. The questionnaire consisted of the following sections, stratified in a semi-quantitative manner: the consumption of major food groups and drinks, the amount of physical activity and smoking before and during pregnancy. GDM was diagnosed according to the IADPSG criteria. Maternal blood was sampled for further genotyping of single nuclear polymorphisms (SNPs) in MTNR1B (rs10830963 and rs1387153), GCK (rs1799884), KCNJ11 (rs5219), IGF2BP2 (rs4402960), TCF7L2 (rs7903146), CDKAL1 (rs7754840) and IRS1 (rs1801278). Binary logistic regression (forward conditional) was accomplished to identify the contribution of «classical» risk factors for GDM (advanced maternal age, higher body mass index (BMI), history of GDM, impaired glucose tolerance, arterial hypertension, family history of diabetes), lifestyle parameters and the above mentioned SNPs to the assessment of GDM risk.
Results
After automatic lineal modeling the following factors proved to be associated with the increased GDM risk: age (OR = 1.11, 95% CI = 1.06–1.16, $P < 0.001$), BMI (OR = 1.09, 95% CI = 1.05–1.14, $P < 0.001$), the presence of G allele of rs10830963 (OR = 2.1, 95%CI = 1.4–3.1, $P = 0.001$), T allele of rs1799884 (OR = 2.1, 95%CI = 1.3–3.4, $P = 0.003$) and consumption of sausage > 3 times a week (OR = 2.55, 95%CI = 1.36–4.78, $P = 0.004$) compared to less consumption. Legumes consumption 1–2 times a week was associated with the decreased risk of GDM, when compared to less consumption (OR = 0.59, 95%CI = 0.36–0.97, $P = 0.036$).
Conclusion
MTNR1B and GCK variants, some eating habits along with an increment in maternal age and BMI were associated with the increased risk of GDM.

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GP79

The rs2292239 polymorphism in the *ERBB3* gene is associated with risk for type 1 diabetes mellitus

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Background and Aim
Type 1 diabetes mellitus (T1DM) is an autoimmune disease resulting from the complex interaction among multiple genes, environmental factors and the immune system. Genome-wide association studies identified *ERBB3* (Erb-b2 receptor tyrosine kinase 3) gene as a main susceptibility locus for T1DM. This gene encodes a member of the family of intracellular receptors of protein tyrosine kinases, which activates multiple signaling pathways including PI3K-Akt and MAPK; thus, regulating cell survival and proliferation. Moreover, ERBB3 seems to contribute to T1DM pathogenesis by modulating antigen-presenting cell function and autoimmunity as well as beta-cell apoptosis and insulin production. Therefore, the aim of this study was to investigate the association of the rs2292239 (C/A) polymorphism in the *ERBB3* gene with susceptibility to T1DM in a Brazilian population from Southern-Brazil.
Methods
Frequencies of the rs2292239 polymorphism were analyzed in 461 T1DM patients (cases) and 570 non-diabetic subjects (controls). Genotyping was performed using Real-Time PCR and TaqMan MGB probes (Thermo Scientific).
Results
Genotype distributions of the *ERBB3* rs2292239 polymorphism were in agreement with those predicted by the Hardy-Weinberg Equilibrium in the control group ($P \geq 0.05$), with the A/A genotype being more frequent in T1DM patients compared with non-diabetic subjects ($P = 0.007$). The A allele frequency was 39.7% in the T1DM group and 32.8% in the control group ($P = 0.008$). Moreover, the A allele was significantly associated with T1DM risk when taking into account additive (OR = 1.67, 95% CI 1.07 – 2.61; $P = 0.023$) and recessive (OR = 1.58, 95% CI 1.04 – 2.40; $P = 0.031$) inheritance models, adjusting for T1DM high-risk *HLA- DR/DQ* haplotypes. In conclusion, our data confirms the association between the *ERBB3* rs2292239 and risk for T1DM in a population from Southern-Brazil.

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GP80

Trace elements as an oxidative stress marker in women with gestational diabetes and their neonates

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Background and aims
Gestational diabetes (GD) is closely related to unbalanced zinc (Zn) and cooper (Cu) serum levels. The aim of this study was to investigate serum zinc and cooper levels in relation to the metabolic profile, and the impact on fetal development in a cohort of gestational diabetes GD(N) neonates and their mothers GD(M) compared to normal pregnancies.
Material and Methods
Prospective controlled study in a tertiary Academic medical center. The study population included 101 mother/neonate pairs; 50 control group (C) and 51 GD group. Intervention: Diet and/or insulin administration in GD(M). Anthropometric, metabolic parameters, and trace elements serum levels were assessed.
Results
Age and body weight change during pregnancy (ΔBW) were similar in both groups. HbA1c was comparable between C and GD group (5.37 ± 0.34 and 5.39 ± 0.48%, for C and GD respectively, $P = 0.844$). Mean serum Cu levels were (150.1 ± 45.85, 32.16 ± 43.37)μg/dl in C and (203.53 ± 65.63, 23.62 ± 13.42) μg/dl in GD, mean Zn levels (87.8 ± 17.48, 120.47 ± 37.16)μg/dl in C and (88.1 ± 27.1, 113.76 ± 36.77)μg/dl in GD, for mothers and neonates, respectively. Neonates had statistically significantly lower serum Cu levels but higher Zn levels compared to their mothers ($P < 0.0001$, $P < 0.0001$). Serum cooper levels in mothers (Cu(M) levels were statistically significantly higher in GD(M) compared to C(M) ($P < 0.0001$). There was a negative correlation between Zn(M) and insulin levels(M) in C ($r = -0.284$, $P = 0.045$), between Zn(M) and insulin(N) in GD ($r = -0.372$, $P = 0.012$), and between Zn(N) and head circumference in C group ($r = -0.423$, $P = 0.013$). There was a positive correlation between Cu(N) and insulin(N) in GD ($r = 0.365$, $P = 0.019$), and between Cu (M) and birth weight in C ($r = 0.304$, $P = 0.042$).
Conclusions
Serum cooper levels are higher in women with gestational diabetes and independently of diabetes control. Both serum trace element levels in neonates seem to correlate with neonatal head circumference and birth weight only in control group.

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GP81

Abstract withdrawn.

GP82

Reduced level of soluble TLR2 in type 2 diabetes despite increased TLR2 monocyte expression

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Background
Chronic low-grade inflammation is a major factor in the pathogenesis of type 2 diabetes. One way for promoting inflammatory cytokines secretion is through activation of toll-like receptors (TLR). Their overexpression on monocytes has been demonstrated in insulin resistance and type 2 diabetes. Soluble forms of toll-like receptors (sTLR) are considered a regulatory mechanisms of their activation. Their role has been described in modulation of bacteria-induced infective diseases but has not been analysed in diabetes. The aim of the study was to evaluate the place of sTLR2 in type 2 diabetes and compare it with monocyte expression.
Subjects and methods
We performed a cross-sectional study that included 63 patients with type 2 diabetes and 25 controls. All were assayed for soluble forms of TLR2 through Enzyme-Linked Immunosorbent Assay. We evaluated monocyte expression of TLR2 in 28 diabetic patients and 14 control subjects through direct immunofluorescence with conjugated monoclonal antibodies. All participants were assayed for Interleukin 6 (IL-6) through Electro-Chemiluminescence Immunoassay and high sensitivity C-reactive protein (hs-CRP) through Particle Enhanced Immunoturbidimetric Assay.
Results
TLR2 expression in patients with type 2 diabetes was higher compared to controls ($89.85 \pm 9.66\%$ vs. $50.20 \pm 36.91\%$ for CD14++CD16+ monocytes, $P=0.003$ and $34.54 \pm 12.38\%$ vs. $17.12 \pm 15.39\%$, $P=0.011$ for CD14+CD16++ monocytes) but sTLR2 was significantly lower in diabetic subjects (1.15 ± 0.65 ng/ml vs 1.44 ± 0.60 ng/ml, $P=0.019$). Inflammatory status between groups was confirmed significantly different concerning hs-CRP (2.79 ± 2.89 mg/l vs. 0.70 ± 0.89 mg/l, $P=0.000$) and IL6 (2.65 ± 2.46 ng/ml vs 1.44 ± 0.22 ng/ml, $P=0.005$) with higher values in diabetic group, although correlations with TLR2 expression were not established ($P>0.05$).
Conclusion
Type 2 diabetes-associated chronic inflammatory state is characterised by elevated monocyte expression of TLR2 but decreased serum sTLR2 level. This poses the question about presence of an impaired immunomodulation of TLRs' activation in diabetes.

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Diabetes & complications 2

GP83

Vitamin D metabolites and IL1β RS16944 polymorphism in type 2 diabetes patients: evidence for functional interaction

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We investigated the SNP rs16944 in German type 2 diabetes (T2D) patients and healthy controls (HC) and correlated the findings with concentrations of VD metabolites.
Methods
504 T2D patients and 447 HC were genotyped by a Taqman assay. Additionally $25(OH)D_3$ and $1,25(OH)_2D_3$ plasma levels of 76 T2D patients and 267 HC were measured by radioimmunoassay.
Results
The AA genotype was significantly less frequent in T2D compared to HC whereas GG and AG genotypes were more frequent in T2D (AA: 48.5 vs 37.95%; AG 40vs 49.7%; GG: 11.4 vs 12.4%; $P=0.003$). Furthermore the allele A was less (68.6 vs 62.7% OR = 0.77; 95% CI: 0.64–0.93) and allele G was more frequent (31.4 vs 37.3% OR = 1.3 95% CI: 1.07–1.57, $P=0.008$) in T2D patients compared to HC. Both T2D patients and HC with IL1β genotypes AA and AG did not differ for the VD metabolites. However T2D patients with the GG genotype showed significantly lower levels of $25(OH)D_3$ (median 34.95 vs 13.7 ng/ml $P=9\times10^{-6}$) and $1,25(OH)_2D_3$ (median 59.05 vs 41.15 pg/ml $P=0.006$) compared to HC with the same genotype.
Conclusion
We describe an association of the IL1β with T2D in German patients. Significantly lower $25(OH)D_3$ and $1,25(OH)_2D_3$ levels were observed in T2D patients with the GG genotype. Whereas the major allele A appears to be protective, the minor allele G is may predispose to T2D in combination with a vitamin D deficiency. Our results suggest that VD deficiency enhances the genetic risk for T2D conferred by the genotype GG of IL1β SNP rs16944. Whether and how vitamin D interacts with IL1β through this polymorphism is subject to further studies.

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GP84

Antidiabetic medication use and the risk of fracture in type 2 diabetic patients: a nested case-control study

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Background
Patients with type 2 diabetes mellitus (T2DM) have an increased risk of fragility fractures. Anti-diabetic oral agents and insulin may also impact on fracture risk. There is however scarce data available on the effect of such therapies combined as usually prescribed in real-life practice conditions.
Objectives
The objective of this study was to compare the risk of fracture among T2DM patients who are users of different antidiabetic treatments.
Methods
A nested case-control study was conducted using incident T2DM patients registered in computerised primary care records in the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) between 2006–2012, with follow-up available until end/2013. Each case (incident fractures of the hip, spine, wrist, or proximal humerus in 2006–2013) was risk-set matched with five controls of the same gender, calendar year of T2DM diagnosis and age at index date (± 10 years). Study exposure included metformin mono-therapy (reference category) and other antidiabetic medications (alone or in combination as prescribed in actual practice) in the 180 days before the index date. Conditional logistic regression analysis was used to estimate odds ratios and 95% confidence interval adjusting for the following confounders: age, gender, HbA1c level, body mass index, history of fracture, co-morbidities, and concomitant medication use.
Results
Data on 12,277 T2DM patients (2,049 cases and 10,2280 controls) was analysed. Insulin use was associated with increased fracture risk (adj OR 1.63 [95%CI 1.30–2.04]), as was the combination of metformin + sulphonylureas (adj OR 1.29 [1.07–1.56]). No significant association was found with other antidiabetic medications and/or combinations.
Discussion
Insulin and sulphonylureas use appear to be associated with an increased fracture risk when compared to metformin amongst recently diagnosed T2DM patients. Residual confounding cannot be ruled out, and more studies are needed to confirm these findings. Given their impact, risk of fracture should be taken into account in the management of T2DM patients.

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GP85

Abstract withdrawn.

GP86

Increased incidence of diabetes mellitus 30 years after the radiation impact in persons exposed to ionizing radiation during the Chernobyl NPP accident

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Several million people in Ukraine and other countries had been exposed to ionizing radiation during the Chernobyl nuclear power plant accident (ChNPPA) on April 26, 1986. The ChNPPA clean-up personnel involved in emergency and recovery works in the 30-kilometer exclusion zone of power plant in the nearest days or months and/or for a long time had received the highest radiation doses due to external gamma-exposure and from incorporated radioactive isotopes with high affinity to endocrine organs, including the thyroid, pancreas, and cerebral endocrine structures. Consequently a dramatic elevation in non-cancer endocrine morbidity emerged due to thyroid disease, pre-diabetes, diabetes mellitus, and obesity. Despite pancreas was previously considered resistant to ionizing radiation the recent research however suggests high sensitivity of endocrine cells, particularly pancreatic beta cells to radiation exposure. It just explains a high prevalence of diabetes mellitus (up to 23%) in the ChNPPA survivors, whilst the respective value for population of Ukraine is much lower, i.e. from 3 to 7% depending on data source. According to retrospective review of endocrine system data from the ChNPPA clean-up workers ($n = 13{,}158$) the prevalence of pre-diabetes and diabetes mellitus had increased dramatically 10 years upon the accident and continues to increase 30 years later. Now it is in average $\sim$16% and $\sim$12% respectively. At that not only a radiation dose but also the duration of moderately intensive gamma-exposure, namely 0.082 ± 0.01 Gy, is critical for the onset of type 2 diabetes mellitus. Persons involved in recovery operations for more than 4–6 months are of concern here. Survey results in the ChNPPA emergency workers demonstrate an increased incidence of latent autoimmune diabetes in adults (LADA).

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GP87

Baicalin lowers glucose intolerance by controlling pancreatic hormone in high fat-induced obese diabetic rats

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Objective
Bacalin was known as an allosteric modulator of the benzodiazepine sites of the γ-aminobutyric acid A receptor ($GABA_AR$), which produce anxiolytic effects in mice without myorelaxant or sedative effects. Baicalin occur flavonoid found in naturally in the genus Scutellaria. It has been recently shown to exert metabolic effects by attenuating hyperglycemia-induced mitochondrial damage in β-cells in diabetic rats, high-fat diet- (HFD-) induced body weight gain, and lipid deposits in the liver and systemic inflammation in mice. This study investigated the effects of baicalin on islet functions and diabetic status in HFD-induced obese diabetic mice.
Methods
C57BL/6 mice were grouped into normal control, HF control, HF sham, and 4 different baicalin dose-administered groups (25, 50, 100, and 150 mg/kg). HFD containing 60% fat and water were fed *ad libitum* for 24 weeks. Designated doses of baicalin or 0.9% saline were administered intraperitoneally 5d/wk. Body weight (BW) and conventional glucose homeostasis parameters (FPG, FPI, AUC-glucose, AUC-insulin, and etc.) were monitored; in addition, *ex vivo* glucose-stimulated insulin secretion (GSIS) and glucagon secretion (GSGS) with isolated islets were performed.
Results
Insulin secretion in response to high glucose stimulation (16.7 mM) was significantly higher in islets isolated from the groups administered 50, 100, 150 mg/kg baicalin compared to HF control; glucagon secretion was significantly suppressed by high glucose stimulation in islets from the same groups.
Conclusion
This study showed that baicalin had positive effects on glycemic control by regulating secretion of insulin and glucagon, possibly through $GABA_AR$ mediation.

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GP88

Effect of insulin on neurotrophins' levels in the muscular wall of mice intestine and colon

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Background
Neurotrophins are implicated in the physiology and pathophysiology of the mature gastrointestinal tract (GIT) such as motility and inflammatory bowel disease. Moreover, GIT disturbances has been attributed to hyperinsuliemia. Insulin-neurotrophins interactions in the (GIT) have not been investigated yet.
Aim
To test the effect of Insulin on the expression of neurotrophins in the muscular wall of mice intestine and colon.
Methods
Total protein extracts from intestinal and colonic muscular wall treated for 24 hours with insulin were subjected to ELISA assays specific for different neurotrophins and data were analyzed using suitable statistical test with graph pad.
Results
Insulin treatment resulted in significant reduction of neurotrophin-3 (NT-3) protein levels in the muscular wall of both mice intestine and colon. Moreover, neurotrophin-4 (NT-4) levels were significantly reduced in response to insulin treatment in muscular tissue from both intestine and clone as well. Interestingly the effect of insulin was more profound in the colon on NT-3 and NT-4.
Conclusion
These results indicate that changes in GIT structure and function seen in hyperinsulinemia might be due to the effect of insulin on neurotrophins expression levels. However, functional studies are needed to elucidate the exact interactions between insulin and neurotrophins in the GIT.

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GP89

Clinical assessment of trabecular bone microstructure in type 2 diabetes mellitus with Trabecular Bone Score (TBS)

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Introduction
Type 2 diabetes mellitus (T2DM) is a risk factor for osteoporotic fractures although bone mineral density is increased. As such, there is a need for improved approaches to estimate fracture risk in such individuals. The Trabecular Bone Score (TBS) is a new technique to determine the trabecular bone micro-architecture.
Objective
Our aim was to evaluate evaluate the usefulness of TBS in T2DM patients.
Methods
We compared TBS values in T2DM group (n: 31) and control group (n: 25) and we analized its relationship with bone mineral density (BMD), history of prior fractures and glycemic control. BMD was evaluated by conventional bone densitometry (DXA) and 3D (3D-DXA).TBS values were determined using TBS InSight® software.

Results
T2DM patients had lower TBS than controls (1.14±0,17 vs 1.25±0,16, $P=0.013$). However, there were no differences in the densitometric or volumetric parameters measured by conventional DXA and 3D-DXA. In T2DM group, TBS at the lumbar spine showed degraded microarchitecture (TBS $\leq$ 1.2) in 16 patients (51.6%); 13 patients (41.9%) had partially degraded structure (TBS $>$ 1.20 & $<$ 1.35); and only 2 patients (6.5%) had normal TBS values (TBS $\geq$ 1.35). TBS results differed between groups close to statistical significance (Default 1). We did not find diferences in TBS values according densitometric diagnosis of osteoporosis (Tscore $\leq$ 2.5 S.D.) or history of prior fracture in either group. We found a significant correlation of TBS with age, body mass index and lumbar spine BMN both in diabetic patients and controls ($P < 0.05$). Finally, we did not observe relationship with glycemic control or duration of diabetes in T2DM group.
Conclusion
TBS is shown as a promising method in the clinical assessment of trabecular bone microstructure in T2DM.

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GP90

The G allele of the *BDKRB1* rs12050217 polymorphism is associated with protection for diabetic retinopathy

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Background
Diabetic retinopathy (DR) is a chronic diabetic complication occurring in most diabetic patients after 20 years of disease. Progression of DR to its sight threatening stages is usually associated with worsening of underlying retinal vascular dysfunction and disease. The plasma kallikrein kinin system is activated during vascular injury, mediating important functions in inflammation, blood flow, and coagulation. Bradykinin B1 receptor (B1R) is expressed in human retina, and retinal B1R levels are increased in murine models of diabetes. Furthermore, experimental studies reveal that B1R antagonists ameliorate retinal functional abnormalities caused by diabetes in rodents. Thus, B1R gene (BDKRB1) is a candidate gene for DR.
Objective
To investigate the association between rs12050217A/G polymorphism in the BDKRB1 gene and DR in patients with type 2 diabetes mellitus (T2DM).
Methods
We analyzed 1129 T2DM patients and 416 non-diabetic subjects. T2DM patients were categorized by the presence of non-proliferative DR (NPDR, $n=476$), proliferative DR (PDR, $n=275$) and absence of DR ($n=200$). The local ethic committee approved the study, and all subjects signed a consent form. The BDKRB1 rs12050217A/G polymorphism was genotyped by Real-Time PCR using TaqMan MGB probes.
Results
The genotype frequencies of the BDKRB1 rs12050217A/G polymorphism are in Hardy-Weinberg equilibrium, and did not differ between T2DM patients and normoglycemic subjects ($P>0.05$). The presence of the minor G allele of the rs12050217 polymorphism was less frequent mainly in patients with PDR when compared to patients with NPDR and without DR (31.5, 41.8 and 41.2%, $P=0.034$; respectively). Interestingly, we observed that the presence of the G allele was associated with protection for PDR, which was confirmed after correction for the presence of hypertension, ethnicity, diabetes duration and age ((95% CI) $=0.580$ (0.398–0.843); $P=0.004$).
Conclusions
The BDKRB1 rs12050217 G allele is associated with protection for the advanced stage of DR in T2DM patients.

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GP91

Dipeptidyl peptidase-4 inhibitor therapy and risk of diabetic retinopathy: a population based study

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Background
Given the possible association between dipeptidyl peptidase-4 (DPP-4) inhibitor and risk of diabetic retinopathy (DR), we examined whether DPP-4 inhibitors are beneficial or harmful for DR compared with other glucose-lowering agents.
Methods
From a Korean population-based cohort, we identified 67,743 adults with type 2 diabetes treated with oral glucose-lowering agents between 2008 and 2013. Matching (1:1) was done for comparative groups: ever-used (case) and never-used (control) DPP-4 inhibitors ($n=14,522$ each group). Cox regression analyses assessed the risk of DR events: vitreous hemorrhage, vitrectomy or photocoagulation, intravitreal agent use, and blindness.
Results
During a median follow-up of 28·4 (14.0–45.2) months, there were 305 (control group) and 342 (case group) composite DR events, respectively. Use of DPP-4 inhibitors was not associated with overall risk of composite DR events (adjusted hazard ratio [HR] 1.08, 95% CI 0.93–1.26). Each DR events including vitreous hemorrhage, vitrectomy or photocoagulation, use of intravitreal agents, and blindness were also not increased with DPP-4 inhibitor therapy. The results were consistent according to baseline retinopathy. However, in the analyses by duration of treatment, a DPP-4 inhibitor treatment duration of <12 months was associated with increased risk of composite DR events (adjusted HR 1.95, 95% CI 1.61–2.36).
Conclusion
DPP-4 inhibitor treatment did not increase the overall risk of DR compared with other oral glucose-lowering agents. Given that short-term DPP-4 inhibitor use was associated with increased risk of DR, the need to assess the aggravation of retinopathy in the early phase of DPP-4 inhibitor use is warranted.

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GP92

Non-genetic rat model of nephropathy in type 2 diabetes with attenuated streptozotocin-induced tubular alteration

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Non-genetic animal models of diabetic nephropathy (DN) are most commonly reproduced by using streptozotocin (STZ) which preferentially gets into β-cells via GLUT2 transporters. However, STZ administration results in nephrotoxic effects as well, due to expression of GLUT2 by renal tubular epithelial cells. We hypothesized that nicotinamide (NA), which is considered to attenuate the severity of STZ-induced β-cell damage, could also prevent tubular alteration. Starting at 3 weeks after unilateral nephrectomy, thirty adult male Wistar rats were fed the high-fat diet for 5 weeks and then successively received either NA (230 mg/kg) and STZ (65 mg/kg, NA-STZ-group) or STZ in a low dose (40 mg/kg, LD-STZ-group) intraperitoneally in 15-min interval. Control nondiabetic uninephrectomized rats received vehicle and were fed normal chow (C-group). At weeks 10, 20, and 30 (the end of the study), metabolic parameters, creatinine clearance, albuminuria, and urinary tubular injury markers (NGAL, KIM-1) were evaluated as well as renal ultrastructural and light microscopic changes at weeks 20 and 30. NA-STZ-group showed higher reproducibility and stability of metabolic parameters. By week 10, NA-STZ-injected rats showed overweight (328.9±22.7 g (NA-STZ) vs 285.4±20.5 g (C)), mild hyperglycemia (HbA1c 5.39±0.24% vs 3.6±0.29%), significant increase in insulin resistance (HOMA-IR 3.2±0.39 vs 1.93±0.29),and

dyslipidemia (total cholesterol 2.89 ± 0.25 mmol/l vs 1.55 ± 0.35; triglycerides 1.05 ± 0.18 mmol/l vs 0.57 ± 0.1), $P < 0.05$ each, that were observed until the end of the study. At 20 weeks, development of early stage of DN was confirmed by glomerular basement membrane thickness, gradual decline in creatinine clearance, and mild albuminuric status (478.4 ± 63.3 μ/24 h vs 35.8 ± 3.6 μ/24 h), with progression by week 30, when light microscopic features of DN were observed. Morphofunctional renal changes in NA-STZ appeared to be more pronounced than those in LD-STZ despite lower levels of KIM-1 and NGAL (2535.8 ± 303.9 ng/24 h (LD-STZ) at week 30) vs 1704.4 ± 444.7 ng/24 h in NA-STZ, $P = 0.037$. We have described a model of type 2 diabetes and DN with attenuated STZ-induced tubular alteration in rats that is characterized by stable metabolic disorders and renal morphofunctional changes similar to relatively early stages of human DN.

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Diabetes therapy & complications 1

GP93

microRNA expression profile in plasma from patients with diabetic kidney disease

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Introduction
Diabetic kidney disease (DKD) is the major cause of end-stage renal disease; however, the pathogenesis of this disease is not fully understood. Currently available therapies are not totally efficacious in the treatment and prognosis of DKD, suggesting that further understanding of the molecular mechanisms underlying the pathogenesis of this disease is necessary to improve its management. Recently, research on microRNAs (miRNAs) has become a hotspot because of their critical role in regulating posttranscriptional levels of protein-coding genes. Several miRNAs were found to participate in DKD pathogenesis; nevertheless, results are still inconclusive. Therefore, the identification of miRNAs involved in DKD may help in the diagnosis and treatment of this disease.
Objective
To identify a miRNA expression profile associated with DKD in plasma from patients with type 1 diabetes mellitus (T1DM) with different degrees of this diabetic complication.
Design
Expressions of 48 miRNAs were investigated in the plasma from 46 T1DM patients: 24 patients in group 1 [patients with T1DM for more than 10 years, with urinary excretion of albumin (UEA) < 30mg/g and estimated glomerular filtration rate (eGFR) ≥ 60 ml/min/1.73 m^2)], 11 in group 2 (patients with T1DM with UEA 30–300mg/g or eGFR 45-59 ml/min/1.73 m^2) and 11 in group 3 (patients with T1DM with UEA > 300 mg/g or eGFR 15-29 ml/min/1.73 m^2), using Stem-loop RT-PreAmp Real-time PCR and TaqMan Low Density Array cards (Thermo Scientific Inc).
Results
Eighteen miRNAs were differently expressed between T1DM patients without DKD (controls) and T1DM patients with different levels of DKD (cases). Seventeen miRNAs were downregulated (miR-126, miR-146a, miR-155, miR-192, miR-200a, miR-200b, miR-204, miR-216a, let-7b, miR-29c, miR-200a, miR-20b, miR-216a, miR-25, miR-320, miR-92a and miR-638) and one miRNA was upregulated (miR-124) in cases compared to controls. In addition, miRNAs let-7b, miR-155, miR-200a, miR-20b, miR-216a, miR-25, miR-29c, miR-320 and miR-92a were downregulated in T1DM patients with severe DKD (group 3) compared to controls.
Conclusion
Our preliminary results show that some circulating miRNAs are differentially expressed between T1DM patients with and without DKD.

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GP94

The A allele of the -866G/A polymorphism in *UCP2* gene decreases high glucose-induced *UCP2* expression in HUVECs

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Uncoupling protein 2 (UCP2) is a mitochondrial protein located in the mitochondrial inner membrane, and it uncouples substrate oxidation from ATP synthesis, thereby dissipating the membrane potential energy and consequently decreasing reactive oxygen species (ROS) formation by mitochondrial respiratory chain. ROS overproduction is related to diabetic retinopathy (DR), a chronic complication of diabetes mellitus (DM). Recently, our group reported that the -866A/55Val/Ins haplotype (-866G/A, Ala55Val and Ins/Del polymorphisms) of the *UCP2* was associated with risk for proliferative DR in both type 1 and type 2 diabetic patients. Additionally, this haplotype influenced *UCP2* expression in human retina samples. Indeed, some studies suggest that the -866G/A polymorphism directly affect *UCP2* expression; however, its effect on endothelial cells under different glucose concentrations is not well defined.
Objective
To investigate the effect of -866G/A polymorphism on *UCP2* expression in an endothelial cell line under different glucose concentrations.
Methods
HUVECs cells were transfected with pGL3 plasmids containing the promoter region of *UCP2* gene and the coding sequence of firefly luciferase, using LTX Lipofectamine (Life Technologies). The test conditions were: 1) transfection with the wild-type allele-containing plasmid (pGL3-UCP2-G); and 2) transfection with the mutated allele (pGL3-UCP2-A), under conditions of normoglycemia (4 mM) or hyperglycemia (25 mM) after 24 h and 48 h. Plasmid pCMV encoding renin luciferase and pEGFP were co-transfected as internal control and transfection control, respectively. Luciferase levels were measured with Luminescent Dual-luciferase Assay (Promega).
Results
HUVECs cells transfected for 24 h and 48 h with the plasmid containing the -866A allele under normal glucose conditions had 47% and 37% decrease in *UCP2* expression than cells transfected with the plasmid containing the G allele ($P = 0.011$ and $P = 0.0001$; $n = 3$). Interestingly, under high glucose conditions, cells containing the A allele had a more drastic decrease in *UCP2* expression (70% and 54%) compared to cells with the G allele ($P = 0.0001$ and $P = 0.028$; $n = 3$) after 24 and 48 h.
Conclusion
Our preliminary results demonstrate that the UCP2 -866A allele decreases *UCP2* expression in HUVEC cells, which is exacerbated under high glucose conditions. The -866G/A polymorphism of the *UCP2* gene is associated with increased UCP2 protein concentrations in human retina, which may explain the previous reported association between the -866A/55Val/Ins haplotype and risk for DR.

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GP95

The relation between PON-1 activity and 25-OH hydroxyvitamin D3 levels and other biochemical parameters in diabetic patients with respect to obesity and diabetic complications

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Objective
To evaluate the relation of mean platelet volume (MPV) levels with serum paraoxonase-1 activity in diabetic patients with respect to obesity and diabetic complications.
Methods
A total of 201 diabetic patients grouped with respect to obesity obese ($n = 89$) and non-obese ($n = 112$) and diabetic complications with ($n = 50$) or without ($n = 150$) microvascular complications and with ($n = 91$) or without ($n = 108$) macro-vascular complications groups were included. Data on demographic and lifestyle characteristics of patients, anthropometric measurements, diabetes related microvascular and macrovascular complications, Correlation of MPV values to paraoxonase and arylesterase activities.

Results
Mean(SD) paraoxonase and arylesterase values were 119.8±37.5 U/l and 149.0±39.9 U/l, respectively in the overall population, with no significant difference with respect to obesity and macrovascular diabetic complications, whereas significantly lower values for paraoxonase 107.5±30.7 vs. 123.9± 38.8 U/l, ($P=0.007$) and arylesterase 132.1±30.2 vs. 154.±41.2 U/l ($P=0.001$) were noted in patients with than without diabetic microvascular complications. Mean(SD) MPV values were 9.10±0.87 fL in the overall population, with no significant difference with respect to obesity and diabetic complications. No significant correlation of MPV values to paraoxonase and arylesterase activities. A significant positive correlation was determined with plasma 25-(OH) hydroxyvitamin D3 levels ($r=0.398$, $P=0.001$ and $r=0.484$, respectively $P=0.001$). HOMA-IR exhibited a significant negative correlation with PON and arylesterase in the groups.
Conclusion
In conclusion, our findings revealed a significant decrease I PON-1 activity in diabetic patients with microvascular rather than macrovascular complications, whereas regardless of obesity and diabetic complications, no increase in thrombogenic activity and no relation of thrombogenic activity with PON-1 activity. PON-1 activity exhibited a significant negative correlation, independent of obesity, sex and age, with plasma glucose, HbA1c and HOMA-IR values in all patients and a significant positive correlation with 25-OH vitamin D3 values. Low PON-1 activity and 25 OH vitamin D3 levels may be a marker of inadequate glycemic control independent of obesity in diabetic patients They may play an important role for early atherosclerosis who had only in obese diabetic especially microvascular diabetic complications well glysemic control of the most factor that it prevents diabetic complications and also well glysemic control and apropiate vitamin D levels have good affect on diabetic complications.

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GP96

High prevalence of lower extremity peripheral artery disease in type 2 diabetes patients with diabetic nephropathy and the role of netrin-1 levels

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Background
Netrin-1 is an early biomarker of acute kidney injury. Besides, recent studies have showed that netrin-1 promotes angiogenesis; but its usefulness for peripheral artery disease (PAD) in type 2 diabetes patients is unknown.This study aimed at investigating whether netrin-1 levelsare increased in peripheral artery disease among patients with type 2 diabetes and also investigating possible associationsbetween diabetic nephropathy (DN) and PAD.
Material and Methods
This was a cross-sectional observational clinical study. This study involved a total of 84 adults with type 2 DM, who underwent ABI (low ankle-brachial index) measurement in an outpatient clinic. PAD was defined as ABI <0.9 in either leg. ABI of 42 patients with PAD were compared with 42non-PADpatients. Diabetic nephropathy was evaluated by estimated glomerular filtration rate and urinary albumin-creatinine ratio (ACR).
Results
Compared with control group, the levels of Netrin-1 levels and diabetic nephropathy subjects were significantly increased in the PAD group. As regards similar GFR values, patients with higher urinary albumin-creatinine ratio (ACR) values had significantly lower ABI parameters than the patients without albuminuria.(Right: 0.96±0.1 vs 1.05±0.01, Left: 0.94±0.1 1.04±0.01vs $P<0.01$).Binary logisticregression analysis revealed that diabetic nephropathy (vs non-DN) was associated with PAD (OR =2.94, 95%CI: 1.2–7.1; $P=0.017$) .In multivariate models, adjusted additionally for the mean duration of diabetes, gender, BMI, HbA1c, hyperlipidemia and hypertension, theassociations with netrin-1and PAD persisted (beta: 0.238, $P=0.042$).
Conclusion
Our study in patients with type 2 DM demonstrated that PAD was associated with diabetic nephropathy and netrin-1 levels. In conclusion, changes in netrin-1 levels are likely to be used as a biomarker for monitoring the risk of PAD in patients with Type 2 diabetes.

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GP97

Comparison of current perception threshold measured by Neurometer in patients with type 2 diabetes mellitus to a group of normal individuals

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Purpose
To determine the proportion of abnormal current perception threshold (CPT) in patients with type 2 diabetes mellitus.
Methods
A total of 1360 patients with type 2 diabetes mellitus involved in an epidemiological study received an examination of CPT measured by Neurometer® CPT/C (Neurotron, Inc., Baltimore, Maryland, USA) on a supine position. The measurement was taken for three frequencies, i.e., 5, 250 and 2000 Hz at three sites: the preauricular area (trigeminal nerve), the index finger (median nerve) and the great toe (superficial peroneal nerve) on both sides. The three frequencies measure small unmyelinated C fiber (5 Hz), small myelinated Aδ fiber (250 Hz), and large myelinated Aβ fiber (2000 Hz), respectively. The normative data from 75 normal individuals were used as control and an "abnormal CPT" was defined as a value greater than the normal mean plus 3 standard deviations derived from the normal individuals. Age, sex, body height and body weight were treated as potential confounders. Student's t test, Chi-square test, correlation coefficient and stepwise regression were used for statistical analyses and a P value <0.05 was considered as statistically significant.
Results
Accept for a significantly older age in the diabetes group, the distribution of sex, body height and body weight were not different significantly. CPT measurements on the right and left sides correlated significantly with correlation coefficients mostly >0.7 ($P<0.0001$) in the diabetes patients. The trigeminal nerve had the most commonly reported "abnormal CPT" that involved approximately 60% of the diabetes patients, followed by the superficial peroneal nerve (50%) and the median nerve. The median nerve showed frequency-dependent abnormality with higher proportion of "abnormal CPT" involving lower frequency. For the frequency of 2000, 250 and 5 Hz, "abnormal CPT" was observed in 15–20, 30–33 and 56–59%, respectively. In stepwise regression analyses, diabetes and age were consistently predictive for CPT.
Conclusions
Patient with type 2 diabetes mellitus have higher CPT values than normal individuals in all anatomical sites. The application of Neurometer® for screening of diabetes neuropathy awaits further confirmation.

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GP98

Gestacional diabetes mellitus: the new screening criteria and its outcomes

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Background
Gestational Diabetes Mellitus (GDM) is one of the most common illness of pregnancy. Despite its frequency, there's no worldwide accepted screening criteria for GDM. In 2011, Carpenter and Coustan (CC) screening (50-g glucose challenge test (GCT) followed by 100-g glucose tolerance test (OGTT) if GCT screen was positive) was abandoned and began the implementation of the screening of the International Association of Diabetes and Pregnancy Study Group (IADPSG) 2010 (75-g OGTT).
Aims
Asses and compare perinatal outcomes of these two screening criteria.
Materials and methods
We undertook a retrospective study, of gestacional diabetes followed on Endocrinology department. Two groups were constituted: CC (followed in 2009 and 2010) and IADPSG (followed in 2014 and 2015). All patients were treated with nutrition and exercise. When target glucose levels were not met, insulin was initiated, no oral antidiabetic agents were used. Analysed data included birthweight, premature delivery, macrosomia, mode of delivery, maternal parity, body mass index (BMI) and insulin treatment.
Results
In 2009 and 2010, of 4705 childbirths in the hospital, 259 (5.5%) women met the CC criteria, of which 134 were included in this study. In 2014 and 2015, of 3496 childbirths in the hospital, 348 (9.9%) women met the IADPSG criteria, of which 221 were included in this study. Those with GDM per IADPSG criteria had more

insulin treatment (46.6 vs 23.1%; $P<0.0001$), fewer large for gestacional age fetus (3.6 vs 9.0%, $P=0.038$) and less premature delivery (1.4 vs 5.2%, $P=0.033$).
Conclusions
Although the application of the IADPSG criteria increased the number of women diagnosed with GDM, there was an increase in insulin treatment, and an overall better newborn outcomes. This could mean that the IADPSG criteria identified a group of women with a increased risk of perinatal outcomes that were not recognized by the CC screening.

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GP99

Higher levels of adiponectin might contribute to lower bone mass observed in patients with type 1 diabetes, through alterations in osteocalcin energy circuit signaling of bone cells.

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Introduction
Recent advances in energy homeostasis revealed a significant interconnection between bone and adipose tissue through osteocalcin. Reduced bone mass documented in type 1 diabetes mellitus (T1D) could be related to disregulation of adipokine signaling on bone.
Materials and Methods
We evaluated 40 children and adolescents with T1D (mean $\pm$ s.d. age 13.04 $\pm$ 3.53 years, mean $\pm$ s.d. T1D duration 5.15 $\pm$ 3.33years) and 40 healthy age- and gender-matched controls (mean $\pm$ s.d. age 12.99 $\pm$ 3.3years). Adiponectin, leptin and bone metabolism markers were measured, while lumbar spine (LS) and total body (TB) Bone Mineral Density (BMD) were evaluated with dual energy X-ray absorptiometry (DXA).
Results
Lower BMD values have already been documented in patients, as well as lower osteocalcin (log(osteocalcin) 3.44 $\pm$ 0.5 vs 3.6 $\pm$ 0.51). Patients had higher levels of adiponectin (18078 $\pm$ 8645 vs 13536 $\pm$ 6703 ng/ml, $P=0.007$) while leptin levels were comparable between groups (8.85 $\pm$ 8.73 vs 10.03 $\pm$ 8.75 pg/ml, $P=0.13$). Both adipokines were associated with Body Mass Index (BMI) in both groups. Adiponectin was positively associated with osteocalcin only in controls (Rho $=0.31$, $P=0.05$) possibly indicating altered energy signaling in bone of T1DM patients, whereas in patients it was negatively associated with IGF1 (Rho $=-0.30$, $P=0.05$) and positively associated with HbA1c (Rho $=0.38$, $P=0.01$) and i-phosphorus (Rho $=0.39$, $P=0.01$). No associations of leptin with bone markers were observed.
Conclusion
Increased adiponectin might contribute to lower bone mass observed in young T1D patients with altered interconnection of energy signaling in bone cells, through osteocalcin circuit.

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GP100

Type 1 diabetes and hearing loss: a meta-analysis

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Objective
Evidence shows type 1 diabetes leads to vascular damage and neuropathy. The purpose of this study was to perform a systematic review and a meta-analysis to asses the evidence of the effects of type 1 diabetes on hearing function.
Methods
Three different electronic databases were used to identify eligible studies including a manual searching of references. The articles obtained were independently reviewed by two authors using predefined inclusion criteria to identify eligible studies. Meta-analysis was performed on pooled data of hearing loss incidence, PTA thresholds and ABR wave latencies.
Results
Fifteen articles fulfilled the inclusion criteria and passed the quality control evaluation. In most studies, hearing loss (HL) was defined as pure tone greater than 25 dB in the worse ear of at least one frequency. The incidence of HL ranged between 0 and 48% for diabetics, which was higher than in controls (OR $=12.43$ 95% CI 3.09–49.95). The tendency of mean PTA (pure tone audiometry) thresholds were greater in diabetics than in controls for higher frequencies, however the results were not significant. Auditory brainstem response (ABR) latencies were longer in diabetic patients compared to controls. Statistical significance was obtained in wave III and V ($Z=3.18$, $P=0.001$ $I^2=82\%$; $Z=2.55$, $P=0.01$, $I^2=89\%$ respectively).
Conclusions
Patients with type 1 diabetes have a significantly greater incidence of HL compared to the control group. However, hearing thresholds seems to be not significantly different from control subjects. Mean PTA thresholds were greater at 6000 and 8000 Hz. Despite a trend of higher threshold difference at higher frequencies tested, the mean differences between groups at any frequency were not statistically significant. A significant prolonged ABR of waves III and V latencies in the diabetic group suggest a retro-cochlear involvement in hearing damage in type 1 diabetes.

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GP101

Abstract withdrawn.

GP102

Comparison of the effects of combinations of different antihypertensive therapies on microalbuminuria and renal functions in type 2 diabetic patients

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Renin angiotensin system blockers are currently used in the treatment of diabetic nephropathy. Carvedilol, 3. generation beta-blockers, may provide additional benefits in diabetic patients. Its antiproteinuric activity is not investigated in patients with diabetic nephropathy. We aimed to compare short-term additive effects of losartan with cilazapril or carvedilol combination on blood pressure, proteinuria and renal functions in microalbuminuric patients with type 2 diabetes mellitus and hypertension.
Methods
Thirty patients with type 2 diabetes, stage 1 hypertension and albuminuria of 30–300 mg/day, were enrolled in the study. After the 2 week follow-up period, all patients were started on losartan 50 mg/day for 6 weeks. Then, they were randomized to three groups for 6 weeks: 1st group (n:10) on losartan 100 mg/day, 2nd group (n:10) on carvedilol 25 mg/day + losartan 50 mg/day and 3rd group (n:10) on cilazapril 5 mg/day + losartan 50 mg/day treatment.
Results
Characteristics of groups were similar. In all groups, systolic and diastolic blood pressures (BP) were significantly decreased. Greatest decrease in systolic (16.5 $\pm$ 7.4 mmHg) and diastolic (10.5 $\pm$ 2.8 mmHg) BPs were seen in group 3 and smallest decreases were seen in group 1 (systolic BP: 9 $\pm$ 6.1 mmHg, diastolic BP: 3 $\pm$ 4.8 mmHg). Microalbuminuria levels in all groups decreased significantly when compared to the period of 50 mg losartan alone ($P<0.05$). Renal functions of the groups did not change significantly. But creatinine clearances significantly increased in all groups after the randomization, although there was no significant difference between groups.
Conclusion
We observed that the combination of carvedilol in hypertensive type 2 diabetics patients with microalbuminuria safely controlled blood pressure more effectively without additional benefit in reducing microalbuminuria

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Diabetes therapy & complications 2

GP103

Abstract withdrawn.

GP104

Non-stimulated c-peptide is independently associated with requirement at 1 year for insulin therapy in patients with diabetes: a retrospective cohort study of 872 patients

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Introduction
C-peptide is frequently used in clinical practice to estimate insulin secretion, and guide need for future insulin treatment. Present practice is based on studies with small patient numbers.
Aim
To explore the association between non-stimulated c-peptide and progression to insulin therapy in patients with diabetes.
Patients and Methods
1971 patients with c-peptide measurements were identified (February 2007–December 2016) within a single health board. 940 individuals also appeared on national diabetes database. 872 individuals within this dataset have a defined diabetes diagnosis and were analysed. The date of first encashed insulin prescription for each individual was extracted from the national diabetes dataset. Insulin-free survival (time to first insulin prescription or end of follow-up) in individuals who were insulin-naive at the time of c-peptide measurement was investigated using survival analysis. Individuals with c-peptide values below median were compared with those above median value. Time to insulin prescription was analysed using cox proportional hazard model with age and BMI as covariables. The positive predictive value (PPV) of c-peptide for predicting insulin use at 1 year was calculated in 0.2 nmol/l increments.
Results
458 individuals had BMI data available, and were insulin-naive at the time of c-peptide measurement. In this cohort a c-peptide in the lower half of the range of observed values (<0.76 nmol/l) is associated with a significantly decreased insulin-free survival time ($P<0.001$, HR 3.0). PPV for initial c-peptide(nmol/l) increments were: c-peptide 0.01-0.2 PPV = 0.95, 0.2–0.4 PPV = 0.67, 0.4–0.6 PPV = 0.6, 0.6–0.8 PPV = 0.43, 0.8–1.0 PPV = 0.3.
Conclusion
Unstimulated c-peptide is independently associated with increased probability of requiring insulin at 1 year. This is a simple test which offers potentially useful information allowing patients to plan for future treatment.

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GP105

Ceramide synthase 6 inhibition as a novel therapeutic approach for obesity and type 2 diabetes

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Excess consumption of saturated fatty acids may lead to an increased production of ceramides that contribute to development of insulin resistance and type 2 diabetes. Substantial research demonstrated that inhibition of ceramide biosynthesis ameliorates atherosclerosis, hepatic steatosis, insulin resistance and obesity. However, as ceramides and their sphingolipid products are involved in multiple fundamental cellular processes, concerns exist about possible risks or adverse effects resulting from overall inhibition of sphingolipid synthesis for treatment of chronic diseases. Therefore, the inhibition of specific ceramide species represents a new strategy for pharmaceutical intervention. Recent research demonstrated that specifically CerS6 mediated C16 ceramide synthesis plays a key role in the development of obesity mediated insulin resistance.
In the current study, we investigated the effects of specifically knocking-down CerS6 in ob/ob mice using CerS6 anti-sense oligonucleotides (ASO). In this animal model, CerS6 expression is significantly higher vs. lean control mice ($\sim$2 fold in the liver and BAT) which correlates with a 4-fold increase of C16 ceramide in the plasma and a 2-fold increase in the liver. CerS6 ASO treatment led to selective and significant $\sim$80% knockdown of the CerS6 expression in the liver and correlated with a significant 50% reduction of C16 ceramide in the liver and plasma compared to control ASO-treated ob/ob mice. CerS6 knockdown protected against body weight gain and was associated with a significant reduction in fat mass and blood glucose levels. Moreover, insulin resistance was significantly improved by ASO treatment as evidenced by oral glucose tolerance and insulin tolerance tests ($\sim$50% reduction in AUC during oGTT).
In conclusion, CerS6 dependent C16 ceramide synthesis represents a distinct sphingolipid species, which contributes to the development of obesity and insulin resistance and therefore may represent a unique and attractive novel target to treat obesity and type 2 diabetes.

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GP106

Outcomes of integrating personal continuous glucose monitors with insulin pumps in a University Diabetes Unit

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Objective
Personal continuous glucose monitoring (pCGM) with interstitial fluid glucose sensing is rapidly becoming the standard of care for real-time, intensive insulin therapy of diabetes. We report our experience of glycemic control in patients in an academic setting using minimally invasive pCGM with continuous s.c. insulin infusion (CSII, or insulin pump) vs CSII alone.
Methods
Over a two-year period, we reviewed all patients treated with insulin pumps at the Diabetes Unit of the Palmetto Health-University of South Carolina Medical Group. Group A (CSII alone) used only meters to self-monitor blood glucose, and while Group B additionally used pCGM integrated with CSII to adjust pump settings, including basal rate and/or short-acting bolus insulin doses, and change insulin-to-carbohydrate ratio and supplemental factor. The data was analyzed with respect to age, gender, glucose control as assessed by glycosylated hemoglobin (HbA1c), and severe hypoglycemia.
Results
There were 54 patients in group A and 59 in group B. They were comparable in mean age and gender breakdown (47.3 vs 45.2 years, and 66.8% vs 62.7% females, respectively). The average glycosylated hemoglobin (HbA1c) changed from 8.8% to 8.2% and from 8.2% to 7.3% from baseline to the end of one year in the two groups respectively. The number of severe hypoglycemic episodes per patient during the one year was 0.2 and 0.07 respectively.
Discussion
CSII patients who used pCGM were similar in demographics to those who used insulin pumps alone, but had a lower baseline A1c, exhibited a larger decrease in A1c at one year (0.9% vs 0.6%), and had fewer severe hypoglycemic events.
Conclusions
The better outcomes with pCGM-integrated pump therapy may be explained by a higher motivation ability for self-monitoring and care, and by the pCGM being a valuable informational tool in assessing glucose trends when used in properly chosen insulin pump patients who are managed by qualified experts.

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GP107

Specific Oct1 gene variants are associated with changes in the risk of cardiovascular death in metformin users

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Aim
Increased cardiovascular incidents and a high risk for microvascular complications are associated with type 2 diabetes. Worldwide, metformin is the most commonly prescribed antidiabetic drug. Polymorphisms in the *Oct1* gene can alter the function or activity of organic cation transporter 1 (Oct1), thus changing metformin efficacy (Oct1 acting as its main transporter) as well as influencing the actions of Oct1 physiological substrates. In the past, polymorphisms in *Oct1* were associated with cardiovascular risk factors, thus they might contribute to cardiovascular risk development.
We investigated, whether the Oct1 polymorphism rs3777392 is associated with increased risk for cardiovascular death in a cohort of patients with and without type 2 diabetes (T2DM) on various therapies.
Methods
Data from the LURIC study ($n=3316$), a prospective cohort study of Caucasians scheduled for coronary angiography were analysed. We identified 1820 non-diabetics, 1220 T2DM patients, including 73 metformin users (Met), 154 sulfonylurea users (SF) and 967 T2DM individuals without medication. Cardiovascular mortality was assessed in all groups according to Oct1 rs3777392 genotypes using Cox proportional hazard models and associations with cardiovascular biomarkers were investigated.
Results
Cardiovascular mortality risk for each minor allele copy was HR 2.08 (95% CI: 1.01, 4.28) only in metformin users. Variants of rs3777392 were associated with BMI, baseline insulin values and triglyceride levels in all T2DM patients ($P=0.016$, $P=0.048$ and $P=0.007$, respectively), patients without medication ($P=0.006$, $P=0.041$, $P=0.008$, respectively) and non-diabetics ($P=0.021$, $P=0.074$, $P=0.125$, respectively) but not in the Met and SF groups.
Conclusion
In our study, the minor allele of rs3777392 in the Oct1 gene was associated with an increased cardiovascular mortality risk in T2DM patients on metformin therapy, which might be due to loss of association with cardiovascular parameters. Besides very positive effects in the majority of metformin users, some individuals may profit from a pre-treatment genotyping and careful monitoring.

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GP108

Liraglutide improves carotid intima-media thickness in pre-elderly and elderly patients with type-2 diabetes: an 18-month prospective, real life study

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Introduction
Liraglutide exerts cardio-protective effects beyond of those on glucose metabolism, affecting several cardio-metabolic parameters, such as subclinical atherosclerosis. However, it is not known if those effects differ in the long-term between pre-elderly and elderly subjects with type-2 diabetes (T2DM).
Methods
We included 135 subjects with T2DM divided in 2 groups: i) 71 pre-elderly subjects (46 men and 25 women, 55 ± 7 years), and ii) 64 elderly subjects (33 men and 31 women, 70 ± 5 years). All subjects were naïve to incretin-based therapies and treated with liraglutide as add-on to metformin, 0.6 mg/day for two weeks, followed by a dose of 1.2 mg/day. At baseline and every 6 months fasting samples were taken for laboratory analyses and carotid-intima media thickness (cIMT) was assessed by B-mode ultrasound. Statistical analysis was performed by ANOVA and the Spearman correlation method.
Results
After18 months of liraglutide therapy HbA1creduced significantly in both groups (from 9.02 ± 1.06 to 6.93 ± 1.25 and from 8.50 ± 0.71 to 6.74 ± 0.90%, respectively) as well as fasting glycemia (from 9.57 ± 3.33 to 7.16 ± 2.83 mmol/l; and from 9.14 ± 3.71 to 7.28 ± 2.29 mmol/l, $P<0.0001$ for all. Anthropometric parameters changed although not significantly. Lipids, with the exception of HDL-cholesterol, reduced significantly only in pre-elderly subjects (triglycerides from 1.94 ± 1.48 to 1.57 ± 0.80 mmol/l, $P=0.0458$; total cholesterol from 4.90 ± 1.57 to 4.27 ± 1.04 mmol/l, $P=0.0025$; LDL-cholesterol from 2.92 ± 1.44 to 2.34 ± 0.91 mmol/l, $P=0.0054$. cIMT significantly decreased in both groups (from 0.96 ± 0.18 to 0.78 ± 0.20 mm; and from 0.98 ± 0.17 to 0.79 ± 0.20 mm, respectively; $P<0.0001$ for both). Changes in cIMT were positively associated only with changes in triglycerides in both pre-elderly ($r=0.245$, $P=0.0398$) and elderly ($r=0.566$, $P<0.0001$) groups.
Conclusion
Liraglutide significantly reduced cIMT in both pre-elderly and elderly subjects with T2DM, beyond glycemic control.

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GP109

Treatment of diabetic ketoacidosis at type 1 diabetes mellitus presentation: 13 year experience from a tertiary centre (2004–2016)

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Introduction
Diabetic ketoacidosis (DKA) is an endocrine emergency and the leading cause of morbi-mortality in children with type 1 diabetes mellitus (1DM). DKA treatment is still controverse, mainly regarding hydroelectrolytic replacement and insulin dose.
Aims
To evaluate efectiveness and safety of our tertiary centre protocol in DKA treatment, which included initial volume expansion with isotonic saline in the first two hours followed by 0.45% sodium chloride with 5% glucose and insulin infusion (0.1 U/kg per h). Potassium replacement with potassium phosphate in the first 12 h.
Methods
Retrospective study of all children with moderate and severe DKA 1DM presented from 2004 to 2016. Data collected: insulin infusion dose, glycemia, pH. Osmolarity, corrected sodium, potassium and phosphate along the first 12 h of treatment. Statistic analysis with SPSS21 ($P<0,05$).
Results
179 new cases of 1DM were admitted and 45 (25%) had DKA at presentation (15 severe, 12 moderate and 18 mild DKA). Within moderate and severe DKA (N=27), 18(67%) were female and mean age at diagnosis was 8.5 ± 3.8 years. Means at admission were: 528 ± 138 mg/dl glycemia, 310 ± 12 mosm/kg osmolarity, 146 ± 5 mmol/l corrected sodium, 4.5 ± 0.73 mmol/l potassium and 1.5 ± 0.5 mmol/l phosphate. Mean insulin infusion dose at treatment start was 0.08 ± 0.03 U/kg per h. Along the first 12 h mean replacement doses were 4.3 ± 1.3 gr/U per h of glucose, 0.13 ± 0.04 mmol/kg per h of potassium, 0.33 ± 0.1 mmol/kg per h of sodium and 0.06 ± 0.02 mmol/kg per h of phosphate. There were 12(45%) cases of hypokalemia and 10(37%) of hypophosphatemia. There was no hypocalcemia nor cerebral edema. There was statistical significance in variation regarding glucose, pH, corrected sodium and osmolarity along the 12 h ($P<0.0001$). Sodium decreased in the first 8 h. Potassium decreased along the first 4 h and rose from 8 h forwards.
Conclusions
Our protocol allowed a safe treatment of DKA at 1DM presentation, with gradual correction of dehydration and acidosis. However, sodium and potassium replacement should be adjusted, leading to our actual protocol.

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GP110

The method of reporting hypoglycemia in Randomized Control Trials (RCTs): a systematic review on RCTs conducted for SGLT-2 inhibitors

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Background
Hypoglycemia is an important side effect in pharmacotherapy of patients with diabetes mellitus. Medical organizations have tried to define hypoglycemia in clinical practice and RCTs with scientific statements and guidelines.
Objective
To explore the method of reporting hypoglycemia conducted on SGLT-2 inhibitor RCTs.
Methods
A systematic review using PubMed to find data on RCTs conducted for SGLT-2 inhibitors, limited to English language.
Results
Of 155 RCTs, 95(61.3) (n(%)) were found to have defined and reported hypoglycemia. The results showed that 8(5.2) RCTs were reported as event/arm, 15(9.7) as event/combined all arms, 69(44.5) as event/patient/arm and 3(1.9) RCTs reported as both event/arm and event/combined all arms. Additionally, 3(1.9) RCTs defined hypoglycemia but did not report it. Hypoglycemia was neither defined nor reported in 57(36.8) of the RCTs. In addition, 41(26.5) RCTs had hypoglycemic episodes that were confirmed, by glucose threshold, whereas only 24(15.5) RCTs had episodes that were reported as symptoms from patients. Hypoglycemic episodes were reported and confirmed in 5(3.2) of the RCTs and 27(17.4) showed that the episodes were reported or confirmed.
Conclusion
This study illustrates that around 40% of RCTs on SGLT-2 inhibitors did not define and report hypoglycemia. The method of reporting hypoglycemia was variable among the RCTs. Almost half the RCTs reported as event/patient/ arm. Additionally, a quarter of RCTs only reported hypoglycemic episodes with confirmation of glucose threshold. Future RCTs should unify the reporting of hypoglycemia for safety assessment of diabetic medication.

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GP111

Hepatic effects of GLP-1 receptor agonist Liraglutide in patients with type 2 diabetes

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Introduction
The aim of this study was to analyze the effects of Liraglutide in hepatic steatosis as well as clinical and biochemical data before and after 6 months.
Methods
We have retrospectively analysed epidemiological, anthropometric and laboratory data of 83 type 2 diabetic patients treated with Liraglutide and followed at different endocrinology units across east Andalusia. We have evaluated nonalcoholic fatty liver disease using liver enzymes and hepatic steatosis index (HSI). HSI > 36 reflects fatty liver, < 30 absence, and intermediate values are considered indeterminated.
Results
Of the 83 cases evaluated, 54.2% were male, mean age 56.76 ± 9.87 years, time from diagnosis 9.46 ± 5.46 years. Prior to treatment, patients had BMI 37.68 ± 6.82 kg/m^2, blood pressure 138.80/82.87 mmHg, fasting glucose 187.33 ± 55.11 mg/dl, glycated hemoglobin (HbA1C) 8.62 ± 1.3%, total cholesterol 178.1 ± 35.74 mg/dl (c-LDL 97.66 ± 32.16 mg/dl, c-HDL 44.54 ± 13.78 mg/dl), triglycerides 197.64 ± 24.19 mg/dl, AST 29 ± 20.311 U/l, ALT 39.88 ± 31.69 U/l and HSI 46.44 ± 6.48.
Clinical and biochemical figures at 6 months were: BMI 36.08 ± 6.32 kg/m^2, blood pressure 132.76/77.41 mmHg, fasting glucose 165.16 ± 56 mg/dl, HbA1C 7.73 ± 1.33%, total cholesterol 170.6 ± 39.19 mg/dl (c-HDL 46.25 ± 15.03 mg/dl, c-LDL 87.74 ± 30.5 mg/dl), triglycerides 198.29 ± 22.29 mg/dl, AST 24.97 ± 12.49 U/l, ALT 32.76 ± 18.24 U/l, and HSI 43.98 ± 6.38.
Statistically significant differences were found regarding several variables, such as BMI, HbA1C, fasting glucose, blood pressure and c- LDL, as well as in ALT and HSI, showing an amelioration in hepatic steatosis. No differences were found in total cholesterol, c-HDL, triglycerides and AST.
Conclusion
In our study, six- month therapy with Liraglutide improves, not only risk factors for cardiovascular disease, but also hepatic steatosis as shown by a decrease in HSI index and ALT.

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GP112

Exenatide treatment causes suppression of serum fasting ghrelin levels in patients with type 2 diabetes Mellitus

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Aim
Ghrelin plays an important role in the stimulation of food intake and long-term regulation of body weight. In present study we investigate the long term effect of exenatide treatment on serum fasting ghrelin levels in patients with type 2 diabetes mellitus.
Methods
Type 2 diabetic patients who were using metformin with and without the other oral antihiperglycemic drugs on a stable dose for at least 3 months were enrolled in the study. Body mass index (BMI) > 35 kg/m^2 and hemoglobin A1c (HbA1c) > 7.0% were the additional inclusion criteria. Oral antihyperglycemic drugs other than metformin were stopped and metformin treatment was continued at 2000 mg per day. Exenatide treatment was initiated at 5 mcg per dose sc twice daily and after one month the dose of exenatide was increased to 10 mcg twice daily. Changes in anthropometric variables, glycemic control, lipid parameters, and total ghrelin levels were evaluated at baseline and following 12 weeks of treatment.
Results
Thirty-eight patients (male/female = 7/31) with type 2 diabetes mellitus entered to the study. Mean age of patients was 50.5 ± 8.8 years with mean diabetes duration of 8.5 ± 4.9 years. Mean BMI was 41.6 ± 6.3 kg/m^2 and mean HbA1c of patients was 8.9 ± 1.4%. Percentage change in weight of patients was −5.2 ± 3.7% following 12 weeks of treatment. BMI and HbA1c levels of patients were decreased significantly ($P < 0.001$ and $P < 0.001$; respectively) while there was no change in lipid parameters. Serum fasting ghrelin levels were suppressed significantly after 12 weeks of exenatide treatment compared with baseline values (328.4 ± 166.8 vs 245.3 ± 164.8 pg/ml) ($P = 0.024$).
Conclusion
These results suggest that the effect of exenatide on weight loss may be related with the suppression of serum fasting ghrelin levels, which is an orexigenic peptide.

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Endocrine Nursing

GP113

Impact of the socio-economic level on the management in type 2 diabetes

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Diabetes is a chronic disease whose associated comorbidities are largely influenced not only by pathology but also by socio-economic conditions. The aim of this study is to investigate the influence of social conditions on the evolution of diabetes. A retrospective, comparative study of 111 patients with type 2 diabetes Follow-up in the Endocrinology-Diabetology department in hospital Hedi Chaker of Sfax. Patients were divided into two groups with unfavorable (G1) and good (G2) socio-economic conditions, both groups had 58 and 53 patients, respectively. The average age of our patients was 54 in G1 and 49 in G2 ($P = 0.7$). A female predominance was noted in the G 1/64% while the male sex was predominant in the G 2: 80%. The age of diabetes was comparable between the two groups (12.5 years vs 11 years, $P = 0.09$). Fasting glucose was significantly higher in G 1 (15 mmol / l) versus 9 mmol / l in G2 ($P < 0.0001$). The number of hospitalizations was higher in G1: 2.8 versus 1.3 in G2 ($P = 0.005$). The food investigation showed a higher caloric intake in G2 estimated at

2615 Kcal/d versus 2184 Kcal/d for the G1. Infectious complications and amputation were significantly more frequent in G 1 compared to G2. Similarly, microangiopathic complications were more frequent in G1 patients. This imbalance was related to management difficulties, so no patient of G1 group was placed under insulin analogs versus 23% of G2 patients. Socioeconomic status seems to play a crucial role in the glycemic balance and the occurrence of chronic complications of diabetes. This is mainly due to the restriction of access to health care structures and therapeutic, sometimes expensive, and the level of instruction of these disadvantaged classes.

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GP114

Outcomes of a nurse-led thyroid clinic at a tertiary-care endocrine centre

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Introduction
A Nurse-led Thyroid Clinic (NLTC) in a tertiary-care Endocrinology centre (EC) in Oxford was set up in 2005. The patients were managed by an Endocrine Advanced Nurse Practitioner.
Aims
To evaluate standard of clinical care (SOCC) quality of service provision (QOSP) and cost effectiveness (CE) of the NLTC.
Methods
Three aspects of service were assessed:

a) *SOCC*: Data were collected for patients managed over 12 months between 1/2014 and 1/2015. Diagnosis, investigations and management plans for individual patients were compared against accepted regional and national guidelines.
b) *QOSP* was evaluated from standardised patient feedback questionnaires (PFQ) that were anonymised for confidentially
c) *CE* was analysed through collection of retrospective data of filed patients clinic lists between 1/2014 and 1/2015. A new patient (NP) tariffed at £120, follow-up, at £90 per visit according to finance department protocol. Annual data recorded of non-face-to-face-telecommunication (NFTFT) costed at £30 per call.

Results

a) *SOCC*: 214 patient appointments for 134 patients were reviewed; 112 patients had Graves' disease, 10 subacute thyroiditis,10 toxic nodular diseases and two subclinical thyrotoxicosis. Patients were managed with a departmental protocol based on British Thyroid Association guidelines 2006.
b) *QOSP:* 50 out of 60 PFQ were returned (34 women/16 men, median age 52.3 years, range 21–85). Majority of the patients expressed high satisfaction with the quality of services provided, with 86% "Extremely Likely" to recommend the TNLC to friends and family.
c) *CE*: New and follow-up patients generated an annual income of £20,490. NFTFT calls (908 patients) generated an income of £27,240. 41 empty NP clinic slots, 22 follow up cancellations and 19 patients who failed to attend the clinic, amounted to a loss of £8610.

Conclusions
The audit supports the value of NLTCs in EC's with a significant thyroid-dysfunction workload. These clinics can provide high quality of clinical care and potentially be cost-effective.

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GP115

Education, patient empowerment and admission avoidance

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It is paramount to educate our patients, thereby empowering them to manage their chronic conditions. This is an evidence based fact. As healthcare professionals our challenge is to provide and ensure patients have been well informed in order to understand and manage their condition successfully on a daily basis.
In today's healthcare service patient education has become a casualty of the reduced resources; there are ever increasing restrictions on both the length and frequency of consultations.
Endocrine teams and in particular the specialist nurses role involves teaching patients with new diagnosis as well as building on information they have gained from their consultations etc. We wanted to see how many patients with pituitary/adrenal failure have gaps in the understanding of their condition, particularly in relation to their sick day rules.
We surveyed 18 patients on hydrocortisone replacement who completed a questionnaire assessing their knowledge and understanding of their condition. When asked what action they would take if they had flu and a high temperature, nine would double their steroid dose, three would triple it. This leaves six patients at potential risk of admission. When asked about vomiting and/or diarrhoea, six said they would double their dose, one would triple it and one would take their emergency hydrocortisone injection, potentially leaving ten patients at risk of an Addisonian crisis. Within this group of patients seven had been given intra muscular hydrocortisone, but only four had been shown how to use it.
The national annual admission rate for patients with Addison's disease/syndrome is 8%. Within this sample group the admission rate was 27.7%.
We need more resources to build on our initial and ongoing education/teaching programme to work on patient awareness of their condition as a whole, including sick day rules.

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GP116

Recovery of the hypothalamus-pituitary-adrenal axis after transsphenoidal surgery for pituitary adenomas

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Purpose
Hypopituitarism is frequently associated with lifelong replacement therapy. However, it has been suggested that recovery from hypopituitarism after transsphenoidal surgery (TSS) for pituitary adenomas may occur during follow up. The aim of this study was to assess the frequency of hypothalamus-pituitary-adrenal (HPA) axis recovery after TSS in patients with non-functioning pituitary adenomas and acromegaly.
Methods
Over the 3-year observational study-period, 146 patients underwent transsphenoidal pituitary surgery. The metyrapone test was used to assess the HPA-integrity after 1 week and after 3–12 months after TSS. The pituitary-thyroid, -gonadal and growth hormone axis were measured one week after TSS.
Results
Patients with Cushing's disease and panhypopituitarism were excluded from the study. 44 subjects had a sufficient HPA-axis one week after surgery. 14 subjects with an insufficient HPA-axis were excluded, as the 11-deoxycortisol after metyrapone was <100 nmol/l. Eighteen patients were eligible to re-assess the HPA-integrity. In 10 out of 18 patients, insufficiency of the HPA-axis appeared to be reversible. Eight patients had persistent secondary adrenal insufficiency. The number of other pituitary hormone insufficiencies one week after TSS was associated with recovery of the HPA-axis after TSS.
Conclusion
After TSS, recovery of the HPA-axis over time does occur in a proportion of subjects. Therefore it is recommended to re-assess the HPA-integrity during follow up to prevent unnecessary glucocorticoid replacement therapy. Pituitary adenoma, reversible hypopituitarism, recovery HPA-axis, pituitary surgery, adrenal insufficiency.
Key words
Pituitary adenoma, reversible hypopituitarism, recovery HPA-axis, pituitary surgery, adrenal insufficiency.

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GP117

The Swedish Pituitary Register Nursing Group (SPRNG) Projects and Experiences

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Background
The Swedish Pituitary Register (SPR) is a national quality register founded in 1991 by the Swedish Pituitary Group and it provides important data in the

continuous quality assessment and improvement work within the Swedish health care system.
The Swedish Pituitary Register Nursing Group (SPRNG) was formed by nurses at the University Hospitals, working with the register, in 2011.
Purpose
To increase the coverage rate and improve the data quality in the register.
To strengthen the endocrine nurse role and encourage and promote the nurses to own register projects.
Methods
The SPRNG, consisting of endocrine nurses, one responsible for the register at each University Hospital. Meetings are performed 1–2 times /year. The SPRNG is working for the same routines considering the register and is actively working with projects in the SPR.
Results
Since the SPRNG was started the coverage rate and the reporting speed in the SPR have increased. Several nurse projects during 2016. Implement PREM and disease-specific PROM variables. User Survey in the register. Register data template for the hospitals operations managers and for the public to increase the knowledge of this patient group.
A study 'Time from first symptoms to diagnosis', where approximately 600 patients with pituitary tumours (Acromegaly, Mb Cushing, NFPA and Prolactinomas) are included, will be compiled 2017. The purpose of this study is to find these patients earlier and to identify how we can do that.
The SPRNG have been active at international conferences with several abstracts. Meeting and sharing experiences of the register with finish endocrine nurses.
Conclusion
The SPRNG has contributed to increase the data quality and coverage rates in the SPR.
The SPRNG is a good example of how nurses can be supported by each other and share experiences, skills and knowledge but also operate their own project.

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Endocrine Tumours

GP118

Luteinizing hormone receptor mediated GATA4 induction promotes adrenocortical tumorigenesis in gonadectomized mice

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The role of luteinizing hormone (LH) and its receptor (LHCGR) signaling in the adrenal gland remains unknown. Gonadectomy-induced chronically elevated LH levels trigger neoplastic transformation in genetically susceptible mouse strains (DBA/2J) or transgenic mice expressing the Simian Virus 40 T antigen (SV40Tag) oncogene under inhibin-α promoter (inhα/Tag). In order to study the functional role of LHR and GATA4 in the onset and progression of adrenocortical tumors in ovariectomized (OVX) inhα/Tag females *in vivo* and *in vitro*, we crossbred the inhα/Tag with *LHR* knockout (LuRKO) mice. Additionally we knocked out *Lhr* (*Lgr*–ko) and *Gata4* (*Gata4*-ko) in the Cα1 cell line derived from an adrenal tumor of inhα/Tag mice. In inhα/Tag mice, we identified two distinct types of SV40Tag expressing neoplastic cells. The first type, subcapsular non-steroidogenic spindle-shaped A-like cells, which never developed to tumors, were found in both intact and OVX inhα/Tag females. The second type, parenchymal tumor cells in the topmost layer of zona fasciculata, later forming tumor foci, were found only in OVX inhα/Tag mice. Lack of LHR in OVX inhα/Tag/LuRKO mice adrenals prevented tumor formation. Histological and immunohistochemical analyses revealed the presence of hyperplastic cells expressing SV40Tag in parenchyma. These cells were devoid of GATA4 and showed signs of apoptosis. *In vitro*, a complete inactivation of *Gata4* significantly decreased cell proliferation, expression of tumor markers (*Inha*, *SV40Tag*, *Lhcgr* and *Esr1*) and gonadal-like steroidogenic phenotype of Cα1 cells. Our results suggest that at first, the tumor formation was LH-dependent, but later on became LH-independent. GATA4 is responsible for the *Inha/SV40Tag* expression, gonadal steroidogenic phenotype and possibly pro-survival pathways. Identifying GATA4 downstream targets in the adrenocortical tumors in both, inhα/Tag and human could be of importance to find potential therapeutic targets for human adrenocortical tumors.

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GP119

Targeted molecular analysis in adrenocortical carcinomas: a way towards personalized medicine

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Adrenocortical carcinoma (ACC) is a rare tumor with heterogeneous outcome and no available targeted therapy. The aim of the study is to identify prognostic molecular markers and novel potential drug targets.
A total of 43 FFPE tumor samples were retrospectively investigated for somatic mutations and copy number variations (CNV) by next-generation sequencing (160 cancer-related genes, Qiagen). Gene expression was evaluated by quantitative RT-PCR in a subgroup of 25 ACC samples (84 cancer drug targets, Qiagen). The major clinical endpoint was progression free survival (PFS).
We observed 123 protein-altering mutations in 47 genes (median 2 per sample), with the most frequent known to be ACC-related: TP53 (28% of samples), *CTNNB1* (26%), *ZNRF3* (19%), *NF1* (16%) and *GNAS* (14%). Notably, we also detected recurrent mutations in genes previously not clearly associated with ACC (i.e. *ABL1*, *KDM6A*, *TSC1*, *FBXW7*, *DNMT3A*, *BRCA1*, *BRCA2*). Some focal CNV were found in >30% samples (i.e. gains of *CDK4*, *MDM2*, *IL7R*, and losses of *TNFRSF14*). A noisy pattern was associated to a shorter median PFS than chromosomal or quiet pattern (4.5 vs 7 vs 14 months, respectively, $P=0.07$). Most affected genes were involved in p53/Rb or Wnt/β-catenin pathway or chromatin remodeling, but also in immune response or DNA repair mechanisms. Patients with alterations in DNA repair genes had longer PFS than others ($P=0.067$, HR = 1.78). At mRNA level, most frequently overexpressed genes (> 2.5 fold change) were *IGF2* (92%), *TOP2A* (92%), *CDK1* (72%) and *PLK1* (60%). Tumors with increased *BUB1B-PINK1* (>5.9) were associated with a trend to worst PFS ($P=0.16$, HR = 1.98).
This pilot study demonstrates the feasibility of molecular analysis in FFPE samples. We identified some genetic variants previously not associated with ACC and new potential drug target genes. These results will be validated in a larger series in order to path the way to a personalized medicine in ACC.

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GP120

Evaluation of the occurrence of the manifestations of Carney complex in a french cohort of 70 patients during a three years standardized follow-up

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Introduction
The Carney Complex is a multiple endocrine and non endocrine neoplasia mostly due to PRKAR1A mutations. Spectrum of manifestations and genotype-phenotype correlations have been previously described by retrospective studies. A prospective study evaluating the occurrence of the different manifestations was needed to precise the optimum follow-up.
Methods
Multi-center national prospective study (Clinical Trials NCT00668291) including 70 patients mutated or wild-type for PRKAR1A followed prospectively during 3years with screening of the different manifestations by annual clinical, biological and radiological evaluation.
Results
The cohort was compound of 50 females and 20 males with a mean age at 35.4years +/−16.7. Prevalence of cardiac myxomas at the end of the follow-up was 22.9% with newly diagnosis during the study period for 3 patients. Forty-four% of patients with myxomas had related stroke attack and 56% had recurrences. Median delay between recurrences was 3.8years (minimum-maximum: 0.8–24). Primary pigmented adrenal nodular disease was diagnosed in 57.1%. Skin manifestations, abnormal somatotroph hormonal tests and thyroid tumors were observed respectively in 58.6, 21.4 and 12.9%. Four% had melanotic shwannomas confirmed by histology. Spinal magnetic resonance imagery revealed lesions for 8.6%. Characteristic multiples calcified tumors on testicular ultrasonography were present in 35% of male patients. Ten% of female patients had surgery for breast myxoma or adenofibroma. Forty% had lesions classified ACR2-3 at mammography. Interestingly, four patients (8%) had breast adenocarcinomas (11.1% of female older than 30years). Eighty-three% of patients had PRKAR1A mutations. Patients carrying the mutation c.709-7del6 (34% of the cohort) had no manifestation or phenotype restricted to adrenal, lentigines and abnormal somatotroph test.
Conclusion
The penetrance of the disease is high after screening except for patient carrying the c.709-7del6 mutation. This study highlights the importance of an annual follow-up, with especially annual cardiac imaging for patients with history of cardiac myxomas and earlier and regular senologic evaluation.

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GP121

Immunity in adrenocortical carcinoma patients – interplay between anti-cancer immunity and steroid hormones

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Adrenocortical carcinoma (ACC) is one of the most aggressive endocrine malignancies. By applying a 'multiple omics' approach, we recently identified two distinct subgroups of ACC patients, a good prognosis "immune" and bad prognosis "steroid" phenotype.
We hypothesized that the steroid phenotype is associated with glucocorticoid-induced suppression that can be 'rescued' by reactivating the immune system using immune checkpoint inhibitors and inhibitors of steroidogenesis.
To assess changes induced by ACC on circulating immune cells we isolated PBMCs from blood of 19 healthy controls = HC and 163 ACC patients (41: tumour free = TF, 82: tumour present without cortisol excess = TP and 40: tumour present and cortisol excess = CE) and performed FACS analyses to quantify T-cells (CD3 + CD4 + and CD3 + CD8 +), B-cells (CD19), monocytes (CD14) and regulatory T-cells (T-reg) as a sign of immune suppression (CD4 + $CD25^{high}FOXP3+$). Using immunofluorescence, we analysed the presence of tumour infiltrating T-cells, Tregs, B-cells, dendritic cells (CD209 +) in full FFPE from 58 primary ACC tumours. Furthermore, expression of immune checkpoint-markers programmed death 1 (PD1) and its ligand PDL1 was analysed by IHC. From the peripheral cells the percentage of Treg in the circulating T-cell population correlated significantly with tumoural and steroid secretion status (4.4 ± 1.2 in HC, 7.9 ± 6.1 in TF, 9.0 ± 7.9 in TP and 11.0 ± 7.8 in CE, $P < 0.01$). Using median as cut-off, patients with increased percentage of peripheral Treg had a lower survival rate (HR = 1.8, 95%CI 1.0-3.1, $P = 0.02$). Most tumours presented a tumour infiltrate (T-cells: 80%, 37 ± 65 cells/HPF, cytotoxic T-cells: 72%, 24.9 ± 53.0, T-helper: 57%, 19.3 ± 16.9 cells/HPF, Treg: 48%, 3.8 ± 3.8, dendritic cells: 73%, 5.8 ± 3.7, B-cells: 0%, PD1: 36%, 14.7 ± 30.1, PDL-1: 83%, 34.6 ± 81.6). The only tumour infiltrating cells associated overall survival were the CD4 + T-helper cells (HR for death: 0.34, 95%CI 0.12–0.95, $P = 0.005$).
In conclusion, ACC patients are characterized by increased circulating immune inhibitory Tregs and tumour infiltrating CD4 + T-helper cells have a positive influence on patient survival.

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GP122

The natural history of adrenal incidentaloma – results from the international prospective multi-centre EURINE-ACT study

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Background
Adrenal masses are discovered in 5% of abdominal imaging scans. Work-up aims at exclusion of malignancy and hormone excess. However, estimates of these risks derive from retrospective studies only, mostly small and with significant selection bias.
Methods
Prospective multi-centre study (2011–2016) in 14 centres (11 countries) of the European Network for the Study of Adrenal Tumours (ENSAT) with prospective consecutive enrolment of patients with newly diagnosed adrenal mass. Extra-adrenal malignancy and phaeochromocytoma were exclusion criteria. Diagnosis was confirmed by histology or imaging follow-up.
Results
We enrolled 1994 patients, 1746 (87.6%) with a benign adrenocortical adenoma (ACA), 83 (4%) with other benign masses (e.g. adrenomyelolipoma, cyst), 106 (5.3%) with adrenocortical carcinoma (ACC) and 59 (3%) with other malignant masses (e.g. metastases, sarcoma). Risk of ACC was highest in young patients (< 40yrs:13%; 40–60yrs:6%; > 60yrs:3%, $P < 0.0001$) and in large masses (> 4 cm:21%, < 4 cm:0.4%, $P < 0.0001$). Of 1746 patients with ACA, imaging for exclusion of malignancy included unenhanced CT in 1301 patients, with tumour density < 10HU indicative of a benign tumour in 69%, with 16% borderline (10–20HU) and 15% suspicious (> 20HU) results. MRI with chemical shift results in 271 ACA patients were indicative of a benign lesion in 79%. In 829/1746 (47%) ACA patients, two or more imaging studies were performed; 19% underwent three or more. Upon re-imaging after ≥ 6 months, the adrenal mass appeared stable in size 601 of 629 ACA patients (96%). Mild autonomous cortisol excess (MACE) was detected in 547/1316 (42%) patients with ACA. Adrenalectomy was performed in 21% (370/1746) of ACA patients. Of those, 222 (60%) had overt hormone excess and 64 (17%) had MACE (70; 18%); the remaining 84 patients (23%) had non-functioning ACA.
Conclusions
Overall risk of ACC is 5.3% and is highest in young patients with adrenal mass size > 4 cm. ACAs are frequently misclassified as malignant by routine imaging, resulting in a high rate of interval imaging and unnecessary adrenalectomies.

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GP123

Outcome of patients with adrenocortical cancer after discontinuation of adjuvant mitotane therapy

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Background
Adjuvant mitotane therapy is frequently used in Europe following surgery for adrenocortical carcinoma (ACC). Management of adjuvant mitotane is mainly empirical and a major open question is the optimal duration of therapy, because no study has ever addressed this issue.
Objective
We aimed to assess the outcome of ACC patients who were treated with adjuvant mitotane for at least one year following surgery and then discontinued therapy for other reasons than ACC recurrence.
Design
We did a retrospective analysis of 132 patients (91 F, 41 M; median age 44 years) with histologically confirmed ACC who were treated at 9 European centres and 1 centre in Canada since 1999.
Results
Tumour stage was ENSAT I, 11%; ENSAT II, 79%; ENSAT III, 20%; hormone secretion was present in 44% and resection status was R0, 83% and Rx, 17%. Median Ki-67 was 10% and Weiss 6. Duration of adjuvant mitotane therapy was 34 months (12–141). Median duration of follow-up was 79 months (31–280), including 34 months after discontinuation (1-263). Seventeen patients (13%) recurred after treatment discontinuation with a recurrence-free survival from surgery of 74 months (31–277) and tumour-free survival after mitotane discontinuation of 32 months (1–263). The only difference in prognostic characteristics between patients with recurrent ACC and the remainders was a higher number of secreting tumours. Interestingly, no recurrence was observed among the 41 patients (31%) treated for >48 months; such patients had similar prognostic characteristics and follow-up duration after mitotane discontinuation than the remainders.
Conclusions
These first results suggest that a prolonged duration of adjuvant mitotane therapy may be associated with better recurrence-free survival.

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GP124

VHL Genotype and risk stratification of pancreatic neuroendocrine tumors in patients with von hippel-lindau disease

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Background
About 8–20% of patients with von Hippel-Lindau disease (vHLd) develop pancreatic neuroendocrine tumors (PNETs). However, prognostic markers for these tumors are lacking. The VHL gene mutation type is associated with the clinical phenotype of vHLd. Hence, we aimed to determine whether VHL mutation characteristics may be associated with PNETs phenotype in patients with vHLd.
Methods
A prospective study of patients with vHLd and PNETs with follow-up imaging. *VHL* mutation type and position were defined using Sanger sequencing of germline DNA.
Results
182 patients (476 PNETs) were followed for a median of 52 months (range 3–84). The *VHL* gene was sequenced in 154 patients: 75 patients (48.7%) had a missense mutation [MisM], 51 (33.1%) - deletion, 12 (7.8%) - nonsense, one (0.6%) - rearrangement, and 15 (9.7%) had frameshift mutations. Patients with a largest lesion diameter <1.2 cm had a lower risk for metastases (Log-Rank test, $P=0.006$) compared with larger diameters, whereas those with diameter >3 cm had higher risk for metastases compared with other patients (Log Rank test, $P=0.007$). Patients with MisM had a higher risk of requiring an intervention (Log-Rank test $P=0.01$) and for developing metastases during follow-up ($P=0.007$) compared to those with other mutation types. Among patients with a largest lesion diameter between 1.2 and 3 cm, those with MisM had higher risk for metastases (Log-Rank test, $P=0.048$) compared to other mutation types, and patients with mutation positioned in exon 3 of the *VHL* gene had higher risk for requiring intervention both in univariate ($P=0.03$) and multivariate analysis (Hazard ratio 2.9, 95% confidence interval 1.2–7.2, $P=0.02$).
Conclusion
Lesion diameter should be the pivot factor in directing PNETs management in vHLd. Among patients with a largest PNET diameter >1.2 and <3 cm, *VHL* genotyping may be useful for risk stratification.

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GP125

GPER-stimulation increases proliferation in colorectal cancer via the Hippo signalling pathway

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Colorectal cancer (CRC) is the 2nd most commonly diagnosed cancer in Europe. Previously, we have shown steroid sulphatase (STS), the enzyme that converts conjugated oestrogens to their active forms, is significantly upregulated in human CRC tissue. Furthermore, increased STS activity substantiates greater CRC tumour burden in mouse models. Here we demonstrate that this oestrogen-induced increase of CRC proliferation is mediated by G-protein coupled oestrogen receptor (GPER) via Hippo pathway signalling through the yes-associated protein 1 (YAP1), transcriptional coactivator with PDZ-binding motif (TAZ), and connective tissue growth factor (CTGF).
To examine how GPER effects CRC proliferation we employed *in vitro* BrdU proliferation assays and in vivo mouse models of CRC treated with G1, a GPER agonist, oestrogens and G15, a GPER antagonist. To investigate whether YAP1, its target gene CTGF, and its transcriptional co-activator TAZ, were altered by oestrogen-induced GPER signalling, we used immunoblotting and immunohistochemistry. YAP1 knockdown cells were also examined by treating them with G1, oestrogens and verteporfin, a YAP1 inhibitor, to assess the role of YAP1 on proliferation.
GPER-stimulation by G1 and oestrogen increased CRC proliferation in a dose-dependent manner, with this effect inhibited by G15 *in vitro* and *in vivo* CRC xenografts. YAP1 mediated this pro-proliferative response in CRC cells in contrast to colon adenoma cells. These findings were underpinned by increased phosphorylation of YAP1 and increased protein expression of TAZ and CTGF after oestrogen and G1 treatment. Intriguingly, CTGF up-regulation correlated with elevated GPER in human CRC tissue. In line with the above results, pharmacological inhibition of YAP1 and YAP1 knockdown blocked G1-induced cellular proliferation supporting the functional pro-proliferative role of YAP1 in CRC.
Taken together, our results propose a new oestrogen-driven pro-proliferative GPER-stimulated pathway through Hippo signalling in CRC. Further studies are required to establish whether this early metabolic response translates into increased cellular viability and cancer development.

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GP126

Inhibition of hRAS and CDK4/6 leads to an antiproliferative activity, blocks cell cycle and induces cell death in anaplastic thyroid cancer cell lines

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The unresponsiveness of anaplastic thyroid carcinomas (ATCs) to multimodal therapy represents the major challenge in thyroid cancer treatment. Our group previously showed that genes involved in cell cycle are differentially expressed in ATCs compared to normal thyroid, and that the most common mutations found in

these tumours are related with proliferation and cell cycle genes, namely *TP53*, *RAS*, *CDKN2A* and *CDKN2B*. Therefore, these genes are promising new targets in ATCs.
Here, we investigated if the inhibition of HRAS by Tipifarnib (TIP) and CDK4/6 by Palbociclib (PD) could be an option in ATC treatment. Different ATCs cell lines with distinct mutational patterns for *RAS, CDKN2A* and *CDKN2B* were used to evaluate the cytotoxic effects of these drugs. The IC50 for TIP and PD were determined, and the effects of these compounds in cell cycle, cell death and cell proliferation were analysed.
Cell culture studies demonstrated that low doses of TIP, at 48 h, induced cell cycle arrest in G2/M phase (50%, $P<0.01$), cell death (20%), and inhibition of cell viability ($P<0.001$), only in the *HRAS* mutated cell line. PD at low concentration increased significantly cell cycle arrest on G0/G1 phase (80%, $P<0.05$), only in cell lines with deletion/mutation in *CDKN2A* or *CDKN2B* genes, however only higher doses induced more than 50% of cell death. The inhibition of cell viability was more pronounced in cell lines with deletion/mutation in *CDKN2A* or *CDKN2B* genes than in wild type thyroid cancer cell lines or in normal thyroid cells ($P<0.05$).
In conclusion, this study suggests that TIP and PD, which are currently in clinical trials for other types of cancer, could play a relevant role in inhibiting the progression of ATC, depending on the specific molecular profile of the tumour.

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GP127

Benign prostatic hyperplasia is associatied with liver inflammation: it's time for prevention?

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Metabolic Syndrome (MetS) has been frequently associated with an overall inflammation status, called "metaflammation", including atherosclerosis and non-alcholic steatohepatitis (NASH), In this study we aimed to evaluate the relationship between intra-prostatic inflammation and NASH in a cohort of patients affected by BPH. Between January 2012 and January 2016, 132 consecutive patients with BPH-related lower urinary tract symptoms (LUTS) who underwent transurethral resection of the prostate were prospectively enrolled. The presence of NASH was evaluated using the NASH score: 1.18*MetS (yes = 1) + 0.45*Diabetes (yes = 2) + 0.15*fasting serum insulin + 0.04*serum AST − 0.94*(AST/ALT) − 2.89. A cut-off of 1.05 was set to predict NASH (AUC: 0.82). Prostate samples were anlaysized for the evaluation of inflammation and this was classified accordindg to Irani score (score from 0 to 6). Patients with viral hepatitis or alcohol steatohepatitis were excluded. A final cohort of 132 patients were included. The median age was 70.8 (interquartile range (IQR) 64.65–73.97), the median IPSS was 24.0 (IQR; 20.0–25.75) and the median prostate volume was 50.5 (IQR: 40.0–72.25). The prevalence of patients affected by MetS alone was 56.8% (76/132), by NASH in 56.8% (76/132) and by severe intraprostatic inflammation (Irani ≥ 4) in while by the both disease in 27.3% (36/132). When considering patients with Irani score ≥ 4, we observed significant increase of NASH score (-0.45 vs -1.01; $P<0.01$). The age-adjusted linear regression analysis demonstrated that waist circumference ($r=0.35$; $P<0.01$), fasting glucose ($r=0.32$; $P<0.01$), LDL ($r=0.15$; $P<0.05$), tryglycerides ($r=0.42$; $P<0.01$) and Irani score ($r=0.12$; $P<0.05$) were associated with increase in NASH score. The age adjuested logistic regression analysis revealed that Irani score ≥ 4 (OR: 3.06; $P<0.05$) was an independent risk factor of NASH. Further, the combination between MetS and NASH was significantly associated with severe intra-prostatic inflammation (OR: 10.8; $P<0.01$) while vs MetS as single alteration. Patients with BPH are more frequently associated with a parallel liver inflammation. These findings can be explained by the metaflammation condition, associated with metabolic aberration. Further studies should be conducted with the scope to revert or prevent prostate related inflammation.

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GP128

Peptides derived from the sst5TMD4 extracellular domain increase malignancy of endocrine-related cancer cells

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A growing number of studies suggest that extracellular fragments derived from plasma membrane receptors can play relevant functional roles in the development and progression of certain tumoral pathologies which might, therefore, serve as novel tools in the diagnostic and prognostic of such pathologies. In this scenario, the truncated somatostatin receptor sst5TMD4, which is overexpressed in various endocrine-related cancers (i.e. breast, prostate, neuroendocrine, liver and pituitary), is an aberrant splicing variant with only 4 transmembrane domains, wherein its C-terminal tail is exposed towards the extracellular matrix and could, therefore, be the substrate for proteolytic enzymes. Thus, to explore the plausible generation of soluble peptides derived from the sst5TMD4 extracellular domain and their potential patho-physiological implications, in silico and *in vitro* approaches were implemented using several cancer-derived cell lines (i.e. breast, prostate, neuroendocrine and liver). Firstly, in silico analysis predicted the existence of two cleavage sites for metalloproteases (MMP) 2, 9, 14 and/or 16, which could generate the release of three possibly soluble peptides. We, then, chemically synthetized these sst5TMD4-derived peptides and demonstrated that they were able to enhance malignancy features (proliferation, migration and dedifferentiation processes) in all the tumoral cell lines tested, probably acting through PI3K/Akt and/or MEK/ERK signalling pathways. Moreover, treatment with sst5TMD4-derived peptides altered the expression pattern of several genes involved in cancer development and progression (e.g. certain MMPs, Ki67, ARP2/3 or CD24/44). Therefore, based on these results, it is possible that sst5TMD4-derived peptides could be linked to the pathological role of sst5TMD4 previously observed in these tumoral pathologies. Altogether, these studies provide new information about the patho-physiological role of this truncated variant of sst5 and suggest that sst5TMD4-derived peptides could be potential candidates for future studies aimed to identify novel diagnostic, prognostic and/or therapeutic targets in certain endocrine-related cancers.

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GP129

Androgen receptor activation inhibits endothelial cell proliferation through an extra-nuclear signaling pathway

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The effect of androgen on angiogenesis has been documented. However, its molecular mechanisms underlying has not been well illustrated. Here, we show that treatment with an androgen receptor (AR) agonist, metribolone (R1881) at a range of concentrations (0.05–5 nM) or dihydrotestosterone (DHT) at a range of concentrations (0.4–40 nM) caused concentration-dependent inhibition of proliferation in human umbilical venous endothelial cells (HUVEC). The R1881-induced proliferation inhibition was also observed in human dermal microvascular endothelial cells (HDMVE). Blockade of the AR activity by pre-treatment with HF (5 nM), an AR antagonist, or knockdown of AR expression using the shRNA technique abolished the R1881-induced proliferation inhibition in HUVEC, suggesting that AR receptor activation can inhibit endothelial cell proliferation. To further delineate the signaling pathway involved in the AR activation-induced proliferation inhibition, our data indicate that R1881 inhibited proliferation in vascular endothelial cells through activating the AR/cSrc/AKT/-p38/ERK/NFκB signaling pathway, which in turn up-regulated the expression of p53, p21 and p27 protein, and finally reduced endothelial cell proliferation. Using the zebrafish model, we also demonstrate that R1881 inhibited angiogenesis through the AR-mediated pathway *in vivo*. The findings of the present study highlight the molecular mechanisms underlying AR activation-induced proliferation inhibition in vascular endothelial cells.

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GP130

Long non-coding RNA expression profiles in human parathyroid tumors

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Aberrant epigenetic signatures have been preliminary detected in parathyroid tumors, in terms of microRNAs (miRNAs) and methylome deregulation. In this study, we profiled the expression of 90 long non-coding (Lnc) RNAs in 4 parathyroid carcinomas (PCas), 12 parathyroid adenomas (PAds) and 2 parathyroid glands from normocalcemic patients (PaNs). Matched miRNA profiles were available for a subset of cases. Unsupervised clustering distributes samples in two groups clearly distinguishing PCas from PaNs. Further analyses identified 9 LncRNAs significantly deregulated between PCas and PaNs, 12 LncRNAs between PAds and PaNs, and 23 LncRNAs between PAds and PCas. Five LncRNAs with a fold change > 2.0, namely *MEG3*, *SGNH6* and *KCNQ1OT1* downregulated in PCas, *NEAT1* and *HAR1B* upregulated in PAds, were validated by qPCR in an independent series of 3 PCas, 4 atypical PAds, 22 PAds and 2 PaNs. PCas and atypical PAds showed similar expression levels of the 5 LncRNAs, whereas PAds were distinguished in two clusters with 10 PAds similar to PaNs. Clinically, PAds with the LncRNA profile similar to normal glands had lower mean serum calcium and ionized calcium than PAds with the LncRNA profile similar to PCas and PAds with intermediate profile (10.2 ± 0.5 vs 12.1 ± 0.2 vs 11.5 ± 0.8 mg/dl; $P = 0.006$ and 1.36 ± 0.06 vs 1.81 ± 0.11 vs 1.51 ± 0.08 mmol/l; $P = 0.0001$). Correlating LncRNA and miRNA profiles, we detected an association between the 5 deregulated LncRNAs and a set of miRNAs, including miR-296-5p, previously identified signifcantly downregulated in PCas. Finally, 10 PAds were characterized for the *MEN1* gene expression level: PAds with lower nuclear menin expression had decreased expression of two LncRNAs mapping on chromosome 11: *KCNQ1OT1* on 11p15.5 and *NEAT1* on 11q13.1. In conclusion, LncRNAs are deregulated in parathyroid tumors and identify 3 clusters of parathyroid tumors with different clinical activity. Moreover, LncRNAs deregulation in PAds may be modulated by the genetic background, while they may be involved in miRNAs deregulation.

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Female Reproduction

GP131

Neurokinin 3 receptor antagonism as a novel treatment for menopausal hot flushes: a phase 2, randomised, double-blind, placebo-controlled trial

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Background
Hot flushes affect 70% of menopausal women, can be long-lasting, and often severely impact on physical, psychosocial, sexual, and overall wellbeing. Hormone replacement therapy is effective but not without risk. Neurokinin B is an important mediator of hot flushes in rodents and elevated hypothalamic expression occurs in menopausal women. Neurokinin B acts via the neurokinin 3 receptor. We therefore hypothesised that neurokinin 3 receptor antagonism could be a novel treatment for menopausal hot flushes.
Methods
This phase 2, randomised, double-blind, placebo-controlled, crossover trial assessed the effectiveness of an oral neurokinin 3 receptor antagonist (MLE4901) on menopausal hot flushes in an ambulatory setting (Clinicaltrials.gov NCT02668185). Sixty-eight women were screened between February and October 2016 in a single-centre, of which 37 were randomised and included in an ITT analysis. Twenty-eight participants (aged 49–62yrs, experiencing >7 hot flushes/24 h some of which were reported as bothersome or severe), completed the trial, and were included in a Per-Protocol analysis. They received 4 weeks of MLE4901 and placebo in random order separated by a washout period. Randomisation was completed by a central computer, and participants were allocated to treatment number in numerical order. Primary outcome was total number of hot flushes during the final week of both treatment periods.
Findings
MLE4901 significantly reduced the total weekly number of hot flushes by 45% compared to placebo (adjusted means: placebo 49.01 (CI: 40.81–58.56), MLE4901 19·35 (CI: 15.99–23.42), $P < 0.0001$) (ITT). MLE4901 also significantly reduced weekly hot flush severity, bother, and interference compared to placebo by 41% ($P < 0.0001$), 45% ($P < 0.0001$), and 58% ($P < 0.0001$) respectively. Treatment was well tolerated.
Interpretation
Treatment with a neurokinin 3 receptor antagonist (MLE4901) could be practice changing as it safely and effectively relieves hot flush symptoms without the need for oestrogen exposure. Larger scale studies of longer duration are now indicated.
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GP132

Testosterone administration decreases insulin sensitivity (IS) in adult female sheep born to testosterone treated mothers

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Different animal models have been used to study the postnatal effect of a prenatal exposure to an androgen excess on the female offspring. We have established a sheep model to test the hypothesis that the intrauterine environment of the PCOS mother may play a role in the etiology of the PCOS. In this regard, our sheep model for the study of PCOS has the advantage that provides mainly an androgenized milieu to the fetus in comparison to pregnant PCOS women who offers a hyperandrogenic and hyperinsulinemic intrauterine environment to the fetus. Previous results from our laboratory have demonstrated that female sheep born to mothers receiving testosterone (T) during part of their pregnancy exhibit features from early postnatal life until adulthood resembling those of PCOS women. In the present work the programming effect of prenatal T on the IS was explored in adult females born to T treated mothers (T-females), and born to untreated mothers (C-females). Our aim was to establish if exogenous T may exacerbate the insulin resistance due to programming effect of prenatal exposure to T. Both groups were injected with T, twice weekly (40 mg per dose), for 8 weeks, beginning at 30 weeks of age. Females were estrous synchronized with prostaglandin and 48 hours after the last T dose, an IVGTT was carried out. On the day of the IVGTT, there was no difference in plasma concentration of estradiol, progesterone and T between groups. IS indexes were calculated with the plasma insulin and glucose concentrations during the IVGTT. Plasma levels of glucose were not different during the IVGTT but T-females secreted more insulin ($P < 0.05$) than C-females. The ratio insulin/glucose before the IVGTT tended to be higher in T-females ($P = 0.054$) and the IS Index-C tended to be lower in T-females compared to C-females ($P = 0.054$). Results show that T administration to T-females amplifies the effect of a glucose challenge on the insulin secretion compared to C-females, suggesting an exacerbation of the insulin resistance induced by fetal programming.

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GP133

Influence of BMI on AMH levels in non-PCOS women

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Introduction
Anti-Müllerian Hormone (AMH) is a useful marker of ovarian reserve (OR), since it remains stable inter/intra-cycles and presents a good correlation with ultrasonographic antral follicular count. Obesity/overweight are increasing and may affect the reproductive health. However, previous studies regarding the effect of body mass index (BMI) on AMH levels are discordant. Our main goal was to evaluate the influence of BMI in AMH levels in women with infertility.
Methods
Revision of medical records of 995 women who performed AMH determinations as part of their fertility workup, between 2011–2016. Women diagnosed with polycystic ovarian syndrome (Rotterdam criteria) were excluded. We analysed the influence of BMI, age, ethnicity, smoking and previous ovarian surgery on AMH levels.
Results
Median AMH concentration was 1.75(0–26)ng/dL and median age at AMH determination was 35(19–40)years. These women evidenced a median BMI of 23(15–39) kg/m^2 and had been struggling with infertility for 60(7–432) months. The majority [700(70.4%)] presented primary infertility. Caucasian women were more represented [889(89.3%)]. Smoking habits (present/past) were present in 359(36.1%), and 147(14.8%) harboured a history of ovarian surgery. On univariable analysis AMH was not correlated with BMI ($r=0.52/P=0.10$); the only factors influencing AMH were age ($P<0.001$), ethnicity ($P=0.005$) and previous surgery ($P<0.001$). On multivariable analysis, age was the only variable significantly associated with AMH, evidencing a reduction of 6.2% for each additional year ($P<0.0001$). Furthermore, we verified a trend suggesting an AMH reduction of 22% ($P=0.08$) in melanodermic patients comparing with the caucasian ones, when controlling for the other variables.
Conclusion
We report one of the largest series evaluating the influence of BMI on AMH levels and, consequently, on OR. BMI does not seem to affect AMH levels. The reported concerns on infertility in overweight/obese women may be related to follicular development/endometrial disorders, rather than decreased OR.

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GP134

Relugolix, an oral gonadotropin-releasing hormone (GnRH) receptor antagonist, in women with endometriosis (EM)-associated pain: Phase 2 safety and efficacy 24-week results

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Objective
The objective of this Phase 2 study was to evaluate the safety of relugolix when administered for 24 weeks in women with EM-associated pain. Efficacy was exploratory assessed using leuprorelin as a reference.
Design
This was an open-label extension study evaluating safety of 3 doses (10 mg, 20 mg, and 40 mg) of relugolix administered orally once daily for a total of 24 weeks in women with EM-associated pain, who had participated in a preceding 12-week study.
Materials and methods
Premenopausal women with EM-associated pain who completed a preceding 12-week study and were eligible to continue for an additional 12-week treatment were enrolled. The primary endpoint was the safety including assessment of change in bone mineral density using dual energy x-ray absorptiometry. Analysis sets were defined as all patients who were administered the study drug.
Results
Among the randomized patients in the preceding study (N=487), 397 were enrolled in this extension study; 77 to placebo, 78 to 89 to relugolix groups, and 69 to leuprorelin. Baseline characteristics were similar between randomized patients and all patients who entered the extension study. The incidences of adverse events including metrorrhagia, menorrhagia, and hot flush in the relugolix 40 mg group were similar to those in the leuprorelin group. Dose-dependent bone density loss was observed with relugolix treatment, with the relugolix 40 mg result consistent with the leuprorelin result. The change from baseline in mean visual analogue scale score for pelvic pain (in mm) during the last 4 weeks of treatment period was −3.222 in the placebo group, −6.849, −9.032, and −11.924 in relugolix 10 mg, 20 mg and 40 mg groups, respectively, and −12.552 in the leuprorelin group. Estradiol levels decreased with increasing dose of relugolix and were maintained below the postmenopausal levels throughout the 24-week relugolix 40 mg treatment period.
Conclusion
Treatment with relugolix for 24 weeks was generally well tolerated and demonstrated similar pelvic pain reduction as leuprorelin in women with EM. Relugolix, a once-daily oral nonpeptide GnRH receptor antagonist, demonstrated similar benefit to injectable leuprorelin in this Phase 2 study.

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GP135

Brown adipose tissue thermogenesis in women with polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive age women and is characterized by reproductive, metabolic and psychological features exacerbated by weight gain. Weight management in PCOS is challenged by propensity to weight gain and lack of sustainable dietary interventions. Body weight is regulated by calorie intake and the rate of energy expenditure. Metabolically active brown adipose tissue (BAT), contributing to energy dissipation, has been described in humans. The thermogenic activity of BAT is controlled by the sympathetic nervous system (SNS). Sex hormones also play role in modulating BAT. Human studies confirm association of supraclavicular skin temperature, where most human BAT is located, with BAT activity. This observational study aimed to explore BAT thermogenesis and its associations, for the first time, in PCOS. Cutaneous wireless temperature probes (2 cm diameter, 0.5 depths) were taped to supraclavicular (BAT) and upper arm (muscle) regions of 49 premenopausal women with PCOS, over 96 hours, (mean age: 29.85±5.93, mean BMI: 29.02±5.43), recruited from community. Multiunit muscle SNS activity (by microneurography) and plasma noradrenaline levels were measured as markers of SNS activity. Fasting lipids, serum androgens, markers of insulin resistance and inflammation were measured. Recorded temperature data from both regions were available in 41 participants. Supraclavicular temperature was significantly higher than arm temperature (33.87±0.65 vs 32.23±0.85, $P < 0.0001$). Supraclavicular temperature correlated with testosterone ($r=-0.410$, $P=0.011$), noradrenaline ($r=-0.488$, $P=0.005$) and triglycerides ($r=-0.393$, $P=0.015$) which remained significant after adjustment for BMI. Arm temperature did not correlate with testosterone, noradrenaline and triglycerides. This is the first study of BAT thermogenesis in PCOS using cutaneous temperature probes. The negative correlation of BAT temperature with noradrenaline levels could implicate a maladaptive thermogenic response to chronic SNS activation in PCOS. Chronic sympathoexcitation and hyperandrogenism play potential roles in modulation of BAT thermogenesis in PCOS.

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GP136

Dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin improved beta cell function and prevented a conversion rate to MTG and DM2 in metformin intolerant PCOS with high metabolic risk

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Objective
Metformin is the first-line therapy for PCOS with high metabolic risk, yet a large proportion of patients cannot tolerate it due to associated gastrointestinal adverse events. The alternative pharmacological strategy when metformin cannot be tolerated is not well established in this population. Our aim was to evaluate whether sitagliptin (SITA) preserves metabolic profile in metformin (MET) intolerant PCOS with high metabolic risk.
Design and methods
A 12-week prospective randomized open-label study was conducted with 30 obese MET intolerant women with PCOS (aged 35.0±7,2 years, BMI 36,9±5.5 kg/m^2). They were randomized to lifestyle intervention and SITA 100mg QD or lifestyle intervention alone as controls (CON). All participants underwent standard anthropometric, endocrine measurements and OGTT. Model derived indexes of insulin resistance (IR) and β-cell function were calculated.
Results
SITA improved beta cell function as assessed by HOMA beta for 45,9±35,8 (P=0,001), modified beta cell function index (MBCI=I0XG0/(G120+G60-7)) for 7,9±7 (P=0,002) and QUICKI for −0,03±0,03 (P=0,002) and increased IR as assessed by HOMA-IR and insulin action index (IAI=1/G0XI0) for 1,8±1,7 (P=0,002) and −0,01±0,01(P=0,003). By contrast, beta cell function decreased in CON arm. The between group differences were significant for HOMA-beta (P=0,000), MBCI (P=0,010) and QUICKI (P=0,025). The conversion rate from normal glucose tolerance to impaired glucose tolerance (IGT) or T2DM was prevented in SITA (3/15 of subjects with MTG before and after the study). In CON 4 women had IGT at the beginning. After 12 weeks IGT was observed in 2 and T2DM in 3 subjects.
Conclusion
SITA improved beta cell function and prevented a conversion rate to IGT and T2DM in metformin intolerant PCOS with high metabolic risk when compared to lifestyle alone.

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GP137

Genetic susceptibility for adrenal hyperandrogenism in polycystic ovary syndrome

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Background
Hyperandrogenism is a main feature of the polycystic ovary syndrome (PCOS). Although its ovarian origin is well recognized, laboratory investigation suggested the contribution of adrenal gland, albeit of unknown mechanism.
Aim
To understand the contribution of genetic factors in adrenal hyperandrogenism (AH) we investigated genome wide SNPs in subgroups of PCOS patients stratified as function of DHEAS levels in two ethnic populations (Romanians and French).
Subjects and methods
Patients recruited during European MEDIGENE program (FP7-279171) with PCOS (n=307) of 18–42 years old were stratified in two groups as function of DHEAS level greater than 95th percentiles in age-matched controls. Genotyping was performed with customized MEDISCOPE microarray chip with 759 000 SNP. Influential SNPs were determined by correlation trend (CT) test and then by genetic association in two subgroups of patients.
Results
Despite no difference in total-testosterone levels, in PCOS with AH (n=58, 18.9%) the SHBG (27.6±3.6 vs 44.5±3.3 nmol/L, P< 0.0002) was lower and FAI (14.0±2.2 vs 8.7±0.7, P< 0.002), 2-h insulin in OGTT (111.2±26.0 vs 77.3±6.9 mUI/L, P<0.044) and systolic BP (123.7±4.26 vs 114.4±1.8 mmHg, P<0.045) were higher than in PCOS without AH. SNPs corresponding to at least 15 genes were positive in CT test with DHEAS levels. Among them, INSR and CDH13 were the most significant with numerous SNPs having a P value < 1.0×10-5 after Bonferroni correction. In genetic association by logistic regression between two groups, other genes were also confirmed, the most influential being IL2RA, PTER, SORCS1, LGR4 and KSR2. For instance, LGR4 (Chr 11) was associated with P< 0.005, OR 5.6, 95%CI [1.6–19].
Conclusion
These data indicated that, in PCOS patients, AH may be in part explained by genetic susceptibility. Despite a full array of genes involved, the insulin-resistance appears as potential actor of AH in PCOS.

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GP138

Turner's syndrome and abnormal liver chemistry: relationship with karyotype in a large dedicated clinic

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Introduction
Abnormal liver function tests (↑LFTs) are frequently observed in Turner's syndrome (TS), although the aetiology is unclear. Obesity is reported as one of the causes; recently an increased prevalence of elevated GGT was found in TS patients with a ring X karyotype.
Aim
To analyse the association between abnormal LFTs and TS-related conditions, and in particular their relationship with the different TS-karyotypes.
Methods
Data on adult TS-patients were collected. ↑LFTs was defined as elevated aminotransferases ± GGT and ALP, for more than 6 months. TS-karyotypes were classified in eight groups.
Results
109 TS women were studied: mean age 36(±13.1)y, BMI 28.3(±6.9)Kg/m^2. 45,X was found in 47 patients (46.1%), mosaicism 45,X/46,XX or 45,X/47,XXX in 15 (15.7%), 4 (3.9%) del(X)(p), 1 (1%) del(X)(q), 10 (9.8%) isochromosome(X)(q), 10 (9.8%) ring X, presence of Y in 4 (3.9%) and 10 (9.8%) other TS-karyotypes.
38/109 (35%) presented with ↑LFTs, most frequently a ↑GGT. Differences between the normal-LFTs-group versus the ↑LFTs-group were found for age (33.8 vs 41y, P=0.008), Tot-Chol (4.9 vs 5.5 mmol/L, P=0.005), LDL-Chol (2.7 vs 3.2 mmol/L, P=0.006), and triglycerides (1.1 vs 1.5 mmol/L, P=0.02). No differences were noted analysing anthropometric values, HbA1c, history of diabetes, hypertension or autoimmunity.
The prevalence of ↑LFTs was significantly higher in the isochromosome(X)(q)-group (P=0.0003); the mosaicism-group had a decreased prevalence of ↑LFTs (P=0.0092). Using the stringent ALT cut-off of 19UI/L, this was commoner only in the i(X)(q)-group (P=0.0134). The i(X)(q)-group showed a similar clinical phenotype compared to 45,X and no increased prevalence of autoimmune disease.
Conclusions
This study shows 1) ↑LFTs are common in TS; 2) the prevalence of ↑LFTs increases with age and is associated with increased cholesterol and triglycerides; 3) for the first time, a relationship between ↑LFTs and karyotype was found, suggesting that liver biochemical abnormalities could be triggered by over-expression of Xq genes escaping inactivation.

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GP139

Sensitivity of hypothalamo-pituitary-adrenal axis in women with PCOS

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Introduction

Increased adrenal androgen production is present in 20–60% of women with polycistic ovary syndrome (PCOS). Possible mechanism is not clarified yet and could be related to altered hypothalamic-pituitary-adrenal-axis (HPA) activity or a consequence of adrencortical steroidogenic abnormalities. The aim of the study was to assess HPA sensitivity in PCOS women using different doses of dexamethasone.

Methods

We analyzed 359 women with PCOS diagnosed using ESHRE/ASRM criteria (age: 25.6±5.3 years, BMI: 25.1±6.4 kg/m^2), and 58 BMI-matched healthy controls (age 28.79±6.1 years, BMI 23.7±6.1 kg/m^2). In all subjects serum ACTH, morning serum cortisol (SC), and DHEAS were measured, and SC and DHEAS determined after overnight dexamethasone test with 0.5 mg ($Dex_{0.5mg}$) and 1 mg (Dex_{1mg}), and marked as $SC_{dex0.5}$, SC_{dex1}, $DHEAS_{dex0.5}$ and $DHEAS_{dex1}$, respectively. Differences between groups were age adjusted and data are presented as ANCOVA-mean (95%CI).

Results

SC was borderline higher [437.9(421.6–454.3) vs. 395.7(356.7–437.8)nmol/l, $P=0.052$] and DHEAS significantly higher [7.7(7.3–8.2) vs. 5.6(4.6–6.7)nmol/l, $P<0.001$] in PCOS than in controls. There was no difference in ACTH among groups. After dexamethasone tests, both groups significantly lowered SC and DHEAS in comparison to basal analyses. In comparison to controls, PCOS had borderline higher $SC_{dex0.5}$ [49.9 (22.9–76.9) vs. 78.5(67.8–89.1)nmol/l, $P=0.055$] but similar percentage of SC suppression [86.5 (80.6–92.3) vs. 82.8(80.4–85.3)%, $P=0.26$]. PCOS had lower SC_{dex1} [26.8 (23.5–30.2) vs. 22.9(21.6–24.2)nmol/l, $P=0.055$] and suppressed SC more than controls [92.5(91.6–93.5) vs. 94.5(94.1–94.9)%, $P<0.001$]. There were no differences in $DHEAS_{dex0.5}$ and $DHEAS_{dex1}$ between groups. Suppression of DHEAS was similar after $Dex_{0.5mg}$ ($P=0.92$), but PCOS suppressed DHEAS after Dex_{1mg} less than controls [32.1 (25.9–38.3) vs. 47.7(34.0–61.4)%, $P=0.04$].

Conclusions

Our women with PCOS, in comparison to BMI-matched controls have increased age-adjusted HPA axis sensitivity to 1 mg but not to 0.5 mg of dexamethasone. DHEAS production in PCOS seems to be more independent of ACTH than in controls.

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GP140

Nonalcoholic fatty liver disease liver fat score (NAFLD-LFS) could be used for the assessment of NAFLD in women with PCOS

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Introduction

A relation between polycystic ovary syndrome (PCOS) and nonalcoholic fatty liver disease (NAFLD) was demonstrated recently. Both NAFLD and PCOS are associated with increased risk for type 2 diabetes and cardiovascular disease. NAFLD liver fat score (NAFLD-LFS) has been implicated as a non-invasive surrogate marker for NAFLD. The aim of this study was to identify the prevalence of NAFLD in different PCOS phenotypes using NAFLD-LFS.

Methods

We evaluated 489 obese PCOS women (PCOS: 33.2±5.7 kg/m^2; 25.6±6.2 years) diagnosed using ESHRE/ASRM criteria and 97 BMI-matched obese healthy women (controls: 32.5±5.5 kg/m^2; 31.7±5.1 years). PCOS group was divided into 4 phenotypes: A [anovulation (ANOV), hyperandrogenism (HA), polycystic ovary morphology (PCOM)], B (ANOV,HA), C (HA,PCOM) and D (ANOV,PCOM). NAFLD was assessed using NAFLD liver fat score (NAFLD-LFS) cutoff > -0.640. Differences between groups were age adjusted.

Results

NAFLD was more prevalent in PCOS in comparison to controls (59.7 vs 44.4%, $P=0.009$). Our PCOS group consisted of 268 women with phenotype A, 129 with phenotype B, 47 with phenotype C and 35 with phenotype D. Prevalence of NAFLD in phenotypes were: A: 59%, B:61%, C:53% and D:66%. There were significant differences in the prevalence of NAFLD between controls and phenotype A ($P=0.015$), phenotype B ($P=0.015$) and phenotype D ($P=0.028$). There were no significant differences between phenotypes.

Conclusions

NAFLD is more prevalent in obese PCOS women than in obese BMI-matched controls. All four phenotypes have the same risk for NAFLD which confirms susceptibility of PCOS as a whole to develop metabolic derangements.

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GP141

Effects of central sympathoinhibition with moxonidine on the elevated sympathetic nervous activity and downstream metabolic abnormalities observed in polycystic ovary syndrome

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The role of the sympathetic nervous system (SNS) in the pathophysiology of PCOS and associated cardiometabolic risks is emerging. Previous studies support increased SNS activity in PCOS, potentially contributing to metabolic features via multiple mechanisms including insulin resistance. Moxonidine is a second-generation imidazoline I_1 agonist, acting centrally, inhibiting sympathetic outflow at the level of rostral ventrolateral medulla with known beneficial effects on hypertension, insulin sensitivity, dyslipidemia and inflammation. This study aimed to explore pharmacological modification of SNS activity, for the first time, in women with PCOS, using moxonidine. 51 premenopausal women (mean age: 29.8±5.9 years, mean BMI: 29.0±5.4 kg/m^2) with PCOS were recruited, from a community setting, in a double blind placebo controlled clinical trial. 48 women were weaned off any interacting medication for 3 months then randomized to moxonidine (0.2mg daily initially, up titrated to 0.4mg daily in 2 weeks) ($n=23$) or placebo ($n=25$) for 3 months. Multiunit muscle SNS activity (MSNA by microneurography), heart rate variability (HRV) and endothelial function (ischaemic reactive hyperaemia index (RHI)) were examined. Fasting lipids, serum androgens, markers of insulin resistance and inflammatory markers were measured prior to and following intervention. 45 women completed the trial (19 moxonidine and 23 placebo). Change in MSNA (−3.23±6.71 vs −2.81±8.2 bursts per minute, P=NS), HRV (5.26±13.56 vs 2.95±15.37 nu in low frequency component, P=NS) and endothelial function (0.10±0.70 vs 0.06±0.67 in RHI, P=NS) did not differ significantly with moxonidine compared to the placebo. Mean changes in BP, fasting lipids, HOMA-IR, hs-CRP and androgens were similar in both groups. In women on moxonidine, change in BMI correlated positively with change in MSNA ($r^2=0.593$, $P=0.03$). Central sympathoinhibition with moxonidine does not modify higher SNS activity and downstream metabolic abnormalities in PCOS. Sympathoexcitation in PCOS may be driven peripherally or from other brain regions with further research needed.

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GP142

Steroid receptors involvement in enamel hypomineralization resulting from exposure to low-dose DEHP and bisphenol A

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The environment has become increasingly contaminated by various pollutants including endocrine disrupting chemicals (EDCs). This has led to an increase in the incidence and gravity of known pathologies and the emergence of new ones, including dental pathologies as the Molar Incisor Hypomineralization (MIH). Among the thousands of EDCs, bisphenol A (BPA) and phthalates (DEHP) are widely used by the plastic industry and responsible to frequent contaminations.

We previously showed a link between experimental exposures to low-dose BPA and enamel defects similar to MIH (1). The characterization of enamel defects may be helpful to propose them as early markers of exposure to EDCs thanks to enamel unique properties.
The aims of the present work are 1) to compare mouse enamel defects resulting from exposure to low-dose BPA and/or DEHP and, 2) to approach the mechanism, of action of both EDCs during amelogenesis.
The study was carried out on mice exposed to 5 and 50 mg/kg per day DEHP with or without 5 μg/kg per day BPA. Exposed animals present enamel defects on their incisors with similar characteristics than those of MIH affected teeth. In addition, 11% of DEHP mice presented enamel breakdown suggesting a weak enamel structure. As both EDCs act through steroid receptors, their presence and expression levels were investigated in ameloblasts by immunofluorescent assays and RT-qPCR respectively. We found that dental epithelium express a specific combinatory of steroid receptors (AR, ERs, ERRs, RARα/RXRα, VDR, GR, MR and PGR) depending on their stage of differentiation. These data suggest that depending on their nature and the time of exposure, phthalates and BPA could affect enamel quality (through AR) and/or quantity (through ERRγ and ERα). Studies are currently driven to decipher the functional role of AR in the mechanism of action of both EDCs in ameloblasts.
References
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Male Reproduction and Endocrine Disruptors

GP143

In vitro effects of Bisphenol A on two metabolic receptors signaling: MC4R and FFAR1

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Metabolic diseases (type 2 diabetes (T2D) and obesity) prevalence is increasing in the world. This is partly related to a change in lifestyle with an increase of caloric intake and a decrease of physical activity. Environmental causes are also involved among them exposure to bisphenol A (BPA). The mode of action of the latter is unknown. Beyond a suggesting effect relayed by nuclear receptors, we propose that BPA can act by modulating the functionality of G protein-coupled receptors involved in the pathophysiology of metabolic disorders. In order to test this hypothesis, we analyzed the effect of BPA on the activity of MC4R and fatty acid receptor FFAR1 (GPR40). MC4R is involved in obesity by regulating dietary intake and energy balance. There are two ligands of MC4R: αMSH (agonist) and AgRP (inverse agonist). FFAR1 increases the glucose-dependent insulin secretion. It is a new therapeutic target in T2D.
Each receptor is transiently expressed in HEK293, and its activity is assessed by measuring cyclic AMP (cAMP) for MC4R, using a biosensor kit, or calcium for FFAR1, using a fluorimetric calcium sensor.
At a concentration of 10 nM, BPA increased by up to 30% the cAMP production induced by αMSH and reduced by half the inhibition induced by AgRP, without modifying the basal activity. These effects are specific for MC4R as BPA did not change the activity of the downstream effectors of cAMP pathway (adenylate cyclase, G protein or phosphodiesterases) or one of endogenous adenosine receptor (negative control).
In addition, 10 pM BPA decreased by one-third the calcium mobilization stimulated by GW9508 (a synthetic agonist of FFAR1).
We show here new effects of BPA with a disruption of G protein-coupled receptors activity, which may be worth to take into account when addressing the question of the link between endocrine disruptor and metabolic diseases.
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GP144

Altered protein expression of cell cycle- and EMT-associated genes by bisphenol compounds in MCF-7 CV human breast cancer cells via estrogen receptor dependent pathway

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Bisphenol-A (BPA) has been considered as an endocrine disrupting chemical (EDC) because it can exert estrogenic properties. For bisphenol-S (BPS) and bisphenol-F (BPF) that are BPA analogs and substitutes, their risk to estrogen-dependent cancer has been reported rarely compared with the numerous cases of BPA. In this study, we examined whether BPA, BPS, and BPF can lead to the proliferation, migration, and epithelial mesenchymal transition (EMT) of MCF-7 clonal variant (MCF-7 CV) breast cancer cells expressing estrogen receptors (ERs). In a cell viability assay, BPA, BPS, and BPF significantly increased proliferation of MCF-7 CV cells compared to control (DMSO) as did 17β-estradiol (E2). In Western blot assay, BPA, BPS, and BPF enhanced the protein expression of cell cycle progression genes such as cyclin D1 and E1. In addition, MCF-7 CV cells lost cell to cell contacts and acquired fibroblast-like morphology by the treatment of BPA, BPS, or BPF for 24 h. In cell migration assay, BPA, BPS, and BPF accelerated the migration capability of MCF-7 CV cells as did E2. In relation with the EMT process, BPA, BPS, and BPF increased the protein expression of N-cadherin, while they decreased the protein expression of E-cadherin. When BPA, BPS, and BPF were co-treated with ICI 182,780, an ER antagonist, proliferation effects were reversed, the expression of cyclin D1 and cyclin E1 was down-regulated, and the altered cell migration and expression of N-cadherin and E-cadherin by BPA, BPS, and BPF were restored to the control level. Thus, these results imply that BPS and BPF also have the risk of breast cancer progression as much as BPA in the induction of proliferation and migration of MCF-7 CV cells by regulating the protein expression of cell cycle-related genes and EMT markers via ER-dependent pathway. (This work was supported by a grant from the Next-Generation BioGreen 21 Program (no. PJ011355-2015), Rural Development Administration, Republic of Korea.)
Keywords: Human breast cancer cells, endocrine disrupting chemicals, bisphenol-A, bisphenol-S, bisphenol-F, epithelial-mesenchymal transition, migration
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GP145

Reproductive toxicity of low dose nonylphenol in mice: a two-generation study

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Nonylphenol (NP), a member of alkylphenol family, has been widely used in both industry and household. NP is classified as an endocrine-disrupting chemical and is known to act as an agonist of the GPER (GPR30). The aim of this study was to address the two-generational effects of para-nonylphenol (NP) on the body weights, reproductive organ weights and histopathologies of ICR mice. We also test the potential reproductive toxicity of octylglucuronide (OG), a substitute candidate for NP. The testing drugs were administered as drinking water (50 and 500 ug/l) throughout the pre-mating period of P0 animals and lactation of F2 animals. Significant decreases were found in the weights of testis, prostate and seminal vesicle in the F1 NP500 group, in the weights of testis and epididymis in F2 NP50 and NP500 groups. There was no weight change in the OG-treated groups. In female, significant decreases in the weights of ovary and uterus in F1 NP50 group, uterus of F1 NP500 group, and F2 NP500 group were found. The weights of ovary in F1 OG50 and OG500 were also significantly decreased. Histopathological studies revealed that the numbers of Leydig cells were reduced in the testes of F1 and F2 NP50 groups. There were no changes in the Leydig cell numbers of OG groups. In F1 NP500 mice, the increased numbers of primary and secondary follicles and decreased number of corpora lutea were observed. There was no change in OG-treated group gonad. Finally, vaginal opening was delayed in F1 NP50 and NP500, and F2 NP50 animals. Present study demonstrated that the potential reproductive toxicity in animals long-term exposed to low dose NP (approximately 15–150 ng of daily intake). Our study also show that OG seems to be a promising alternative to NP, and further studies are warranted. This work was supported by the National Research Foundation of Korea Grant funded by the Korean Government (NRF-2016904200).
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GP146

Psychological rather than organic and/or relational components are involved in sexual dysfunction in Young/Middle aged human immunodeficiency virus (HIV)-Infected Men

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Background
HIV-infection is associated to an increased prevalence of erectile dysfunction (ED). In HIV-infected men ED seems to be less related to serum Testosterone (T), depending from other factors.
Aim
To investigate the role of different components (organic, relational, psychological) of erectile function by using validate questionnaires in HIV-infected men with normal serum T.
Methodology
Prospective, cross-sectional, observational study on eugonadal HIV-infected male patients with ongoing Highly Active Antiretroviral Therapy (HAART) attending the Clinic of Infectious Diseases. The International Index of Erectile Function (IIEF)-15, IIEF-5 and Structured Interview for Erectile Dysfunction (SIEDY) were used to assess sexual function. Sexual desire was further evaluated through a direct question during the visit. LC-MS/MS was used to assess gonadal status.
Results
225 HIV-infected patients were enrolled (mean age 45.19 ± 5.36 years). SIEDY scores at appendix and scale 3 were significantly higher in patients with ED at IIEF-15 ($n=136$, 60.4%) compared with those without ED ($P<0.001$ and $P=0.015$, respectively). Conversely, scale 1 ($P=0.448$) and 2 ($P=0.503$) of SIEDY did not differ between patients with or without ED, suggesting a predominance of the psychological basis of ED in our cohort. The erectile function domain at IIEF-15 was directly correlated with IIEF-5 score (0.778, $P<0.001$). Similarly, the score at SIEDY appendix was significantly different among ED degrees at IIEF-15 ($P<0.001$). In particular, lower score was found in HIV-infected men without ED compared to those with mild, moderate and severe ED ($P<0.001$, $P=0.001$, and $P<0.001$, respectively), confirming the reliability of these tools. Sexual desire was impaired in 73 patients (31.33%) at interview with a good correlation with the specific item of IIEF-15 ($P<0.001$).
Conclusions
The psychological component impacts in a significant manner on ED in HIV-infection context. Despite the high prevalence of comorbidities in these patients, the organic component does not affect erectile function. All the three validated questionnaires seem to be trustworthy in the diagnosis of ED in this setting.

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GP147

Effects of physical exercise or metformin on testosterone deficiency and erectile dysfunction associated to metabolic syndrome

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Metabolic Syndrome (MetS) is a cluster of clinical conditions, associated to an increased cardiovascular and metabolic risk, to hypogonadism and erectile dysfunction (ED). Lifestyle modification (including physical exercise, PhyEx) and metformin (MET) are well-known treatments for the condition. We established an animal model of MetS that recapitulates the human phenotype, including andrologic derangements.
The aim of this study was to investigate in experimental MetS the effect of PhyEx or MET on penile erection and on hormonal and metabolic parameters.
Control (RD) and MetS rabbits were treated with MET (the last 18 days) or exercise-trained to run on a treadmill for 12 weeks. Penile tissue was collected for *in vitro* contractility study or gene expression.
MET, but not PhyEx, induced a reduction in visceral adiposity, blood pressure, triglycerides, glucose level and tolerance. MET increased testosterone (T), whereas PhyEx completely restored it. Ach-induced relaxation, hampered in MetS rabbits, was significantly ameliorated by MET and completely normalized by PhyEx. HFD determined a net reduction of electrical field (EF)-vasorelaxation in CC. The relaxant response to sildenafil, abolished in HFD rabbit CC, was restored by PhyEx. PhyEx normalized sodium nitroprusside (SNP)-induced relaxation, that was enhanced in MetS rabbits. Genes related to NO signaling were up-regulated by PhyEx, but not by MET. Similar results were obtained for smooth muscle-related genes. PDE5 expression was decreased in MetS rabbits and completely restored by PhyEx. Accordingly, sildenafil-induced increase in SNP relaxation was completely normalized by PhyEx.
In conclusion, PhyEx more than metformin, completely restored T levels and responsiveness to Ach and sildenafil in experimental MetS, even though it was less effective than metformin in reducing metabolic abnormalities. The effect of exercise training is most probably related to an improved NO signaling, including PDE5. Hence, PhyEx can be considered a new strategy to treat hypogonadism and ED related to MetS.

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GP148

Impacts of a single ablative dose of radio iodine therapy for differentiated thyroid carcinoma on testicular function: results from the SAPIRA study

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Background
Radioactive iodine therapy (RAI) is a classical therapeutic approach in patients with differentiated thyroid carcinoma (DCT). Few data are currently available on RAI's potential impacts on testicular function.
Design
A longitudinal prospective multi-center study (PHRC N°P040419) included male patients before a single radioiodine dose of 3.7 GBq of I^{131} (V0), at 3 months (V3) and 13 months (V13) post treatment.
Method and Patients
Hormonal assessments (FSH, LH, Testosterone, inhibin B) as well as sperm parameters (number, mobility and morphology), DNA fragmentation and sperm FISH analysis in order to detect chromosomal abnormalities were performed at V0, V3 and V13.
Results
Thirty six patients were included in the study. At V0, all patients had normal gonadal function. At V3, FSH median levels were significantly increased as compared to V0, respectively 9 UI/l ± 4.8 (*N*: 3–7 UI/l) versus 4 UI/l ± 3 ($P<0.0001$). Between V3 and V13, FSH levels decreased but remained higher than baseline levels. Inhibin B median levels decreased significantly at V3 ($P<0.0001$) and returned to V0 levels at V13. LH and T levels were not modified at V3 or V13.
Median sperm concentration significantly decreased at V3 as compared to V0 (20 vs 48 million/ml; $P<0.0001$) and returned to V0 levels at V13. In parallel, a statistically significant decrease in sperm morphology was observed at V3. Sperm mobility and DNA fragmentation were not modified after RAI. However sperm chromosomal abnormalities were increased at V3 ($P<0.0005$) and V13 ($P<0.01$), as compared to V0.
Conclusion
In this prospective study, RAI transiently altered FSH, inhibin B and sperm number. Furthermore, chromosomal abnormalities observed at V3 were found to persist 13 months after RAI. Therefore, our study illustrates that counseling about fertility could be interesting in male patients with DCT treated by a single dose of radioiodine.

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GP149

Presentation, clinical features and long-term follow-up of Leydig cell tumours of the testis: 77 cases from a single center experience

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Introduction
With the improved imaging techniques, Leydig cell tumours (LCTs) are frequently found, accounting up to 22% of testicular tumours. The natural history of LCTs is relatively unknown, because of the small size and heterogeneity of available studies. Since LCTs are often removed, long-term follow-up is missing. The aim of this study was to report the experience with a large cohort of prospectively collected LCTs.
Materials and methods
Patients with LCTs were enrolled from 2005 to 2016. Clinical and biochemical features of LCTs were compared with two matched cohorts: patients with seminomas and patients without testicular lesions (noL) randomly selected among patients referred in the same period.
Results
77 patients had LCTs, 90 had seminomas, and 1420 had no lesion (noL). Groups were matched for age and BMI. Infertility was the reason for referral in more than half of LCTs. Testicular volumes ($P=0.002$), sperm concentration ($P=0.001$) and morphology ($P<0.001$) were significantly lower in LCTs compared to noL; gonadotropins were higher ($P<0.001$) and testosterone was lower ($P=0.008$) in LCTs vs noL. No differences were found in gonadal steroid after hCG test, between groups. When compared to seminomas, LCTs did not show differences in hormonal status except for higher SHBG levels ($P=0.028$), LH/Te ratio ($P<0.001$), and lower sperm concentration ($P=0.04$). LCTs lesions were smaller compared to Sem ($P<0.001$). Cryptorchidism ($\chi^2=45.658$ $P<0.001$) and gynecomastia ($\chi^2=54.923$, $P<0.001$) were associated with a higher risk of LCTs. After a median follow-up of 32.5 months, no metastases have been detected. Non-operated LCTs developed subclinical hypogonadism ($P=0.018$) compared to surgically removed LCTs.
Conclusions
LCTs have a good prognosis when correctly recognized. Based on the largest existing series, we showed that infertility, gynecomastia,low testicular volume, and cryptorchidism are frequently associated with LCTs, supporting the hypothesis that testicular dysgenesis syndrome could play a role. Active surveillance, as an alternative to surgical removal, appears to be a safe option, but monitoring of Leydig cell failure remains necessary.

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GP150

Semen quality in patients with adult-onset hypogonadotropic hypogonadism

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Introduction
Gonadotropins from the pituitary gland are essential for testosterone production and spermatogenesis. However, little is known about semen quality in patients with adult onset gonadotropin insufficiency.
Aim
To investigate semen quality in men with adult onset hypogonadotropic hypogonadism requiring testosterone replacement therapy.
Patients and method
A single center study comprising all hypogonadal men with pituitary disease (year 2003–2016, $n=28$, (median(IQR) 30 (27–37) years), who accepted cryopreservation of semen before initiation of testosterone therapy. On the day semen samples were cryopreserved, reproductive hormone levels were measured. Semen parameters, hormone levels and size of testicles were compared to those of young men ($n=340$, 19 (18–20) years) from the general population.
Results
Patients vs controls had lower serum testosterone 5.6 (3.5–7.8) vs 19.7 (15.5–24.5) nmol/l ($P<0.001$), free testosterone index 33.3 (18.1–55.1) vs 73.7 (57.8–91.7) ($P<0.001$), luteinizing hormone 1.5 (1.1–2.1) vs 3.1 (2.3–4.0) U/l ($P<0.001$), and inhibin-B 142 (126–187) vs 229 (176–285) ng/l ($P<0.001$). Levels of follicle stimulating hormone were unchanged 2.3 (1.4–4.4) vs 2.2 (1.5–3.3) U/l ($P=0.47$). There were no differences on semen volume 3.0 (1.5–5.0) vs 3.2 (2.3–4.3) ml ($P=0.33$), sperm concentration 35 (6–62) vs 43 (22–73) mill/ml ($P=0.1$), or total sperm counts 102 (8–236) vs 136 (65–235) mill ($P=0.09$). Forty-seven percent of patients and 77% of controls had normal semen quality, WHO criteria (volume >1.5 ml, concentration >15 mill/ml and AB-motile sperm $>42\%$) ($P=0.001$). Three had azoospermia. Testicular size was unchanged 18 (13–25) vs 20 (19–25) ml ($P=0.46$).
Conclusion
Patients with acquired pituitary insufficiency had reduced semen quality, supporting the need for early cryopreservation of semen in this group of patients. However, despite severe Leydig cell insufficiency almost half of patients had normal semen quality based on determination of three variables. This finding is in contrast to men with hypergonadotrpic hypogonadism where spermatogenesis is often severely compromised before Leydig cell insufficiency occurs.

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Neuroendocrinology & Growth Hormones

GP151

Growth hormone-releasing hormone (GHRH) antagonists, MIA-602 and MIA-690, inhibit survival and proliferation of human pleural mesothelioma cells

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Human malignant pleural mesothelioma (MPM) is a rare but aggressive neoplasm, arising from pleural mesothelial cells, generally due to asbestos exposure. Different growth factors are involved in the pathogenesis of MPM and in resistance to therapy; moreover, chemotherapy with cisplatin and antifolates, like pemetrexed (PEM), is the first-line treatment for inoperable MPM. Growth hormone-releasing hormone (GHRH), apart from stimulating GH secretion in the pituitary, exerts many extrapituitary functions, including stimulation of cell proliferation and survival. GHRH and GHRH receptor (GHRH-R) are expressed in different cancer cell types, where they modulate their proliferative effects. Moreover, GHRH-R antagonists were found to inhibit the proliferation of different cancer cells *in vitro* and *in vivo*; however, the role of GHRH antagonists in MPM remains unknown. Thus, in the present study, we investigated the effects of the GHRH antagonists MIA-602 and MIA-690 on survival, proliferation and apoptosis of human MPM cells. Our results show that MIA-602 and MIA-690 reduce survival and proliferation of MSTO-211H (biphasic) and REN (epithelioid) MPM cells, but have no effect in MeT-5A (human non-malignant mesothelial cells). Moreover, MIA-602 and MIA-690 promoted apoptosis and reduced the expression of the antiapoptotic protein Bcl-2 in MSTO-211H and REN cells. Cell cycle analysis of REN cells treated with GHRH antagonists showed an increase in the Sub-G1 apoptotic phase and a decrease in the G2 pre-mitotic phase. Furthermore, MIA-602 and MIA-690 inhibited cell migration in REN cells and increased the cytotoxic action of PEM in both MPM cell lines. These results suggest a novel therapeutic role for GHRH antagonists in the treatment of MPM, alone or in combination with standard therapies, by reducing the chemotherapy doses and their associated side effects.

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GP152

Somapacitan expected to provide IGF-I levels suitable for once-weekly dosing in children

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Somapacitan is a long-acting growth hormone (GH) intended for once-weekly subcutaneous administration. As for GH, the mechanism of action of somapacitan is either directly or indirectly via insulin-like growth factor I (IGF-I). A PK/PD model of somapacitan was developed from the pharmacokinetics (PK) and IGF-I levels from three phase 1 trials data: a single dose/multiple dose trial (0.02–0.24 mg/kg per week) in healthy adults, a multiple dose trial in adults with growth

hormone deficiency [GHD] (0.02–0.12 mg/kg perweek) and a single dose trial in children with GHD (0.02–0.16 mg/kg). Somapacitan exposure-response was described with a non-linear relationship between dose and exposure and a delay in response observed between C_{max} PK and C_{max} IGF-I. Somapacitan PK levels and IGF-I response was found to correlate to body weight bridging exposure and response between children and adults. The PK/PD model was based on goodness of fit judged adequate to describe somapacitan exposure and IGF-I levels and simulate the expected IGF-I profiles after multiple doses in children. Descriptive IGF-I exposure-response analysis of single dose data in GHD paediatric patients indicated that the dose range 0.04–0.16 mg/kg provided change in IGF-I comparable to daily hGH. Based on the PK/PD model of somapacitan, once-weekly dosing of 0.04 mg/kg per week are expected to provide C_{max} IGF-I levels that match the average daily human GH (hGH) treatment; 0.08 mg/kg per week are expected to provide C_{avg} IGF-I levels that match the average daily hGH treatment; and 0.16 mg/kg per week are expected to provide higher IGF-I levels than with daily hGH, with average concentrations not exceeding +2 SDS. In conclusion, the PK/PD of somapacitan is well characterised in adults and children in GHD in support of once-weekly dosing.

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GP153

Evaluating CHARGE syndrome in CHD7-positive CHH patients: clinical implications

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Context

Congenital hypogonadotropic hypogonadism (CHH) and CHARGE syndrome are clinically and genetically overlapping syndromes, with mutations in the *CHD7* gene presenting in both disorders. However systematic evaluation of CHARGE features in *CHD7*-positive CHH patients is seldom performed.

Objective

This study aims to systematically evaluate CHARGE features in CHD7-positive patients and explore the phenotype-genotype correlation.

Design

Whole exome sequencing was performed on 130 CHH probands to identify mutations in 24 CHH genes, including *CHD7*. Putative mutations were defined as rare sequence variants (RSVs, minor allele frequency <1%) that were either protein-truncating variants (PTVs) or missense variants predicted to be deleterious by SIFT and/or PolyPhen2. Missense mutations were also evaluated using Bergman criteria, integrating computational algorithms, population and segregation data (Bergman, Human Mutation, 2012). CHD7-positive CHH patients were evaluated for CHARGE features.

Results

We identified 16 CHH patients harboring heterozygous mutations (two PTVs and 14 missense), of whom 14 were available for re-evaluation. After detailed phenotyping, three probands (one PTV and two missense) were re-classified as CHARGE syndrome. Four probands with missense mutations present additional CHARGE features, while the remaining seven probands exhibit no additional CHARGE feature (one PTV and six missense). Both the missense mutations underlying CHARGE syndrome were categorized as pathogenic using Bergman criteria, while the other missense mutations were classified as either benign or of unknown significance. Of note, 3/4 CHH patients with additional CHARGE features also had mutations in other CHH genes, contributing to the variable expressivity.

Conclusions

50% of *CHD7*-positive CHH patients exhibit additional CHARGE features, with 21% meeting the clinical diagnosis of CHARGE syndrome. While the Bergman criteria accurately predict the most severe mutations resulting in CHARGE syndrome, it is unable to distinguish isolated CHH from CHH with additional CHARGE features. The results of this study have diagnostic and genetic counseling implications for *CHD7*-positive CHH patients.

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GP154

The effect of chronic hypothalamic-pituitary-adrenal axis activation on hypothalamic glucagon-like peptide-1 action in an animal model of depression and *in vitro* studies

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Hypersensitivity of hypothalamic–pituitary–adrenal (HPA) axis is considered to be an important factor in the pathogenesis of depression. Interestingly, glucagon-like peptide-1 (GLP-1) – an incretin hormone involved in the maintenance of glucose homeostasis in the periphery is known to activate HPA axis. The aim of the present study was to investigate whether prenatal stress (an animal model of depression) may influence levels of GLP-1 and GLP-1 receptor (GLP-1R) in the hypothalamus. Since prenatal stress may not change the level of the investigated factors in basal conditions, but may change the response to adverse factors in the adulthood, our studies were also conducted on animals subjected to acute stress and oral glucose administration (1 g/kg). In parallel in order to study the direct influence of GLP-1 receptor agonists on the activity of corticotropin-releasing hormone (CRH) promoter gene, a hypothalamic cell line mHypoA-2/12 was stably transfected with plasmid DNA containing the sequence (from −663 to +124 bp) of human CRH promoter gene conjugated with luciferase reporter gene. The cells were treated with GLP-1 and exendin-4 (20 and 200 nM) for 6, 24 and 48 h. The amount of GLP-1 in the hypothalamus was not altered by prenatal stress in basal conditions, however it was significantly lower in a group subjected to acute stress. Prenatal stress and glucose loading significantly decreased the concentration of GLP-1R in the hypothalamus. Obtained results suggest that attenuated central incretin hormone signaling may contribute to metabolic disturbances, evident in depression. In contrast, transfected mHypoA-2/12 cells treated with selected GLP-1R agonists displayed no significant differences in reporter gene activity, which may suggest that GLP-1R activation does not stimulate CRH expression in this experimental model.

Acknowledgments

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GP155

A novel purified polyclonal antibody towards T-Pit is a reliable marker of corticotroph cell differentiation

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Classification of pituitary neuroendocrine tumours (NETs) or pituitary adenomas is based on the expression of the anterior lobe pituitary hormones (FSH, LH, GH, Prolactin, TSH, ACTH and alpha-subunit of the glycoprotein hormones). Assessment of the transcription factors SF-1, Pit-1 and T-Pit has been a complement to the classification. Tumours negative for both pituitary hormones and transcription factors have been designated as null-cell adenomas. However, lack of sensitive and specific antibodies towards T-Pit has presented difficulties for the inclusion of these transcription factors into the classification system of pituitary endocrine tumours. Here, we present a novel purified polyclonal antibody (HPA072686) towards T-Pit and demonstrate its high sensitivity and specificity for immunohistochemistry-based identification of the cells with corticotroph differentiation. In an immunohistochemical study of a large cohort of pituitary adenomas of different types from 246 patients, a distinct nuclear expression of T-Pit was demonstrated in all ACTH-immunolabelled tumours, silent and clinically functioning, as well as in a proportion of tumours previously diagnosed as null-cell adenomas. None of the tumours that were immunoreactive for Pit-1, SF-1 or pituitary hormones, other than ACTH, expressed T-Pit. We expect that the availability of a reliable T-Pit antibody as a marker of corticotroph cell differentiation will contribute to: i) more precise classification of pituitary neuroendocrine tumours, particularly, those with sparse or no hormone expression, ii) better identification of silent corticotroph tumours that may have more aggressive clinical behaviour than silent gonadotroph tumours, and which are at the moment difficult to identify in cases with sparse or no ACTH

expression, iii) more cost effective immunohistochemical screening of pituitary tumours based primarily on the use of the three transcription factors and iv) identification of potential corticotroph cell differentiation in non-pituitary NETs.

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GP156

Liraglutide treatment prevented the increased expression of proinflammatory cytokines in the hippocampus of male pups in a perinatal stress model of food restriction

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Adverse events during gestation in rodents, results in an enhancement of immune function, including elevated levels of inflammatory cytokines in the brain. Liraglutide is a GLP-1 receptor agonists known to exert neuroprotective effects in brain. The aim of this study was to elucidate if liraglutide given to food restricted (FR) pregnant rats may prevent the deleterious effects of FR in the hippocampal inflammatory status of male and female pups at 21 days of age (D21). 20 Sprague-Dawley pregnant rats were included. Controls (CT) were fed ad libitum, whereas dams in restricted group were fed with 50% (50FR) daily intake of control dams. Pregnant rats were treated with liraglutide (100 μg/kg per 12 h; 50FR/LIR, CT/LIR) or vehicle (50FR/VEH, CT/VEH) from gestational day 14 to 21. During lactation FR was increased to 30%. At D21 and before weaning, pups were sacrificed. The hippocampi were obtained and stored at −80 °C until analysis. mRNA expression levels of IL1β, IL6,NFKβ,IL 10 and Arginase1 in the hippocampus were assessed by RT-PCR. Immunohistochemistry analysis for Iba1 (marker of microglia) was performed in dentate gyrus (DG). The FR-mothers model promoted a proinflammatory state in the hippocampus just in male but not in female pups. 50FR male rats displayed increased mRNA expression of IL1β, IL6 and NFKβ compared to control males. LIR treatment decreased the expression of these cytokines and increased IL6 in control males. Furthermore, LIRA treatment increased the anti-inflammatory cytokine IL10 in 50FR male and CT female rats and the mRNA expression of the arginase1 (marker of microglia M2-like phenotype) in 50FR male rats. The number of IBA1 immunopositive cells were increased in the DG of 50FR males compared to controls, and were reduced by the treatment with LIRA. In conclusion, LIRA prevents the proinflammatory status induced by FR of the mother in male pups and enhanced anti-inflammatory markers.

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GP157

Predictors of permanent, transient and three-phase postoperative diabetes insipidus

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Objectives
To evaluate predictors of permanent, transient and three-phase diabetes insipidus (DI) in patients undergoing endoscopic endonasal transsphenoidal surgery.
Patients and methods
The study included 154 patients undergoing endoscopic endonasal transsphenoidal surgery (122 women and 32 men) age from 18 to 65 years (median 40 (31;52)). 73 patients with Cushing disease, 66 patients with acromegaly, four patients with prolactinomas, nine patients with non-functioning pituitary adenomas, one patient with thyrotropinoma, one patient with Nelson's syndrome and three patients with multihormonal secreting adenomas we examined. Patients were monitored for hormones, balance of fluids, serum electrolytes, plasma and urine osmolality.
Results
Postoperative permanent DI occurred in 27 patients, among them four as three-phased disturbances. Transient DI occurred in 42 patients, among them nine as three-phased disturbances. Onset arised on the 1th day–2nd month after surgery (median 1 day (1;5)) for the permanent DI's and on the 1th day–4th month for transient DI's (median 1 day (1;5)). Duration for transient DI was 1 day–1 year and 3 month (median 2 (1;30)), in 38% patients transient DI occurred as single polyuria-polydipsia episode. Adrenal insufficiency incrised risk of transient and three-phased DI development (RR 0.516 (0.287; 0.927), $P=0.02$, RR 0.056 (0.008; 0.42), $P=0.0003$, respectively), panhypopituitarism increased permanent DI onset risk (RR 0.264 (0.132; 0.53), $P=0.02$). Patients with corticotropinomas and somatotropinomas had higher risk of transient and three-phased DI (RR 0.212 (0.061; 0.734), $P=0.02$, RR 0.459 (0.311; 0.677), $P=0.04$, for corticotropinomas, respectively; RR 4.559 (1.049; 19.813), $P=0.03$, RR 1.977 (1.033; 3.783), $P=0.07$ for somatotropinomas, respectively). Macroadenoma also increased risk of transient and three-phased DI (RR 5.739 (1.32; 24.962), $P=0.01$, RR 2.593 (1.357; 4.955), $P=0.02$, respectively).
Conclusions
ACTH- and GH-secreting adenomas, macroadeomas and postoperative adrenal insufficiency can be considered as predictors of transient and three-phased diabetes insipidus. Panhypopituitarism can be considered as predictor of permanent diabetes insipidus.

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GP158

The effect of chronic tianeptine administration on NLRP3 inflammasome pathway – study in an animal model of depression

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Introduction
Recently, the immune hypothesis of depression has gained a new dimension because of inflammasomes. NLRP3 inflammasome is a protein complex and its activation leads to stimulation of the enzyme caspase 1 responsible for generation of active form of pro-inflammatory cytokines: IL-1 β and IL-18. Recently postulated 'inflammasome theory of depression' assumes that depression is based on a disturbance of the mechanisms regulating NLRP3 complexes and uncontrolled synthesis of IL-1β.
Aim
The aim of present study was to examine whether prenatal stress influence the inflammasome NLRP3 system (subunits: NLR, ASC, protease caspase-1) in the frontal cortex and hippocampus of adult rats offspring. Furthermore the impact of chronic antidepressant drug – tianeptine administration on the above-mentioned parameters were evaluated.
Methods
Pregnant rats were subjected to restraint stress. At 3 months of age, control and prenatally stressed rats were tested for behavioural changes in forced swimming test. After that male offspring were administered i.p. for 14 days with tianeptine or vehicle. The animals' behaviour were tested again and rats were sacrificed. The protein level of all NLRP3 inflammasome subunits was determined by Western blot analyses.
Result
Prenatal stress procedure cause long-lasting behavioral alterations expressed as an increase in immobility and a decrease in swimming and climbing time measured in the forced swim test. Chronic treatment of tianeptine normalized all above-mentioned changes in prenatally stressed offspring. Prenatal stress procedure increased concentration of all NLRP3 subunits in frontal cortex. In hippocampus prenatal stress affected caspase-1 levels but had no effect on the other NLRP3 inflammasome subunits. Chronic tianeptine treatment attenuated all evoked by stress changes.
Conclusion
Prenatal stress procedure leads not only to persistent behavioral disturbances but also malfunction in brain NLRP3 inflammasone pathway. NLRP3 pathway can be indicate as an potential attractive target for antidepressant drug action.
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GP159

Pituitary androgen receptor signalling is a novel negative regulator of prolactin production

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The classical paradigm of lactotroph prolactin production and release is based around tonic inhibition by hypothalamic dopamine and stimulation by factors such as estrogen. We have recently shown that conditional ablation of pituitary androgen receptor (Foxg1-Cre ARKO) surprisingly does not change the concentration of circulating gonadotrophins but increases circulating prolactin

in male mice; highlighting androgen signalling as a novel negative regulator of prolactin production. We aimed to refine our knowledge of the site and mechanism of action of this control by performing further genetic, pharmacological and surgical experiments to ablate the production and/or action of prolactin and/or androgens. Male mice with a genetic ablation of AR in neurons (Nestin-Cre ARKO) do not have an increase in circulating prolactin, confirming that the increase in prolactin seen in the Foxg1-Cre ARKO mouse is not due to loss of hypothalamic AR, but specifically pituitary AR. However, Foxg1-Cre ARKO mice treated with the dopamine agonist bromocriptine show a decrease in circulating prolactin levels suggesting that the mechanism of prolactin increase originates with the hypothalamic dopamine system that normally controls prolactin. Male mice with postnatal AR ablation in ~50% lactotrophs (Prolactin-Cre ARKO) do not show an increase in circulating prolactin, suggesting that either the mechanism is not lactotroph-specific or that ablation of AR needs to occur earlier or in a greater number of lactotrophs to result in an increase in circulating prolactin. Mice castrated in adulthood do not show an increase in circulating prolactin which suggests that the control mechanism is not an acute response to changes in androgens but is programmed during the pre-adult development of the pituitary. Further experiments are currently being undertaken to ablate AR in other pituitary cell populations and at earlier time points with the aim of pinpointing the spatio-temporal mechanism of control of prolactin production by androgen receptor signalling.

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GP160

Somatic mutations in USP8 are frequent events in pituitary tumors causing Nelson's syndrome

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Recent studies have reported a high prevalence of *USP8* mutations in corticotroph adenomas causing Cushing's disease. Nelson's syndrome is a potentially life-threatening complication of bilateral adrenalectomy in patients with refractory Cushing's disease that is caused by the development of an ACTH-secreting tumor in the pituitary gland. Whether *USP8* alterations are also present in Nelson's tumors has not been studied in detail so far.

Methods

We have screened for mutations in the exon 14 of *USP8* in tumors from 32 patients who were diagnosed with Nelson's syndrome (28 females, four males). Genomic DNA was extracted from fresh-frozen or FFPE adenomas. The presence of mutations was analyzed by Sanger sequencing. Mutational status was correlated to clinical data.

Results

In our cohort, 15/32 tumors presented a mutation in the exon 14 of *USP8*, a prevalence similar to that reported in Cushing's disease, with c.2159C>A (p.Pro720Gln) being the most frequent (8/32), followed by c.2155_2157delTCC (p.Ser718del, 4/32) and c.2152T>C (p.Ser718Pro, 3/32). Two *USP8* WT cases were categorized as atypical pituitary tumors and excluded from subsequent analyses. Mutations were found exclusively in females (15/27, 55%; vs 0/3 males). Other variables, such as age at diagnosis of Nelson's syndrome, BMI, hyperpigmentation, visual field defects, adenoma size or mortality did not significantly differ between patients with WT and mutant tumors. Regarding the hormonal status, patients with mutant tumors tended to exhibit higher levels of plasma ACTH at time of Nelson's diagnosis (median WT 1335 pg/ml vs mutant 1668 pg/ml; $P=0.098$; $n=25$) and significant changes after surgery (median 131 vs 639, $P=0.043$; $n=22$). Postoperative normalization of plasma ACTH was reached more frequently in patients with WT tumors (4/12, 33% vs 1/10, 10%) but without statistical significance ($P=0.323$). No differences were observed in tumor control after surgery.

Conclusion

Somatic mutations in the *USP8* gene are common in Nelson's syndrome and may be related to a more severe hormonal phenotype.

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Obesity

GP161

The association between olfaction and taste functions with serum ghrelin and leptin levels in obese women

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Aim

Olfaction and gustation have great importance on feeding behavior and food preferences. Recent published data suggests that olfaction and taste functions are modulated in response to changing levels of various molecules such as ghrelin and leptin which are play important roles on feeding and energy balance. We aimed to investigate the olfaction and taste functions in obese female patients and the association between serum ghrelin and leptin levels compared with healthy controls.

Methods

Fifty two obese women who have body mass index >30 kg/m^2 and 15 healthy women were included in to the study. After 8 h of fasting, blood samples were taken for serum biochemical parameters, ghrelin and leptin levels measurement. For the quantitative assessment of olfactory function, all participants underwent on N-butanol threshold test and odor identification test by using 12 Sniffin' Sticks ready-made fragrance sticks. The gustatory function was tested by administering a whole-mouth above-threshold test using sucrose solutions.

Results

The sucrose taste threshold score in obese women was significantly higher than the controls ($P=0.004$). N-butanol smell threshold was not significantly different between the two groups ($P=0.149$) while the Sniffin' Sticks smell test scores were significantly lower in obese women compared with the controls ($P=0.007$). Serum leptin levels were also significantly higher in obese women ($P<0.001$) although there was no significant difference in serum ghrelin levels between the two groups ($P=0.768$).

Conclusion

No significant association was observed between olfaction and taste functions and serum ghrelin levels of obese individuals. It was found that serum leptin levels were increased while taste and smell functions were decreased in obese women. These results might suggest that leptin, which is an anorexigenic peptide, may have a negative effect on taste and smell functions.

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GP162

Sarcopenic obesity and associated factors in older adults with diabetes: the 2009–2010 Korean National Health and Nutrition Examination Survey

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Objective

Sarcopenic obesity is a double burden for older people because it carries the cumulative risk of functional abnormality, metabolic, cardiovascular risk, and mortality compared to either sarcopenia or obesity alone. Diabetes is related to an increase in visceral adiposity and is associated with the risk of sarcopenia. The objective was to explore the association between sarcopenic obesity and diabetes and determine the associated factors with sarcopenic obesity in older people with diabetes.

Research design and methods

This study was based on data from the Korean National Health and Nutrition Examination Survey (KNHANES), conducted by the Korean Ministry of Health and Welfare, from 2009 to 2010. Out of 19,491 participants, the analysis included data for 3,206 older people. Multivariate logistic regression analyses were used to identify

independent associated factors with sarcopenic obesity. The complex sample analysis was used for the KNHANES data for weighting all values following the guidance of statistics form the Korea Centers for Disease Control and Prevention.
Results
The Prevalence of nonsarcopenic nonobesity, nonsarcopenic obesity, sarcopenic nonobesity, and sarcopenic obesity were 43.2, 7.7, 23.5 and 25.6%, respectively, in all subjects. The prevalence of sarcopenic obesity in older people with diabetes was significantly higher than those without diabetes (33.9% vs. 23.4%, P-value <0.001). Diabetes was an independent associated factor with sarcopenic obesity after fully adjusting for confounding factors, including chronic disease, sociodemographic influences, and lifestyle. Among the older people with diabetes, undiagnosed diabetes, diabetes duration with more than 10 years, elevated diastolic blood pressure, known hypertension, increased intake of protein, and number of comorbidity were independent associated factors with higher risk of sarcopenic obesity. History of stroke and increased vitamin D level were independently associated with a lower risk of sarcopenic obesity.
Conclusion
Diabetes influenced the risk of sarcopenic obesity in older people. Undiagnosed diabetes, diabetes duration with more than 10 years, elevated diastolic blood pressure, known hypertension, increased intake of protein, number of comorbidity, history of stroke, and vitamin D level were independently associated with sarcopenic obesity in older people with diabetes.

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GP163

Resistance training reduces skeletal muscle inflammation even after 4-week detraining in obese rats

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The ingestion of high-fat diet has been considered a crucial factor in the genesis of subclinical systemic inflammation and insulin resistance. The resistance training (RTr) can be an effective tool for the prevention and treatment of immune-metabolic disorders through physiological and morphological adaptations. The purpose of the present study was to analyze the effects of RTr and cessation of training on muscle inflammation and expression of genes related to glucose metabolism in obese rats. Thirty male Wistar rats aged 2 months were subdivided into three groups: High-Fat Diet (DH), Trained High-fat Diet (DHT) and Detrained High-fat Diet (DHD). RTr was performed for 12 weeks (wk), 3×/wk, three sets of 12 repetitions per session. In the 8th wk, DHD group interrupted training for 4 wk. RT-PCR was performed to analyze genes code TNFα, AMPK, GLUT4 and MEF2A, and Western blotting was assayed to analyze the expression of TNFα in the soleus muscle. Additionally we analyzed the insulin sensitivity by ITT, and muscle fiber area by HE staining. The results showed that RTr (DH vs. DHT) caused increase of muscle fiber area ($P<0.05$), and insulin sensitivity by 34% ($P<0.05$), increased AMPK gene levels by 23% ($P<0.05$), GLUT4 by 24% ($P<0.05$) and MEF2A by 20% ($P<0.05$), and reduced protein and gene levels by 51 and 28% of TNFα ($P<0.05$), respectively. Detraining (DHD vs DHT) increased body weight ($P<0.05$), and provoked reduction of muscle fiber area ($P<0.05$). However, TNFα expression remained reduced even after cessation of training. We conclude that RTr exerts positive effects on reduction of the local inflammation, and improves the expression of genes related to glucose metabolism in the oxidative skeletal muscle. These adaptations are maintained even after 4-week detraining.

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GP164

miR-26b is decreased in obesity and is associated with insulin resistance and visfatin levels

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Obesity is one of the major causes of morbidity and mortality worldwide and is considered a risk factor for metabolic syndrome, type 2 diabetes and cardiovascular disease (CVD). miRNAs are epigenetic regulators of several aspects of metabolism and energy homeostasis and are involved in obesity and regulation of insulin sensitivity. miR 26b is among the obesity-related micoRNAs and is differentially expressed in preadipocytes and mature adipocytes in humans and is upregulated during adipocyte maturation. Visfatin which is implicated in insulin resistance and metabolic syndrome is a target of miR-26b. The aim of this study was to investigate the levels of miR-26b levels in obesity and its association with insulin resistance and metabolic parameters.
Methods
Seventy children and adolescents (35 controls; 35 obese), between the ages of 8 and 18 years, were selected and clinically evaluated. The expression of miR-26b was measured after microRNA extraction from plasma samples. The extracted microRNAs were elongated using poly A polymerase reaction followed by cDNA synthesis. Real-time PCR was performed using SYBR green and delta Ct was calculated by the formula: Ct (reference gene)-Ct (target gene). miR-16 was used as the reference gene. Insulin and visfatin levels were measured using ELISA, and insulin resistance was calculated by the homeostasis model of assessment of insulin resistance (HOMA-IR). Fasting plasma glucose, triglyceride, total cholesterol, LDL-C and HDL-C were also measured colorimetrically.
Results
miR-26b expression were significantly lower in obese subjects compared with control group and were also lower in subjects with insulin resistance compared to those without insulin resistance. miR-26b was significantly correlated with insulin levels and HOMA-IR. It also showed a significant negative correlation with visfatin which was higher in obese subjects compared with control subjects.
Conclusion
Decreased miR-26b expression in obese children and adolescents may be involved in insulin resistance and increased visfatin levels.

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GP165

The effect of FTO polymorphism rs 9939609 on obesity and metabolic disturbances in Polish people from Lower Silesia

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Background
The association between fat mass and obesity-associated gene (FTO) polymorphism rs 9939609 and obesity was found in some European countries. However, the data concerning Polish population is insufficient. The relationship between FTO and metabolic disorders remains unclear.
Methods
The study group consisted of 686 women and 418 men from Lower Silesia in Poland, aged 30–80 years (mean age 54.2±9.26 years). The examination included anthropometric measurements, blood pressure, lipid profile and fasting blood glucose analysis. The group was genotyped for *FTO* rs9939609 polymorphism.
Results
Mean BMI was 28.2±5.0 kg/m^2 and was slightly higher in men. Prevalence of obesity (BMI >30 kg/m^2) was around 31% with no sex differences. Minor allele frequency was 0.44. In whole study group, mean BMI was higher in risk allele carriers (AA, AT) than TT homozygotes (AA – 28.45 kg/m^2, AT – 28.41 kg/m^2 vs TT – 27.8 kg/m^2), but the difference was not statistically significant. The association between *FTO* polymorphism and obesity traits were stronger in men than in women (p-values, respectively: for body weight 0.0005 vs >0.1, for BMI <0.01 vs >0.1, for waist circumference 0.0005 vs >0.1 in co-dominant model). We did not observe any association between *FTO* polymorphism and dyslipidaemia, hypertension or higher blood glucose concentration.
Conclusions
FTO polymorphism is one of many factors influencing body mass in Polish population. The effect on other metabolic disturbances is not significant. The reasons why the association between *FTO* and obesity were more pronounced in men than women remain unclear. Probably age, degree of obesity or other hormonal factors modify the clinical presentation of genetic predisposition.

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GP166

Role of Elovl6 in brown and beige adipose tissue during β3-adrenergic receptor activation

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Anti-obesity therapeutics based on increasing the amount of brown fat have received more attention from industry as the biology and regulation of brown fat are better understood than that of beige fat. Cold exposure and treatment with β3 adrenergic receptor agonist are known to activate brown/beige adipose tissue. Many transcriptional pathways regulating brown/beige adipose tissue have been identified, the role of lipid biosynthetic enzymes in brown/beige adipose tissue has been less investigated. In this study, we investigated the role of Elovl6, the enzyme responsible for converting C16 non-essential fatty acids (FAs) into C18 species, in brown/beige adipose tissue. We have observed upregulation of Elovl3, 4, 6 and 7 in BAT and inguinal WAT of mice treated with β3-adrenergic receptor agonist CL-316243 as well as cold-expose. These elongases are responsible for the conversion of C16 FAs into C30 saturated FAs, indicating the relevance of very long chain FAs in the activation process of brown/beige adipose tissue. It was reported that Elovl6 KO mice have impaired mitochondrial function and hence impaired thermogenic capacity of BAT when exposed to cold temperature (Cell Rep. 13:2039, 2015). When exposed to chronic CL-316243 treatment we observed that Elovl6 KO mice compensate its impaired BAT function by increased development of functional beige fat contributing to its increased energy expenditure. Interestingly, these metabolic changes are appearing to be mediated by increased type-2 cytokine signalling and macrophage polarization in the inguinal WAT of Elovl6 KO mice, as per our preliminary results. We have observed increased expressions of markers for cell proliferation (Ki67), macrophage (F4/80, CD68, Itgax-1, Arg-1, Clec-10) in the beige fat of Elovl6 KO mice compared to WT mice stimulated with CL-316243. These results suggest that Elovl6-regulated FA chain length is important for beiging and M2 macrophages are playing a mediator role in beige adipogenesis.

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GP167

A link between sex hormones, obesity and gut microbiota

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Sex steroids are involved in the development of obesity and metabolic disorders. The interrelationship between sex steroid balance and metabolism is complex, and the underlying mechanisms are still unclear. The impact of gut microbiota in development of obesity, inflammation and metabolic dysregulation has been suggested in humans and demonstrated in mouse models. Less is known about the interactions between sex steroids and gut microbiota. Based on available evidence, it is, however, pertinent to ask if sex steroids participate in the regulation of the composition or function of gut microbiota, or if gut microbes regulate sex steroid balance. The aim of the present study was to define the interplay between sex steroid balance and gut microbiota, in the context of obesity and metabolic dysregulation. First, we showed that non-obese human aromatase expressing (AROM+) male mice, with increased circulating estradiol to testosterone ratio and impaired liver lipid metabolism, have a female-type intestinal microbiota and higher ratio of *Firmicutes* to *Bacteroidetes*. Treatment with aromatase inhibitor restored estradiol/testosterone levels, followed by a slight improvement in their microbiota ecology. Second, in a mouse model reporting the expression of human aromatase (*CYP19A1*) gene (hARO-Luc mouse), ovariectomy-induced obesity, accompanied with elevated *Firmicutes* to *Bacteroidetes* ratio, altered gut homeostasis and increased aromatase reporter gene expression in the mammary adipose tissue. In conclusion, by applying two gene-modified mouse models, we showed that changes in sex steroid balance are linked to altered gut microbiota composition, and on the other hand, sex steroid – related obesity is linked to increased expression of human aromatase gene reporter. Further experiments, such as fecal transplantation from mice with altered sex steroid balance to WT mice, are needed to confirm the causality between sex steroids, gut microbiota and metabolic disorders.

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GP168

Effects of short sleep duration on energy metabolism and energy balance in subjects with overweight and obesity

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Introduction
The chronic reduction of sleep duration is associated to an increased risk of weight gain, but mechanistic aspects remain to be fully elucidated. The aim of our study was to examine the relationship between short sleep duration and energy metabolism, fuel selection and energy balance in overweight and obesity. Methods: Inclusion criteria were: age 18–65 years, BMI $\geq$25 kg/m^2. Use of any CNS medications, any psychiatric disorders and night shift work were considered as exclusion criteria. Body composition was evaluated by DXA. All participants underwent indirect calorimetry. The respiratory quotient (RQ) was calculated from gas exchanges. The equations by Weir and by Frayn were used to calculate the resting energy expenditure (REE), and carbohydrate and fat oxidation, respectively. Sleep duration, total daily energy expenditure (TDEE) and the level of physical activity (METs/day) were objectively assessed (Sensewear Armband). A 3-day dietary record was administered. Participants were divided into two groups, "regular sleep" (RS): >300 min/day or "short sleep"(SS): $\leq$300 min/day. Results: 88 women and 30 men were included (age:49.6$\pm$12.1 years), of whom 30.5% exhibited a short sleep duration. BMI (39.7$\pm$7.1 vs. 36.2$\pm$5.0 kg/m^2, $P=0.03$) and truncal body fat (18.7$\pm$6.2 vs. 16.1$\pm$4.6 kg, $P=0.04$) were higher in the SS group than the RS group. Subjects with short sleep had a lower RQ (0.71$\pm$0.12 vs. 0.76$\pm$0.12, $P=0.004$) and oxidized more fat (113$\pm$55 vs. 95$\pm$56 g/min, $P=0.006$) than regular sleepers. The METs/day were higher in the SS group compared to the RS group (1.56$\pm$0.55 vs. 1.35$\pm$1.24, $P=0.04$). RQ was positively associated to sleep duration ($P=0.04$, adj. for age, sex, and body fat). No difference emerged in TDEE or energy intake (SS group: 23$\pm$10 vs. RS group: 25$\pm$6 kcal/kg/day, $P>0.05$).
Conclusion
Short sleep affects energy substrate metabolism and adiposity distribution in overweight and obese subjects.

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GP169

Blood mercury concentration in relation to overweight or obese among Korean children and adolescents: KNHANES 2009–2013

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Background
Harmful effects of mercury on cardiovascular disease have been suggested in many epidemiologic studies. However, reports on harmful effect of mercury in relation to overweight or obesity have shown inconsistent findings.
Methods
A total of 1577 children and adolescents (10–18 years of age) from the Korean National Health and Nutrition Examination Survey (KNHANES) 2009–2013. Overweight or obese group was defined as over the 85th percentile of the age- and sex-specific BMI norms or BMI over 25. Subjects were categorized into three groups by age and gender specific blood cadmium, lead, and mercury concentration. Multivariate logistic regression stratified by gender was performed to estimate the odd ratio (OR) and 95% confidence interval (CI) for investigate the association.
Results
Compared to non-obese group, blood mercury concentration of was higher in obese group. Blood levels of cadmium and lead were not significantly different according to obese status. After adjustment for confounders, subjects in the highest tertile group of blood mercury levels were more likely to have overweight or obesity (OR 2.65, 95%CI 1.13–6.26) compared to subjects in the lowest tertile group in girls. No significant association was found in boys.
Conclusions
Blood mercury concentration is positively associated with overweight or obesity among Korean children and adolescents. Further longitudinal studies will be needed to confirm the causality.

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GP170

Association of the FTO gene rs9939609 polymorphism with obesity in the Republic of Tatarstan

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Aim
To investigate the possible association of the rs9939609 polymorphism in the FTO gene with obesity in the Republic of Tatarstan (RT).
Materials and methods
The study involved 63 adult patients (21 men and 42 women; 38–77 years old) with overweight or obesity and 515 healthy young people (157 men and 358 women; 16–35 years old) with normal weight. We assessed clinical and biochemical parameters (blood lipid profile). The analysis of the rs9939609 T/A polymorphism of the FTO gene in buccal cells was performed using Sintol kits (Russia) for RT-PCR. All the patients were tested by bioelectrical impedance analysis.
Results
The distribution of genotypes of the FTO gene polymorphism (TT – 11%, TA – 65% AA – 24%) and alleles (T – 44% A – 56%) in the group of patients with overweight and obesity was significantly different from those of the control group (TT – 42,9%, TA – 45,4%, AA – 11,7%; T – 65,6%, A – 34,4%; OR = 2.43, $P < 0.0001$), confirming that the A allele is a risk factor for obesity. In the group of obese patients we found an additive effect of the A allele on the increase of the average waist-hip ratio (lowest value in TT carriers, maximum value in AA carriers). We found that the number of patients with arterial hypertension and dyslipidemia was higher in the group with AA and TA genotypes compared with group with TT genotype.
Conclusion
We found a significant association of the T/A polymorphism of the FTO gene with the obesity. Obese patients with the risk allele of the rs9939609 FTO gene polymorphism have significantly higher values of absolute and relative body fat mass and BMI, total cholesterol, low-density lipoprotein, and triglycerides.

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GP171

Effect of bariatric surgery on sexual function and sex hormone levels in obese patients: a meta-analysis

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Objective
The aim of this meta-analysis is to evaluate the effect of bariatric surgery on sexual function and sex hormone levels in obese patients.
Methods
Two independent investigators conducted a literature search of PubMed, Medline and Cochrane databases using the terms *bariatric surgery*, *sexual function and sex hormone* to identify appropriate human studies published in English about the effect of bariatric surgery on sexual function and sex hormone levels in obese patients. The search was restricted to data from January 1, 1990 to December 1, 2016. Bibliographies of recent review articles and systematic reviews were searched to identify any additional trials. Two investigators according to the inclusion and exclusion criteria independently select literature, extract data and evaluate quality, then using RevMan 5.3.5 software for Meta analysis.
Results
In all, 31 studies met all criteria, including 1150 patients. The types of bariatric surgery performed included laparoscopic Roux-en-Y gastric bypass, laparoscopic gastric banding surgery, laparoscopic adjustable gastric banding, laparoscopic sleeve gastrectomy, Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding, vertical gastric banding, biliopancreatic diversion. The time to follow-up after surgery varied from 1 months to 115 months. Of the 31 studies, 5 reported the IIEF in obese men in 154 of 1150 patients (MD = 4.84, 95%CI (2.92, 6.75), $P < 0.00001$); 7 studies reported the FSFI in obese women in 369 of 1150 patients (MD = 4.10, 95%CI (−0.28, 8.48), $P = 0.07$). The changes of sex hormone levels in obese male patients before and after bariatric surgery as following: total testosterone (MD = 8.55, 95%CI (6.59, 10.52), $P < 0.00001$); free testosterone (MD = 6.52, 95%CI (3.09, 9.94), $P = 0.0002$); estradiol (MD = −7.03, 95%CI (−11.05, −3.01), $P = 0.0006$); luteinizing hormone (MD = 0.92, 95%CI (0.64, 1.20), $P < 0.00001$); follicle-stimulating hormone (MD = 1.29, 95%CI (0.65, 1.94), $P < 0.0001$); sex hormone-binding globulin (MD = 23.85, 95%CI (18.44, 29.26), $P < 0.00001$). The changes of sex hormone levels in obese female patients before and after bariatric surgery as following: total testosterone (MD = −0.78, 95%CI (−0.84, −0.71), $P < 0.00001$); free testosterone (MD = −5.53, 95%CI (−10.47, −0.59), $P = 0.03$); estradiol (MD = −25.10, 95%CI (−36.92, −13.27), $P < 0.0001$); luteinizing hormone (MD = 4.50, 95%CI (−1.04, 10.05), $P = 0.11$); follicle-stimulating hormone (MD = 1.68, 95%CI (0.50, 2.86), $P = 0.005$); sex hormone-binding globulin (MD = 34.79, 95%CI (22.63, 46.96), $P < 0.00001$).
Conclusion
This meta-analysis indicates that bariatric surgery has a significant improvement on the sexual function in both genders.

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GP172

Lipolytic effects of endogenous 3-iodothyronamine (T1AM) and synthetic analog SG-2 *in vivo* and in cultured adipocytes

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3-Iodothyronamine (T1AM) is a hormone like molecule structurally similar to TH, that has been reported to modulate energy metabolism by favoring lipid over glucose catabolism. To better understand the role played by T1AM on the regulation of lipid metabolism, in the present study we administered spontaneously obese mice with T1AM at two different dosages (10 and 25 mg/kg per day) for 7 days and the effects on body weight (BW) and lipid profiles were examined. In addition a fluoro-labeled version of T1AM (FL-T1AM) was synthesized and utilized to assess T1AM intracellular localization in 3T3-L1 mouse adipocytes.
Administration of 10 or 25 mg/kg per day T1AM showed a BW loss of 10% or 18% of initial BW by day 7 of treatment. T1AM treatment at both dosages produced a significant increase in total plasma triglycerides ($P < 0.05$) and a significant decrease in plasma cholesterol ($P < 0.05$), without any significant change in glycaemia. At present, the specific mechanism of T1AM entry into the cell, as well as its internal targets remains unknown. Cellular imaging revealed rapid intercellular uptake of FL-T1AM without localization to the lipid droplet or nucleus of mature adipocytes. This rapid rate of uptake was further evaluated via flow cytometry, with peak detection of FL-T1AM steadily rising until reaching peak signal and equilibrium at ∼20 min. We also observed that when 3T3-L1 adipocytes were treated with T1AM or its synthetic halogen free analog SG-2 (1–10 μM), both compounds decreased lipid accumulation in mature adipocytes, with SG-2 showing a potency significantly higher than T1AM ($IC50_{SG\text{-}2} = 5$ μM; $IC50_{T1AM} = 20$ μM).
In conclusion T1AM and its synthetic analog show a significant lipolytic activity, both in cultured adipocytes and *in vivo*.

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Pituitary

GP173

A comparison of single-dose effects of short acting somatostatin analogs: octreotide vs pasireotide in patients with active acromegaly after surgical debulking

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Acromegaly is a rare endocrine disorder caused by growth hormone (GH) secreting pituitary adenoma. The treatment of choice is transsphenoidal surgery. In patients with persistent disease after surgery medical therapy is recommended.

First-line medical treatment include first generation long-acting somatostatin analogs: octreotide LAR and lanreotide autogel. Recently, pasireotide – a second generation somatostatin analog has been investigated in patients with acromegaly. The aim of this study was to compare the effectiveness of the single-dose of short-acting somatostatin analogs: octreotide vs pasireotide in patients with active acromegaly after surgical debulking who were resistant to first generation long-acting somatostatin analogs.

Eighteen patients after debulking surgery without biochemical control of acromegaly on medical therapy were enrolled in the study. All patients had short-acting octreotide and pasireotide administered on different days. GH concentration was measured before and 60, 120 and 180 min after drug administration. Nadir GH concentrations and decreases in GH concentrations were compared.

Nadir GH values in octreotide test were reached 60 min after drug administration, while in pasireotide test – 180 min after drug administration. The median nadir GH concentration was 2.765 μg/l (IQR: 1,885–4.07) vs 1.51 μg/l (IQR: 0.95–2.555) respectively, $P<0.001$. The decrease in GH concentration was more significant after pasireotide administration compared to octreotide administration ($P<0.001$). The median decrease in GH concentration in octreotide test was 1.255 μg/l (IQR: 0.918–1.75) vs 2.805 μg/l (IQR: 1.523–5.043) after pasireotide administration. Octreotide was generally better tolerated than pasireotide.

Short-acting pasireotide is more effective than short-acting octreotide in GH supression in patients with uncontrolled acromegaly. Pasireotide may be a promising alternative for patients resistant to first-generation somatostatin analogs.

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GP174

Efficacy and safety of switching to pasireotide LAR alone or in combination with pegvisomant in acromegaly patients controlled with combination treatment of first-generation somatostatin analogues and weekly pegvisomant (PAPE study): a prospective open-label 48 week study, preliminary results 24 weeks

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Background

Efficacy and safety of combination treatment of pasireotide LAR with pegvisomant (PEGV) has not been studied yet. Switching to Pasireotide LAR in patients previously controlled with long-acting somatostatin analogues (LA-SSAs) and PEGV could reduce the required PEGV dose to normalize serum IGF1 levels, while the effect on glucose metabolism is unknown.

Methods

We enrolled 60 acromegaly patients >18 years with acromegaly who had normal IGF1 levels ($\leq 1.2\times$Upper Limit of Normal (ULN)) using combination treatment of high dose LA-SSAs and weekly PEGV for ≥ 6 months. After enrollment LA-SSA treatment was continued, and the PEGV dose was reduced by 50% for 12 weeks. If IGF1 levels remained normal after 12 weeks, patients were switched to pasireotide LAR 60 mg monotherapy, every 4 weeks. If IGF1 levels $>1.2\times$ULN patients were switched to pasireotide LAR 60 mg and continued with the 50% reduced PEGV dose. The primary endpoint was the percentage of patients achieving normal IGF1 levels at 24 weeks. The key secondary endpoint was the frequency diabetes at 24 weeks.

Results

At baseline, median IGF1 was $0.94\times$ULN with a median PEGV dose of 80 mg/week, and 30.6% of patients had pre-existing diabetes. After the 50% dose reduction of PEGV, median IGF1 levels increased to 1.43 ULN, while IGF1 remained normal in 33% of patients. At 24 weeks, 73% of patients achieved normal IGF1 levels with a median IGF1 $0.98\times$ULN. Cumulative PEGV dose reduction between baseline and 24 weeks was 66%. At 24 weeks, IGF1 levels were normal in 88% of patients on pasireotide LAR monotherapy, and 68% of patients on combination treatment. Pasireotide LAR was well tolerated. At 24 weeks, the most common adverse event was diabetes which occurred in 70.2% of patients. Two patients withdrew prematurely due to hyperglycemia requiring insulin treatment.

Conclusion

Pasireotide LAR alone or in combination with pegvisomant controls IGF1 in 73% of patients after 66% reduction in cumulative dose of weekly pegvisomant. The frequency of diabetes was 70.2% and is in line with previous studies.

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GP175

Resistance to somatostatin analogues is associated with GSTP1 gene methylation and AHR rs2066853 variant in acromegaly patients

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Evidences suggest that environmental contaminants exposure and/or the impairment of intracellular xenobiotic metabolizing system could affect pituitary pathophysiology. Glutathione-S-transferase-P1 (GSTP1) gene encodes for an enzyme that is involved in cellular detoxification mechanisms. GSTP1 altered activity or expression has been reported in some tumours.

We aimed to assess the GSTP1 gene promoter methylation status in acromegaly patients and its contribution to their clinical features.

Seventy-seven WT AIP gene acromegaly patients (50 women) have been screened for germline AHR rs2066853 variant and GSTP1 promoter methylation. Epidemiologic, clinical, biochemical and radiological parameters at diagnosis have been compared after patients' stratification according to GSTP1 methylation status and the presence of AHR rs2066853 variant. We also evaluated the response to somatostatin analogues (SSA) administered either before or after surgery in 71 cases.

Seventeen patients were found to carry AHR rs2066853 variant and 26 methylated GSTP1 (GSTP1met). GSTP1met patients showed a higher prevalence of diabetes mellitus ($P=0.01$), colonic polyps ($P=0.05$), and were more resistant to SSA ($P=0.02$) as compared to GSTP1 unmethylated patients (GSTP1unmet).

On the basis of GSTP1 methylation status and the presence of AHR rs2066853 variant, we identified four groups: group 1, 40 patients GSTP1unmet and AHR WT; group 2, 20 patients only GSTP1met; group 3, 12 patients carrying only AHR rs2066853 variant; group 4, five patients with both GSTP1 methylation and AHR rs2066853 variant. Group 1 patients were more sensitive to SSA than other groups ($P=0.02$). Patients of group 4 were more resistant to SSA ($P=0.02$) and showed higher GH ($P=0.03$) and IGF1 ($P=0.04$) levels and lower percentage of GH decrease ($P=0.04$) after SSA than other groups.

In conclusion, GSTP1 methylation and AHR rs2066853 variant associate with resistance to SSA in acromegaly patients.

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GP176

Minimally Invasive Diagnosis and Direct Transnasal Surgery: a single centre series of 100 children with Cushing's Disease with long term follow-up

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Introduction

Trans-sphenoidal surgery (TSS) with minimally invasive techniques is the first choice in the treatment of paediatric Cushing's disease (CD). The question is how can high remission rates be achieved with less invasive investigations and TSS. The developments in our centre treating 100 pediatric Cushing patients with long-term follow-up may add some helpful ideas.

Material and methods

Data from our first series 1 ($n=55$) will be compared with new data from the recent series 2 ($n=45$) until 2009. All patients were operated by one surgeon by direct transnasal microsurgery (TNS). Special diagnostic methods such as inferior petrosal sinus sampling (IPSS) were replaced by ACTH measurement from the cavernous sinus (CSS) restricted to unclear cases without increase of salivary cortisol in the CRH-test, difficult sella anatomy and/or negative MRI. Multiple direct micro-cytology, micro-doppler and adequate visualization will be described.

Results

In our first series of 55 cases, IPSS was performed in 13 (24%) of whom 46% had false adenoma lateralization. All adenomas could be removed with extensive pituitary exploration and all had intraoperative pathology. Two patients had early successful re-surgery. Recurrence rate 15%. In the second series with more

refined MRI and endocrinology: easy repeat CRH saliva tests and CSS sampling used in only 7 patients (15%), all micro-adenomas were initially detected. Early repeat-TNS was necessary and successful in three. Recurrence rate 11%. Side effects of TNS were minimal, as such, children and parents readily accepted re-TNS. Thus, including re-TNS in recurrences, 98 of 100 patients had long-term remission. TNS in recurrences had a better outcome in the last series with less pituitary dysfunction using more intraoperative minute biopsies.
Conclusions
Invasive pre-surgical investigations could be reduced. 98% remission rate could be achieved with advanced investigations, refined TNS, early re-TNS and re-TNS in recurrences. Only two children (2%) were irradiated – only one was indicated by the senior surgeon.

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GP177

Octreotide subcutaneous (s.c.) depot, a novel ready-to-use formulation, provides higher exposure and maintains response in patients with acromegaly and functioning neuroendocrine tumours (NETs) previously treated with long-acting octreotide: Results from a phase 2, open-label, multicentre, randomized study

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Background
Octreotide s.c. depot is a novel, ready-to-use formulation administered via a thin needle, which may allow self-administration. In a phase 1 study in healthy volunteers, octreotide s.c. depot provided greater bioavailability with faster onset and greater IGF1 suppression than long-acting octreotide. Here, we present data from a phase 2 study evaluating pharmacokinetics (PK), efficacy, safety, and tolerability of octreotide s.c. depot in patients with acromegaly and neuroendocrine tumours (NETs).
Methods
Adult patients with acromegaly or functioning, well-differentiated NETs treated with long-acting octreotide 10 mg/20 mg/30 mg every 4 weeks (q4w) for $\geq$2 months received the last dose of long-acting octreotide in period 0 (P0). Patients were randomized 28 days later to receive octreotide s.c. depot 10 mg q2w or 20 mg q4w for 3 months (period 1 [P1]).
Results
Twelve patients were randomized to receive octreotide s.c. depot 10 mg q2w (acromegaly, n=3; NET, n=1) or 20 mg q4w (acromegaly, n=4; NET, n=4). Acromegaly: steady state (SS) PK (for octreotide s.c. depot 10 mg, 20 mg vs long-acting octreotide 10 mg, 30 mg, respectively) – $AUC_{0\text{-}28d}$(day*ng/l): 95.6, 78.5 vs 6.23, 24.1; C_{max}(ng/ml): 10.6, 11.3 vs 0.35, 1.41. NETs: SS PK (for octreotide s.c. depot 10 mg, 20 mg vs long-acting octreotide 20 mg, 30 mg, respectively) – $AUC_{0\text{-}28d}$(day*ng/l): 83.3, 135.0 vs 27.8, 39.9; C_{max}(ng/ml): 5.61, 15.7 vs 1.68, 2.48. In acromegaly, control of IGF-1 and GH levels was maintained or improved in P1 vs P0. In NETs, symptoms of carcinoid syndrome were similar or improved in P1 vs P0; symptoms disappeared in two patients in 20 mg group. Adverse events (all grade 1-2) were reported in six and eight patients during P0 and P1, respectively; most common in P1 were GI disorders.
Conclusions
Octreotide s.c. depot provided higher exposure than long-acting octreotide, maintained biochemical control in patients with acromegaly and symptom control in patients with functioning NETs, and was well tolerated with a safety profile consistent with long-acting octreotide.

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GP178

Sleep patterns in patients with non-functional GHRH receptor

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Hypothalamic GH releasing hormone (GHRH) has hypnotic actions by increasing slow wave sleep (SWS) (non-rapid eye movement sleep, non-REM), which account for about 75% of sleep. Conversely, GH may stimulate the rapid eye movement sleep (REM). Patients with GH deficiency (GHD) often exhibit sleep problems leading to daytime fatigue and reduced quality of life (QoL). We have described a cohort of patients with isolated GHD (IGHD) due to GHRH resistance caused by a homozygous null mutation (c.57+1G>A) in the GHRH receptor gene. They have normal QoL and no obvious complaints of chronic tiredness. The aim of this study was to determine objectively and subjectively the sleep quality in these subjects, who have never received GH therapy. A cross sectional study was carried out on 21 adult IGHD subjects, and 21 matched controls. Objective sleep assessment included polygraphic records of the stages wake (W), non-REM: N1 (drowsiness), N2 and N3 (already sleeping) and R (REM). Subjective evaluation included the Pittsburgh Sleep Quality Index, Insomnia Severity Index, and Epworth Sleepiness Scale. Compared to controls, IGHD subjects exhibited lower sleep efficiency (77.7 (27.5) vs 87.5 (10.1) %, $P=0.007$), total sleep time (330.0 (127.5) vs 385.5 (56.0) min, $P=0.028$) and higher percentage of the non-REM 1 stage (14.6 (18.9) vs 7.3 (8.1) %, $P=0.022$). There was no difference between the groups in REM sleep and in quality questionnaires. These data show an extension of the drowsiness period, with a reduction in the total sleep time, suggesting a preponderant role of GHRH resistance over GHD in the sleep quality of these IGHD subjects. The objective reduction in the sleep efficiency and total sleep time seem have minimal subjective consequences, as it was not reflected in differences of quality sleep questionnaires.

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GP179

Correction of sustained hyponatremia secondary to SIAD by the use of chronic tolvaptan therapy is associated with a reduction in Emergency Room visits, hospital admissions and days of hospitalization over a 3-year period

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Introduction
Hyponatremia (HN) is associated with worse clinical outcomes, and longer hospital lengths-of-stay than seen in eunatremic patients. The Syndrome of Inappropriate Antidiuresis (SIAD) is the most common cause of hyponatremia in hospitalization. We studied the relationship between correction of sustained SIAD-induced hyponatremia and visits to the Emergency Room (ERv) as well as hospital admissions (HA) in a case series.
Methods
Retrospective, cross-sectional study of patients whose HN was corrected with chronic tolvaptan therapy (CTV) for a minimum of 3 years. Serum Sodium levels(SNa) in mmol/l. Descriptive statistics expressed as median (IQR). SPSS 15, non-parametric tests (Wilcoxon for paired data), univariate analysis.
Results
16/25(64%) patients fulfilled inclusion criteria. Nine patients not completing 1 year of follow-up were excluded. Median age: 82 (74–87). Women: 11/16(69%) . HN was first detected a median of 51 months (IQR 29–56) prior to initiation of therapy. SIAD etiology: 9/16(56%) idiopathic, 3/16 (19%) drug-induced (19%), 2/16 (3%) respiratory, 1/16 (6%) abdominal, 1/16 (6%) cancer. The year before HN correction, Nadir SNa:120(115–125) mmol/l, with a median of 2(1–4) ERv/patient, HA:1(1–2) with 18(10–32) days of hospitalization (DH). During year 1 of CTV, Nadir SNa rose to 136(133–137) mmol/l ($P=0.001$), ERv dropped to 1(0-3)($P=0.03$), HA to 0(0-0)($P=0.003$), DH to 0(0,0)($P<0.001$). The benefits were sustained when comparing the second and third years to the year prior to HN correction. Second year: ERv: 0(0-1)($P=0.004$), HA: 0(0-1)($P=0.001$), DH: 0(0-1)($P<0.001$). Third year: ERv: 1(0-2)($P=0.05$), HA: 0(0-1)($P=0.009$), DH:

0(0-4)($P=0.01$). Three years before start of therapy vs 3 years post: Total median ERv/patient: 3(1-5), HA: 2(1-4), DH 18(10-34) vs total ERv: 2(1-4) ($P=0.03$), HA: 1(0-2)($P=0.006$), DH 0(0-4)($P=0.006$). No patient developed hypernatremia. Tolvaptan doses were lowered if thirst developed or SNa reached 141 mmol/l. Final weekly TV dose was 34 mg (23–105).
Conclusions
Correction of sustained hyponatremia secondary to SIADH with chronic TV therapy was safe, and associated with a significant and sustained reduction in ER visits, hospital admissions, and days of hospitalization.

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GP180

Outcome of non-functioning pituitary adenomas that regrow after primary treatment: a study from two large specialist UK centers

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Introduction
Despite the significant risk of regrowth of non-functioning pituitary adenomas (NFAs) after primary treatment, systematic data on the probability of further tumour progression and the effectiveness of management approaches are lacking.
Aims
Assess the probability of further regrowth(s), predictive factors and outcomes of management approaches in patients with NFA diagnosed with adenoma regrowth after primary treatment (surgery combined or not with radiotherapy) in two UK referral centers.
Methods
The records of the patients with NFA who during their follow-up had adenoma regrowth were reviewed. The period covered for the primary NFA surgery was between 1/1963 and 12/2011 and the follow-up period ended in 6/2016.
Results
We identified 237 patients (median follow-up after 1st regrowth of 5.9 years (range 0.4–37.7)). The 5-year 2nd regrowth rate was 35.3% (36.2% after surgery; 12.5% after radiotherapy; 12.7% after surgery combined with radiotherapy; 63.4% with monitoring). Of those managed by monitoring, 34.8% eventually were offered intervention. Type of management and sex were risk factors for 2nd NFA regrowth, whereas age at diagnosis of primary NFA and type of adenoma immunostaining were not. Amongst those with 2nd adenoma regrowth, the 5-year 3rd regrowth rate was 26.4% (24.4% after surgery; 0.0% after radiotherapy; 0.0% after surgery combined with radiotherapy; 48.3% with monitoring). Overall, patients with a NFA regrowth had probability of a 3rd regrowth 4.4% at 5 years, and 10.0% at 10 years, and the type of management of the 1st regrowth was the only risk factor. Malignant transformation was diagnosed in two of 237 patients (one gonadotroph and one silent ACTH adenoma).
Conclusions
Patients with regrown NFA after primary treatment continue to carry considerable risk of tumour progression necessitating long-term follow-up. Management approach of the regrowth is the major factor determining this risk; monitoring alone is associated with high progression rates and a substantial number of patients will ultimately require intervention.

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GP181

Targeting either GH or IGF-I levels during somatostatin analogue treatment in patients with acromegaly: A randomized, investigator-initiated multicenter study

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Context
Assessment of disease control in acromegaly depends on GH and IGF-I, but discordant values frequently occur. Further, the role of OGTT-suppressed GH (GH_{nadir}) in somatostatin analogue (SA) treated patients is debated.
Objective
To evaluate the effect of targeting either IGF-I or GH during SA treatment.
Design
A randomized, investigator-initiated, multicentre trial.
Patients and methods
84 patients controlled with either SA ($n=61$) or surgery-only ($n=23$) underwent a 3 h GH profile including a 2 h OGTT at baseline, after 6 months (SA treated patients only) and after 12 months together with IGF-I. SA patients were randomized to be monitored by either IGF-I ($n=33$) or GH_{nadir} ($n=28$). SA dose increase were allowed at baseline and after 6 months. Symptoms and quality of life (QoL) were assessed by disease-specific questionnaires (PAQ12 and AcroQoL).
Main outcome measures
GH and IGF-I at baseline and 12 months, symptoms and QoL, and SA dose increases.
Results
IGF-I and fasting GH levels at baseline were comparable between the two groups, whereas GH_{nadir} (μg/l) was lower in the surgery group (GH_{nadir} 0.7 ± 0.1 (SA) vs 0.3 ± 0.1 (surgery), $P<0.01$). At baseline, 31% of SA patients had concordant controlled GH and IGF-I, 43% had elevated GH and 3% elevated IGF-I. Significantly more patients in the surgery group had concordant controlled values (65%), $P<0.01$. SA dose increase was performed in 20 patients in the GH target group as compared to eight patients in IGF-I target group ($P=0.02$) and resulted in a higher proportion of controlled patients ($P=0.01$). SA patients had suppressed insulin levels and elevated glucose and FFA levels during the OGTT compared to surgery. QoL was only mildly affected at baseline and did not change consistently.
Conclusions
i) Discordance between GH and IGF-I is more prevalent during SA treatment as compared to surgery, mainly due to elevated GH_{nadir} levels, ii) targeting discordant GH or IGF-I levels in SA patients translates into SA dose increase and a higher degree of concordance, iii) Our data suggest that a sizable proportion of SA patients are undertreated.

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GP182

Brain white matter damage and volumes of hippocampus and hypothalamus correlates to cognitive function in craniopharyngioma

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Introduction
Adult patients with craniopharyngioma (CP) and hypothalamic (HT) damage have impaired cognitive function. The white matter (WM) changes behind these findings remain to be elucidated. Diffusion tensor imaging (DTI) is a MRI technique that quantifies microstructural damage in the WM. This is the first study of DTI, hippocampal (HC) and HT volume in relation to cognition in CP patients.
Methods
A cross-sectional study of childhood onset CP was performed at median 22 years after first operation. After exclusions, 36 patients and 31 controls remained in the MRI study. Main outcome measures were comparison of cognitive tests, volume measurements of HC and HT and the DTI parameters median diffusivity (MD) and fractional anisotropy (FA) between patients and controls.
Results
CP patients have WM damage in the left dorsal cingulum and right uncinate fasciculus. No significant difference was found on DTI measurements of the HC. Correlations were found between DTI results from the right uncinated fasciculus (MD, $P=0.035$ and FA, $P=0.005$) and the left HC (MD, $P=0.035$ and FA, $P=0.001$) with long term memory reflecting general knowledge. DTI in the cingulum correlated with visual memory (MD, $P\leq0.04$ and FA, $P\leq0.04$) and short term memory (MD, $P=0.004$). DTI in the HC correlated with long term memory (MD, $P=0.03$ and FA, $P\leq0.046$) and short term memory (FA, $P=0.02$). HT volume correlated negatively with MD of right uncinate fasciculus ($P=0.015$). The CP patients had a smaller HC volume which correlated with long term memory ($P=0.016$).
Conclusions
A structure to function relationship is established between cognition and WM damage detected with DTI in CP. CP patients have a smaller HC compared to controls. Whether the cognitive deficits are a direct consequence of HT damage or an indirect effect on frontotemporal network remains to be elucidated.

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GP183

Copeptin – a sensitive marker of an altered CRH-axis in pituitary disease

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Background
Copeptin (pre-proAVP) secreted in equimolar amounts with vasopressin (AVP) closely reflects AVP release. Previously it was shown that copeptin is stimulated in standard pituitary function tests acting through hypothalamic centres. Furthermore, copeptin has been shown to subtly mirror stress potentially mediated via CRH. To further test a potential direct interaction of CRH with copeptin release which could augment AVP effects on pituitary function, we investigated copeptin response in a standard CRH test, both in healthy controls and patients with pituitary disease.
Patients and methods
18 healthy controls and 29 subjects with history of pituitary disease were subjected to a standard CRH test and in addition to ACTH and cortisol we measured copeptin by standard assays (ThermoFisher).
Results
Patients with previous pituitary disease were subdivided in a group passing the test (P1) and failing (P2). The latter group included five patients with diabetes insipidus. The overall copeptin response was higher in controls than in subjects with pituitary disease (area under the curve, $P=0.04$ for P1 + P2) with a maximum increase in controls from 3.84 ± 2.86 pmol/l, to 12.65 ± 24.87 pmol/l, $P=0.04$, at 30 min). In contrast, both groups of pituitary patients lacked a significant CRH response. The mean increase in P2 was from 1.93 ± 1.44 pmol/l to 3.37 ± 3.49 pmol/l, at 30 min, $P=$ns, and even in P1 where ACTH concentrations increased four-fold (mean 21.48 vs. 91.53 pg/ml, $P<0.01$) copeptin did not respond (e.g. 4.35 ± 5.81 pmol/l vs. 5.36 ± 6.79 pmol/l, at 30 min, $P=$ns).
Conclusions
CRH is able to stimulate copeptin release in healthy controls suggesting a direct interaction of CRH and AVP/vasopressin. Interestingly, this relation is altered already in the group of pituitary patients who pass the standard CRH test indicating i) that the CRH-ACTH-cortisol response is largely independent from the AVP system, but ii) the CRH-AVP interaction reflected by copeptin may be much more sensitive to reveal subtle alterations in the regulation of pituitary function.

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GP184

Hormonal and metabolic effects of long-term cabergoline withdrawal in patients with hyperprolactinemia

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Hyperprolactinemia is associated with abnormalities in glucose and lipid profile with development of insulin resistance and metabolic syndrome (MetS), which have been found to be improved by treatment with cabergoline (CAB). The current study aimed at investigating hormonal and metabolic effects of long-term CAB withdrawal in patients with prolactinomas. In 46 patients (37 F, 9 M, aged 34.5 ± 11.5 yrs, 36 microadenomas and 10 macroadenomas) anthropometric (weight, BMI, waist circumference (WC)) and metabolic (fasting glucose (FG) and insulin (FI), total (TCHO), HDL and LDL cholesterol, triglycerides (TG), HOMA-IR, HOMA-β, ISI0, VAI, and prevalence of MetS) parameters, and PRL levels were evaluated at baseline, at CAB withdrawal (TWD), and 12 (T12) and 60 (T60) months after CAB discontinuation. CAB treatment (median duration = 72 months) induced PRL normalization in all patients, and a significant improvement of BMI ($P<0.0001$), WC ($P<0.0001$), FI ($P=0.007$), HDL ($P<0.001$), LDL ($P<0.001$), HOMA-IR ($P=0.012$) and ISI0 ($P=0.05$) compared to baseline. CAB withdrawal resulted in prolonged and sustained normoprolactinemia, with only 8 (17.4%) patients requiring treatment restarting within 12 months. In 38 patients permanently discontinuing CAB, compared to TWD BMI ($P<0.0001$), WC ($P<0.0001$), TCHO ($P<0.001$) and VAI ($P<0.0001$) significantly impaired at T12, and similarly BMI ($P<0.0001$), WC ($P<0.0001$), TCHO ($P<0.05$) and VAI ($P<0.0001$) at T60. Compared to TWD no further changes were seen in FI, HOMA-IR, HOMA-β, ISI0. MetS prevalence significantly increases from T0 (23.9%) to T60 (41.3%, $P<0.0001$), with 8 patients (17.4%) developing MetS after CAB withdrawal. In conclusion, CAB discontinuation significantly worsens lipid profile and MetS prevalence in patients with prolactinomas.

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Pituitary & Endocrine Tumours

GP185

Localization of benign insulinomas using glucagon-like peptide-1 receptor (GLP1-R) SPECT/CT and PET/CT and MRI in a prospective clinical study

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Purpose
We aim at prospectively comparing the detection rate of GLP1-R PET/CT vs GLP1-R SPECT/CT vs standardized contrast enhanced 3T-MRI in patients with suspected insulinoma.
Methods
40 patients with neuroglycopenic symptoms due to endogenous hyperinsulinemic hypoglycemia were enrolled.
3T-MRI was performed. Afterwards patients received SPECT/CT after injection of ^{111}In-DOTA-exendin-4 and PET/CT after injection of ^{68}Ga-DOTA-exendin-4 in a randomized order. Three blinded nuclear medicine physicians and three blinded radiologists reviewed the scans.
Standard of comparison was the histological diagnosis after surgery.
Results
Previously performed cross-sectional imaging was negative or inconclusive in 27/40 patients. So far 29 patients have been operated. The histological diagnosis of a benign insulinoma was confirmed in 25 patients, one patient had a nesidioblastosis. In one patient no lesion could be found intraoperatively. In two patient symptoms of endogenous hypoglycemia ceased postoperative but histological diagnosis did not confirm a benign insulinoma or nesidioblastosis. These two patients were excluded from evaluation as the final diagnosis remained unclear. Two patients refused surgery. Three patients are awaiting surgery. In five patients all performed imaging modalities did not find any suspicious lesion and were thus not operated up to date. One patient showed signs of malignancy in MRI, thus did not meet the inclusion criteria and was excluded. In this interim

analysis of 27 operated patients PET/CT showed an overall pooled sensitivity of 92%, SPECT/CT at 72 h a sensitivity of 71% and 3T-MRI a sensitivity of 76%.
Conclusion
1) These preliminary data suggest that PET/CT performs better as standardized MRI imaging and SPECT/CT at lower irradiation dose and much shorter investigation time than the latter.
2) GLP-1R PET/CT will be a useful diagnostic tool in patients where CT/MRI fails to localize the insulinoma.

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GP186

24 hour urinary 5-hydroxyindoleacetic acid (5-HIAA) doubling-time (DT) is associated with disease-specific mortality (DSM) and progression-free survival (PFS) in patients with neuroendocrine tumors (NETs)

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Background
Biochemical biomarker DT is used clinically for prognosis prediction in several solid malignancies. The aim of the current analysis was to determine whether biomarker DT has any prognostic utility in patients with NETs.
Methods
Patients with NETs ($n=184$) were enrolled in a prospective study with comprehensive biochemical analysis. The current analysis included subjects with increasing 5-HIAA levels in at least two consecutive measurements. DTs for each biomarker were calculated using the formula DT = $[\log_{10}(2)$*(time interval between tests)]/$[\log_{10}(2^{nd}$ value)–$\log_{10}(1^{st}$ value)]. Log-rank test was used to assess differences in DSM or PFS risk by DT. The *c*-statistic of 5-HIAA predictive utility for DSM was calculated using receiver operating characteristic (ROC) curve analysis. DSM and PFS were compared by 5-HIAA DT using Kaplan-Meier survival analysis and multivariate analysis was performed using Cox regression.
Results
91 patients had increasing 5-HIAA levels. Four patients died during a median follow-up of 8 months (interquartile range, 12). The c-statistic for DSM prediction by 5-HIAA was 0.76 (95% CI 0.62–0.90), and 5-HIAA DT <434 days had positive and negative predictive values for DSM of 75 and 76%, respectively. Patients with a 5-HIAA DT <434 days had higher risk for DSM during follow-up (Log-Rank test, $P=0.02$). In sub-group analysis this difference was found only among patients with a non-pancreatic NET ($P=0.002$). In the entire cohort, PFS were comparable between patients with 5-HIAA DT longer vs. shorter than 434 days. However, patients with small-intestine NET with 5-HIAA DT $<$ 434 days had a higher risk for progression ($P=0.006$), also in multivariate analysis (Hazard Ratio 15.3, 95% CI 1.01–232.6, $P=0.049$).
Conclusions
Short 5-HIAA DT is associated with increased DSM and lower PFS in patients with NET, and specifically among those with SINET, and can be used as a prognostic measure in NET patients.

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GP187

Pasireotide alone or in combination with cabergoline effectively controls urinary free cortisol levels: results from a prospective study in patients with Cushing's disease (CAPACITY)

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Background
Pasireotide is a multireceptor-targeted somatostatin analogue that predominantly binds to somatostatin receptor subtype 5 (SSTR5) and provides sustained control of urinary free cortisol (UFC) levels in some patients with Cushing's disease (CD). Cabergoline is a dopamine D2 receptor agonist with efficacy in some patients with CD. Most corticotropinomas co-express SSTR5 and D2, providing rationale for combination treatment with pasireotide and cabergoline. Results are reported from a Phase II study of pasireotide alone or combined with cabergoline in patients with CD.
Methods
Open-label, multicentre, non-comparative study. Patients with persistent/recurrent or *de novo* (if not surgical candidates) CD who were pasireotide-untreated at screening were enrolled. Patients initiated treatment with pasireotide (subcutaneous) 0.6 mg bid. If mean UFC (mUFC; from two consecutive 24h collections) remained $>$ULN after 8 weeks, the pasireotide dose was increased, if tolerated, to 0.9 mg bid for 8 weeks. If mUFC remained elevated, cabergoline 0.5mg qd was added for 8 weeks, increasing to 1.0mg qd for another 8 weeks if mUFC$>$ULN. Primary endpoint: proportion of patients with mUFC$\leq$ULN at week 35.
Results
Sixty-six patients (median 40.5 years; 59 females) were enrolled. Twenty-seven patients received pasireotide monotherapy; 39 received combination therapy. At week 35, mUFC$\leq$ULN was achieved in 25 patients (37.9%, 95%CI 26.2–50.7), 13 of whom received pasireotide monotherapy, with a further 12 achieving the primary endpoint after cabergoline addition. The most common ($>20\%$) AEs were hyperglycaemia (51.5%), nausea (47.0%), diarrhoea (45.5%), headache (28.8%), dizziness (24.2%) and cholelithiasis (24.2%). Sixteen (24.2%) patients discontinued before week 35 (10 on pasireotide monotherapy); seven (10.6%) because of AEs (five on pasireotide monotherapy). Two on-treatment deaths occurred, both unrelated to study treatment.
Conclusions
Pasireotide alone or combined with cabergoline effectively controlled mUFC. Results suggest that addition of cabergoline in patients with persistently elevated mUFC is an effective strategy to enhance the control of CD.

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GP188

Vertebral fractures are prevalent among patients with acromegaly in spite of normal bone mineral density reflecting overall duration of disease regardless of biochemical control or cure

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Introduction
Skeletal complications of acromegaly are among its most persistent and invalidating impacts. Dual-X-ray absorptiometry (DXA) alone might be insufficient or even misleading for bone health assessment in acromegaly.
Patients and methods
Patients with acromegaly ($N=170$) were classified as active ($N=104$), operatively cured ($N=34$) or medically controlled ($N=32$). 57 males and 113 females were included, 52.8 (22.0–78.5) years old. Bone mineral density (BMD) was assesed at L1-L4 and Femoral neck (FN) using DXA Hologic Discovery-W-QDR. BMD results were expressed as Z score, accounting for age and gender. Vertebral fracture assessment (VFA) on Th4-L4 was performed in 71 patients (24 male, 47 female) to identify number, type, location and degree of severity of vertebral fractures (VFs).
Results
L1-L4 BMD was normal in all patients and not significantly different in active (Zsc: 0.61 ± 0.13) cured (Zsc: 0.32 ± 0.25) or controlled acromegaly (Zsc: 0.17 ± 0.32). FN BMD was normal in all and not significantly different in active (Zsc: 0.61 ± 0.11) cured (Zsc: 0.59 ± 0.19) or controlled acromegaly (Zsc: 0.49 ± 0.22). VFs were identified in 23.9% (17/71) of patients. Prevalence in males was significantly higher than in females (33.3% vs. 19.2%; $P<0.01$). Patients with and without VFs did not differ in BMD L1-L4 Zsc (0.98 ± 0.06 vs. 1.04 ± 0.02) or FN Zsc (0.83 ± 0.05 vs. 0.86 ± 0.02). Duration of the disease in patients with VFs was significantly longer (14.1 ± 1.9 vs. 9.6 ± 1.2yrs) then in those without VFs ($P<0.05$). Prevalence of VFs was significantly higher in controlled (62.5%) and cured (40.0%) compared to active (17.8%) acromegaly ($P<0.01$).
Conclusion
Considerable prevalence of vertebral fractures (24%) was identified in a large cohort of patients with acromegaly, irrespective of normal bone mineral density. Duration of the disease was the main determinator of VFs prevalence, regardless of the biochemical control or cure. VFs are important, persistent and invalidating yet often under-recognized complication of acromegaly.

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GP189

Evaluation of pituitary toxicity after radiotherapy for cerebral chondrosarcomas in adult patients

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Pituitary dysfunction can be a consequence of cranial radiotherapy. It usually occurs years after the treatment. However little is known on risk factors for pituitary dysfunction. The object of this study was to evaluate radiation induced pituitary toxicity of proton beam therapy in a cohort of adult chondrosarcoma patients.
The files of 113 patients were reviewed. Mean age at the beginning of radiotherapy was 43 years old (18–76). Mean dose delivered to the tumor was 67 Gy and mean dose delivered to the pituitary gland was 59 Gy. Mean post-radiotherapy follow-up time was 7 years (4–17). Pituitary dysfunction was observed in 78 patients, within the delay of 4 years after radiotherapy. The prevalence of hyperprolactinemia was of 40%, thyrotrophic insufficiency was 36%, corticotropic insufficiency 31%, and gonadotropic insufficiency 25%. No significant differences were shown in the delay of dysfunction between the pituitary axes. In multivariate analysis, risk factors known to increase the risk of vascular side-effects of radiation (sex, age, smoking, high blood pressure, dyslipidemia and diabetes mellitus) were not associated with an increase of pituitary dysfunction.
Conclusions
Pituitary toxicity of radiotherapy is frequent after 4 years. The high prevalence of hyperprolactinemia pinpoints a possible hypothalamic origin of post radiotherapy pituitary insufficiency. A prospective follow up is necessary to complete these observations and propose relevant guidelines. Our study analyses the largest cohort of patients with chondrosarcomas after proton beam therapy. Our results emphasize the importance of careful and long term endocrine follow-up of these patients.

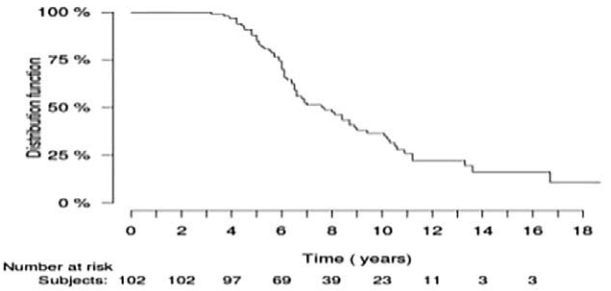

Figure: Kaplan-Meyer curve for pituitary dysfunction.

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GP190

Safety of long-term growth hormone (GH) treatment in adults with GH deficiency (GHD): an analysis from the NordiNet® International Outcome Study

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Background
Long-term safety data (1998 to mid-2016) are reported for adult patients with GHD treated with GH (Norditropin® (somatropin), Novo Nordisk) as prescribed by treating physicians in the real-life clinical setting and enrolled in NordiNet® International Outcome Study (IOS) (NCT00960128), a non-interventional, multicentre study.
Objective and hypotheses
To describe and report safety data and incidence rates (IRs) (events/1000 patient-years) of adverse drug reactions (ADRs), serious adverse events (SAEs) and serious ADRs (SADRs).
Method
Events were classified by MedDRA Preferred Term/System Organ Class (SOC). IRs during GH treatment were calculated.
Results
Data for 2438 patients (adult-onset, 90.1%; female 44.0%; mean (S.D.) age at treatment start, 43.3 (17.8) years; duration of follow-up, 5.8 (4.7) years; GH dose, 0.41 (0.32) mg/day) were analysed. Overall, 197 adverse events (AEs) were reported in 150 patients. Among these patients, mean (S.D.) treatment duration to first AE was 4.7 (4.1) years and GH dose at AE onset was 0.36 (0.31) mg/day. After the first AE, GH dose was unchanged in 55.3%, discontinued in 26.4% and decreased in 7.6% of patients (not reported/other for 10.7%). IRs were 11.91 for SAEs, 1.89 for SADRs and 5.52 for ADRs. Most frequently reported ($n \geq 10$) AEs by SOC (n, %) were nervous system disorders ($n=43$, 21.8%), neoplasms (benign, malignant and unspecified) ($n=35$, 17.8%), musculoskeletal and connective tissue disorders ($n=20$; 10.2%); general disorders and administration-site conditions or infections and infestations (each $n=15$, 7.6%); and cardiac disorders ($n=14$, 7.1%). Type 2 diabetes was reported as an AE in four patients. Twelve deaths (one possibly related) were reported.
Conclusions
IRs of SAEs, ADRs and SADRs were low. Data from NordiNet® IOS revealed no new safety signals, further supporting the favourable safety profile of GH replacement in adults with GHD.

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GP191

GH and IGF-1 levels at 12 weeks predict long-term responses to lanreotide Autogel in treatment-naïve acromegalic patients: *post-hoc* analyses from the PRIMARYS study

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Background
In PRIMARYS, lanreotide Autogel (LAN) 120 mg/28 days reduced tumour volume (TV), and GH/IGF-1 levels in patients with GH-secreting macroadenomas. In *post-hoc* analyses, we investigated predictive factors for treatment responses.
Methods
PRIMARYS, a 48-week, international, open-label study, involved 90 treatment-naïve patients with GH-secreting macroadenomas receiving LAN. Factors predictive for hormonal control (HC; GH ≤ 2.5 μg/L + normal IGF-1) at last post-baseline value available (LVA) or $\geq 20\%$ TV reduction (TVR) at week 48/LVA were investigated using univariate logistic regression. Week-12 GH, IGF-1 and TV cut-off values for predicting responses were obtained from ROC curves, maximising the Youden index. Analyses used intention-to-treat populations and $P<0.05$ as significant.
Results
From univariate analyses, HC was more likely in women (odds ratio: 2.9 times higher for women vs. men), and older patients (2.2 times higher for each 10-year higher age), and with lower baseline IGF-1 (1.1 times higher for each 10% lower IGF-1 level [% upper limit of normal, ULN]), but no association with GH levels was shown. HC was determined by week-12 hormonal response: optimal cut-offs were 1.19 μg/L for GH (sensitivity, 0.79; specificity, 0.89; area-under-the-curve [AUC] value, 0.87) and 110% ULN for IGF-1 (0.89, 0.85 and 0.93, respectively). Univariate analyses revealed no baseline factors influencing TVR. TVR was, however, determined by changes from baseline to week 12 in GH, IGF-1 and TV: optimal cut-offs were -69% for GH (sensitivity, 0.74; specificity, 0.67; AUC, 0.74), -61% for IGF-1 (0.58, 0.80, 0.75), and -21% for TV (0.81, 0.97, 0.93).
Conclusions
Based on *post-hoc* PRIMARYS data, treatment-naïve patients with GH-secreting macroadenomas are more likely to achieve long-term hormonal control with LAN 120 mg/28 days if GH levels are <1.2 μg/L and IGF-1 levels $<110\%$ ULN at 12 weeks, and more likely to achieve clinically significant long-term reductions in TV with $>60\%$ reductions in GH/IGF-1 levels by week 12.

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GP192

Long-term treatment with pegvisomant (Somavert®): Observations from 2090 acromegaly patients followed in ACROSTUDY

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Introduction
Pegvisomant (PEGV) is approved for the treatment of acromegaly since 2003. This is the second interim analysis of data from ACROSTUDY, with the majority of patients treated for at least five years (yrs).
Methods/design
ACROSTUDY is an international, open-label, prospective, non-interventional, post-marketing surveillance study monitoring the long-term safety and efficacy of PEGV. Patients were enrolled in the study on an ongoing basis.
Results
As of May 31, 2016, data from 2090 patients (51% men) from 15 countries were available. Mean treatment duration was 7.6 yrs (median 8.1 range: 0.0–19.1 yrs). Patients were followed in ACROSTUDY for a mean of 6.3 yrs (median 6.8, range 0.1–12.1). At ACROSTUDY start, there were 12 patients in the 0–18 yrs category and 203 patients in the >70 yrs category. At PEGV start, pituitary insufficiencies were observed for gonadotrophins (37.9%), TSH (29.1%) and ACTH (28.3%). 54.4% of patients experienced adverse events (AEs) with most common AE being IGF-I increased (10.5% of patients), headache(4.9%), vitamin D deficiency(4.6%) and arthralgia(3.7%). SAEs were experienced in 22% of patients (2.3% were treatment related, while 7.0% of patients discontinued treatment due to the SAE). A total of 78 deaths were reported (all non-treatment related). Locally assessed MRIs showed that most patients (72.2%) had no change in tumour size relative to last exam; 16.8% had decrease in tumour size, 6.8% had an increase, and 4.3% had both increase and decrease. Shift analysis demonstrated that of the 1245 with reported normal LFTs (AST/ALT) at baseline, 3% developed elevations > 3xULN. Administration site reactions were reported for 3.4% of patients.
Conclusions
This second interim analysis of long-term follow up showed that PEGV is an effective and safe treatment in patients with acromegaly. Data indicate low occurrence of reported pituitary tumor changes, liver test elevations and site administration reactions.

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GP193

Amenorrhea without vasomotor symptoms in women over 40: A sign of pathological hyperprolactinemia?

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Background
Hyperprolactinemia is often seen in women of reproductive age (20–35 years), most often due to microprolactinoma. However, prolactinomas do occur in older women.
Objective
To analyze clinical features of hyperprolactinemia in women >40 years
Material and methods
Clinical and biochemical data of 185 women with pathological hyperprolactinemia were analyzed.
Results
Seventy (37.8%) patients had microprolactinomas (MI), 57 (30.8%) – macroprolactinomas (MA), and 58 (31.4%) – non-tumoral hyperprolactinemia (NT). Among them, 26(36.1% of corresponding subgroup) with MI, 27(46.6%) with NT and 37(64.9%) with MA were >40 years of age. Menstrual disturbances and infertility issues are key factors for prolactin measurement but among these women, it was a reason to visit doctor only in few cases. In most cases with onset of hyperprolactinemia within 40–50 years of age, women themselves or their gynecologists considered amenorrhea as a natural postmenopause, missing the correct diagnosis. It was characteristic for hyperprolactinemic women that they did not experience vasomotor climacteric symptoms. Weight gain was common (68% women) but was also considered as climacteric and result of ageing. Headache and visual impairment were common causes for referral later on, and hyperprolactinemia was found due to hormonal investigation after MR-visualization of pituitary tumor. In some cases with prolactin levels 1300–1900 mMU/l, differential diagnosis was required between hyperprolactinemia due to pituitary stalk compression and prolactinomas with moderate secreting activity ("hook" phenomena was excluded). However, significant tumor shrinkage and (in some cases) restoration of regular menstrual cycle after 3–6 months of cabergoline treatment confirmed prolactinoma.
Conclusion
If a woman over 40 has menstrual irregularity or amenorrhea and does not experience any vasomotor symptom, it is a reason to prove a natural menopause by measuring high FSH levels (>25 MU/l). In cases of lower FSH levels it is reasonable to consider pathological hyperprolactinemia.

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GP194

Serotonin, ATRX and DAXX as differential diagnostic markers of neuroendocrine tumours (NETs) in the sellar region. An immunohistochemical study in a large series of pituitary adenomas and in a non-pituitary NET

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We present a case of a patient with a locally invasive, serotonin- and ACTH-reactive tumour in the sellar region, filling the sphenoid sinus and expanding into the epipharynx. Clinical examination completed by 68-Gallium-DOTA-TOC PET revealed tracer uptake in the sellar tumour as well as in a 7 mm lesion in the pancreatic tail. A differential diagnosis between silent corticotroph adenoma and another primary or secondary neuroendocrine tumour (NET) with ACTH-expression was difficult.
As serotonin was strongly positive in the tumour cells and its expression in pituitary endocrine tumours has not been systematically studied, we performed immunohistochemical analysis of serotonin in a large series of pituitary adenomas of different hormonal types from 246 patients. In addition, ATRX and DAXX, which mutations are associated with a subset of pancreatic NETs have been studied by using immunohistochemistry in the same cohort of pituitary tumours. None of the examined pituitary tumours expressed serotonin. There was normal expression of ATRX and DAXX corresponding to a lack of ATRX/DAXX mutations in the pituitary tumours.
Thus, serotonin-immunolabelling tumours in the sellar region most probably represent primary or secondary neuroendocrine tumours of non-pituitary origin. ATRX and DAXX do not seem to be involved in the pathogenesis of pituitary adenomas. Demonstration of ATRX or DAXX mutations in a neuroendocrine tumour of the sellar region excludes pituitary adenoma and suggests a non-pituitary NET, probably of pancreatic origin.

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GP195

Long-term follow-up of a family with a large *AIP* gene deletion: variable phenotypes and challenges in the management

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Introduction
Germline aryl hydrocarbon receptor-interacting protein (*AIP*) mutations are responsible for 15–30% of familial isolated pituitary adenomas (FIPA). We report

a 4-generation FIPA kindred with a heterozygous *AIP* gene deletion in exon 2, highlighting the benefits of genetic screening and management challenges in affected subjects and asymptomatic carriers.

Patients

A 45y woman died of a spinal ependymoma (obligate carrier). Her 18y son showed lethargy over the following months attributed to grief. However, investigations due to headache revealed hypopituitarism and a clinically non-functioning PA was diagnosed. Two years later, his 185 cm 18y-brother was diagnosed with a sparsely-granulated PA co-expressing PRL&GH. Fourteen-years after operation his IGF-1 was repeatedly raised with small increase in his tumour remnant. Lanreotide treatment was started and surgery is planned. A Rathke's cyst was detected in a bulky gland in their eupituitary 17y mutation carrier sister when she was first screened, which is now regressed. However, after 8y follow-up a 4 mm-microadenoma became visible, with normal PRL, IGF-1 and OGTT-GH nadir 0.38 µg/l. Their 27y second-cousin presented amenorrhoea after cessation of oral contraceptive, hyperprolactinaemia and 2xULN IGF-1. Her MRI showed 2 pituitary microadenomas, corresponding to a 6 mm-somato-tropinoma on the right and a 4 mm-prolactinoma on the left, confirmed histologically.

Discussion

Of 14 subjects with *AIP* mutations, 4 have PA, 1 ependymoma and 7 are asymptomatic (penetrance 29%). Ependymomas were described with loss of genetic material at 11q13-locus, but has not been described in patients with *AIP* mutations. The slow regrowth of the tumor in the brother suggests that long-term follow-up is needed. Bulky pituitary and not fully suppressed GH on OGTT can represent challenges in *AIP* mutation carrier teenager females. Multiple PAs with different secretory profiles may arise in the pituitary of these patients. Genetic screening and baseline review with follow-up of younger subjects is recommended in *AIP* mutation-positive families.

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GP196

Diagnosis of acromegaly: Sex and BMI are the major determinants of growth hormone suppression during oral glucose tolerance test (OGTT)

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GH suppression during OGTT is the gold-standard test in diagnosis and monitoring of acromegaly. However, discrepancies between GH nadir and IGF-I have been described and have triggered search for factors modifying the extent of GH suppression. Cut-offs at 1.0 or 0.4 ng/ml are currently recommended with modern, highly sensitive GH assays. To establish assay specific GH nadir cutoffs for the 22kD GH specific IDS-iSYS assay, we examined 381 subjects (319 females, 62 males) with normal pituitary function. We analyzed the impact of age, body mass index (BMI), menstrual cycle and hormonal contraceptive therapy.

In 96% of all subjects the GH nadir was <0.4 ng/ml (92% <0.3 ng/ml, 81% <0.2 ng/ml and 56% <0.1 ng/ml). In all sex- and age-groups BMI was the major determinant, with lower GH nadirs in subjects with higher BMI. In 4 different BMI groups (A: <20 kg/m^2, $n=30$, B: 20–25 kg/m^2, $n=174$, C: 25–30 kg/m^2, $n=99$ and D: >30 kg/m^2, $n=77$) mean GH nadirs were as follows: A: 0.29 ng/ml, B: 0.15 ng/ml, C: 0.10 ng/ml and D: 0.07 ng/ml with significant differences between all groups except group C vs. D (A vs. B: $P=0.0043$, A vs. C, A vs. D, B vs. C, B vs. D: $P<0.0001$, C vs D: $P=0.057$). While age had no impact, men exhibited significantly lower mean GH nadirs compared to women (0.09 vs 0.14 ng/ml, $P<0.0001$). Premenopausal women on estrogen containing oral contraception (OC) ($n=20$) had significantly higher mean GH nadirs (0.36 ng/ml) compared to women not taking estrogen containing OC ($n=272$, 0.13 ng/ml, $P<0.044$), while the phase of the menstrual cycle had no impact.

Our findings confirm the need for lower cutoffs for the GH nadir if new sensitive GH assays are used, but also suggest adjustment to sex- and BMI can improve diagnostic sensitivity and specificity.

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Thyroid 1

GP197

Cognitive functions in primary hypothyroidism on selenium supplementation

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Introduction

Selenium (Se) is a trace element that plays key roles in thyroid pathology. In patients with Hashimoto thyroiditis (HT), Se supplementation might reduce antibody levels and may provide additional beneficial effects, such as on cognition.

Aim

To evaluate cognitive function (cognitive decline) in patients on long-term levothyroxine replacement for primary hypothyroidism with and without selenium supplementation.

Design

Cross-sectional, case-control study.

Patients and methods

Sixty nine patients with HT (mean age 43.52 ± 14.33 yrs) on long-term levothyroxine replacement and 57 euthyroid healthy controls, matched for age, sex, and educational level, were included. HT patients were divided into 2 groups, 25pts with (Se+) and 44pts without selenium supplementation(Se-). Neuropsychological evaluation assessed general cognitive function(cognitive screening: MMSE, Visual- and Digit Span), attention span in visual and verbal modality (Numbers from WAIS and Visual span from WMS-R), conceptual tracking (TMT A and B), verbal divergent thinking (Phonemic fluency test, Listing of animals from BDEA, TMT B, Verbal fluency test).

Results

Selenium levels were within the normal range in all groups, but significantly higher in HT(Se+)vs controls (94.88 ± 20.63 vs 86.95 ± 14.95 mcg/l, $P<0.05$). TSH concentrations were higher in patients (both HT(Se+) and HT(Se-)) when compared to controls: (3.01 ± 1.66 and 3.01 ± 1.90 vs 1.77 ± 0.88 mU/l, $P<0.000$), but FT4 concentrations were not different: (12.81 ± 4.01 vs 12.46 ± 2.64 vs 12.93 ± 2.88 ng/l, $P>0.05$). TPOab concentrations were different, both between HT(Se+) and HT(Se-), as well as between patients and controls (1399.25 ± 1968.30 *vs* 4290.96 ± 3177.13 *vs* 20.48 ± 30.73 U/ml, $P<0.001$). Global cognitive function (MMSE) was not different between groups (29.16 ± 1.31 vs 29.16 ± 1.61 vs 29.54 ± 0.93, $P>0.05$), but conceptual tracking and verbal divergent thinking was different between all groups (TMTA:36.40 ± 12.85 vs 40.89 ± 21.89 vs 29.81 ± 11.57, $P<0.001$, TMTB:89.00 ± 27.88 vs 103.93 ± 48.81 vs 73.02 ± 24.10, $P<0.001$, KF:21.88 ± 5.61 vs 19.07 ± 5.65 vs 21.44 ± 5.11, $P<0.05$, FF:11.28 ± 3.37 vs 9.22 ± 3.69 vs 11.05 ± 3.44, $P<0.05$).

Conclusion

Patients treated for primary hypothyroidism according to routine clinical care guidelines show persistent impairments in cognitive functioning which were, in certain domains, improved with selenium supplementation. Future studies are still needed in order to provide reliable evidence to support selenium supplementation in a clinical practice.

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GP198

Which is the best tool to use when initiating the differential diagnosis of a thyrotoxic patient? A challenge to current guideline recommendations

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Aim

Differential diagnosis (DD) of thyrotoxicosis is critical as the treatment of the three main causes of this condition (Graves' disease [GD], Toxic Multinodular

Goitre [TMG], and Thyroiditis [TS]) differs substantially. Recently published diagnostic algorithms investigating hyperthyroidism embrace the presence of thyrotropin receptor (TSH-R) antibodies (TRab) as the first and most cruicial diagnostic step. Although TRab measurement has important limitations (some can block or be neutral to TSH-R, or pass undetected by the assay), Guidelines recommend thyroid radionuclide scan (TRS) when TRab are absent. Our objective was to compare the TRab vs. TRS values in the DD of hyperthyroidism. We sought to analyse limitations of the current diagnostic Guidelines which could lead to misdiagnosis and improper treatment of thyrotoxicosis.
Methods
We conducted a retrospective study of 235 outpatients attended at our Centre from 2006 to 2016. Inclusion criteria were patients with overt or subclinical hyperthyroidism from whom TRab and TRS levels were taken at the time of diagnosis. SPSS 20.0 was used for statistical analysis. Pearson's correlation was applied to quantify the relationship between the two diagnostic tools.
Results
We grouped the sample in Gr. A: 89 (37.8%) those with positive TRab; Gr. B: 102 (43.4%) those with diffuse TRS uptake; and Gr. C: 146 (62.2%) those with negative TRab. All groups were partially overlapped. In Gr. A, the TRS reported a diffuse increase uptake (consistent with GD) in 63 (70.8%), heterogeneous uptake consistent with TMG in 21 (3.6%), and absent or low uptake consistent with TRS in 5 (5.6%). In Gr. B, only 63 (61.8%) had positive TRab. In Gr. C, up to 39 (26.7%) of individuals had a diffuse increased uptake in TRS. Pearson's r analysis between positive TRab and diffuse increased uptake was: 0.431 ($P = <0.001$).
Conclusions
Provided that a high diffuse uptake by TRS can only be associated with GD, our study suggests that the DD of thyrotoxicosis should not rely initially on TRab, as this approach may leave a third (29%) of patients misdiagnosed, and consequently, improperly treated. Our results support the value of thyroid scintigraphy as the first step in the DD of thyrotoxicosis.

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GP199

Cardiovascular risk factors in patients with autoimmune thyroiditis

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Background
Overt thyroid dysfunction is associated with an increased cardiovascular risk. The impact of subclinical hypothyroidism and autoimmunity in the increased cardiovascular risk remains controversial. Aim: To evaluate the interrelations between thyroid function, thyroid autoimmunity and cardiovascular risk factors, in patients with autoimmune thyroiditis (AIT).
Methods
353 subjects with AIT were evaluated. We defined three groups based on TSH levels: TSH < 2.5 μUI/ml, TSH 2.5–5.0 μUI/ml and TSH > 5.0 μUI/ml. We recorded thyroid function tests, thyroid autoimmunity, insulin resistance markers including Homeostasis Model Assessment for Insulin Resistance (HOMA-IR), lipid profile, homocysteine, C-reactive protein (CRP) and vitamin B12 levels. Statistical analysis was performed using Kruskal-Wallis test and Spearman correlations.
Results
Our sample comprised 94% females with a mean age of 47 ± 16.3 years. The group TSH > 5.0 μUI/ml presented higher levels of HOMA-IR when compared to the other two groups [2.96(1.76–4.59) in TSH > 5.0 μUI/ml vs 1.86(0.97–2.56) in TSH 2.5–5.0 μUI/ml and 1.58(1.06–2.46) in TSH < 2.5 μUI/ml, $P = 0.002$]. In the total group we observed positive correlations between free T3 (FT3) and both HDL ($r = 0.118$, $P = 0.028$) and ApoA1 ($r = 0.129$, $P = 0.024$); TSH was positively correlated with HOMA-IR ($r = 0.146$, $P = 0.018$) while free T4 (FT4) was negatively correlated with homocysteine ($r = -0.119$, $P = 0.041$). In the group TSH < 2.5 μUI/ml, positive correlations were found between TSH and both HDL ($r = 0.136$, $P = 0.031$) and homocysteine ($r = 0.147$, $P = 0.028$), FT4 and CRP ($r = 0.136$, $P = 0.037$) and also anti-thyroglobulin and ApoB ($r = 0.165$, $P = 0.013$); anti-thyroglobulin was negatively correlated with homocysteine ($r = -0.186$, $P = 0.006$). Negative correlations between anti-thyroglobulin, total cholesterol ($r = 0.371$, $P = 0.004$), LDL ($r = -0.325$, $P = 0.011$), ApoB ($r = -0.342$, $P = 0.022$) and lipoprotein(a) ($r = -0.470$, $P = 0.001$) were revealed in the group TSH 2.5–5.0μUI/ml. Regarding the group TSH > 5.0 μUI/ml, we found positive correlations between FT3 and HDL ($r = 0.358$, $P = 0.030$), vitamin B12 ($r = 0.398$, $P = 0.024$) and HOMA-IR ($r = 0{,}424$, $P = 0{,}031$); and between anti-thyroglobulin and homocysteine ($r = 0.383$, $P = 0.033$).
Conclusion
We observed significant correlations between thyroid function, thyroid autoimmunity, insulin resistance, lipid profile and homocysteine that may contribute to an increased cardiovascular risk in AIT.

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GP200

Evaluation of the effectiveness of personalized radioiodine treatment in Graves' disease

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Aim
Radioiodine activities for the treatment of Graves' disease hyperthyroidism are still subject to discussion, as is the use of a fixed approach over a dosimetric one. We aimed to evaluate our success rate using a personalized dosimetric approach: instead of the "(MBq I-131 × g gland mass × 100)/(percentage uptake at 24 h)" activity calculation, we further adjusted for factors such as gender, age, diagnosis, 2 h and 4 h radioiodine uptake, previous medication, and clinical history.
Materials and methods
We reviewed data from all patients treated with radioiodine therapy (RIT) for hyperthyroidism at our department ($n = 179$), from January 2008 to January 2016, selected those with Graves' disease ($n = 118$), and excluded the ones without follow-up ($n = 11$). RIT was considered successful if either euthyroidism or hypothyroidism were achieved. We evaluated success rates differences between lower and higher activities. All statistical analyses were carried out using IBM SPSS version 21.0 for Mac. A type I error 0.05 was considered.
Results
107 patients were included (44.346 ± 13.07 years; 89 female). RIT was successful in 91.6% ($n = 98$), while 8.4% ($n = 9$) remained hyperthyroid. If we consider the success after the first RIT, 72.0% ($n = 77$) succeeded, while 28.0% ($n = 30$) remained hyperthyroid. 87 (81.3%) were submitted to a single therapy whereas 20 (18.7%) were submitted to multiple RIT. There were no significant outcome differences between the lower and higher activities used ($P = 0.061$).
The used activities ranged between 148 MBq and 703 MBq (335.92 ± 101.60 MBq).
Conclusion
Our results confirm RIT effectiveness in Graves' disease hyperthyroidism treatment. Although using inferior activities to those generally prescribed (200–800 MBq), we achieved higher success rates – comparable to the best reposted in the literature. There were no statistically significant outcome differences between the lower and higher activities used, highlighting the importance of tailored treatment approaches to warrant the best therapeutic outcome and while avoiding unnecessary exposure.

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GP201

Abstract withdrawn.

GP202

Citrus flavanones naringenin and hesperetin induced mild functional alteration in thyroids of old-aged Wistar rats

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Aging is a complex process characterized by a progressive decline in cellular function, alterations of the endocrine system and the increased incidence of thyroid diseases. Citrus flavanones naringenin (NAR) and hesperetin (HES) may contribute to maintenance of health at old age however they may also affect thyroid hormone economy. The aim of this study was to test weather NAR or HES administration alter thyroid functioning. NAR or HES were administrated orally (15 mg/kg) to male 24-month-old Wistar rats during 4 weeks. Control groups received vehicle, sunflower oil. Immunohistochemical staining of thyroglobulin (Tg), thyroxine (T_4) bound to Tg (T_4-Tg) and sodium iodide sysmporter (NIS) were performed. Immunopositivity of Tg or T_4-Tg in thyroid follicles were measured as intensity of optical density (OD) or relative intensity of fluorescence (RIF). Thyroid stimulating hormone (TSH) and total T_4 concentrations were measured in serum. After citrus flavanones treatments, thyroids showed Tg and T_4-Tg immunopositivity mainly in the colloid of the follicles. The obtained results showed increased ($P < 0.05$) intensity of OD for Tg and T_4-Tg RIF after both flavanones treatments, while NIS expression did not change. Serum TSH increased ($P < 0.05$) only after NAR, although T_4 remained unchanged after both treatments. In conclusion, citrus flavanones induced stronger expression of thyroid-specific proteins in gland of old-aged males. However, only NAR elevated serum TSH, being more potent than HES. This alteration is in line with preserved capacity of the thyroid to compensate the mild interference of flavanones treatments with thyroid hormone production in old-aged males.

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GP203

The oxford multidisciplinary thyroid eye disease (TED) clinic; can short waiting times and use of steroid sparing agents (SSA) reduce total steroid dose and requirement for surgery/radiotherapy?

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Introduction
The Oxford multidisciplinary thyroid eye disease (TED) clinic comprising an oculoplastic surgeon, rheumatologist and endocrinologist with access to orthoptics, neuroradiology and radiotherapy was established in 2013. The aim was to facilitate rapid referral and treatment in a specialist centre in keeping with Amsterdam Declaration. Early use of steroid sparing agents (SSA) and recently rituximab forms part of the treatment regimen.
Methods
A retrospective, 4-year, single-centre, consecutive case series of patients with TED audited both outcomes (in terms of severity and activity) derived from the VISA classification and treatment modalities, at presentation and 1 year follow-up.
Results
104 patient records were analysed. Mean wait from referral to first review was 1 month with 42% of referrals originating from endocrinology departments. Mean age was 51.2 years. 26.0% ($n=27$) of patients were male and 35% were current/ex-smokers. Where thyroid biochemistry was available at referral ($n=80$): 51% were euthyroid, 45% hyperthyroid and 4% hypothyroid. TSHRAb was positive in 85% of patients checked compared to 62% of TPO Ab. Presenting signs included: ocular surface disease (68%), exophthalmos (53%), diplopia (45%), eyelid retraction (38%) and reduced vision (7%). Presenting activity was mild (VISA $\leq$3/10) in 69% and severe in 16% ($\geq$7); severity mild in 47.1% and severe in 20.2%. 1 year data ($n=36$) showed mild activity at 1 year in 95% (38.9% at referral) and 0% severe disease (33% at referral).
Intravenous methylprednisolone was administered to 30 patients; 47% required $\leq$1.5 g total with use of SSAs: methotrexate ($n=30$), azathioprine ($n=6$), ciclosporin ($n=10$) and Rituximab ($n=8$). Orbital decompression surgery was performed in 12.5% ($n=13$), squint surgery 12.5%, eyelid surgery 22% and orbital radiotherapy 8%.
Conclusion
Early use of SSAs has significantly reduced the overall steroid load in patients when compared to established European guidance (EUGOGO). This regimen confers a low orbital decompression and orbital radiotherapy rate.

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GP204

24-month efficacy of a single radiofrequency ablation on autonomously functioning thyroid nodules

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Background
Radiofrequency ablation has been advocated as an alternative to radioiodine and/or surgery for the treatment of autonomously functioning benign thyroid nodules. However, only a few studies have measured radiofrequency ablation efficacy on autonomously functioning benign thyroid nodules. The aim of this work was to evaluate the 24-month efficacy of a single session of radiofrequency ablation (performed with the moving shot technique) on solitary autonomously functioning benign thyroid nodules.
Methods
Thirty patients with a single, benign autonomously functioning thyroid nodule, who were either unwilling or ineligible to undergo surgery and radioiodine, were treated with radiofrequency ablation between April 2012 and May 2015. All the patients underwent a single radiofrequency ablation, performed with the 18-gauge needle and the moving shot technique. Clinical, laboratory, and ultrasound evaluations were scheduled at baseline, and after 1, 3, 6, 12, and 24 months from the procedure.
Results
A single radiofrequency ablation reduced thyroid nodule volume by 51, 63, 69, 75%, and 76% after 1, 3, 6,12, and 24 months, respectively. This was associated with a significant improvement of local cervical discomfort and cosmetic score. As for thyroid function, 33% of the patients went into remission after 3 months, 43% after 6 months, 50% after 12 months, and 70% after 24 months from the procedure. This study demonstrates that a single radiofrequency ablation allowed us to withdraw anti-thyroid medication in the majority of patients, who remained euthyroid afterwards.
Conclusions
This study shows that a single radiofrequency ablation was effective in 70% of patients with autonomously functioning benign thyroid nodules. Most importantly, patients responded gradually to the treatment, such that it is possible that longer follow-up studies might show greater response rates.

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GP205

Association of vitamin D levels with thyroid function and autoimmunity

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Introduction
Vitamin D is a hormone that acts through the Vitamin D receptor (VDR) not only on the skeletal system but on a great number of target tissues, including thyroid gland. In recent years the association of vitamin D with autoimmune thyroid diseases (AITD), has been suggested.
VDR gene polymorphisms had been associated with an increased risk of AITD. In addition a recent meta-analysis showed that AITD patients had lower level of 25-hydroxyvitamin D. However some studies have not confirmed the association between vitamin D levels and AITD. Furthermore, data on the effects of vitamin D in thyroid hormones and TSH serum levels are very poor.
The aim of our study was to evaluate the association of vitamin D levels with thyroid function and positivity for thyroid antibodies.
Material and methods
PORMETS is a nationwide, cross-sectional study in Portugal comprising a sample of 4095 adults. Five hundred participants were randomly selected to be included in the present study. A fasting venous sample was collected and serum calcium, PTH, 25-hydroxyvitamin D [25(OH)D], TSH, FT_4, FT_3 and thyroid antibodies were measured.
Results
Our study included 286 women and 214 men with a mean age of 53.4 years.
Free thyroxine (FT_4), free triiodothyronine (FT_3), TSH and thyroid antibody levels did not present any significant linear correlation with 25(OH)D levels.
After adjustment for sex and age, TSH, FT_4 and FT_3 levels did not present any significant association with 25(OH)D levels or with low vitamin D status.
Logistic regression analysis did not show any significant association of low vitamin D status with thyroid antibodies positivity, even after adjustment for several possible confounding variables.
Conclusion
Our results do not confirm the association of vitamin D levels with thyroid function and positivity for thyroid antibodies.

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Thyroid 2

GP206

Early use of steroid-sparing agents in treatment of moderate-to-severely active thyroid eye disease

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Introduction
The management of active thyroid eye disease (TED) remains controversial. High dose intravenous methylprednisolone (IVMP) is the current recommended first-line treatment based on EUGOGO guidance. Such therapy has the potential for serious adverse effects. We present the outcomes of an alternative approach in the management of moderate-to-severely active TED, using steroid-sparing agents (SSAs) in conjunction with IVMP. Methotrexate is used as the first-line SSA alongside ciclosporin and rituximab depending on activity score.
Methods
Presented is a retrospective, 4-year, single-centre, consecutive case series of patients with moderate-to-severe TED treated using the Oxford protocol. Treatment modality, disease activity (derived from the VISA classification) and adverse effects are reported at initial presentation, 6- and 12-month follow-up.
Results
104 consecutive case notes were reviewed of TED patients treated by the TED MDT. 24 patients with moderate-to-severely active disease were identified (mean age 46.8 years; 12 female) with a mean pre-treatment VISA activity score of 5.5/10 (S.D. = 1.98; range 1–9). IVMP and an SSA was commenced in all patients. Mean total steroid dose was 2.72 g (S.D. = 1.4; 1.0–6.9). 38% of patients ($n = 9$) received 1.5 g of IVMP or less. Only two patients required >4.5 g of IVMP equating to the EUGOGO treatment protocol dose for this patient group. There was significant improvement in VISA activity score both at the intermediate review (mean score 2.7; S.D. = 2.8; $P < 0.001$; mean follow up 25.2 weeks) and at one year or last follow up (mean score 1.4; S.D. = 1.5; $P < 0.001$; mean follow up 48.0 weeks). Three patients stopped methotrexate due to a non-specific chronic cough, deranged liver function or nausea. No serious or long-term adverse effects were reported.
Conclusion
Based on our experience and outcomes, the initiation of an SSA with limited adjuvant IVMP is as an effective and safe therapy for moderate-to-severely active TED. This approach results in a significant reduction in disease activity with reduced total steroid load.

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GP207

Prediction of response to methimazole based on clinical symptoms in new onset graves' patients, using neural networks

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Introduction
Anti-thyroidal drug (ATD) therapy is a treatment of choice for Graves' disease because of its effectiveness and low rate of adverse effect. Response to ATD or remission rate varies among individuals, although there were few useful clues for prediction of treatment response. We applied neural network model to predict response to methimazole, based on clinical symptoms at initial clinical symptoms.
Methods & Design
We reviewed 20 new onset Graves' patients and used their symptoms at initial diagnosis. A total of 12 symptoms were classified into 5 categories (general, cardiac, neuromuscular, psychologic, and gastrointestinal). In each category, the number of positive symptoms was considered the score of the category. Response to methimazole was defined as whether serum TSH normalized within 3 months. A total of six variables, 5 symptom categories and sex, were used for a 2-layer neural network model. Among 20 subjects, 15 subjects used in training set, and the other 5 subjects were use in model validation.
Results
The mean age of subjects was 49.3 ± 12.2 years and male subjects were 6 (30%). Our neural network model with 15 subjects as a training set showed sensitivity of 1.0 and specificity of 0.545 with AUC of 0.75 to predict normalization of serum TSH within 3 months. With same model, the estimated scores of the other 5 subjects corresponded to their actual outcomes.
Conclusion
Despite the limitation of small sample size, our neural network model showed promising performance to predict response to methimazole with patients' clinical symptoms in new onset Graves' patients.

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GP208

Serum Interleukin-37 (IL-37) levels were increased and correlated with oxidative stress parameters in Hashimoto's Thyroiditis (HT) patients

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Background
IL-37, member of the IL-1 family, is a natural suppressor of immune and inflammatory responses. Increased serum IL-37 levels were observed in several autoimmune diseases, including Graves' disease. No data on TH are available from the literature.
Materials and methods
We enrolled 45 euthyroid HT patients (5 M e 40 F, mean age 38.5 ± 12.6) and 50 age- and sex-matched healthy controls. None was on LT-4 therapy. Smokers, subjects with kidney failure, history of cancer or autoimmune, inflammatory and infection comorbidities were excluded. Serum IL-37 levels were measured by ELISA (kit IL-37 DuoSet Elisa, R&D System, Minneapolis, USA; minimum detectable dose 10 pg/ml). Specific serum tests, such as d-ROMs (derived Reactive Oxygen Metabolites) test and BAP (Biological Antioxidant Potential) test (Diacron International, Italy), were performed in all

subjects to investigate the changes in oxidative balance, and AGEs (Advanced Glycation End Products) were determined as a specific marker of oxidative stress.
Results
IL-37 levels were significantly higher in TH (mean ± s.d.: 999.59 ± 1064.93 pg/ml) than in controls (448.02 ± 498.96 pg/ml; $P=0.018$). In both groups, these values correlated negatively with age (TH, RS = −0.377 $P=0.016$; controls, RS = −0.404; $P=0.06$) and were tendentially higher in men than in women ($P=0.063$). Furthermore, there was a positive correlation between serum IL-37 levels and TSH, statistically significant in TH (RS = 0.412 $P=0.008$; in controls, RS = 0.418; $P=0.053$). The regression analysis showed a significant positive association between IL-37 and d-ROMs ($P=0.029$) and AGEs ($P=0.014$): if serum d-ROMs and AGEs levels increased, serum IL-37 levels also increased. A significant direct correlation between serum IL-37 levels and AGEs was also observed (RS = 0.578; $P=0.006$).
Conclusion
Serum IL-37 levels were significantly increased in TH patients and correlated with oxidative stress parameters. Given the anti-inflammatory properties, IL-37 could be an innovative research strategy for TH pathogenesis and therapy.

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GP209

The increased immunohistochemical expression of IL-23 in Hashimoto's thyroiditis but not in Graves' disease patients

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Introduction
Recently, Th17 cells and their cytokines were identified to play an important role in the pathogenesis of thyroid autoimmunity. IL-23, produced by antigen presenting cells, is required for survival and differentiation of Th17 cells, and is known to guide T cells toward the Th17 phenotype. Its serum levels are increased in several autoimmune diseases, including Hashimoto's thyroiditis (HT), however, the expression level of IL-23 within thyroid tissue assessed by immunohistochemistry has not been addressed thoroughly before. The aim of our study was to estimate the levels of immunoexpression and distribution of IL-23 within thyroid tissue of patients with HT and Graves' disease (GD) and compare them with controls.
Materials and Methods
Forty seven adult patients presenting 21 cases of HT, 8 of GD, and 18 cases of ordinary colloidal goiter without autoimmune component, which served as control group, were enrolled in this study. Immunostaining was performed using an anti-IL-23 antibody (Santa Cruz Biotechnology, CA, dilution 1:50). Levels of immunopositivity for IL-23 were defined semiquantitatively.
Results
In HT patients the expression of IL-23 was detected both in the abundant inflammatory lymphocytic infiltrates characteristic of HT and follicular epithelial cells, whereas tissues obtained from GD patients demonstrated the weak thyrocytic expression predominantly. Majority of patients in controls showed negative or occasional expression of IL-23. The highest IL-23 immunopositivity was observed in HT patients, furthermore, it was significantly higher compared to the control group and GD ($P<0.001$; $P=0.043$, respectively). No difference was found between the expression of IL-23 in GD patients and the control group ($P=0.324$). Additionally, weak expression of IL-23 was observed in connective tissue septae and blood vessels in most HT patients.
Conclusion
Overexpression of IL-23 might play a role in the pathogenesis of HT, guiding T cells towards the Th17 phenotype and promoting the autoimmune inflammation of the thyroid gland.

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GP210

Laser ablation of benign thyroid nodules without anesthesia: clinical tolerance, hazards and complications

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Laser ablation of thyroid nodules has been used for the last two decads (Pacella et al, 2000). Surprisingly, complications are less frequent in patients treated without anesthesia, probably because eventual pain is an useful alarm symptom, leading the operator to repositioning the fiber during the procedure (Pacella et al., 2015).
Material and methods
A total of 32 patients were included, without using local anesthesia. Nodules were solid, 5–72 ml volume, age 36–84 years, gender female (84%). Procedure included three phases: (1) Preparation 30 min (informed consent and final decision about anatomic approach); (2) Laser ablation 30 min (usually 3–8 paths, 3–5 illuminations each and total energy of 50–500 joules/cc); and (3) Observation 60 min (with ice collar and vital constants monitoring). A 1064 nm Nd-YAG laser from an EchoLaser generator (Elesta, Florencia-Italy) was used. Triple thyroid image (Ultrasound, Doppler and Elastography) was monitored using an Acusson 2000 Hellix platform (Siemens, Forchheim-Germany).
Results
30 of 32 patients (93.75%) would accept another ablation if necessary. Pain was refered as 1–6 of 10 (arithmetic mean 3.5; median 2). Difficulties were: cervical discomfort (4), excessive time of manipulation because short neck (1), transient mild hypertension (1), mild vasovagal reaction (1), small intra-thyroid hematoma (1) and a partial and transient Horner syndrome (1) resolved 3 months later.
Discussion
Clinical tolerance in general was spectacular. Major complaints were postural. Complications were mild and transient, although potentially risky. No cases of severe pain, voice change, fever, skin burn or cough were observed. In the future, preventive specific strategies (like careful identification of risky patients, laser cauterization of large feeding vessels or protective hydrodissection to protect vital organs) will be considered before laser ablation.
Conclusions
Clinical tolerance was very good. Complications were few, mild and transient, but potentially risky. This highlights the importance of identifying properly risky patients as well as the need of including preventive strategies.

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GP211

Orbital ectopic thyroid mistaken for mestastases

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Introduction
Ectopic benign thyroid tissue outside the normal migration path of the thyroid is an extremely rare condition that, to our knowledge, has never been described in the orbit.
Clinical case
75-year-old woman with nodular thyroid was referred to Vilnius University Hospital Santariskiu Klinikos for fine needle aspiration biopsy. Her complaints were palpitations, difficulty swallowing, diplopia, *exophthalmos* with medial and –superior dislocation. Symptoms were progressing for 2 years, although laboratory testing always showed euthyreosis. Her thyroid-stimulating hormone (TSH) was 1.04 mU/l (normal 0.4–4.1 mU/l), anti-TPO antibodies – 1.9 kU/l (<5.61 kU/l) on admission. Fine needle aspiration biopsy and histological examination suggested diagnosis of Hurthle cell carcinoma and subject was referred to surgery.
Management and Outcome
After thyroidectomy histology revealed nodular thyroid hyperplasia and follicular adenoma. To exlude orbital malignancy head MRI was performed. Imaging

showed 18×14 mm in size, non-homogenic, contrast accumulating mass with well-defined margins in the inferior –lateral part of the orbit. Orbital tumor excision was performed and histological examination revealed tumor composed of micro-/macrofolicules with colloid. Folicular epithelium had no atypical changes, as confirmed by three independed pathologists. These criteria supported diagnosis of ectopic thyroid tissue. Due to patients noncompliance further postoperative period is unknown. A 5-year follow-up showed normal TSH levels of 3.07 mU/l, with 75 mcg/day levothyroxin therapy, anti-TPO antibodies – 0.2 kU/l, thyroglobulin 0.91 mgk/l (normal 0.83–55 mgk/l). Once no primary or secondary tumors were detected we concluded that the thyroid tissue in the orbit of our patient was ectopic.

Conclusion

Ussualy ectopic benign thyroid tissue could be found in the normal migration path of the thyroid. However, we are presenting the extremely rare case of benign thyroid tissue located in the orbit, suggesting the extensive diagnostic approach in unclear cases.

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GP212

Association of the Period3 clock gene polymorphism with autoimmune thyroid diseases

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Background

Circadian rhythmicity is generated by a set of genes including Period3. Changes in the expression of Period3 and other clock genes have been linked with regulation of the immune system. Period3 polymorphisms have been associated with circadian disruption and so immune system dysregulation and altered secretion of several cytokines, which can lead to inflammatory and autoimmune disorders.

Aim

To investigate the influence of a polymorphism in Period3 gene on susceptibility and severity of autoimmune thyroid diseases (AITD).

Methods

A total of 125 unrelated patients (mean age 35.94±9.9 years) with AITD (GD, 69; HT, 56) and 115 unrelated healthy controls (mean age 31.3±8.7 years) were included. Serum levels of IL-6 (pg/ml) and TNF-α (pg/ml) were determined by ELISA method. Period3 gene polymorphism rs2797685 was identified by PCR-RFLP.

Results

Subjects expressing the GA+AA genotype of the selected polymorphism in Period3 gene demonstrated a significantly higher risk of AITD compared to the population expressing the GG genotype (OR = 1.83, CI: 1.04-3.20; $P = 0.033$). No significant associations of genotypes were detected with the age of onset of disease, presence and severity of orbitopathy in GD and thyroid function status at diagnosis and daily dose of thyroxine per kg body weight in HT. AITD and control groups were similar in terms of mean IL-6 levels, but mean serum IL-6 level was significantly lower in the group with GA genotype than in the group with GG genotype in GD ($P = 0.013$). Mean level of TNF-α was significantly higher in patients with AITD compared with controls ($P < 0.001$) but TNF-α levels were not significantly different in the groups of different genotypes of the selected polymorphism of the Period3 gene.

Conclusion

This study provides the first evidence for a genetic association between AITD and the Period3 gene, highlighting the possible relevance of polymorphisms in clock genes in the etiopathogenesis of AITD.

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GP213

IgG4-related fibrous variant of Hashimoto thyroiditis in a non-Asian woman

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Introduction

First described in 2009, IgG4-related thyroid disease includes several subcategories: Riedel's thyroiditis, fibrous variant of Hashimoto thyroiditis (FVHT), IgG4-related Hashimoto thyroiditis (HT) and Graves' disease with elevated IgG4. It is rare, with most cases described in Japan and characterized by increased IgG4 plasma cells at immunostaining.

Case Report

A 59-year-old Caucasian women, without known Asian ancestry, was observed at the endocrinology department due to neck swelling over the previous 4 months. She reported dyspnea at some neck positions, fatigue and constipation. She presented a diffusely enlarged very hard thyroid, with some nodules and reduced mobility. Laboratory evaluation revealed primary hypothyroidism, very elevated titles of anti-thyroglobulin and anti-peroxidase antibodies, elevated erythrocyte sedimentation rate and G immunoglobulins (3400 mg/dl, reference range, RR: 751–1560), elevated IgG4 (267 mg/dl, RR: 4–86) and κ-dominant light chains. There was no monoclonal band; IgA and serum calcium levels were normal. Ultrasound confirmed an enlarged heterogeneous thyroid, with nodules and small calcifications. Cytology was compatible with lymphocytic thyroiditis. The CT scan additionally revealed multiple latero-cervical ganglia, esophageal diversion, airway impression and reduction of the nasopharynx lumen. There was no evidence of malignancy, infection, other autoimmune disorders or non-neck involvement. Euthyroid state was obtained with levothyroxine reposition and total thyroidectomy was performed. Histology revealed a FVHT with elevated IgG4-positive plasma cells and IgG4/IgG ratio. After surgery, serum IgG levels decreased and IgG4 levels became normal.

Discussion

The very hard rapidly enlarging thyroid, short disease duration, high antibody titers, hypothyroidism, diffuse thyroid involvement, no evident extrathyroidal invasion, increased inflammatory parameters, IgG and k dominant profile and elevated IgG4 that normalized after surgery, suggested a fibrous IgG4-HT. Histology and immunostaining confirmed an IgG4-related FVHT. Although very rare in non-Asian countries, it is important to suspect and confirm an IgG4-related thyroid disease, allowing an adequate diagnosis, treatment and follow-up.

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GP214

Thyroid hormones deficiencies and poor outcome in chronic heart failure outpatients

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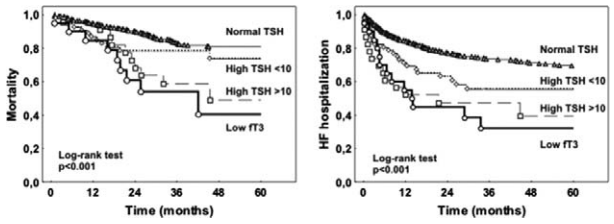
Background
Hypothyroidism and low T3 syndrome frequently occur in HF patients.
Aim of the study
To evaluate in a large sample of CHF patients the association between thyroid hormone deficiencies and poor outcome.
Methods and results
From 2006 to 2015, we screened 712 consecutive CHF outpatients (551 males, 64 ± 14 years, left ventricular ejection fraction (LVEF) 33 ± 10%, NYHA class 2.3 ± 0.6, NTproBNP 2153 ± 4696 pg/ml, GFR-EPI 71 ± 25 ml/min*1.73 m^2) in stable clinical conditions (> 1 month) and in conventional therapy. All patients underwent assessment of thyroid function. A total of 34 patients were excluded for hyperthyroidism; among the remaining 678, 58 (9%) showed a TSH level above the upper normal limit, but below 10 microU/ml, 23 (3%) a TSH value above 10 microU/mL, and 20 patients (3%) low fT3 (LT3) levels without changes in TSH levels. During a mean follow-up of 38 months, 122 patients died (101 for cardiovascular causes) and 202 experienced at least one admission for acute decompensated heart failure. TSH > 10 microU/mL (HR:2.96; 95%CI: 1.54–5.68; *P*: 0.001) and LT3 (HR: 3.79; 95%CI: 1.91–7.54; *P* < 0.001), but not high TSH < 10 microU/mL (HR: 1.59; 95%CI: 0.871–2.91; *P*: 0.13), were associated with an increased risk of death at univariate analysis. At multivariate Cox regression analysis, after correction for the presence of NYHA class 3, LVEF < 35%, NTproBNP > 1000, systolic arterial pressure < 100 mm Hg and GFR-EPI < 60 ml/min, only LT3 remained significantly associated with events (HR: 2.75; 95%CI:1.38–5.49; *P*: 0.004). When the occurrence of heart failure hospitalization was considered, high TSH levels with a value < 10 microU/ml (HR 1.82; 95% CI: 1.18–2.83; *P* < 0.01), TSH > 10 microU/ml (HR 2.84; 95%CI:1.61–5.01; *P* < 0.001) and LT3 (HR: 3.33; 95%CI: 1.89–5.88; *P* < 0.0001) were all associated with events at univariate regression analysis. At multivariate regression analysis TSH > 10 microU/ml (HR: 1.91; 95%CI:1.06–3.46; *P*:0.03) and LT3 (HR: 2.39; 95%CI: 1.36–4.24; *P*:0.002), but not high TSH with value < 10 microU/ml, remained associated with HF hospitalization.
Conclusions
In this observational study on a large cohort of CHF outpatients, we found that impaired thyroid function, particularly when high levels of TSH (> 10 microUI/ml) and low T3 levels are considered, has an independent adverse impact on CHF events.



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GP215

Hypothyroidism and heart failure outcome: a study with a long-term follow-up

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Background
Hypothyroidism (HT) has been demonstrated to be associated to heart failure (HF) progression.
Aim of the study
To evaluate the impact of HT on the progression of HF during a long-term follow-up.
Methods
From 2006 to 2015, we evaluated 675 consecutive CHF outpatients (523 males, 64 ± 13 years) in stable clinical conditions (> 1 month) and in conventional therapy. They underwent a clinical evaluation, 12-lead ECG, echocardiogram, blood pressure measurement and a routine chemistry. They have been carefully evaluated for the presence of thyroid diseases. The follow-up was extended on a median value of 47 months, for a maximum of 123 months. Thyroid function has been evaluated every 4 months, more frequent (every 6 weeks) for patients receiving levothyroxine. The onset of HT during follow-up was defined as detection of TSH values above the upper limit. When HT was detected, thyroid replacement therapy was started according to guidelines. During follow-up were also evaluated hospitalizations related to exacerbation of HF and death.
Results
Four hundred and fifty-five patients (67.7%) were euthyroid at the enrolment and showed a normal thyroid function during the follow-up; in 80 patients (11.8%) there was a previous diagnosis of HT; in 40 patients (5.9%) the HT was detected at the time of enrolment; 52 patients (7.7%) developed HT during the follow-up. To avoid confounding factors, we compared patients in euthyroid status at the enrolment and during follow-up and patients with HT at the enrolment. At univariate Cox regression analysis, a significant association between HT and the events, i.e. mortality for all causes (HR: 1.60; 95% CI: 1.08–2.38; *P*:0.019) and hospitalization for HF worsening (HR: 2.13; 95% CI: 1.54–2.96; *P*: < 0.001) was found. At multivariate Cox regression analyses, HT remained associated only with HF hospitalization (HR: 1.58; 95% CI: 1.09–2.29; *P*:0.015), but not with mortality (HR: 1.05;95% CI:0.67–1.65; *P*:0.819), after correction to LVEF < 35%, GFR < 60 ml/min/m^2, NTproBNP > 1000 pg/ml, NYHAIII, PA 95 mmHg.
Conclusion
In a long-term follow-up, HT is independently associated with hospitalization due to HF worsening, but not with mortality. We hypothesise that HT is able to induce hemodynamic instability leading to hospitalization, but, probably, its correction with thyroid hormone therapy could in part blunt its impact on patients' survival.

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GP216

The correction of TSH with thyroid replacement therapy is associated with a better outcome in chronic heart failure patients

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Background
It has been previously demonstrated that thyroid hormone deficiency is associated with a worse outcome in patients affected by chronic heart failure (CHF). However, few data are available about the effects of thyroid replacement therapy on the prognosis of patients.
Aim of the study
The aim of the study was to evaluate the relationship among thyroid replacement therapy, correction of thyroid stimulating hormone (TSH) serum levels and outcome of a series of CHF outpatients.
Methods
We screened CHF outpatients in stable clinical conditions (> 1 month) and in conventional therapy. All patients underwent a baseline clinical evaluation, a 12-lead ECG, an echocardiogram and routine blood tests. Thyroid hormones were assessed at the enrolment and routinely during follow-up (every 3–4 months or every 6–8 weeks if TSH level was altered at the previous control). All patients with history or newly diagnosed hypothyroidism were managed by endocrinologists. We considered hypothyroidism corrected when TSH serum levels were normalized by thyroid replacement therapy (levothyroxine).
Results
Hypothyroidism was diagnosed in 180 patients (121 males, 67 ± 12 years, left ventricular ejection fraction, LVEF, 33 ± 10%, NYHA class 2.5 ± 0.5, NTproBNP 2125 ± 2975 pg/ml, GFR-EPI 64 ± 22 ml/min*1.73 m^2) out of 712 patients. Twenty-four patients were excluded because they were lost at follow-up or died within the first 3 months or because endocrinologists did not prescribe

levothyroxine for TSH values not high enough. Among the remaining 156 patients in which levothyroxine was prescribed, in 111 patients a normal TSH value was obtained. During a mean follow-up of 38 months, 29 patients died (25 for cardiovascular causes) and 62 experienced at least one admission for acute decompensated heart failure. The failure in TSH correction was associated with an increased risk of all cause of death (HR: 3.31; 95% CI: 1.59–6.86; *P*: 0.001) and of heart failure hospitalization (HR: 2.27; 95% CI: 1.36–3.79; *P*: 0.002). At Cox multivariate analysis the failure in TSH correction remained associated with all cause mortality (HR: 2.57; 95% CI: 1.20–5.51; *P*: 0.002) and with heart failure hospitalization (HR: 1.78; 95% CI: 1.05–3.01; *P*: 0.03) after correction for NYHA class 3, LVEF $<$ 35%, NTproBNP $>$ 1000, systolic blood pressure $<$ 100 mmHg and GFR-EPI $<$ 60.

Conclusion

Our results support the possibility that hypothyroidism correction could improve the prognosis of CHF patients, although randomized controlled trials should be designed in order to demonstrate this hypothesis.

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Thyroid 3

GP217

Thyroid function in heart failure with preserved ejection fraction (HFpEF) – evaluation of serum and myocardial thyroid hormones in an animal model of HFpEF

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Introduction

Thyroid hormones play a central role in the regulation of the cardiovascular system. Heart failure with preserved ejection fraction (HFpEF) is responsible for more than 50% of all heart failure cases and its main pathophysiological alteration is diastolic dysfunction. Diminished thyroid function is known to predominantly impair diastolic function, however the thyroid hormone status in HFpEF remains largely unknown.

Methods

We evaluated an animal model of HFpEF, ZSF1 Obese rats (ZSF1-Ob, $n=13$), and their control group, ZSF1 Lean rats (ZSF1-Ln, $n=11$), with serial echocardiography followed by invasive hemodynamic recordings and tissue collections at 20 weeks. Serum TSH was quantified by ELISA. Thyroxine (T4) and triiodothyronine (T3) were quantified in serum, left ventricle and visceral adipose tissue by radioimmunoassay (RIA).

Results

At 20 weeks of age, ZSF1-Ob group developed HF with diastolic dysfunction, as shown by an increased E/E' on echocardiography, a prolonged time constant of isovolumetric relaxation, an elevated end-diastolic pressure and upward shifted end-diastolic pressure-volume relationship on invasive hemodynamic evaluation. Serum levels of thyroid hormones were significantly decreased in ZSF1-Ob rats (T3: 5.96 ± 4.65 vs 35.85 ± 9.39 ng/dL in ZSF1-Ln, $P<0.001$; T4: 1.51 ± 0.64 vs 3.49 ± 1.35 µg/dl in ZSF1-Ln, $P<0.001$), while the levels of serum TSH were not significantly different between the two groups (0.65 ± 0.38 ng/ml in ZSF1-Ln vs 0.79 ± 0.57 ng/ml in ZSF1-Ob, $P=0.531$). Left ventricle levels of thyroid hormones were significantly decreased in ZSF1-Ob rats (T3: 3.87 ± 0.85 vs 10.51 ± 7.91 ng/g in ZSF1-Ln, $P=0.012$; T4: 0.99 ± 0.43 vs 2.02 ± 0.60 ng/g in ZSF1-Ln, $P=0.016$). The levels of T3 and T4 in visceral adipose tissue were not significantly different between the two groups.

Conclusion

We observed a decrease in serum and myocardial thyroid hormone levels in an animal model of HFpEF. This may contribute to impaired diastolic function and, therefore, may constitute an interesting therapeutic target in HFpEF.

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GP218

STAT6 deficiency ameliorates Graves' disease severity by suppressing thyroid epithelial cell hyperplasia

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Signal transducer and activator of transcription 6(STAT6) is involved in epithelial cell growth. However, little is known regarding the STAT6 phosphorylation status in Graves' disease (GD) and its role in thyroid epithelial cells (TECs). In this study, we found that STAT6 phosphorylation (p-STAT6) was significantly increased in TECs from both GD patients and experimental autoimmune Graves' disease mice and that STAT6 deficiency ameliorated GD symptoms. Autocrine IL-4 signalling in TECs activated the phosphorylation of STAT6 via IL-4R engagement, and the downstream targets of STAT6 were Bcl-xL and cyclin D1. Thus, the IL-4-STAT6-Bcl-xL/cyclin D1 pathway is crucial for TEC hyperplasia, which aggravates GD. More importantly, *in vitro* and *in vivo* experiments demonstrated that STAT6 phosphorylation inhibited by AS1517499 decreased TEC hyperplasia, thereby reducing serum T3 and T4 and ameliorating GD. Thus, our study reveals that in addition to the traditional pathogenesis of GD, in which autoantibody TRAb stimulates thyroid-stimulating hormone receptors and consequently produces T3, T4, TRAb could also trigger TECs producing IL-4, and IL-4 then acts in an autocrine manner to activate p-STAT6 signalling and stimulate unrestricted cell growth, thus aggravating GD. These findings suggest that STAT6 inhibitors could be potent therapeutics for treating GD.

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GP219

Delayed TSH recovery after dose adjustment during TSH-suppressive levothyroxine therapy in patients with differentiated thyroid cancer

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Background

Delayed thyroid-stimulating hormone (TSH) recovery during treatment of Graves' disease is caused by long-term excessive thyroid hormone, which results in down-regulation of pituitary thyrotropic cells. However, it is unknown whether delayed TSH recovery exists after levothyroxine (LT4) dose adjustment in patients with differentiated thyroid cancer (DTC) who are taking a suppressive dose of LT4.

Methods

We retrospectively reviewed 97 DTC patients who had a reduced LT4 dose while receiving excessive LT4 for TSH suppression. TSH levels at baseline (point 1), 6 months (point 2), and 12-18 months (point 3) after LT4 dose adjustment were compared with each other. A delayed TSH recovery group whose TSH levels exceeded target TSH levels (according to recent guidelines) between points 2 and 3 was identified.

Results

In patients with LT4 reduction, the median TSH level at point 3 was significantly higher than that at point 2 [0.17 vs 0.09 µIU/ml; $P<0.001$). The delayed TSH recovery group (44.3%, 43 of 97 patients) showed increased body weight during follow-up (60.84–62.73 kg; $P=0.01$), although TSH levels remained in the target range. A lower LT4 dose per body weight (LT4 dose/weight) after reduction [HR (95% CI), 0.01 (0.00–0.54); $P=0.03$], greater changes in the LT4 dose/weight [1.10 (1.00–1.22); $P=0.04$], and higher BMI before surgery [1.19 (1.03–1.38); $P=0.01$] predicted the occurrence of delayed TSH recovery.

Conclusions

Delayed TSH recovery was commonly observed after LT4 dose adjustment was performed as recommended by dynamic risk stratification. Six months may not be enough time to evaluate real thyroid hormone status by TSH levels.

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GP220

Analysis of a large cohort of subjects with thyroid hemiagenesis (THA) reveals random seasonality in the dates of birth

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Introduction
In the etiology of thyroid dysgenesis (TD) an interplay between genetic and environmental factors is thought to play a crucial role. Data from previous studies on association between the season of birth and the incidence of TD causing congenital hypothyroidism (mainly agenesis and ectopy) are conflicting. To date, seasonality of births have not been analysed yet in regard to congenital absence of one thyroid lobe (thyroid hemiagenesis, THA).
Patients and Methods
Dates of birth of 102 patients diagnosed with THA were analysed and compared to 102 control subjects with no thyroid pathology matched for age and gender. Both groups were subdivided according to the month of birth (I-XII), season of birth (spring, summer, autumn, winter) and quarter (1–4) of the year. The differences were analysed statistically.
Results
Distribution of the months of birth in the group of patients with THA was asymmetric; smaller number of patients were born in the 4th (X-XII) quarter of the year (19 patients) vs 1st (28 patients), 2nd (29 patients) and 3rd (26 patients). Similarly, smaller number of patients were born in autumn (IX-XI) – 19 patients if compared to other seasons of the year (winter – 27 patients, spring – 27 patients, summer – 29 patients). However, if the studied group was compared to the control group, the difference in the distribution of the months of birth was at the border of statistical significance ($P < 0.0923$). Furthermore, if the studied and control group were subdivided into four quarters or seasons, and then compared, the difference was definitely not statistically significant.
Conclusions
An analysis of the largest so far reported cohort of patients with THA indicate that environmental factors including intrauterine exposure to maternal seasonal viral infections or variable vitamin D availability seem not to play a significant role in pathogenesis of THA.

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GP221

Thyroid hormone T3 protects mice from fasting induced skeletal muscle atrophy by counteracting autophagy

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Purpose
Skeletal muscle has been recognized as a thyroid hormones (THs) target for contractile function, regeneration, metabolism and glucose disposal. Despite a role in regulating muscle development has been described, little is known about the role of THs in regulating muscle homeostasis in a pathological state such as food deprivation induced atrophy. The purpose of this study is to evaluate whether thyroid hormones may hamper the fasting induced skeletal muscle atrophy and to investigate the mechanisms involved.
Methods
Preliminary data on C2C12 myotubes have suggested that T3 could counteract the starvation induced atrophy *in vitro.* Based on these results, BALB/C male mice (8–10 weeks) were used for *in vivo* experiments. Animals were food-deprived (STV) for 24 and 48 hours to induce muscle atrophy and daily injected intraperitoneally with T3 (100 ug/kgBW) or vehicle (NaCl 0,95%) as controls. Tibialis anteriors were taken at the end of the experiments. Morphological analyses were performed on hematoxylin/eosin stained sections. ATG7-Mrna was evaluated by Sybr-Green qRT-PCR and LC3II/Lc3I was evaluated by western blot.
Results and conclusions
As a sign of skeletal muscle atrophy, the STV group showed a significant ($P < 0.001$) reduction in the Cross-Sectional-Area of the myofibers, compared to the control group; on the contrary the T3 treated group (STVT3) ensures the maintenance of the fiber size. Protein degradation in skeletal muscle cells is mediated by the autophagic/lysosomal pathway. The core autophagic machinery is composed of ATG (autophagy-related) proteins. One ATG family member, Atg7, activates enzyme facilitating microtubule-associated protein-light-chain3 (LC3)-phosphatidylethanolamine conjugation. The presence of T3 was able to significantly reduce ATG7 mRNA expression, moreover the hormone significantly reduces LC3II/LC3I protein expression, when compared to STV mice ($P < 0,05$). On the whole our results suggest that T3 treatment can reduce fasting induced skeletal muscle atrophy by counteracting the autophagic process.

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GP222

Will it be useful to measure PTH at 4 hours post thyroidectomy to decide for calcium replacement? 1st result of a prospective study

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Introduction
Calcium replacement after Thyroid surgery has been changing along times. The aim for this replacement is to avoid hypocalcaemia effects after thyroid surgery but not all the patients seem to need it. Parathyroid hormone (PTH) has a short half-life after its release into the bloodstream, making it a good marker of calcium metabolism in short time after surgery.
Method
Prospective study of Endocrine Surgery Multidisciplinary group of one Centre between March and December of 2016. Calcium replacement was done according to a protocol defined by multidisciplinary group after PTH measurement. PTH values were considered normal above 15 pg/ml. Data were analyzed using SPSS.
Results
96 patients underwent total thyroidectomy vs totalization of thyroidectomy. 5 were excluded since they were admitted at ICU and protocol was not implemented. PTH was measured 4 hours after surgery.
From the 91 patients, 74 had normal PTH levels. The remaining patients (17) started calcium replacement according to established protocol and showed no symptoms of hypocalcaemia.
Considering group with normal PTH, at day one after surgery, 41 had normal calcium levels (*P* 0,01 on correlation analysis) and 33 had low levels. This last group started the protocol of calcium replacement and at day two after surgery were observed higher calcium levels (*P* 0,001 at linear analysis) and didn't refer hypocalcaemia symptoms.
Our Sample has a significance of 0.05 in the non-parametric, Q-square and Kolmogorov-Smirnov test.
Conclusion
Measuring PTH 4 hours after surgery is helpful to decide which patients should start calcium replacement, using PTH value cut-off of 15 pg/ml.

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GP223

Endogenous TH metabolite 3-iodothyronamine (T1AM) and synthetic thyronamine-like analogues SG-1 and SG-2 induce autophagy in human glioblastoma cells (U-87MG)

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Endogenous TH metabolite 3-iodothyronamine (T1AM) and recently developed thyronamine-like synthetic analogues SG1 and SG2 have emerged as neuroprotective agents. Autophagy has proved to be an effective therapeutic approach for neurodegenerative diseases. Therefore we investigated whether these compounds can induce autophagy in human glioblastoma cells (U-87MG). Cultured U-87MG cells were initially treated with 1 μM T1AM, SG-1, SG-2 or vehicle for 30', 4, 8 and 24 h and autophagy was monitored morphologically by assessing the presence of autophagic vacuoles and LC3-II puncta formation with transmission electron microscopy (TEM) and immunofluorescence (IF) microscopy, respectively. In addition, cellular lysates were subjected to western

blotting to assess the accumulation of microtubule-associated protein 1 light chain 3 (LC3). This protein is widely used as a marker for autophagy because it is a structural protein vital in autophagosome formation. TEM and IF microscopy showed a significant time dependent increase of autophagy-like vacuoles density and LC3 punta formation in U-87MG cells exposed to the treatment with test compounds, with T1AM and SG-1 being the most effective. Along with extensive cytoplasmic vacuolization, western blotting analysis revealed significant up regulation of LC3-II expression ($P<0.01$). Finally, we extended our analysis to examine the role played by our test compounds on the PI3K–AKT–mTOR pathway that has been suggested to play an important role in the regulation of autophagy in mammalian cells. We carried out WB for Akt, phosphorylated Akt (pAkt) and we calculated the ratio pAkt/Akt in vehicle-treated cells following test compounds administration. We found that 1 μM T1AM, SG-1 and SG-2 decreased such a ratio after 30' and 4 h treatment, suggesting that they might induce autophagy through the modulation of pAkt level. In conclusion, T1AM and synthetic analogues induce autophagy in a glioblastoma cell line. The potential pathophysiological and/or therapeutic implications of this finding remain to be determined.

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GP224

Impact of chronic high fat diet consumption on the expression of organic nutrients carriers in the small intestine of mice: role of thyroid hormones in these processes

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Products of carbohydrates, proteins and lipids hydrolysis are absorbed by specific carriers located at the enterocytes apical membrane, but little is known about the mechanisms related to their regulation by own nutrients, especially considering the high consumption of fats. Carbohydrates are transported by SGLT1, GLUT5 and GLUT2 and peptides are transported by PEPT1. Cholesterol is transported by NPC1L1 and long chain fatty acids occur through FAT-CD36 and FATP4. Thyroid hormones have important effects on organic nutrients metabolism, but little is known about their role on the intestine, which led us to evaluate thyroid hormone effects on intestine organic nutrients carriers of mice fed high fat diet (HFD) or standard diet. C57BL/6 mice were fed standard diet (control) or high fat diet (HFD) for 12 weeks. Afterwards, both mice were treated with saline, PTU (antithyroid drug) or T3 for 30 days. They were killed and the jejunum was removed for histological analysis or inverted for intestinal epithelium separation from the mucosa for protein analysis by Western blotting technique. FAT-CD36, NPC1L1 and GLUT2 protein contents reduced in mice fed HFD compared to control mice. SGLT1, PEPT1 and FATP4 remained unchanged among experimental groups. On the other hand, NHE3 protein content, which is important for sodium and peptides absorption, increased significantly in the small intestine of mice fed HFD. PTU or T3 treatment did not affect these parameters. High fat compared to standard diet did not show any alteration of the villus length, but mice fed standard diet and treated with PTU or T3 showed an increased villus length compared to treated-vehicle mice, however this finding have no association with the changes of nutrient carriers described above. Thus, we can infer that HFD affects the expression of some organic nutrient carriers in the small intestine, independently of thyroid hormones treatment.

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Thyroid Cancer

GP225

Prognostic factors for intrathyroidal papillary carcinomas – a multivariate analysis

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Introduction
The aim of this study was to examine prognostic significance of patient-related, tumor-related and treatment-related factors for intrathyroidal papillary thyroid carcinomas (PTC), via multivariate analysis.
Materials and methods
This study included 153 patients with intrathyroidal PTCs (pT1/pT2/pT3) surgically treated in our Institution during two-decade period. Patients with locally invasive tumors (pT4) and initial distant metastases (M1) were excluded. Parameters of interest were: gender (male; female), age (≤ 45; >45 years), tumor size (pTNM classification WHO 1984), multifocality (no; yes), histological type of PTC (pure; microcarcinoma; follicular; poorly differentiated), presence of lymphonodal metastases (pN1a; ipsilateral-pN1b; contralateral-pN1b; total), surgery extent (total thyroidectomy; total thyroidectomy with lymphonodal dissections). Univariate and multivariate analysis of all parameters was performed in order to distinguish factors of significance for disease-free (DFS) and cancer-specific overall survival (cs-OS).
Results
In the follow-up, 10% of patients had locoregional or distant relapse, while 5.2% died due to PTC. Univariate analysis distinguished older age, male gender, tumors over 4 cm in diameter, multifocality and poorly differentiated PTC-types as unfavorable prognostic factors for cs-OS. DFS was significantly shorter in males vs. females, as well as in patients with multifocal vs. solitary PTC. Tumor multifocality was unfavorable prognostic factor for both DFS and cs-OS. Independent prognostic factors for intrathyroidal PTCs, based on Cox multivariate analysis, were multifocality and gender for DFS, and multifocality and age at diagnosis for cs-OS.
Conclusion
Prognostic factors define risk groups within population of differentiated PTCs providing timely, adequate treatment and opportunity for longer quality life of patients with PTCs.

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GP226

Malignancy Rate in Thyroid Nodules: Cytology versus Histology in challenging categories

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Background
To stratify the risk of malignancy, thyroid fine-needle aspiration cytology (FNAC) is an important and cost-effective method to evaluate nodules. The Bethesda System for Reporting Thyroid Cytopathology III, IV and V categories are diagnostic challenges, falling between benign and malignant.
Objective
Determinate the malignancy rates of thyroid nodules classified as Bethesda Categories III-V.
Methods
Retrospective study of patients' records with thyroid nodules classified as III-V by the Bethesda system, between January 2014-June 2016.
Results
Of a total of 2791 cytologies, 176 (6%) were classified as III-V, with the following distribution: 93 (3%) atypia of undetermined significance (AUS, III); 50 (1,8%) suspicious for follicular neoplasm (SFN, IV) and 33 (1%) suspicious for malignancy (SM, V). Malignancy rates for IV and V FNAC diagnostic groups were 27% (10/37) and 85% (22/26), respectively. Among patients in group III, 27 patients underwent surgery after a single AUS report (final diagnosis of malignancy – 33%), 39 repeated the FNAC and the remaining are under surveillance. The second cytology report was as follows: 24 benign, 9 AUS, 4 SM, 1 SFN and 1 unsatisfactory; surgery was performed in 9 patients (5AUS + 1SFN + 3SM) and the final diagnosis of malignancy was 44%. The malignancy rate based on histology was not statistically different between patients with one or two cytologies ($P=0{,}693$).
Conclusions
Incidences of III-V diagnostic categories in our study resemble the predicted by the Bethesda System. The malignancy rate for the AUS category was higher than expected and similar to the one found in SFN. Repeating the FNAC in the former group offered minimal additional benefit.

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GP227

Fine needle aspiration biopsy in pediatric patients with thyroid nodules

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Introduction
Although thyroid nodules (TN) are less common in children than in adults, the risk of malignancy is much higher in pediatric age and therefore representing greater concern in this age group.
Objective
Evaluate a cohort of pediatric patients with TN and search differences between subjects with malignant and benign TN regarding sex, age, compressive symptoms, cervical ultrasound characteristics, family history of differentiated thyroid cancer (FHDTC), radiation exposure and previous/coexisting thyroid disease.
Methods
Retrospective review of patients under 18 years of age with the diagnosis of TN submitted to fine needle aspiration biopsy (FNAB) from 2010 to 2016.
Results
Seventy-three patients [21% males; mean age 13.8(3.2) years] were included. 46.6% had palpable nodules. 84.9% were euthyroid and 12.3% had hypothyroidism. 31.5% of the patients had positive anti-thyroid antibodies. Ultrasound showed that TN had a diameter range of 15.9 ± 9.8 mm, 47.9% patients had a solitary nodule, 31.5% TN were hypoechoic, 5.5% had increased intranodular flow, 10.9% had microcalcifications and 5.5% had irregular margins. We found that 5.5% of patients had undergone previous cervical irradiation and 12.3% had FHDTC. 84.9% of the patients had a conclusive FNAB at first: benign in 39 (colloid ($n=25$), chronic lymphocytic thyroiditis ($n=12$), granulomatous thyroiditis ($n=1$), thymus tissue ($n=1$)), FLUS in 4, suspected follicular neoplasia in 3, suspected malignancy in 1 and papilar carcinoma in 15 patients. Thyroidectomy was performed in 43.8% of the patients. In histology, 71.9% were diagnosed as malignant. One patient developed permanent hypoparathyroidism after surgery. We verified that the FHDTC was more frequently present in the malignant nodules (26% vs 6%, $P=0.024$), while for the other factors mentioned above there were no statistically significant differences.
Conclusion
In most patients a conclusive diagnosis was achieved with FNAB. The high prevalence of malignancy was similar to that described in the literature. FHDTC was the only factor found associated with an increased risk of malignancy.

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GP228

Differentiated thyroid cancer – comparison between patients with and without remission

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Introduction
Differentiated thyroid cancer (DTC) is one of the most frequent forms of malignancy. Because of its favourable outcome and low mortality rates, identifying prognostic factors has been a challenge. Several risk stratification systems have been developed. Most of them include demographic and tumour specific features, as well as extrathyroidal extension. Our objective was to compare clinical characteristics between DTC patients with and without remission.
Methods
Data from patients followed for DTC between 1956 and 2016 was retrieved. Patients with less than 2 years of follow up, those submitted to subtotal thyroidectomy or with positive antithyroglobulin antibodies were excluded. They were divided in two groups, according to the presence or absence of remission criteria (undetectable TSH-suppressed thyroglobulin levels and no evidence of structural disease). Groups were compared for age at diagnosis, nodule dimensions, multicentricity, capsule presence and extrathyroidal involvement as well as the presence of node or distant metastasis.
Results
A total of 814 patients was included, 82.9% of which were female. The median age at diagnosis was 47 years old (min. 11; max. 89). Five hundred patients had criteria for remission (Group 1) and 314 didn't (Group 2 [36 with cancer related death, 55 with persistent or recurrent disease and 223 with indeterminate response]). Median follow up was 10 years (min. 3; max. 50) in Group 1and 9 years (min. 3; max. 57) in Group 2. Patients in group 1 were significantly younger (median 44.5 vs 49.5; $P<0.001$) had more multicentricity (45,7% vs 37.7%; $P=0,041$) and less local (22.7 vs 30.6%; $P=0,016$) and distant metastasis (0.4% vs 5.7%; $P<0,001$). No differences were found in nodule dimensions, capsule presence or extrathyroidal involvement.
Conclusion
Among patients with differentiated thyroid cancer, the older ones, with unicentric tumours, local or distant metastasis at presentation seem to have worst outcome.

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Trends in papillary microcarcinoma prevalence in North of Portugal

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Introduction and Objectives
The incidence of thyroid cancer has increased worldwide. This increase has been attributed to more diagnosed papillary thyroid microcarcinomas. The purpose of this study was to analyse the growing trend of first appointments in our Thyroid Cancer Unit, namely patients with papillary microcarcinomas.
Methods
We performed a retrospective study based on the patients diagnosed with thyroid cancer between 1960 and 2016. We divided these patients into groups, based on the year of first surgical treatment: 1960 to 1996, 1997 to 2001, 2002 to 2006, 2007 to 2011 and 2012 to 2016. We calculated the relative frequency of papillary microcarcinomas comparing to the total cancer diagnostics in each group.
Results
The total count of patients with registered thyroid cancer dimensions was 1146. The mean age was 48.2 ± 15.3 years old. 81.9% were female. We have found that papillary microcarcinoma frequency increased steeply from 11.2% [35/313, 95% confidence interval (CI) 8.2–15.2%] in 1960–1996 to 30.9% (42/136, 95% CI 23.7–39.1%) in 1997–2001. From that time onwards it stabilised around 1/3 of thyroid cancer cases evaluated – 34.0% (54/159, 95% CI 27.1–41.6) in 2002–2006; 34,6% (93/269, 95% CI 29.1–40.4%) in 2007–2011 and 30.5% (82/269, 95% CI 25.3–36.2%) in 2012–2016.
Conclusions
The prevalence of papillary microcarcinomas has increased until the end of the last century. After 2002 our data showed a somewhat stabilised rate of 1/3 of all diagnosed thyroid cancers.

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Radioiodine (RAI) refractory differentiated thyroid cancer (DTC): outcome and prognostic factors for DISEASE progression

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Introduction
Patients diagnosed with DTC have excellent prognosis. A small percentage of patients with disease persistence do not respond to treatment with RAI (RAI-refractory DTC) and have low median survival (3.5 years). We investigated the prognostic factors and the disease course in patients with RAI-refractory DTC.
Methods
Of all DTC patients (n = 1160) followed-up in our department in recent years, 800 received RAI treatment and were classified in 2 groups: RAI-refractory DTC

(5.8%) and RAI responsive DTC (94.2%). Clinical and histological characteristics were compared between the 2 groups.
Results
The incidence of RAI-refractory DTC was higher in patients ≥45yrs and particularly in those ≥65yrs (3% vs 7.4% vs 17.4%, $P=0.001$). Men had RAI-refractory DTC more frequently than women ($P=0.02$). RAI-refractory DTC patients presented higher incidence of capsular, lymph node and extra-thyroid invasion ($P<0.004$), larger size ($P<0.001$), worse histological type (high risk papillary: 34.9% vs 12% and features of poor differentiation: 14%vs0.6% respectively, $P<0.001$,). They presented more frequently distant metastases at follow-up (73.3% vs 1.5%, $P<0.001$). 12 RAI-refractory patients had local persistence. 5/12 had no distant metastasis; all underwent multiple surgeries and 3 locoregional external radiation therapy. The 10-year probability of lack of progression of disease was 27.9% vs 98.8% ($x^2=297$, $P<0.001$). In Cox proportional hazard analysis, the only predictor for disease progression was resistance to RAI (HR 0.032, 95% CI 0.007–0.146, $P<0.001$). Within the RAI-refractory DTC subgroup, when age at diagnosis, gender, tumor size, histological type, lymph node, capsular and tissue invasion were taken into account, the only predictor for disease progression and occurrence of distant metastases was tumor size ($P=0.008$ and $P=0.015$ respectively).
Conclusions
Patients with RAI-refractory DTC present disease progression at high percentage (72.7%). In these patients, tumor size is the most important unfavorable factor predicting disease progression and occurrence of distant metastases. These data may be useful in designing treatment strategy.

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Management and outcome of bone metastasis from differentiated thyroid carcinoma in the real life: the M.OS.CA.TI. study

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Although differentiated thyroid cancer (DTC) has the third highest propensity to spread to the bone after breast and prostate cancer, there is a paucity of data concerning the treatment of bone metastasis (BM) in this setting. The MOSCATI (Metastasi OSsee da Carcinoma TIroideo) was a multicenter, retrospective study investigating the real-life outcome and management of BM in 143 patients (80 F, 63 M; median age 60 years) with DTC involving 10 specialized centers in Italy. One or more skeletal related events (SREs) were diagnosed in 58% of patients in significant association with more aggressive tumor histotype (OR 5.39), higher number of BM (OR 1.36), localization of BM to thoracic spine (OR 2.7), cervical spine (OR 7.47) or skull (OR 2.28), and lack of radio-iodine (RAI) uptake (OR 6.03). RAI treatment was performed in 93% of patients. Bone active drugs were used in 32 patients with SRE (22.4%; zoledronate in 31 and denosumab in one). Bone active drugs were used more frequently in patients with more aggressive histotype of DTC ($P<0.001$), with RAI-refractory BM ($P<0.001$) who did not receive RAI therapy ($P<0.001$) and/or in those with multiple BM ($P=0.006$), malignant hypercalcemia ($P=0.001$), pathological fractures ($P=0.02$) and in those undergoing radiotherapy ($P<0.001$). After treatment, 13.5% of patients developed new SREs and 39 patients (27.3%) died. RAI treatment significantly prevented the second SRE (HR 0.01) and decreased mortality (HR 0.12) as compared to patients treated with anti-resorptive drugs alone. Patients treated with RAI plus anti-resoptive drugs showed less efficacy in preventing second SRE and decreasing mortality as compared to treatment with RAI alone. In conclusion, in the real life, the use of bone active drugs is currently limited to zoledronate in patients with pre-existing SREs. In this specific clinical setting, RAI therapy, but not zoledronate, prevented progression of SREs and mortality. Future studies are needed to clarify the effectiveness of anti-resorptive drugs in primary prevention of SREs and possible advantages of denosumab versus zoledronate in the treatment of BM from DTC.

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Germ-line mutations in RET-790 and RET-791 codons (exon 13) among subjects with sporadic medullary thyroid cancer

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Background
Medullary thyroid carcinoma (MTC) is a rare calcitonin producing neuroendocrine tumour that originates from parafollicular C-cells of the thyroid gland. RET proto-oncogene germline mutations are crucial for the onset and the progression of MTC, and the occurrence of single nucleotide polymorphisms could predispose the clinical course of disease. The objective of this study was to evaluate possible differences in clinical presentation among patients with/without RET codon 790 and codon 791 (exon 13) mutations.
Methods
A non-isotopic polymerase chain reaction based single strand confirmation polymorphism analysis and heteroduplex gel electrophoresis method was used to screen tumour DNA extracted from 132 formaldehyde fixed and paraffin embedded MTC specimens. We analysed clinical data from 69 patients harbouring RET codon 790 and codon 791 mutations (exon 13) (group A) compared with 63 patients with "wild-type" genotype (group B). The study was conducted according to the Declaration of Helsinki, the protocol was reviewed and approved by the institutional independent ethics committee. All patients were provided with written informed consent.
Results
Mean age for the group A was 56.2 ± 11.4 years (range, 44.8–67.6) vrs. 49.4 ± 9.7 (range 39.7–59.1) for the group B. Lymph node metastases were found in all patients (group A, $n=46$ vrs. group B, $n=31$; $P<0.001$), and distant metastases in 11 patients (group A, $n=7$ vrs. group B, $n=4$; $P>0.001$). Postoperatively, 62% of patients in group A vrs. 78% of patients in group B were biochemically cure ($P<0.001$). In the group A, pT-category was: T_0, $n=21$; T_1, $n=16$; and T_2, $n=9$. In the group B, pT-category was: T_0, $n=22$; T_1, $n=7$; and T_2, $n=2$ ($P<0.001$).
Conclusions
Patients with RET codon 790/791 (exon13) mutations have a more aggressive clinical course and lower biochemic cure rate in comparison with patients with 'wild-type' genotype. This information should be considered by genetic counseling or by operative therapy and could have clinical importance when specific targeted therapy is discussed.

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Comparison of clinicopathological features in patients with familial and sporadic papillary thyroid cancer

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Introduction
Although, familial medullary thyroid cancer is a known condition, familial papillary thyroid cancer (PTC) is a rare and less well described clinical entity. While some studies suggest more aggressive features in familial PTC, some do not support these findings. We aimed to compare ultrasonographical, cytopathological and histopathological results of patients with familial and sporadic PTC.
Methods
Data of 194 patients diagnosed with PTC histopathologically between 2007–2016 were retrospectively reviewed. PTC in ≥2 members of the family was defined as familial PTC. Thyroid functions, ultrasonography features, cytological and histopathological findings were compared in familial and sporadic PTC.

Results
There were 35 tumor foci in 20 familial and 253 foci in 174 sporadic PTC patients. Gender, thyroid functions, thyroid autoantibody positivity, mean nodule number, thyroidectomy indications and surgical approach were similar in two groups. Preoperative ultrasonography features were available in 20 familial and 112 sporadic nodules. There was not any difference in mean nodule diameter, echogenity, texture, microcalcification, macrocalcification, presence of hypoechoic halo, taller than wide shape, margin irregularity and vascularization pattern. Cytological results were distributed similarly in two groups ($P=0.433$). In histopathological examination, mean tumor number was 1.79 ± 0.98 in familial and 1.46 ± 0.77 in sporadic patients ($P=0.09$). Mean tumor diameters were 6.26 ± 4.10 mm and 9.87 ± 11.62 mm in familial and sporadic tumors, respectively ($P=0.074$). Multifocality, microcarcinoma rate, variants of PTC, vascular invasion and extracapsular extension were similar ($P=0.155$, $P=0.239$, $P=0.094$, $P=0.617$ and $P=0.743$, respectively). Capsular invasion was significantly increased in sporadic group (19.8% vs 5.9%, $P=0.049$).
Conclusion
Whether familial PTC is more aggressive than the sporadic form of the disease is controversial. Clinical, ultrasonographical, cytological and most of the histopathological features of familial and sporadic PTC were identical in our study. Early detection of cases other than index patients might cause diagnosis at an earlier stage of the disease in familial form.

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Lobectomy as a treatment option for well differentiated thyroid cancer (WDTC) between 1–4 cm: which results should we expect?

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Introduction
The ATA guidelines 2015 suggests lobectomy as an option for low risk thyroid tumors between 1–4 cm, although there remains some controversy once some characteristics become apparent only on pathologic examination.
Objective/methods
Retrospective analysis of patients who underwent thyroid surgery in 2014 and 2015, with a histologic diagnosis of WDTC 1–4 cm in size and revision of the proportion of patients eligible for lobectomy with indication for completion thyroidectomy according to the ATA guidelines 2015.
Results
Three hundred and eighty eight patients who underwent thyroidectomy were analysed. Of these, 85 (21,9%) were include for final analysis. Exclusion criteria: history of cervical radiation, tumors <1 and >4 cm, macroscopic extrathyroidal extension (ETE), cN+, and bilateral thyroid nodules.
The mean age of the cohort was 49 years**,** 83,5% are females, none had an aggressive histology, 12 (14,1%) had vascular invasion, 5 (5,9%) had microscopic ETE, 3 (3,5%) had positive margins and 1 (1,2%) patient had positive lymph node metastasis.
Conclusion
(20%) of the patients with apparently 'low risk' WDTC who are eligible for lobectomy would have indication for completion total thyroidectomy according to the ATA guidelines 2015.

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GP235

Clinical Utility of response to therapy in combination with BRAF in risk assessment of thyroid cancer

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Response to therapy re-stratification approach has been recently included in the 2015 ATA guidelines as a risk-adapted approach to management of thyroid cancer. Our aim was to investigate the clinical utility of response to therapy variables obtained during early follow-up in combination with BRAF, a prominent oncogene in thyroid cancer with prognostic value. This was a retrospective multicenter study of 871 patients at 11 centers in Spain with papillary thyroid cancer followed after total thyroidectomy and radioactive iodine remnant ablation. 685 patients were re-stratified during the first year of follow-up based on response to therapy: excellent (73% of the patients), indeterminate (8%), biochemical incomplete (6%) and structural incomplete (13%). Clinical outcomes were obtained in each group and no evidence of disease (NED) was seen in 95%, 47%, 32% and 24% respectively for a median follow-up of 57 months. BRAF mutation prevalence was 51% and was significantly associated with patients who had no excellent response (31.4% vs 22.9%; HR 1.53 (95% CI, 1.080 a 2.188)). This association remained significant with biochemical incomplete response but not with structural incomplete response. Moreover, BRAF positive tumors were less likely to have distant metastasis compared with BRAF negative tumors. Patients with excellent response and BRAF negative tumors, almost 100% had NED at the end of follow-up. Patients with indeterminate and biochemical incomplete response and BRAF positive tumors, were less likely to have NED compared with BRAF negative, although the difference was not significant due to the small number of patients in each group. Our data show that indeterminate and biochemical incomplete response may not have such favourable clinical outcome as previously shown. In addition, BRAF status informs about the way papillary carcinomas disseminate (locoregional vs distant metastasis) and may help to better assess risk estimates that change over time based on response to therapy.

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Thyroid Cancer & Thyroid Case Reports

GP236

A rare case of medullary thyroid cancer, mesothelioma and meningioma, due to APC and RASAL1 mutations

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Introduction
Patients with "mixed" phenotypes are common among patients with multiple endocrine and non-endocrine neoplasias. Their diagnoses do not fit a given pattern making ge netic counseling difficult and testing impossible to guide. Most of these patients end up getting genome-wide studies for the identification of any predisposing genetic defect. We present a rare case of a 57 year old female who presented clinically with medullary thyroid cancer (MTC), mesothelioma and meningioma. As part of our diagnostic work-up for this category of patients, we performed a SNP microarray (comparative genomic hybridization; CGH) and whole exome sequencing (WES). CGH did not reveal any abnormalities; WES revealed two variants of unknown significance (VUS) in two separate genes, namely APC and RASAL1.
Case presentation
The patient, a 57 year old female patient, was diagnosed with AML at 41y old, peritoneal mesothelioma at 43y old, meningioma at 53y old and medullary thyroid cancer with lymph node metastasis at 53y old. She also suffers from autoimmune atrophic gastritis, alopecia universalis and relapsing perichondritis of the ear.
Results
WES was performed by DNA extracted from blood and revealed two specific VUS, in the APC gene: p.R1103W, c.3307 A>T and in the RASAL1 gene: p.R538H, c.1613 G>A. The APC gene (OMIM #17500) is a tumor suppressor gene involved in Wnt / β catenin signaling pathway; mutations have been reported in Familial Adenomatous Polyposis (FAP), brain tumors and Turcot syndrome. Mutations in the RASAL1 gene (OMIM#604118) have been found in thyroid cancer (both papillary and medullary) and Cowden syndrome. The above two variants found in this patient have not been reported previously as pathogenic. The mutations in the APC and RASAL1 genes are probably involved in thyroid cancer development. In addition, the mesothelioma and meningioma are likely related to mutations in the APC gene. This unique clinical presentation has not been reported before and is being proven by additional immunostaining and molecular studies.
Conclusion
Patients with unique phenotypes may present with a list of clinical manife stations that do not fit any given diagnosis. These patients deserve genome-wide testing

that is often rewarding but also complex. In our patient with MTC, mesothelioma and meningioma two new gene defects were identified that are probable responsible for the phenotype.

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GP237

Thyrotoxic Periodic Paralysis due to Graves' disease: a mandatory differential diagnosis in Asian patients presenting with paralysis and hypokalemia

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Introduction
Thyrotoxic periodic paralysis (TPP) is a potentially life-threatening complication of hyperthyroidism that is underdiagnosed and frequently missed. It is relatively common in Asian men with Graves' disease. TPP attacks are frequently associated with hypokalemia.
Case presentation
We describe a 26-year-old Asian male with an unremarkable past medical history who was admitted following sudden onset of flaccid paralysis of the lower extremities. Signs and symptoms such as weight loss, diaphoresis, palpitations and mild diffuse goitre were present. The electrocardiogram showed a sinus tachycardia and the laboratory evaluation revealed markedly low potassium and phosphorus levels (K^+ 1.5 mmol/l; PO_4^{3-} 1.8 mg/dl). The patient was managed with intravenous potassium chloride with markedly improvement of the neurological deficits, despite a rebound hyperkalemia shortly after replacement. A thyroid profile was taken due to the suspicion of TPP in the context of Graves' disease, and the diagnosis was made (TSH 0.01 μU/ml; free T4 5.21 ng/dl; free T3 15,64 pg/ml; TRABs 37,64 U/l). The patient then started on oral propranolol and tiamazol, with complete remission of the symptoms and sustained normalization of serum potassium.
Conclusion
TPP is an alarming and potentially lethal complication of hyperthyroidism characterized by muscle paralysis and hypokalemia due to a massive shift of potassium into cells. This condition mainly affects male patients of Asian descent. With increasing population mobility and admixture, TPP as the presenting feature of hyperthyroidism is now more common in Western countries. Early diagnosis not only aids in definitive management with nonselective beta-blockers and correction of hyperthyroidism, but also prevents the risk of rebound hyperkalemia due to excessive potassium replacement. We report this case to emphasize the importance of recognizing TPP to avoid missing a treatable and curable condition.

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GP238

A fatal case of fetal goiter: autoimmunity is the key

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Introduction
Fetal goiter is an infrequent and potentially life-threating condition derived from either fetal hypothyroidism or hyperthyroidism. TSH-receptor stimulating antibodies (TSH-R-ABs) can cross the placenta and induce fetal hyperthyroidism and goiter. We describe a rare case of TSH-R-ABs-induced hyperthyroidism in a woman with autoimmune hypothyroidism (AH) without previous hyperthyroidism.
Case Report
A 28 years old pregnant woman under treatment with Levothyroxine (LT4) for 6 years because of AH was referred during pregnancy. She had history of 2 miscarriages: fetal death at 28th gestational week (GW) two years before and fetal loss in 2015 because of corioamnionitis. Blood tests at 12th GW showed undertreated AH (TSH 31.4 μU/mL, fT4L 0.97 ng/dL) and Levothyroxine dose was increased. At 24th GW, blood tests showed a mild hyperthyroidism (TSH 0.05 μU/mL, fT4 1.53 ng/dL) and LT4 dose was reduced. Fetal ultrasound (US) at 25th GW showed a male fetus with bilateral cerebral ventriculomegaly without other alterations. TORCH serologies were negative, amniocentesis revealed a normal karyotype and fetal MRI showed bilateral cerebral ventriculomegaly and fetal goiter.
To study the fetal thyroid function a blood sample by cordocentesis was obtained and a maternal blood test to examine TSH-R-ABs levels was performed. Meanwhile, fetal US at 26th GW showed tachycardia, mild pericardial effusion, hydrothorax, cardiomegaly, hepatomegaly and splenomegaly. Fetal blood sample showed fetal hyperthyroidism (TSH $<$ 0.008, fT4 4.03, fT3 9.92) while maternal TSH-R-ABs were elevated ($>$ 40 mUI/mL). Unfortunately, fetal death occurred before knowing the results and antithyroid drugs could not be started. As far as we know, this is the second reported case of TSH-R-ABs-induced fetal thyrotoxicosis in an AH woman.
Conclusion
TSH-R-ABs plasma determination should be mandatory in pregnant women with any previous autoimmune thyroid disease and fetal goiter or thyrotoxicosis. Antithyroid drugs should be started as soon as fetal hyperthyroidism is suspected.

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GP239

Renal cell carcinoma metastasis to thyroid tumor: a case report

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Introduction
Subacute thyroiditis (SAT) association with papillary thyroid carcinoma (PTC) has been rarely reported in the literature. Metastatic neoplasms to the thyroid are rare in clinical practice. Renal cell carcinomas (RCC) are the most frequent site of origin of thyroid metastases (12 to 34%). Tumor-to-tumor metastases, in which a thyroid neoplasm is the recipient of a metastasis, are exceedingly rare. Tuberous sclerosis (TS) is associated with several renal manifestations (80–85% of the patients) including angiomyolipomas (AMLs) (80%), renal cysts (30%) and RCC (2–4%)
Case report
A 19-year-old male, with personal history of TS, presented in the emergency department complaining of edema, jitteriness and pain in cervical region. SAT diagnosis was established based on complaints, physical examination and laboratory results. After the resolution of SAT, thyroid ultrasonography (US) revealed 2 suspicious nodules. The major nodule was submitted to fine needle aspiration cytology and the report was suspected of malignancy. Total thyroidectomy was performed. Postsurgical pathology evaluation showed a bilateral PTC/follicular variant (pT3N0). Within the PTC were a few nests of a morphologically distinct neoplasm. Immunoperoxidase stains of these cells were positive for CK8/18 and CK7 and were negative for thyroglobulin, calcitonin, vimentin, CK20, CD10 and racemase thus suggesting metastases of RCC. The body CT showed bilateral renal lesions likely to be angiolipomas without distinctive criteria. Suspicious lesions in the liver, lungs and bones were also reported without uptake in a 18F-FDG PET-CT.
Conclusion
This case illustrates an extremely rare occurrence of tumor-to-tumor metastasis where the recipient was a PTC and the donor likely to be an occult RCC.

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GP240

Giant goiter with intrathyroid arteriovenous fistula as a cause of severe pulmonary hypertension

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Introduction
Hyperthyroidism has been described as a rare cause of pulmonary hypertension (PH) as well as systemic arteriovenous fistulas. However, we describe a case of pulmonary hypertension secondary to an intrathyroid arteriovenous fistula, not previously described in the literature.

Case report
A 56 year old woman followed in our consultations with multinodular goiter and a long standing hyperthyroidism, secondary to Graves Basedow disease with difficult management. She required methimazole and low doses of levothyroxine simultaneously to achieve hormonal control, needing multiple admissions for heart failure (HF). In her last admission to Cardiology, she had right HF stage III-IV of NYHA, and physical examination revealed grade III goiter with murmur auscultation and thrill palpation. The blood tests revealed that she was euthyroid. The echocardiogram showed dilatation of both ventricles, ejection fraction 57%, moderate-severe biauricular dilatation, moderate mitral and tricuspid insufficiency, PAPs 73 mmHg. Cervical thoracic CT evidenced large multinodular goiter with intrathoracic extension and tracheal compression, multiple hypervascular nodules and cervico-vascular venous congestion. Right cardiac catheterization showed moderate precapillary PH with high saturations in the venous territory explored and cardiac output 8.1 l/m. These findings were consistent with the diagnosis of PH secondary to intrathyroid arteriovenous fistula. Definitive treatment was made by performing total thyroidectomy. The pathologic study of the piece was reported as multinodular thyroid goiter ($12 \times 13 \times 5$ centimeters and 140 grams) with signs of diffuse hyperplasia and arteriovenous fistula. Two months after surgery the patient had improved her functional class and the PAPs had decreased to 30 mmHg.
Conclusions
This is the first case described in which pulmonary hypertension is secondary to an arteriovenous fistula in a giant goiter. Surgery was a successful treatment, and one year after, the patient has a disease free survival.

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GP241

Thyroid-related adverse events in patients treated with Nivolumab

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Introduction
Nivolumab is an antibody that binds to and blocks the activation of programmed-death-receptor 1(PD-1), promoting the activation of T-cells against tumor cells. Thyroid dysfunction (TD) is one of the most common immuno-related adverse events, with incidence up to 10% in patients treated with PD-1/PD-L1 blockade.
Objective
To report our experience of Nivolumab-TD in patients with advanced cancer.
Methods
All patients diagnosed of nivolumab-induced TD during 2016 were included. Data from thyroid function tests, autoimmunity and imaging study before and during nivolumab therapy were recorded.
Results
Twelve cancer patients (5 lung, 4 melanoma, 3 Hodgkin lymphoma) were evaluated. 75% women, mean age: 56.7 year (19–77). Ten patients were treated with nivolumab 3 mg/kg (with or without chemotherapy) every 15 days, 2 patients received combined immunotherapy (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg). Three patients had previously well-controlled thyroid disease (1 overt primary hypothyroidism, 2 subclinical hypothyroidism). Baseline serum TSH and free thyroxine were evaluated in eleven patients, being normal in ten whereas one showed minimal subclinical hypothyroidism. During follow-up, 7 patients (58.3%) developed hyperthyroidism (4 overt and 3 subclinical). Six of them after cycle(C) 2, and 1 after C3. Thyroid antibodies were positive in 3 patients. One overt hyperthyroidism was treated with high dose steroids (prednisone 0.8 mg/kg per day) and nivolumab was temporarily withdrawn. Four of seven hyperthyroid patients became hypothyroid later, needing levothyroxine. Primary hypothyroidism occurred in 5 patients (41.7%) (3 overt and 2 subclinical), between C4-C7. Autoimmunity was positive in 3 hypothyroid patients. No patient discontinued nivolumab due to hypothyroidism.
Conclusions
In our series, hyperthyroidism is more frequent and appears earlier than hypothyroidism. A pattern consistent with a transient thyroiditis followed by hypothyroidism is seen in one-third of patients. Monitoring thyroid function at baseline and before each therapeutic cycle is warranted to detect and treat TD promptly.

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GP242

False negative fine needle aspiration thyroid cytology: an institutional experience

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Introduction
Fine needle aspiration cytology (FNA) is the most accurate diagnostic method for thyroid malignant nodule diagnosis. According to the literature, the percentage of false negative results (FN-FNA) is less than 1.5%, in tertiary health care centers. In this study we describe the cases reported in this Hospital, between 2014 and 2016, of benign cytology, histologically characterized as malignant. All pathologic specimens were reviewed.
Results
From a total of 299 benign FNA cases submitted to surgery, 6 cases with malignant histopathology were detected (2.0%). FN-FNA was identified in 5 males and 2 females, with ages ranging from 42 to 72 years old. The nodules size varied between 41 to 95 mm.
The ultrasound malignancy risk was between 5 and 20% (ATA 2015 Risk Stratification System).
The benign FNA were described as hyperplasic nodule in 3 cases, cystic hyperplasic nodule in 1 case, cystic colloid nodule in 1 case and colloid nodule in the remaining.
In all the cases the histological diagnosis was of follicular variant of papillary carcinoma, with macrofollicular areas, either predominant or focally, and with a heterogeneous distribution of the distinctive nuclear features of papillary carcinoma.
Four patients were recommended for radioiodine therapy. One of these patients was diagnosed with pulmonary and bone metastases.
Four patients were available for follow-up (mean time = 1.5 years; 9–24 months). There is no imaging evidence of disease in any of the patients.
Conclusions
In our institution, the percentage of FN-FNA was 2.0%, in accordance with that described in the literature.
The ultrasound risk assessment did not significantly change the risk assessed by FNA.
In all the cases the histological diagnosis was follicular variant of papillary carcinoma. The presence of macrofollicular areas, cystic areas and a heterogeneous expression of the typical nuclear features of papillary carcinoma may explain the occurrence of FN-FNA.

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GP243

Risk factors associated with malignancy in thyroid nodules classified as Bethesda category IV (follicular neoplasm/suspicious for follicular neoplasm)

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Background
Thyroid nodules diagnosed as Bethesda category IV (follicular neoplasm/suspicious for follicular neoplasm (FN/SFN)) are recommended for surgery. However, only 25% of these nodules turn to be malignant on histopathology. Therefore, selection of nodules for surgery diagnosed as Bethesda category IV is important. We aimed at to define the predictive factors for malignancy and predictive risk indices for selection of surgery.
Method
The records of all patients with nodules that underwent fine needle aspiration biopsy (FNA) and classified by Bethesda reporting system as FN/SFN between 2011 and 2017 at our institution were reviewed. Univariate and multivariate analysis were performed to select independent factors associated with thyroid cancer. Using independent risk factors for malignancy predictive indices were created.
Results
Among 6,217 nodules which underwent FNA, 163 (2.6%) were diagnosed as FN/SFN. Of the 163 patients classified as FN/SFN, 126 underwent surgery with an associated malignancy rate of 36% (45/126). Age under 45, solid structure, microcalcification, hypoechogenicity and increased vascularization were found to be significant and independent risk factors associated for malignancy. The risk

indices were created by classifying nodules with 0, 1, 2, 3, and ≥4 risk factors as risk indices 0, 1, 2, 3, and 4. There were 17 (14%), 41 (33%), 27 (21%), 22 (17%), and 19 (15%) patients in risk indices 0, 1, 2, 3, and 4, respectively. The estimated malignancy risk in patients with 0, 1, 2, 3, and 4 risk indices were 0% (0/17), 12% (5/41), 26% (7/27), 64% (14/22), and 100% (19/19), respectively.
Conclusions
Using predictive factors for malignancy in Bethesda IV category a small, but important proportion of patients 14% who had nodules without any risk factors could be spared unnecessary surgery. Predictive indices should be considered for informing the patients about the malignancy risk and for selection of surgery in Bethesda IV category.

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GP244

Expressions of miRNAs and BRAF^{V600E} mutation detection in papillary thyroid carcinoma

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Introduction
Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy. For the majority of patients with PTC, the prognosis is very good; however, up to 20% of patients suffer disease recurrence. Currently, the risk stratification for PTC recurrence is based on clinicopathological features which have limited prognostic value. Identification of molecular biomarkers of PTC recurrence such as protooncogene BRAF and miRNAs may help to improve risk-stratified patient management.
Objective
The aim of this study was to detect BRAFV600E mutation and identify miRNA biomarkers for PTC recurrence.
Methods
We selected 3 miRNA (miRNA- 146b, -222 and -21) and measured the expresion levels of these miRNAs in patients with recurrent PTC (Rc-PTC) and without recurrence (NRc-PTC). 106 NR-PTC and 60 Rc-PTC FFPE samples were analysed for selected miRNAs. 114 FFPE PTC samples (31 Rc-PTC and 83 NR-PTC) were analysed for BRAF^{V600E} mutation.
Results
The expression levels of all three miRNAs were significantly increased in PTC when compared to healthy thyroid tissue. miRNA-146b expresion was extremely elevated with 55.6-fold over-expression in PTC ($P<0.001$). miRNA-222 and -21 were over-expressed 13.8-fold and 3.7-fold, respectively ($P=0.001$ and $P=0.16$). In Rc-PTC and NRc-PTC groups miRNA-21, -146b and -222 were significantly differently expressed with 1.4- fold ($P=0.006$), 1.8-fold ($P=0.007$) and 2.1-fold ($P<0.001$) higher expresion in NRc-PTC compared with Rc-PTC tissues. 114 FFPE PTC samples were analysed for BRAF^{V600E} mutation and 66 of them (57.9%) were shown to be positive. Subsequently, DNA samples from Rc-PTC and NR-PTC groups were analysed for BRAF^{V600E} mutation and this mutation was found in 54.8% (17/31) of Rc-PTC samples and 59.0% (49/83) of NR-PTC samples. There was no signifficant difference between these groups ($P=0.686$).
Conclusion
These results suggest that miRNA-21, miRNA-222, miRNA-146b might be potential biomarkers for PTC recurrence. BRAF mutation is not associated with PTC recurrence.

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GP245

A statistical, in silico model predicts polygenic thyroid cancer risk

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Introduction
The detection of a unique genetic marker is not possible for multifactorial diseases, such as thyroid cancer (TC), where the pathological phenotype is given by the contribution of multiple genes, environmental factors and lifestyle. We found a mathematical model for inferring the risk of thyroid cancer, an example of multifactorial disease.
Methods
Genetic data represented by 184 SNPs associated to thyroid tumors were used for Bayesian clustering of 2504 individuals from the 1000 Genomes database, by STRUCTURE software. Numerical values representing the inferred genetic structure of each individual is provided in the output file of the software and were matched with environmental and lifestyle parameters associated to thyroid functions, i.e. iodine exposure and obesity, by principal component analysis (PCA). Data analysis was performed using labels such as geographic origin of individuals, population, sex and thyroid cancer incidence.
Results
We found that seven thyroid tumor-related genetic clusters are differently represented among human populations. The matching of genotype, iodine and obesity data resulted in individuals' gradient distribution by thyroid cancer incidence, revealing that all these components are required to infer the disease risk. Genetic background and, to a lesser extent, environmental factors and lifestyle, are not related per se to a specific range value of cancer risk. An exception is provided by individuals from Tuscany, Italy, which deviates from the overall distribution, preserving high cancer risk independently from obesity or iodine. This could result from a peculiar genetic setting or from the exposure to environmental factors not considered in the analysis.
Discussion
We demonstrated that TC risk may be detected a priori by applying polygenic model to specific population or individuals.
Conclusion
This study provides a novel mathematical approach to infer the polygenic disease risk, as a promising diagnostic tool for personalized medicine.

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Eposter Presentations: Adrenal and Neuroendocrine Tumours

Adrenal Cortex (to include Cushing's)

EP1

Confirmatory tests for diagnosis of primary aldosteronism among Chinese hypertensives

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Objective
Primary aldosteronism (PA) has emerged as the most frequent form of secondary hypertension. For the diagnosis of PA, confirmatory testing is indispensable and different tests are recommended by guidelines, including captopril challenge test (CCT) and saline infusion test (SIT). However, there are sparse studies evaluating and comparing CCT and SIT in Chinese population. Hence, we investigate the diagnostic efficiency of CCT and SIT for PA in Chinese hypertensives in our study.
Methods
In total, 183 patients with essential hypertension and 105 patients with PA were recruited in the study, and their clinical data were analyzed by constructing the receiver operating characteristics (ROC) curve to compare the accuracy of CCT and SIT.
Results
(1) A total of 277 patients underwent CCT. The AUC of post-CCT aldosterone, aldosterone suppression rate and post-CCT aldosterone/renin ratio (ARR) were 0.877 (95% CI 0.833 to 0.921, $P<0.001$), 0.683 (95% CI 0.617 to 0.748, $P<0.001$) and 0.929 (95% CI 0.896 to 0.963, $P<0.001$), and accuracy of ARR post-CCT is highest ($P<0.001$). For post-CCT ARR, at the optimal cut-off value of 30 ng•dl-1/ng•ml-1•h-1, the sensitivity and specificity were 67.6% and 96.2% respectively. (2) The SIT was performed in 116 patients. The AUC of post-SIT aldosterone and post-SIT ARR were 0.829 (95% CI 0.731 to 0.928, $P<0.001$) and 0.923 (95%CI 0.860 to 0.985, $P<0.001$), and post-SIT ARR has higher accuracy ($P<0.05$). The best cut-off value of post-SIT ARR for identifying PA was 60 ng•dl-1/ng•ml-1•h-1, with sensitivity and specificity of 81.8% and 95.2%, respectively. (3) 110 patients underwent both CCT and SIT. In the consistency check of CCT and SIT, kappa value was 0.714, $P<0.001$. The AUC of post-CCT ARR, post-SIT ARR, serial test of post-CCT ARR and post-SIT ARR were 0.937 (95% CI 0.885 to 0.990, $P<0.001$), 0.921 (95% CI 0.858 to 0.984, $P<0.001$) and 0.939 (95% CI 0.881 to 0.881, $P<0.001$), there is no statistical difference among the three indices.
Conclusions
With a good consistency, CCT and SIT are both efficient confirmatory tests for PA, and applying ARR post-CCT or ARR post-SIT make it feasible to diagnose PA more accurately. However, combining two tests fails to further improve the accuracy for diagnosis of PA.

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EP2

The correlation of salivary cortisol values with serum cortisol values

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Aim
The aim of the study was to evaluate the correlation between salivary and serum cortisol values to the healthy people and patients with Cushing's syndrome.
Methods
33 cases: 21 healthy people aged 22 to 53 years old; 12 patients with Cushing's syndrome values were included to our study. All the participants of control group were healthy without known disease. Two samples of salivary and serum cortisol was taken to all the participants of the study in the morning and in the midnight. All the subject respect the rolls of salivary collected samples.
Results
The mean age of the healthy subjects was 31 ± 4.8 years old. Basal salivary cortisol was significantly correlated with serum salivary cortisol in the morning and at the midnight; $P<0.05$ in the morning and $P=0.052$ at the midnight. Pearson coefficients were 0.45 in the morning and 0.42 at the midnight (2300 h). The sensitivity of salivary cortisol values in diagnoses of Cushing's syndrome was 100% for cut off values 2.18 ng/dl and for cut off values 3.14 ng/dl the sensitivity was 100% and specificity 83%. ACU 0.97.
Conclusions
In our study we found a correlation between salivary and serum cortisol values in both samples, at the morning and at the midnight to all participants; in healthy people, patients with Cushing's disease.

Keywords: salivary cortisol; serum cortisol; correlation
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EP3

Adrenocortical virilizing tumor in an adult woman in remission after surgical therapy performed more than 12 years ago

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Introduction
Adrenocortical carcinomas (ACCs) are rare, frequently aggressive tumors. Pure virilizing carcinomas are infrequent, constituting 5 to 10% in most series.
Clinical case
A 36-year-old female consults for 5 years evolution of amenorrhea associated with hirsutism attributed to polycistic ovary syndrome (PCOS) and treated with oral contraceptives during the previous 2 years. There was no other data on virilization, changes in body weight, hypertension or gastrointestinal symptoms. In the biochemical exam the following were observed: total testosterone 405 ng/dl (15–110), free testosterone 26.9 pmol/l (0.19–8.9), DHEA-sulphate 1000 µg/dl (35–430), FSH 2.9 mU/ml and LH 11.4 mU/ml. Basal and urinary cortisol, prolactin, beta-estradiol, 17-OH-progesterone, thyroid, hepatic and renal function, ions, were normal. The response to LHRH and ACTH and ovarian ultrasound were compatible with PCOS and ruled out late onset congenital adrenal hyperplasia. The imaging tests showed a solid adrenal mass in the left $10\times13\times14$ cm, with prominent vascular structures inside it, which were embolized prior to surgical excision performed by bilateral subcostal laparotomy. The histological diagnosis of the tumor which weighed 1.152 kg and measured $20\times12.5\times8.5$ cm, proved to be an adrenocortical tumor of low degree malignancy, without invasion of the capsule or adjacent tissues. Menstruation, hormonal tests and ovarian ultrasound became normal after surgery. The patient did not receive any therapy and the follow-up has not shown recurrence.
Discussion
Overall, survival is poor for ACC. Five-year survival is approximately 45–60% for early stage disease, and 10–25% for advanced stage disease. For patients with stage I to III disease, complete surgical resection as initial therapy is the only potentially curative treatment and open surgery remains the standard approach. Despite the large tumor size, the patient had a good prognosis based on the absence of invasion of the surrounding tissues, the histological grade of differentiation and the complete tumor resection. The interest of her case is due not only to the prolonged survival with an optimal quality of life, but also is a representative example of PCOS secondary to hyperandrogenism that disappears from the functional and morphological point of view after the suppression of its cause.

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EP4

Investigation of atrophic adrenal glands in Cushing's syndrome model rats induced by the administration of dexamethasone

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Cushing's syndrome is a disease caused by excessive glucocorticoids from adrenocortical tumors. In most cases, impaired adrenocortical function is likely caused by atrophy of the normal adrenal tissue as a result of chronic suppression by the low ACTH levels in the hypercortisolism state. Secondary adrenal insufficiency causes with surgical resection of cortisol-secreting tumors. Therefore, we thought that it was necessary to prepare Cushing's syndrome model rats for establishment of a new treatment method to promote improvement of the function of the remaining adrenal glands after adrenalectomy. Cushing's syndrome model rats have already been published and they describe changes in blood pressure and body weight. Regarding atrophy of tissues, it is considered that the atrophy of cells and the appearance of apoptosis are observed in such tissues. However, the weight and histological changes of the adrenal glands are not

described. In this study, we investigate ACTH, the ratio of adrenal cortex to medulla and number of apoptotic cells as evaluation of atrophic adrenal glands in dexamethasone-treated rats ($n=5$) compared to control rats ($n=5$). In the group treated with dexamethasone, an increase in blood pressure (135 ± 24 mmHg), suppression of plasma ACTH (20 ± 12 pg/ml) and the low serum corticosterone levels (7.5 ± 1.1 ng/ml) were observed as compared with the control group. In addition, adrenal gland weight decreased (13.6 ± 1.2 mg), and the low ratio of adrenal cortex to medulla and an increase of apoptotic cells were observed. Compared with control rats, dexamethasone-treated rats showed a significant decrease in hormonal secretory ability both endocrinologically and histologically. Our group is currently conducting experiments to investigate the levels of mRNAs for c-fos in adrenal glands as assessment of the recovery of adrenal atrophy.

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EP5

Long-term assessment of AddiQoL and patient diaries may identify Addison patients at high risk for adrenal crises

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Introduction
Several studies have shown a reduced quality of life (QoL) in patients with Addison's disease (AD). However, by now there are no data investigating the changes of QoL over a long-term course. Adrenal crises (AC) are frequent and potentially life-threatening complications in patients with AD. Since no reliable laboratory indicator can predict impending crises it is difficult to detect patients at increased risk. The purpose of this study was to test whether the repeated use of questionnaires for self-assessment over longer periods can detect possible prodromal periods of an AC.
Methods
137 patients with AD were included. They were asked to complete the disease specific-quality of life questionnaire AddiQoL once monthly over a period of ten months. In addition they also completed a short questionnaire about adverse events during the last month. AC was defined if at least two of the following symptoms were reported: a) hypotension, b) nausea or vomiting, c) severe fatigue, d) documented hyponatremia, hyperkalemia, or hypoglycemia, and subsequent parenteral glucocorticoid administration was carried out.
Results
110 patients completed the study by fulfilling at least 9 of the 10 required sets of questionnaires and not exceeding a time-lag over more than three months. Seven patients suffered an AC, resulting in 7.6 crises/100 patient years. AddiQoL scores in patients with adrenal crises showed a trend ($P=0.058$) to a wider fluctuation over the ten months. 19 Patients reported about severe adverse events not fulfilling the named criteria of AC. In these patients we found a significantly lower median ($P=0.017$) of the AddiQoL scores compared to patients not suffering a pre-crisis.
Conclusions
These are the first data showing the course of QoL during a period of ten months in patients with AD. Prevalence of AC lay by 7.6 per 100 patient years, in accordance with previous data. Our data show, that relevant medical adverse events in patients with AD are associated with a lower QoL. Furthermore, such events affect intraindividual AddiQol-scores over time with a trend to a stronger fluctuation. Long-term assessment of AddiQol and assessment of adverse events, e.g. via patient diaries, may be applied as an additional clinical tool to identify patients at risk for critical events.

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EP6

Impact of Cortrosyn treatment on weight and adrenal structure in the wistar rat

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The corticotropic hormone (ACTH) mainly secreted by the anterior lobe of the pituitary gland which, following a physiological or psychological stress situation, stimulates the adrenal gland and induces the release of glucocorticoids. Many studies have shown their effects on several physiological functions such as immunity, inflammation as well as the cardiovascular system whose action is controlled by ACTH. For this purpose, the study carried out in the wistar rat revealed the effects of a treatment with Cortrosyn (ACTH of synthesis) on the weight and the adrenal structure in the wistar rat. The work was carried out on a lot of rat wistar divided into two lots: one batch of control rat (T) and one batch of treated rat (S) receiving a daily intramuscular injection of Cortrosyn at the rate of 0.01 mg/100 g of weight Body for 20 days. After sacrifice of the animals, the adrenals are taken, weighed and immediately immersed in the fixing liquid in order to carry out the histological techniques. The results show that the intramuscular injection of Cortrosyn resulted in a very significant increase in absolute and relative adrenal weights in treated rats as compared to controls as well as an increase in the number of cells (hyperplasia), a different cell distribution and The appearance of optically empty space. These results to be investigated and could explain why the activation of the adrenal cortex during 20 days by the Cortrosyn would be in favor of an important structural and functional modification of the adrenal gland whose indirect trophic effect of this hormone could be regulated by several factors.

Keywords: Cortosyn; adrenal; ACTH

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EP7

Molecular variability determines subtle adrenal biosynthetic defect in non-classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency

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There is a clinical spectrum of non-classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency (NC-CAH). In addition, *CYP21A2* gene mutations analysis present in homozygosis or as compound heterozygosis.
Objectives
To evaluate the relationship between the genotype and biochemical profiles and also compare with clinical severity in NC-CAH.
Patients and methods
Clinical, hormonal and molecular data of 57 patients (47 female,10 male; 47 children,10 adults) with NC-CAH were retrospectively analyzed.
Results
The majority of children (76%) presented with premature pubarche at the diagnosis and 12% showed clitoromegaly. Among adult patients, hirsutism (90%) and menstrual abnormalities (66%) were observed at diagnosis. The basal and ACTH-stimulated 17OHP mean levels were 1115 ± 919 (97–4125) and 4245 ± 2059 (1115–10648) ng/dl. The most frequent mutation was p.V281L (68% of alleles) being 42% in homozygosis and 39% of the patients were compound heterozygotes for one classic and one non-classical mutation (C/NC).The severe mutations were p.I172N, IVS2-13A/C>G, Δ8, CL6, p.Q318X, p.R356W and LGC. Basal and ACTH-stimulated 17OHP values were higher in patients carrying the C/NC genotype group compared to NC/NC genotype (1549 ± 250 vs 806 ± 162; $P=0.01$ and 4740 ± 577 vs 3355 ± 345 ng/dl; $P=0.04$, respectively). Moreover, ROC curve analyses showed that the basal and ACTH-stimulated 17OHP levels of 610 and 3,913 ng/dl were the best cutoffs to identify NC-CAH patients carrying compound heterozygosis with severe mutations. We observed a higher DHEAS (182 ± 150 vs 85 ± 69 µg/dl, $P=0.03$) and a bone age advancement trend ($P=0.05$) in C/NC genotype group compared to NC/NC. There were no differences in age, height, weight, androstenedione and testosterone levels at diagnosis.
Conclusion
Although no phenotype difference was observed between NC/NC and C/NC genotypes, the present study showed graded severities of adrenal biosynthetic defect reflecting the molecular variability in NC-CAH.

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EP8

Corticoids-therapy related complications in patients with primary adrenal insufficiency

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Introduction
Patients with primary adrenal insufficiency (PAI) require lifelong corticoids replacement and they are at risk of therapy-related osteoporosis and cardiovascular complications.
Objectives
Determine the prevalence of cardiovascular risk factors, osteoporosis, and other toxicities related with corticoids treatment.
Material and methods
Retrospective, descriptive study in patients with PAI follow up in our service during the last 30 years. Information was collected from clinical histories.
Results
Identified 30 patients with PAI. *Clinical characteristics:* 21 were women, mean age at diagnosis of 36.72 ± 5.3 years and mean time since diagnosis 263.8 ± 57.5 months. Etiology: 15 (50%) autoimmune disease; 7 (23.3%) post-surgery; 5 (16.6%) congenital adrenal hyperplasia; 2 (6.7%) tuberculosis and 1 (3.3%) metastatic disease.
Steroid replacement: 26 (86.7%) used hidrocortisone (HC), 3 (10%) dexametasone, 1 (3.3%) prednisone. 25 patients were on treatment with fludrocortisone. Mean glucocorticoid dose (HC or equivalent): 20.58 ± 1.5 mg/day, mean fludrocortisone dose 0.066 ± 0.008 mg/day.
Possible therapy-related complications: 23(76.7%) patients developed at least 1complication during follow-up: osteoporosis 11(36.7%), dyslipidemia 10 (33.3%), prediabetes 8(26.6%), hypertension 7(23.3%), type 2 diabetes 6(20%), 1(3.3%) cardiovascular event. 88% patients with osteoporosis, 78.6% with diabetes or prediabetes, 85.7% hypertension and 70% with dyslipidemia used HC dose ≥ 20 mg/d.
Conclusions
Osteoporosis and cardiovascular complications are frequents in patients with PAI. Patients on treatment with higher corticoid dose are at risk of development therapy-related complication. Adjustment in corticoid to minimal necessary dose could prevent these complications.

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EP9

Severe hypertriglyceridemia in relation to toxic levels of mitotane in a patient with stage IV adrenocortical carcinoma (ACC)

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Introduction
The use of mitotane as ACC therapy is associated with multiple adverse effects including hypercholesterolemia due to increased levels of LDL cholesterol. There are no reported cases of severe hypertriglyceridemia (HTG).
Clinical case
A 59-year-old male with a personal history of dyslipidemia phenotype IV and pulmonary emphysema, former smoker and drinker was diagnosed with non-functioning left-sided ACC. Left adrenalectomy + left nephrectomy and subsequently right adrenalectomy and atypical segmentectomy of the upper right lung lobe due to the presence of metastases was performed. One month later, low-dose (2 g/day) mitotane therapy was initiated in combination with hydrocortisone and oral fludrocortisone replacement therapy. In the first post-mitotane control, triglycerides (TG) level which previously was 325 mg/dl increased to 953 mg/dl, coinciding with serum mitotane of 13.8 mg/l. Other factors that could increase it were overruled. Fenofibrate 145 mg/day was prescribed but in the following control TG were 880 mg/dl with serum mitotane of 14.3 mg/l. The dose of mitotane was then reduced to 1 g/day, its level dropped to 10.5 mg/l and TG were 939 mg/dl. Consequently ezetimibe 10 mg/day was added to the therapy and the mitotane dose was increased to 1.5 g/day and subsequently to 2 g/day because the level was very low and a 4.5 cm unresectable metastatic adenopathy that received radiotherapy appeared in the mediastinum. Coinciding with a mitotane level of 33.8 mg/l, the patient presented severe asthenia attributable to mitotane toxicity and TG of 1,528 mg/dl, without data of pancreatitis, what required a drastic decrease in the dose of drug. In the last review, the mitotane level was 6.7 mg/l, TG were 344 mg/dl, the symptoms disappeared and the mitotane dose was again raised while those of fenofibrate, ezetimibe, hydrocortisone and fludrocortisone remained the same.
Discussion
The presence and type of hyperlipemia prior to therapy is likely to affect the adverse effects of mitotane on lipids and in this patient, TG levels have varied according to mitotane doses and levels despite lipid-lowering therapy. On the other hand, dyslipidemia may induce an overestimation of plasma mitotane measurements, so it is necessary to closely monitor the lipid profile in all patients treated with this drug.

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EP10

Addison's disease presenting as severe hypoglycaemia and cachexia

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Addison's disease (AD), also known as primary adrenal insufficiency, is caused by destruction or dysfunction of the adrenal cortex, resulting in hypocortisolism. The usual clinical features of chronic AD are non-specific and include fatigue, nausea, vomiting and hyperpigmentation. We describe the case of a 58-year-old African black male with AD presenting with recurring severe hypoglycaemia. The patient was admitted several times to the emergency department with hypoglycaemia (blood glucose between 26 and 50 mg/dl) and loss of consciousness, managed with intravenous dextrose. These episodes were associated with anorexia, dizziness, fatigue and progressive weight loss over two years prior to presentation. His past history was significant for pulmonary tuberculosis, and there was no family history of note. Physical examination revealed a cachectic habitus, depressed mood and hyperpigmentation of palmar creases and oral mucosa. He had a body mass index of 14.9, blood pressure 98/57 mmHg and regular pulse of 64 bpm, with no other remarks on systemic examination. Biochemical analysis revealed Hb 11 g/dl, mild hyponatremia (134 meq/l), normokalemia (4.1 meq/l), hypoalbuminemia (32.4 g/l), and normal renal and hepatic function tests. Morning serum cortisol level was 2.3 μg/dl and ACTH 52.2 pg/ml, with normal levels of other pituitary hormones. ACTH stimulation test was performed and confirmed adrenal insufficiency. Computerised tomography scan of the abdomen showed normal shaped and sized adrenal glands. HIV screening was negative and there were no clinical or radiological signs of active tuberculosis. He started treatment with hydrocortisone and fludrocortisone, and his symptoms readily improved. This case illustrates an unusual presentation of Addison's disease and points out the need for a high index of suspicion so that morbidity and mortality can be decreased by a prompt diagnosis.

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EP11

Posterior reversible encephalopathy syndrome (PRES) in a patient with primary aldosteronism

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Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by varied neurological symptoms. There are two leading theories regarding the pathophysiology: hypertension crisis and endothelial dysfunction.
Case report
We report the case of a 42-year-old patient with history of hypertension. She presented to the emergency department with headache and bilateral loss of vision. She described one previous episode of witnessed generalised tonic-clonic seizure at home. She was found to have an elevated blood pressure (BP) of 210/105 mm Hg. An ocular examination revealed a diminished vision and perception of hand movement on both eyes. Laboratory findings were within normal range except for potassium, which was 2.7 mEq/l (normal range 3.5–5). Brain MRI showed bilateral posterior parietooccipital hyper densities in the cortex and subcortical white matter consistent with PRES. Antihypertensive therapy was started. The patient's headache rapidly resolved and her vision improved. The patient was discharged symptom-free on potassium supplements and antihypertensive therapy. After discharge the patient was referred to the Endocrinology service. Aldosterone concentration/plasma renin activity ratio was positive and the saline

infusion test confirmed the diagnosis of hyperaldosteronism. Abdominal MRI revealed a two-centimetre adenoma of the left adrenal gland. The patient underwent surgery to remove the adenoma. After surgery, hypokalemia and hypertension resolved.
Conclusions
Although primary aldosteronism (PA) is not included among the reported causes of PRES, it is important to consider its existence in PRES patients, particularly in those with hypokalemia. The occurrence of PRES in patients with PA might be independent of hypertension since the direct action of aldosterone on the mineralocorticoid receptor may cause endothelial dysfunction.

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EP12

Evaluation of cardiovascular risk in patients with adrenal incidentaloma

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Introduction
Recent studies indicate that patients diagnosed with adrenal incidentaloma may present with cardiovascular disease. The aim of this study was to investigate markers of subclinical cardiovascular disease in patients with adrenal incidentaloma and healthy control group.
Methods
This study included 50 patients with non-functional adrenal adenoma and 30 healthy controls. BMI and waist circumference of the patients were measured. The lipid parameters, glucose, insulin, C-peptide, erythrocyte sedimentation rate, fibrinogen, homocysteine, hsCRP levels and carotid intima media thickness were measured. HOMA levels of the patients were calculated.
Results
Patients with non-functional adrenal adenomas were compared with obese and non-obese control groups. Carotid intima media thickness and erythrocyte sedimentation rate levels of the patients with adrenal incidentaloma were significantly higher than the healthy controls. There was not statistically significant difference between lipid parameters, glucose, insulin, C-peptide, fibrinogen, homocysteine, hsCRP levels of the patients and control group.
Conclusion
In patients with nonfunctional adrenal adenomas the carotid intima media thickness, which is a cardiovascular risk indicator, was found to be thicker than the normal population. At the same time, erythrocyte sedimentation rate, another indicator of cardiovascular risk, was also higher in the adrenal incidentaloma group. These findings suggest that patients with adrenal adenomas have a higher risk for subclinical cardiovascular disease and close follow-up may be necessary.

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EP13

Hair cortisol in patients with primary aldosteronism

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Context
Primary aldosteronism (PA) is a common cause of secondary hypertension, and some PA adrenal tumors co-secrete glucocorticoids, causing subclinical or overt Cushing syndrome (CS). We recently reported correlations between hair cortisol concentration (HCC) and serum and urinary levels of cortisol in patients with CS.
Objective
To determine correlations of segmental hair cortisol and biochemical markers of a referred cohort of patients for the evaluation of PA and to compare to patients with normal cortisol secretion. This pilot study was conducted at the National Institutes of Health Clinical Center.
Methods
Hair samples were collected from 12 study subjects (four with PA, two with PA and cortisol co-secretion, and six controls), with mean age 40.1 ± 21.4 years, mean BMI 28.1 ± 5.3 kg/m^2. Diurnal serum cortisol and ACTH measurements, 24-h-urinary free cortisol corrected by body surface area (UFC/BSA) and 17-hydroxysteroids, corrected for creatinine (17OHS/Cr) were measured. Patients underwent step-wise diagnosis, with measurement of serum aldosterone and plasma renin activity followed by saline suppression and/or oral salt loading tests. Patients without PA or CS were excluded as controls, if midnight serum cortisol >1.8 μg/dl. Segmental hair samples from each patient were processed and analysed for cortisol according to the methods described by Meyer *et al*. (2014).
Results
Age, blood pressure, urinary and midnight cortisol levels were higher ($P<0.05$) in the PA group compared to the controls. Average hair cortisol values in the groups with PA and controls were 30.0 ± 31.0 pg cortisol/mg hair (median: 16.3 pg/mg; interquartile range: 12.6–37.4 pg/mg) and 22.9 ± 27.6 pg cortisol/mg hair (median: 11.3 pg/mg; interquartile range 7.9–26.6 pg/mg), respectively ($P>0.05$). No correlation between hair cortisol and serum and urinary markers of hypercortisolemia was seen in the six patients with PA.
Discussion
We found that no statistically significant difference in hair cortisol between groups and no significant correlation of hair cortisol with urinary or serum cortisol evaluations. We speculate that the lack of correlation may be due to insufficient power. More research is needed on the use of hair cortisol in patients with PA.

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EP14

Salivary steroid levels during diagnostic tests for adrenal insufficiency

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Diagnostic tests of the hypothalamic–pituitary–adrenal axis (HPA axis), measuring of free cortisol and use of other adrenal steroids are the subject of debate. We investigated 15 healthy men with mean/median age 27.4/26 (± 4.8) years, and mean/median BMI 25.38/24.82 (± 3.2) kg/m^2. All subjects underwent four dynamic tests of the HPA axis, specifically 1, 10, and 250 μg synacthen tests and an insulin tolerance test (ITT). Salivary cortisol, cortisone, pregnenolone, and DHEA were analysed using liquid chromatography-tandem mass spectrometry.
During the ITT maximum salivary cortisol levels of over 12.5 nmol/l were found at 60 min. Maximum cortisol levels in all of the Synacthen tests were higher than stimulation in the ITT. Cortisone reacted similarly as cortisol, i.e. we did not find any change in the ratio of cortisol to cortisone. Pregnenolone and DHEA were higher during the ITT, and their peaks preceded the cortisol peak. There was no increase of pregnenolone or DHEA in any of the Synacthen tests.
Our results indicate that a 10 μg Synacthen dose is a safe and cost-effective choice.
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EP15

Assessment of quality of life of patients with Cushing's syndrome depending on the disease course

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Aim of the study
To evaluate effectiveness of pituitary transsphenoidal surgery (TSS) in patients with ACTH-dependent Cushing's syndrome (ACTH-DCS) in Republic of Uzbekistan (RUZ).
Materials and methods
Patients who included in CS register monitored in 2015. All data from 2000 to 2015 analyzed including outpatient, inpatient examines, tests and treatment. To present, 158 patients with ACTH-DCS registered and monitored. Of these 158 patients, 41 males (26%) and 117 females (74%). Mean age of patient varied from 12 to 38 years old. Mean age was 26.38 ± 3.4 and 27.58 ± 3.4 years old for males

and females respectively. Duration of the condition varied from 4 months to 25 years. 73 patients who had TSS were evaluated in 1, 3, 6 and 12 months period of time and the every 3 months for the follow-up period. TSS was performed initially in 73 patients and in ten patients it was carried out after medical treatment.
Results
Of 158 patients, 86 patients (54%) had surgery including 73 cases who underwent TSS. Pituitary surgery performed as a monotherapy in 32 patients (44%) and in 41 cases (56%) patients received combination therapy. Of 73 patients who underwent TSS, in 60 cases (82%) patients had cured, while repeat surgery performed in ten cases (13.7%). After repeat surgery all ten patients (13.7%) had remission, however, four of them relapsed in 15 months in average. After TSS remission was achieved in 82% of patients who included 62 patients with microadenomas (84.9%) and 12 cases with macroadenimas (16.6%). After 3 years of follow-up five patients (6.8%) who had total hypophisisectomy procedure developed no relapse, whereas of 62 patients (84.9%) with selective adenomectomy and of six patients (6.8%) who had hemihypophysisectomy recurrent disease observed in 5 (8.1%) and 1 (16.7%) cases respectively while remission has not developed in 6 (9.7%) and 1 (16.7%) respectively ($P=0.03$).
Conclusion
Of 73 patients with CS who had pituitary surgery, remission observed in 60 patients (82%), whereas six patients (8.2%) relapsed and in seven cases (9.6%) remission has not developed. TSS remains as first treatment choice in CS and contributes to a steady remission in 82% according to our results.

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EP16

Paraneoplastic Cushing's syndrome and nephrotic syndrome in a patient with bronchial carcinoid

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Introduction
We report a case of Cushing's syndrome association with nephrotic syndrome in a patient with occult ectopic ACTH (EAS) secretion by a bronchial carcinoid and resolution of both disorders after bilateral adrenalectomy.
Case report
A 42-year-old man was admitted to our department with the suspicion of EAS. He was in a very good health until several months ago when he developed suddenly nephrotic syndrome, severe hypertension, severe hypokalemia, hyperglicemia and rapidly progressive the full blown picture of severe hypercortisolism: severe mental changes, muscle weakness, bruising, pigmented moon facies, no striae, distal muscular atrophy and weight loss. A renal biopsy showed podocyte foot process effacement and no inflammation/sclerosis; renal function was normal. Serum cortisol was frankly elevated and variable (21–97 μg/dl), because of the heavy and variable proteinuria (1.7–7.5 g/24 h), urinary free cortisol 37.071 nmol/24 h. Serum cortisol did not supress with both low -dose and high-dose dexamethasone and serum ACTH was high (238 pg/ml). A pituitary MRI was normal. Chest CT scan revealed a round subpleural nodule 8–9 mm in the right lung. SRS (111-indium-pentetreotide) and 18-FDG-PET CT scans were negative. Bilateral laparoscopic adrenalectomy was performed. Postoperative course was marked by sepsis and he was treated with antibiotics for three months. All the sign and symptoms of hypercortisolism gradually disappeared but the pigmentation remained; surprisingly the resolution of the nephrotic syndrome was noted. One year later he was in good clinical condition with adrenal replacement therapy. Chest CT scan confirmed the presence of a stable pulmonary nodule and he underwent thoracic surgery. A bronchial typical carcinoid tumour with positive immunostaining for ACTH was diagnosed. Postoperative course was uneventful.
Conclusion
This is a rare case of the association of severe occult EAS with nephrotic syndrome, which has been cured by the resolution of the severe hypercortisolism.

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EP17

Frequancy of diabetes and prediabetes in patients with adrenal incidentaloma without hormonal activity

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Aim of the study
Estimation of the frequancy of diabetes and prediabetes in patients with adrenal incidentaloma (AI) without hormonal activity.
Material and methods
The study comprised patients with AI without hormonal activity, verified by CT. The hormonal function of adrenal glands was determined according to the circadian rhythm of cortisol and/or dexametasone suppression test, ACTH, aldosterone, plasma renin activity, DHEAS, androstenedione, 17hydroxy progesterone, metanephrines in urine.
Physical examination included: the BMI, the waist circumference (norm <80 cm women, <94 cm men), blood pressure. The biochemical assays: fasting glycemia, OGTT (excluded patients with diabetes), fasting insulin and lipids level (total, HDL and LDL cholesterol, triglycerides).
Results
125 patients were examined, aged 61.3 ± 8.8 years, 72 (57.6%) women. Size of tumors were 27.6 mm ±15 mm. Carbohydrates disorders were observed in 62 (49.6%) persons aged 62.9 ± 7.5 years, including 32 (25.6%) women. Abdominal obesity was diagnosed in 87 (69.6%), 56 (44.8%) women and 31 (24.8%) men. Diabetes was regonised in 16 (13%) patients, IFG in 24 (19.2%), IGT in 34 (27.6%). The concentration of fasting insulin was $8.9+/-5.5$ μU/ml, higher in men then in women ($9.16+/-5.65$ vs $8.71+/-4.70$; $P>0.01$). The concentration of total cholesterol was 218 ± 49.7 mg/dl, HDL-cholesterol 59 ± 21.1 mg/dl, LDL cholesterol 134 ± 44.1 mg/dl, triglycerides 116 ± 60 mg/dl; 83 (66.6%) of the patients had been diagnosed positive for dyslipidemia or were administered hypolipemic medications. Additionaly arterial hypertension was diagnosed in 99 (79.2%) patients, with the arterial systolic BP 131 ± 15 mmHg, diastolic BP 80 ± 9 mmHg.
Conclusions
1) Diabetes was observed more often in patients with AI without hormonal activity then in the entire Polish population.
Patients with AI without hormonal activity are a risk group of prediabetes and diabetes.

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EP18

To big to work! Lymphoma presenting with primary adrenal insufficiency

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Background
Primary adrenal lymphoma (PAL) is a rare cause of primary adrenal insufficiency (PAI). Most often patients present with unspecific symptoms. Bilateral adrenal enlargement with signs and symptoms of PAI are clues, percutaneous biopsy after having excluded pheochromocytoma in a situation of high suspicion is diagnostic. Most of PAL are highly malignant B-cell lymphomas with a bad prognosis.
Case
A 71-year-old patient was sent for endocrine workup because of a 2-month history of intermittent dyspnea, thoracic discomfort, weight loss and abdominal pain. An ambulant CT scan to exclude pulmonary embolism showed bilateral adrenal enlargement (right $77\times31\times55$ mm, left $63\times38\times41$ mm, native 25-29HE), which were new compared to a CT scan done one year earlier. On clinical examination, the patient was orthostatic and in an im-paired general condition. He had hyperpigmented hand lines. Laboratory evaluation showed a slight hyponatremia (131 mmol/), potassium in the upper normal range (4.2 mmol/l), pathologic ACTH-stimulation test (peak cortisol level: 153 nmol/l) and elevated ACTH levels (231 ng/l, normal range <46 ng/l). Antibodies for 21-hydroxylase were negative, as well as free metanephrines in plasma, aldosterone-renin ratio was decreased (aldosterone 122 pmol/l, renin 39 mU/l). 17-hydroxyprogesterone was low (3.3 nmol/l, normal range 1.9–6.5 nmol/l). Quantiferon test was negative, and the CT scan did not raise suspicion for tuberculosis. We diagnosed PAI and started substitution with hydrocortisone (initial dose 50 mg/d) and

fludrocortisone (0.1 mg/d). Histology of a CT-guided needle biopsy revealed infiltration of a highly malignant B-cell lymphoma. The patient was sent for oncological evaluation and start of chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP).

Discussion

PAL is a rare manifestation of primary extranodal lymphomas (1/3 of all lymph node neoplasms, PAL < 1% of all extranodal lymphomas). Only about 100 cases are published in the literature worldwide. Conversely, secondary spreading of a lymphoma to the adrenals is quite common (in autopsy studies up to 25%). Other reasons for bilateral adrenal enlargement are adrenal hyperplasia (any cause), metastasis of lung, breast and stomach (>50% of metastasis), bilateral pheochromocytoma, adrenal hemorrhage, adrenal involvement with granulomatous diseases, histicytosis and primary pigmented nodular adrenal dysplasia (PPNAD). Symptoms of PAL are unspecific (asthenia, weight loss, vague abdominal pain, fever). Diagnosis is made by percutaneous biopsy. In nearly 70% of cases PAL are bilateral, causing primary adrenal insufficiency. Average age of affected patients is around 70 years. Most of PAL are diffuse large B-cell lymphomas with BCL6 gene rearrangement and poor prognosis, as in our case. Therapy consists of R-CHOP.

Conclusion

Patients with bilateral adrenal enlargement and PAI need immediate replacement of glucocorticoid (including instructions about dosing in stressful situations) and mineralocorticoid hormones. While PAL is rare, it has a poor prognosis, thus rapid induction of treatment is necessary.

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EP19

Specificity of the posture test for subtyping of primary aldosteronism, a 10 year nationwide summary in Iceland

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Introduction

The posture test (PT), developed to distinguish idiopathic adrenal hyperplasia (IAH) from aldosterone producing adenoma (APA), has been postulated as inaccurate. In 2007, standardized diagnostic methods, including PT for subclassification, were introduced in Landspitali University Hospital (LUH), housing the only endocrine department in Iceland. The aim of this study is to review the results of PT performed in LUH in 2007–2016.

Methods

Charts for all patients ≥18 years old, diagnosed with primary aldosteronism (PA) during 2007–2016 in LUH, were retrospectively reviewed. After screening, verification of PA was made with saline infusion test. During PT, s-aldosterone, s-renin and s-potassium were measured after a 10-h bed-rest and again after subsequent 4-h upright-position. If s-aldosterone increased by >50%, the test was considered positive. Thereafter, patients underwent a CT-scan and adrenal venous sampling (AVS). Adrenalectomy was offered if PA was found unilateral by AVS.

Results

Out of 49 PA-patients undergoing PT during the period, 22 had unilateral disease and 27 bilateral. The unilateral group (UG) consisted of 14 patients with APA and 4 with IAH. Three are awaiting surgery and one histopathological examination was inconclusive. Average increase of s-aldosterone during PT in the bilateral group (BG) was 217±127%, significantly higher than 88±26% in the UG ($P=0.008$). A greater proportion of the BG had a positive PT, 81% (22/27) versus 55% (12/22) of the UG, $P=0.04$. Positive predictive value of the PT with regards to bilateral disease was 0.65 (22/34), sensitivity 0.81 (22/27) and specificity 0.45 (10/22).

Conclusions

In this nationwide study we found the PT to have fairly high sensitivity but low specificity in subclassifying PA, supporting previous reports of inaccuracy. Although the PT is not conclusive, it could be informative in addition to CT-scan for treatment decision if a patient is unable to undergo AVS for practical reasons.

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EP20

Cofilin is a cAMP effector in mediating actin cytoskeleton reorganization and steroidogenesis in mouse and human adrenocortical tumor cells

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The cAMP signaling pathway plays a major role in the pathogenesis of cortisol-producing adrenocortical adenomas (CPA). In adrenocortical cells cAMP induces dramatic changes in cell morphology accompanied by actin cytoskeleton rearrangements that precede steroidogenesis, the causal relationship between these events being still undefined. In this study we investigated cAMP effects on cytoskeleton rearrangements and steroidogenic response in mouse (Y1) and human adrenocortical tumor cells, focusing on the role of the actin-severing protein cofilin, whose inactivation is regulated by phosphorylation on Ser3. Moreover, we tested possible alterations in cofilin phosphorylation status and expression in human CPA vs endocrine inactive adrenocortical adenomas (EIA). We demonstrated that forskolin induced cell rounding and reduced phosphorylated (P)-cofilin/total cofilin ratio in Y1 (−52±16%, $P<0.001$) and primary human CPA cells (−53±18%, $P<0.05$). Cofilin silencing in Y1 cells reduced both forskolin-induced morphological changes (37±8% rounded cells vs 63±7% in control cells, $P<0.05$) and progesterone production (1.3-fold increase in silenced cells vs 1.8-fold in control cells, $P<0.05$), whereas transfection of wild type or S3A (active) cofilin, but not S3D (inactive) cofilin, potentiated forskolin effects on cell rounding (80±6% and 85±14% rounded cells, respectively, vs 69±6% in control cells) and increased about threefold progesterone synthesis with respect to control cells ($P<0.05$). Furthermore, cofilin dephosphorylation by Y27632, a selective inhibitor of ROCK, the kinase that phosphorylates cofilin, potentiated forskolin induced cell rounding (about 90% rounded cells) and steroidogenesis (about twofold increase vs forskolin alone).

Finally, western blot analysis showed a reduced P-cofilin/total cofilin ratio and an increased total cofilin expression in CPA vs EIA (P-cofilin/total cofilin ratio 0.76 and 2.44 respectively, $P<0.05$, total cofilin/GAPDH 1.20 and 0.54, respectively, $P<0.01$).

Overall, these data identified cofilin as a mediator of cAMP effects on both morphological changes and steroidogenesis in mouse and human adrenocortical tumor cells.

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EP21

Primary Aldosteronism in Iceland, nationwide results from 2012–2016

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Introduction

Primary aldosteronism (PA) is an important, potentially curable cause of hypertension (HT) with higher risk of cardiovascular events than essential HT. In 2007, a standardized PA work-up protocol was introduced in Landspitali University Hospital (LUH), housing the only endocrine department in Iceland. The aim of this study is to review characteristics, test results and histopathology for patients diagnosed with PA in 2012-2016 in LUH.

Methods

Charts for PA-patients aged ≥18, diagnosed in 2012–2016 in LUH, were retrospectively reviewed. Screening was considered positive if s-aldosterone and/or 24-h urinary aldosterone excretion was increased and s-renin decreased. Diagnosis was confirmed if s-aldosterone increased by >140 pmol/l on saline

infusion test (SIT) performed by a 4-hour intravenous infusion of isotonic saline, 500 ml/h. Thereafter, patients underwent a CT-scan and adrenal venous sampling (AVS) for distinguishing unilateral (UD) from bilateral disease (BD). Adrenalectomy was offered if UD was diagnosed.

Results

Thirty-six patients were diagnosed with PA during the period; 19 males and 17 females. All had s-aldosterone >300 pmol/l on morning screening and 12 had an elevated 24-h urinary aldosterone ($n=23$). Median (range) s-aldosterone after SIT was 311 pmol/l (202-1715). By the end of 2016, 10 had a confirmed UD (32%), 21 BD (68%) and 5 were awaiting AVS. Six out of 10 UD underwent adrenalectomy by the end of 2016 and all had a cortical adenoma on histopathological examination. CT-scan showed unilateral adrenal nodule in 15 patients, 8 of whom had UD by AVS on that same side (positive predictive value 0.53).

Conclusions

This study indicates that PA is an important cause of HT in Iceland with equal gender distribution. Bilateral hyperplasia proved to be a more frequent cause than cortical adenoma which is consistent with prior Icelandic results from 2007–2011. Interestingly, no-one was diagnosed with unilateral hyperplasia during the study period.

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EP22

Cardiovascular risk factors do not play a role in the risk factor profile of adrenal crisis

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Introduction

Adrenal crises (ACs) are life-threatening events in patients with primary (PAI) or secondary (SAI) adrenal insufficiency, occurring ~4–10 times per 100 patient-years. Major causes of ACs are infections, especially gastroenteritis and tonsillitis/laryngitis. Risk factors for ACs remain ill defined, but could include concomitant endocrine diseases (diabetes mellitus, premature ovarian failure) in PAI, diabetes insipidus in SAI, and concomitant non-endocrine diseases (obesity, asthma, cancer, and cardiac and neurological diseases) in both groups.

Design

We analysed data from the European Adrenal Insufficiency Registry (EU-AIR; NCT01661387) with centres across Germany, the Netherlands, Sweden and the UK. Clinical and biochemical data at enrolment were compared for patients with frequent ($n\geq2$) and infrequent ACs ($n<2$) in each AI subset; 1969 patients were included (727 PAI, 1172 SAI) in the current analysis. Patients with congenital adrenal hyperplasia or tertiary AI were excluded.

Results

To November 2016, 27 patients with frequent ACs were identified (19 PAI, 8 SAI). The number of adverse events/patient was significantly higher in the frequent than the infrequent AC group in both subsets (PAI, 15.3 ± 14.0 vs 3.9 ± 6.5; SAI, 19.6 ± 18.5 vs 2.2 ± 4.3, respectively; $P=0.0024$). Patients with frequent ACs were more likely to be female (PAI, 78.9% vs 65.1%; SAI, 75.0% vs 47.9%), and less likely to have hypertension (PAI, 5.3% vs 21.0%; SAI, 25.0% vs 34.4%), with a lower BMI (PAI, 24.2 ± 4.7 vs 26.2 ± 4.9 kg/m^2; SAI, 26.0 ± 5.7 vs 28.7 ± 5.1 kg/m^2). There were no differences in daily glucocorticoid dose, frequency of diabetes mellitus, HbA1c levels, lipid profiles or use of statins. Interestingly, disease duration was shorter in patients with frequent compared with infrequent ACs in PAI (12.8 ± 13.2 vs 18.9 ± 14.5 years), whereas the opposite was true in SAI (15.6 ± 12.3 vs 13.8 ± 11.2 years).

Conclusions

Data suggest that known cardiovascular risk factors appear not to feature in the AC risk profile.

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EP23

Bilateral adrenal incidentaloma: a diagnostical and therapeutical challenge

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Incidentally discovered adrenal masses (incidentalomas) present challenges both in diagnosis and management. The bilateral adrenal mass carries a risk of hormone hypersecretion, but it could also present a metastasis from another primary carcinoma or be a part of genetic syndrome.

We report a 68 year old patient with bilateral adrenal incidentalomas (revealed accidentally on US, confirmed by abdominal CT in 2015.) left 29 mm, right 33 mm in diameter, radiological characteristics indicating adenoma. Initial diagnostical work up showed subclinical Cushing syndrome with osteoporosis and arterial hypertension as part of clinical presentation. One year later, abdominal CT showed significant enlargement of both adrenal masses (left 50 mm, right 45 mm), still adenomas according to CT characteristics, but post contrast imaging could not be performed due to chronic renal impairment. Her laboratory results were still consistent with subclinical Cushing syndrome, now presenting with osteoporosis, hypertension and glucose impairment with no signs of other excessive hormone secretion but now her chest x-Ray revealed a lesion in her left lung 27 mm in diameter of unknown etiology (although she mentioned lung tuberculosis in her youth). As she did not have any signs of metastatic disease and her tumor markers were normal we decided to perform left adrenalectomy to provide definite diagnosis. Histological finding confirmed adrenal adenoma and hormone reevaluation showed possible excessive cortisol secretion with osteoporosis, but now blood glucose was normal, and anti-hypertensive agents were discontinued due to normal blood pressure. There was no change in the size of the lung lesion on her chest X ray (6 months after) and no signs of metastatic lesions. Thoracic CT and bronchoscopy are planned.

While the initial diagnostic approach is similar to the unilateral incidentaloma, additional testing should be considered in the case of the bilateral adrenal mass and as oppose to unilateral incindentalomas surgery remains the mainstay of treatment in most cases.

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EP24

Are we missing patients with primary aldosteronism (PA) if we require both elevated aldosterone: renin ratio (ARR) and elevated aldosterone levels?

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Introduction

Although the Endocrine Society guidelines recommend using aldosterone: renin ratio (ARR) to screen patients for primary aldosteronism (PA), whether to include a cut-off for aldosterone levels remains controversial. In Singapore, most centres require both an ARR >550 (ng/dl)/(ng/ml per h) and aldosterone ≥15 ng/dl. However, it has been shown that patients with PA may have aldosterone levels <15 ng/dl, and also respond well to mineralocorticoid antagonists. We examined the prevalence of Asian patients with high ARR, and influence of including patients with unsuppressed aldosterone levels >5 ng/dl.

Methods

We determined the prevalence of patients with high ARR >550 (aldosterone, ng/dl; plasma renin activity, ng/ml per hr) in a multi-ethnic Asian population with hypertension being screened for PA in a single tertiary centre, and stratified them by aldosterone levels.

Results

A total of 786 patients were screened for PA from 2015–2016, with 219 of 786 (27.8%) patients having a high ARR. Amongst these 219 patients with a high ARR, 68 of 219 (31.1%) had an aldosterone levels ≥15 ng/dl, 51 (23.3%) had aldosterone levels 10-14.9 ng/dl, 60 (27.4%) had an aldosterone levels 5–9.9 ng/dl, and 40 (18.3%) had aldosterone levels <5 ng/dl. When both ARR> 550 and aldosterone ≥15 ng/dl are required, only 68 of 786 (8.6%) patients will proceed for confirmatory tests as per current practice. However, if all patients with ARR>550 and unsuppressed aldosterone levels ≥5 ng/dl are included, then 179 of 786 (22.8%) of patients should be considered for the diagnosis of PA.

Conclusion

Current practice of requiring a high aldosterone level in addition to a high ARR may underdiagnose patients with PA. However, potential benefit of working-up all patients with a high ARR has to be weighed against increased cost. A possible alternative would be a trial of mineralocorticoid therapy in these patients.

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EP25

Severe hypoglycaemic ketoacidosis in a patient with adrenal crisis

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We present a case of a 26 years old female who was rushed to hospital with 4 days history of abdominal pain, vomiting and dizziness. She also had one episode of diarrhoea. Further history revealed that she had lost 32 kilograms of weight over the last 18 months through diet and exercise. There were no signs suggestive of an eating disorder.

On examination she was peripherally cold, tachycardic (117/min), hypotensive (86/50 mmHg) and sweaty. Her Glasgow Coma Scale was 15. Her chest was clear and she had mild epigastric tenderness. She was fluid resuscitated with 0.9% sodium chloride. Blood test results: pH 7.01, pCO2 (3.2), pO2 (14.6), blood glucose (2.1 mmol/l), HCO3 (12), Na (126), K (5.6), ketones (7.6 mmol/l), urea 15.1 mmol/l and creatinine (79) and CRP (76). 10% Dextrose infusion was started. An adrenal crisis was suspected and she was commenced on IV hydrocortisone. A possible trigger was thought to be gastroenteritis. Her serum cortisol was 13 mmol/l, no baseline ACTH was checked. She remained hypotensive despite aggressive fluids and was subsequently transferred to ITU. Over the next 24 hours her blood pressure was maintained on inotropes however her acidosis was refractory to treatment (pH $<$ 7.2 after 8 hours). She was started on sodium bicarbonate 1.26%; however, the effect was not sustained as her pH continued to drop. Her ketones also remained high (5–6 mmol/l) despite a normal glucose (4–7 mmol/l). She was subsequently commenced on 5%Dextrose infusion to halt ketogenesis. Her HbA1c was 35 mmol/mol. Following 5% Dextrose infusions, her acidosis started to improve with normalisation of ketones. Learning points:

1. Adrenal crisis should be treated promptly
2. Euglycaemic or hypoglycemic ketosis can complicate prolonged starvation, vomiting and eating disorders, so detailed and collateral history is important
3. Although very rare, type 1 diabetes can be masked by adrenal insufficiency and present with euglycemic ketoacidosis. It should be considered in similar scenarios.

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EP26

Assessment of the hypothalamic pituitary adrenal axis in patients receiving adjuvant mitotane treatment after radical resection of adrenocortical carcinoma

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Mitotane, used in the treatment of adrenocortical cancer (ACC), is able to inhibit multiple enzymatic steps of adrenocortical steroid biosynthesis, potentially causing adrenal insufficiency (AI). Recent studies *in vitro* have also documented a direct inhibitory effect of mitotane at the pituitary level.

The aim of the study was to assess the hypothalamic pituitary adrenal (HPA) axis in patients receiving mitotane as adjuvant treatment after radical resection of ACC getting insights on how mitotane affects the HPA axis and looking for markers to assessing AI.

We prospectively enrolled 16 patients on adjuvant treatment with mitotane after radical surgical removal of ACC, who were on stable mitotane dose and cortisol replacement therapy for at least 6 months and were disease free at the time of evaluation. Patients underwent standard hormone evaluation and stimulation test with h-CRH. A group of 10 patients with Addison's disease served as controls for the h-CRH test.

At the time of the study, six patients had mitotane levels within the therapeutic range, one had levels $>$20 mg/l, while nine had levels $<$14 mg/l. The median dose of cortisone acetate was 62.5 mg daily. Basal serum cortisol was reduced in 14 patients, being undetectable in 7 of them, and in the normal range in only two patients (12.5%); one of them had low mitotane concentrations. Only a non-significant trend between mitotane dose and either serum or salivary cortisol was evident. We demonstrated a close correlation between CBG levels and plasma mitotane levels ($P=0.003$) and between serum cortisol levels and salivary cortisol levels ($P=0.005$), while ACTH levels were inversely correlated with the daily dose of cortone acetate ($P=0.006$). ACTH levels were significantly higher in the Addison group than in ACC patients, both in baseline conditions ($P=0.036$) than following CRH ($P=0.041$).

In conclusion, measurement of salivary cortisol did not add useful information for assessing AI in mitotane-treated ACC patients. Assessment of ACTH levels may be of some aid, since levels that are not frankly elevated may herald over-replacement. The observation of lower ACTH levels in ACC patients than in patients with Addison, both in basal conditions and after CRH stimulation, suggests that mitotane may play an inhibitory effect on ACTH secretion at the pituitary level. However, an effect of high-dose cortisol replacement should not be ruled out.

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EP27

Extra-gastrointestinal stromal tumor in the retroperitomeum which had difficulty in differential diagnosis with adrenal cancer

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Extra-gastrointestinal stromal tumors (EGISTs) in the retroperitomeum are extremely rare. A 44-year-old man was referred from a private clinic suspicious of an adrenal tumor that was incidentally detected by abdominal ultrasound. Computed tomography (CT) scan showed a retroperitoneal mass of 12 cm harboring a feeding artery from the left adrenal gland contiguous with the left adrenal gland, which enhanced heterogeneously on post-contrast imaging. By magnetic resonance imaging, the tumor demonstrated heterogeneous low intensity in T_1 weighted images and an extremely heterogeneous lesion composed of high and low signal intensity in T_2 weighted images. PET CT imaging with fluorine-18-fluorodeoxyglucose (^{18}F-FDG) demonstrated ^{18}F-FDG accumulation in the tumor in the early and late phase. Iodine-123-metaiodobenzylguanidine and iodine-131-adosterol scintigram did not detect any accumulation in the tumor. The results of all conducted serum and urinary examinations of adrenocortical hormone and catecholamine were within the normal range. Adrenalectomy was performed. Histopathological diagnosis of the tumor was GIST. Immunohistochemical findings revealed that the neoplastic cells were positive for c-kit and CD34 and negative for S100 protein, alpha-SMA, and desmin. Mitotic activity (2–3/50 high power field) and the labeling index for MIB-1 (about 3.2%) were low. The GIST was diagnosed as a high-risk tumor because its diameter was over 5 cm. We started imatinib 400 mg/day according to the Japan GIST guideline 1 month after operation.

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EP28

Perceptions of medical practitioners' management of addison's disease across Africa: an on-line survey

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Objectives

Addison's disease diagnostic and management challenges in Africa are not well documented. We aimed to identify the specific needs of patients with established Addison's disease, across Africa.

Methods

An online survey of a large pool of medical practitioners was undertaken. The questionnaire covered patient demographics, aetiology, therapy and limitations of diagnosis and treatment.

Results

Of the 36,203 recipients; 661 responded; 246 completed the questionnaire. 151 were actively treating Addison's disease. The total number of patients identified with Addison's disease in this study was 1134 (530 males; 604 females). The highest number were reported from South Africa (748; 66%). Majority of patients were in the age groups of 16-60 years with a slight excess of females (334 vs 403). Associations were reported with hypothyroidism in 15.3%, type 1 diabetes in 11.6%, pernicious anaemia in 6.5%, premature ovarian insufficiency in 4.6% and Graves' disease in 3.0%. Presentation in crisis was reported in 12.1% of cases, otherwise classical symptoms were seen fairly consistently. Over 60% of patients received hydrocortisone only and the remainder received combination of hydrocortisone and fludrocortisone. Fixed doses of steroid replacement were used by 35.3% of physicians, whereas 57.9% of respondents adjust doses on basis of body weight. Appropriate diagnostic investigations, proved to be the greatest

limitation in making the diagnosis, with 73.2% of responders relying on the combination of clinical grounds and compatible electrolytes alone and only 27.9% having access to an ACTH stimulation test. There were few therapeutic options available to the responders outside of South Africa, with overall, 53% indicating non-availability of medication and 58% not having access to a CT scan.
Conclusions
This first continent-wide survey highlighted some challenges in diagnosis and treatment of Addison's disease. Awareness and resources are required for timely recognition and optimal management of Addison's disease in Africa.
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EP29

Improved metabolic outcomes for patients with subclinical Cushing's syndrome treated with surgery: Ten year experience in a tertiary centre
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Introduction
Subclinical Cushing's syndrome (SCS) occurs in up to 12% of patients with incidentally found adrenal masses. Optimal management remains controversial. We report our experience of nine patients with SCS managed at our institution from 2007 to 2016.
Methods
All patients were referred for adrenal incidentalomas (AI) and had no discriminatory clinical features of Cushing's syndrome. SCS was defined using cortisol levels $>$ 138 nmol/l after overnight 1-mg dexamethasone suppression test and one additional abnormal biochemical test. ACTH was suppressed in all. Urinary free cortisol measurements were normal in the majority.
Patients and results
The median age of our patients was 53 years (range 36–63) and all but one were female. Mean size of the adenomas was $2.65 + 0.52$ cm. Majority of our patients had metabolic comorbidities of overweight, hypertension, glucose intolerance or diabetes and dyslipidemia. One patient initially followed up as a non-functioning AI developed SCS over 8 years of surveillance as her adenoma grew. Another patient had bilateral adrenal adenomas. All our patients underwent surgical resection. The patient with bilateral nodules underwent bilateral subtotal adrenalectomy. All but one required a period of postoperative corticosteroid support. Following withdrawal of steroids, there was observable median weight loss of 3.85 kg (0.5–10.7) compared to presurgical weight. Four patients had an improvement of their BMI category from overweight to normal. All six patients with hypertension had sustained improvement in their blood pressure: two became normotensive and the remainder had reduction of doses of antihypertensives. However there was no change to glycemic and lipid status.
Conclusions
In our small series of patients with SCS, surgical intervention resulted in improved metabolic outcomes. We therefore suggest that if patients are surgically fit, surgery should be considered for SCS.
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EP30

Severe hypoaldosteronism after unilateral adrenalectomy for primary hyperaldosteronism
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Introduction
Primary hyperaldosteronism is a known cause of arterial hypertension, classically with hypokalaemia. About 30–40% of the cases are caused by unilateral aldosterone-producing adenoma, and the recommended treatment is adrenalectomy. Hypoaldestoronism is an uncommon complication of unilateral adrenalectomy, but it can be life-threatening. We present a case of severe hypoaldosteronism after unilateral adrenalectomy for the treatment of primary aldosteronism.
Case presentation
A 66 years old male with long term hypertension on triple drug therapy, chronic kidney disease and persistent hypokalaemia was diagnosed with primary hyperaldesteronism. He had increased aldosterone – 3426 pg/ml (normal 34.7–275 pg/ml) and low renin – 4 uUI/l (normal 4.4–46.1 uUI/l). An elevated plasma aldosterone to renin ratio was compatible with diagnosis. A CT scan revealed a right adrenal nodule suggestive of adenoma (21×19 mm). He was submitted to laparoscopic unilateral adrenalectomy. Pathology confirmed an adrenal adenoma. At discharge, all anti-hypertensive drugs were suspended.
3 weeks after surgery he complained of asthenia, anorexia and diarrhea. Blood tests showed severe hyperkalaemia (7.8 meq/l), metabolic acidosis and acute renal failure (creatinine 4.2 mg/dl). The serum aldosterone was low (43 ng/dl) and renin (4.7 pg/ml) normal. We assume the diagnosis of hyporeninemic hypoaldosteronism and he was treated with fludrocortisone (0.1 mg id), sodium bicarbonate and fluids, with improvement in serum creatinine and normalization of potassium levels. 3 months after discharge he remained asymptomatic but fludrocortisone dependent, with stable potassium and creatinine levels and mild hypertension.
Conclusion
Despite uncommon, hypoaldosteronism after unilateral adrenalectomy is known to occur. Usually mild and transitory, it can also be severe, persistent and life-threatening. Long term hypertension and impaired renal function, both present in our patient, are associated with persistent disease. A close and regular follow-up is essential for earlier detection, especially in high risk patients.
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EP31

The role of CYP11B2 polymorphism in the pathogenesis of hypertension in patients with adrenal incidentaloma
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Background
Significant prevalence of hypertension in the world's population and its consequences tend to an intensive search for pathogenesis and etiology of this disease. Epidemic of hypertension is accompanied by an epidemic of adrenal incidentaloma and grows in direct proportion to patients age. Polymorphism of aldosterone synthase (CYP11B2) in -344th region of promoter seems to have much in common with hypertension and adrenal incidentaloma.
Aim
The aim of this study was to assess what role may play CYP11B2 polymorphism in the phenotype of hypertension with associated adrenal incidentaloma. In this study, the analysis of alleles and genotypes focused on incidence of adrenal tumour and impact on the number of antihypertensive medications required to proper control.
Subjects and methods
Study was performed on 106 hypertensive patients with diagnosed adrenal incidentaloma (HAI), on 44 hypertensive patients without adrenal incidentaloma (HWAI) and on 63 healthy individuals forming control group. Groups matched to each other in terms of age, gender. Related patients and those who suffered from disease that may falsely affect the results were excluded. Severity of hypertension was determined by number of antihypertensive medications used to control. The significance of differences between the groups was evaluated through chi-square and Student's *t*-test.
Results
TT genotype and T allel occurred significantly less frequently in HAI in comparison with Control Group (respectively: $P = 0.049$; $P = 0.04$). Patients with TT genotype needed more medication to control hypertension in comparison with CC genotype (3,080 vs 2,361, $P = 0.0439$). Lack of significant differences between HWAI to the rest groups.
Conclusions

- The presence of the C allele in the region of -344 aldosterone synthase promoter predisposes to adrenal tumour, the TT genotype reduced that risk.
- Hypertension in patients with CC genotype is less severe, regardless of its phenotype.

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EP32

Primary aldosteronism: more common than once thought: Two clinical cases
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Introduction
Estimated prevalence of hypertension (HT) in Portugal is 42%. It is a major risk factor for coronary heart disease and cerebrovascular disease, the leading mortality cause in Portugal. Primary aldosteronism (PA) was once recognized as rare cause of secondary hypertension and hypokalemia a condition present in all cases. Nowadays, prevalence of this condition is about 10% in HT patients, being the commonest form of secondary HT. Secondary forms of HT should be excluded in young patients, severe increase in blood pressure, sudden onset or worsening of HT, poor blood pressure response to drugs and organ damage disproportionate to the duration of hypertension.
Case 1
A 69 years old female with a past medical history of HT for the last 20 years, presented with poor blood pressure control on bisoprolol 10 mg *id* perindopril 10 mg *id* and nifedipine 30 mg ER *id* at outpatient department. She had normal electrolytes. Screening tests for PA revealed high plasmatic aldosterone and suppressed renin plasmatic activity with a ratio > 25 ng/ml per h. Diagnosis was confirmed after saline infusion test. CT adrenal scan suggested left adrenal diffuse hyperplasia.
Case 2
A 48 years old female presented at the emergency room complaining of severe headache and four limbs' muscle weakness. There was a past medical history of eclampsia and hypertension diagnosed at the age of 30, and euthyroid multinodular goiter. Labs revealed hypokalemia and she was started on oral KCl 600 mg *bid.* After electrolytes correction, she was screened for PA. High plasmatic aldosterone and low renin plasmatic concentration with a ratio > 3.8 was detected. Diagnosis was confirmed after saline infusion test.
Conclusion
PA is an important cause of secondary hypertension, with a higher cardiovascular event rate than essential hypertension. It is frequently underdiagnosed and a potentially curable form of hypertension.

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EP33

Rapid reduction in left ventricular mass in primary aldosteronism after treatment; a prospective cardiac MRI study

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Background
Primary aldosteronism (PA) patients have increased left ventricular mass (LVM) and increased cardiovascular morbidity compared with those with essential hypertension. Echocardiographic studies have demonstrated that adrenalectomy or spironolactone decreases LVM. The aim of the present study was to use MRI to assess both LVM and cardiac function before and during stress testing, at baseline and after treatment with adrenalectomy or spironolactone, compared with healthy subjects (HS).
Material and methods
Fifteen recently diagnosed PA patients and 24 age- and sex-matched HS performed a baseline cardiac MRI with a 3.0 Tesla scanner. Imaging was performed at rest and during stress-testing with adenosine 140 μg/kg per min. Short-axis images were used for quantifications of LVM and left ventricular volumes. A follow-up MRI was performed in 20 of the HS and 14 of the PA patients, at least one year after starting specific treatment.
Results
Nine patients (60%) had unilateral PA, the remaining bilateral ($n = 5$, 33%) or not representative ($n = 1$, 7%) adrenal vein sampling. The PA and HS did not differ in age or sex. PA patients had higher baseline blood pressure (BP) than the HS (median BP 138/90 vs 118/75, $P < 0.001$). At follow-up, 8/14 PA were adrenalectomized (median 18 months). The remaining 6/14 were on spironolactone (median 21 months). LVM at baseline differed significantly between the PA and HS groups (median 145 vs 97 g; $P < 0.001$). At follow-up, the PA group had a significant reduction in LVM (median -18 g, $P < 0.001$), but no difference in cardiac output (CO) response to stress compared with baseline (follow-up PA median stress CO/rest CO 1.4 vs baseline 1.5, $P =$ ns).
Conclusion
Cardiac MRI showed rapid reduction in LVM in PA after treatment with adrenalectomy or spironolactone. CO response to stress remained unchanged after treatment. Our results underline the importance of early diagnosis and treatment of PA.

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EP34

The treatment with dual release hydrocortisone in patients with adrenal insufficiency: correlation between change of the evening cortisol exposure time profile and change in metabolic profile, depression status and quality of life

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Conventional glucocorticoids (CGCs) are unable to mimic physiological cortisol rhythm in adrenal insufficiency (AI), resulting in increased metabolic morbidity and impaired quality of life (QoL). Non-physiological cortisol pattern and elevated evening cortisol levels may be responsible for the increased risk of metabolic disorders observed in AI patients under CGCs. Once daily dual-release-hydrocortisone (DR-HC), which better reproduces physiological daily cortisol profile, significantly improves metabolic parameters and QoL in primary AI (PAI) and secondary AI (SAI) patients. The aim of the current study was to evaluate cortisol profile and its impact on metabolism, depression status and QoL in PAI and SAI patients switched from CGCs, including cortisone acetate and immediate-release hydrocortisone, to DR-HC. Fourteen AI patients underwent daily cortisol sampling, at 3 h intervals, at baseline (CGCS treatment) and 12 months after switching to DR-HC. Mean cortisol (24 h, 7-7am) AUC was 15.61% lower with DR-HC than with CGCs. In particular, mean (7am-1pm) and (1-7am) were 15.61% and 2.1% higher whereas mean (1-7pm), (7pm-1am) and (7pm-7am) AUC were 18.8% ($P = 0.057$), 58.39% ($P < 0.001$) and 41.87% ($P = 0.004$) lower with DR-HC than with CGCs, respectively. After 12 months of treatment, DR-HC induced a significant improvement in waist circumference ($P = 0.002$), depression status ($P = 0.05$) and QoL ($P = 0.05$). Moreover, the change (Δ) in cortisol 7pm-1am and 7pm-7am AUC appeared significantly correlated with the change (Δ) in glucose 120' after load ($P < 0.005$), depression score ($P < 0.05$) and QoL score ($P < 0.05$). The change (Δ) in cortisol 7pm-1am AUC appeared also significantly correlated with the change (Δ in fasting insulin ($P = 0.045$) and HOMA index ($P = 0.045$). In conclusion, the switch from CGCs to DR-HC in AI patients induces a significant improvement of waist circumference, depression status and QoL, and a significant decrease of late afternoon, evening and night GC overexposure; this reduction is significantly correlated with the improvement in metabolic profile, depression status and QoL.

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EP35

Treatment of adrenal insufficiency with hydrocortisone dual-release formulation: glycometabolic profile and health-related quality of life

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Introduction
Treatment of adrenal insufficiency (AI) in the last years has been object of important changes due to the development of a dual-release preparation of hydrocortisone (Plenadren®). Hydrocortisone dual-release therapy contemplates a once-daily tablet that allows more closely mimicking the physiological circadian rhythm cortisol, thus avoiding overexposure.
Objective
The aim of the study was to value effects of Plenadren administration on the 24-h urinary free cortisol (UFC), the glycometabolic profile and health-related quality of life of patients with AI.
Methods and materials
We enrolled seven adults with secondary AI caused by panhypopituitarism (55.9 ± 3.6 years) and seven adults with primary AI (36 ± 6.2 years). We evaluated BMI, UFC levels, the glycometabolic profile and health-related quality of life (estimated by AddiQol questionnaire) before and 3, 6, 9 and 12 months after Plenadren administration. One patient dropped out the study for personal reasons.
Results
All patients, except one, reported a significant improvement of the quality of life after 3 months of treatment, whereas after 1 year everyone reported individual wellness. After 12 months of treatment, all parameters evaluated improved, though not in statistically significantly manner. The parameters for which there was evidence of a greater improvement were total cholesterol, low-density cholesterol and glycosylated hemoglobin levels.

Conclusions
The once-daily oral hydrocortisone dual-release therapy is a valid option for the treatment of patients with AI. It allows a good glycometabolic balance in the absence of side effects and improving compliance.

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EP36

Transformation from Addison's disease to adrenocortical carcinoma presented as Cushing's syndrome with androgenisation

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We present a female patient 56 years old, who was treated at the endocrinology department from the year 2006. The diagnosis of Addison's disease was established and she was properly treated. At the same time primary hypothyroidism was diagnosed, also started treating it properly. She was regularly controlled more often at the first time, than yearly at outpatient clinic. In September 2015 she was in menopause. A few months before she noticed oedematous legs and arms and diffuse bruising. Hypertension was also noticed for the first time and needed therapy. Her voice was different (became deep), she noticed hair loss and hirsutism, as well. She thought it was all in correlation with menopause. At the control examination she had hypokalemia, hypernatremia, hypertension, osteopenia with clear clinical aspect of Cushing. The abdominal ultrasound, CT scan and FDG-PET scan showed huge (13.8 cm in diameter) heterogeneous tumour mass in the right adrenal gland. The tumour infiltrates inferior vena cava and liver. Pelvic bone metastases were diagnosed also. CT angiography showed tumour thrombus and pulmonary embolism. Tumour biopsy showed adrenocortical carcinoma. The hormonal tests showed co-secretion of cortisol and androgens (Cushing's syndrome and androgenisation). Tumour was inoperable so tumour arterial embolisation was performed with idea of debulking. The patient was treated with mitotane in combination with systemic chemotherapy (EDP regiment: etoposide, doxorubicin), antiandrogen therapy per os and metirapon. Because of the important hepatotoxicity mitotane was discontinued soon. She needed also hydrocortisone supplementation transitory, for the short time. The patient died due to the disease progression after one year.

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EP37

Visinin-Like Protein-1 in the regulation of aldosterone biosynthesis

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Visinin-Like Protein-1 (Vsnl1) is a member of the EF-hand calcium sensor protein family that is expressed in the zona glomerulosa of the rat and human adrenal and upregulated in aldosterone-producing adenomas.
We studied the expression pattern of Vsnl1 and co-localization with the CYP11B2 enzyme and the zona glomerulosa (ZG) marker Dlk1 (ZOG) using double and triple immunofluorescence in the adrenal of rats on a normal, high and low sodium diets. We also studied the role Vsnl1 in aldosterone biosynthesis and calcium in the HAC15 cell.
In the rat adrenal, Vsnl1 was expressed only in cells of the ZG and in cells expressing Dlk1, including undifferentiated cells between the ZG and zona fasciculata. Nearly all of the ZG cells from adrenals of rats on a low sodium diet expressed both Vsnl1 and CYP11B2. However in adrenals of rats on a normal and high sodium diet the staining for Vsnl1 was in many more ZG cells than those expressing CYP11B2. Vsnl1 and Dlk1 immunoreactivity was found not only cells that are steroidogenically active and producing aldosterone, but also in ZG and undifferentiated cells in the rat adrenal subcapsular area.
Human adrenal cortical carcinoma cell line HAC15 was transduced with a lentivirus carrying Vsnl1. Three days after transduction cells were incubated with vehicle, angiotensin II (A-II) 10 nM, Forskolin 10 μM and potassium 16 mM and compared with control cells transduced with an empty lentivirus. Aldosterone and cortisol were measured after 24 h. The basal secretion of aldosterone was not increased, but that of cortisol was. Aldosterone and cortisol secretion were greater after A-II, forskolin and potassium stimulation in cells overexpressing Vsnl1. Proliferation of the HAC15 cells measured by the XXT and crystal violet methods and intracellular calcium, as measured by the Fluo-4 AM dye, were also increased after transduction with Vsnl1.
Transduction of HAC15 cells with shRNA for Vsnl1 that reduced Vsnl1 expression decreased their basal and A-II stimulated aldosterone synthesis. The Vsnl1 has a myristoylation consensus sequence at the N-terminal domain. Site directed mutagenesis of Vsnl1 at the 2 position (G2A) lentivirus transduced in HAC15 cells resulted in a significant decrease in the aldosterone response to A-II. In summary, the Vsnl1 is a zona glomerulosa protein that participates in calcium mobilization and increases the various secretagogue-induced aldosterone synthesis.

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EP38

Metabolic syndrome is common among patients with adrenal incidentalomas, but not associated with functional adrenal status

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Background
Adrenal incidentalomas (AI) have an increasing prevalence during last decades, probably due to the extended use of new imaging techniques and longer life expectancy. Adrenal hormonal hypersecretion, even subclinical, is probably related to cardiovascular disease (CVD).
Methods
We evaluated 100 patients with adrenal masses, incidentally discovered in imaging techniques performed for non adrenal disorders (67 Female, 33 Male, mean 58.1 ± 12.9 years, median 60.5y), according to NIH criteria of 2002 and ESE 2016. IDF 2006 criteria were used for metabolic syndrome (MS) definition.
Results
Mean incidentaloma size was 35.5 ± 20 mm. 20% were bilateral, while 41% were located to the right and 39% to the left adrenal. The majority (70%) was found to be non functional and 30% to be functional. Autonomous cortisol secretion (ACS) was found in 15%, pheochromocytoma (Ph) in 7% and hyperaldosteronism (HA) in 8% of all cases. Non functioning lesions were defined as non functioning adenomas (62%), non malignant cysts (2%), myelolipomas (2%), metastases (1%) and bilateral teratoma (1%). MS prevalence was higher in study group compared with general population (65% vs 23%, $P<0.001$). There was no difference in MS prevalence between patients with functional and non functional tumors (63.3% vs 64.7%, $P=0.53$), while no difference was found between functional tumors (ACS60% vs Ph57% vs HA75%, $P=0.78$). Hypertension had the greatest proportion in cases with hyperaldosteronism, while no difference in central obesity, hyperlipidemia and abnormal glucose metabolism was found between functional tumors.
Conclusions
The prevalence of metabolic syndrome was found to be high in patients with AI. A common pathophysiologic pathway (probably hyperinsulinaemia) must be the underlying mechanism between AI and MS, associated with an increased risk for CVD.

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EP39

The clinical course of patients with adrenal incidentaloma: Başkent University experience

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The prevalance of incidentally discovered adrenal masses increased in last three decades. The major clinical concern is the risk of malignancy and hormone overproduction but most of them are non-fonctional and benign. Current practices in the management of adrenal incidentalomas reevaluated the follow-up suggestions considering low probability of the transformation of a benign and non-functional adrenal mass to a malignant or functional one. Therefore, in the present study we analysed the clinical course of patients with adrenal incidentaloma. We evaluated 203 consecutive patients (139 females, 64 males:mean age 55.8 ± 0.8 years) who were referred to the Department of Endocrinology, Başkent University Hospital, between January 2007 and 2017. Among the 203 patients examined 171 had unilateral, 32 had bilateral adrenal masses. Mean size of tumors was 22.7 ± 10.8 mm. In 157 (%77.3) patients' adrenal mass was benign and non-functional, 21 (%10.3) had autonomous cortisol

secretion, 9 (%4,4) had Cushing syndrome, 5(%2.5) had pheochromocytoma, 9 (%4,4) had primary hyperaldosteronism and, 2(%1) had adrenocortical carcinoma. Twentyone patients went adrenelectomy. Median follow up time was 3 (1–10) years. During the follow up the change in the size of adrenal mass was non significant ($P=0.12$) and there were no changes either in metanephrines and normetanephrines or in the activity of renin–aldosterone axis. There was a significant correlation between adenom size and cortisol levels after dexamethasone supression test in patients with autonomous cortisol secretion. As a result our study suggests that the risk of an adrenal adenoma initially diagnosed as benign or non-functional becoming malignant or hormonally active is low.

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EP40

Predictive baseline morning P-cortisol levels for the response to a Synacthen test in prednisolone treated patients

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Introduction
Evaluation of glucocorticoid production generally requires a dynamic test. Cut-off levels for baseline cortisol concentrations predicting the outcome of a Synacthen test have been proposed for different cortisol assays. With introduction of the new Roche Elecsys Cortisol II assay, P-cortisol concentrations are expected to decrease by 20%. We have investigated cut-off levels for baseline P-cortisol concentrations measured with the Roche Elecsys Cortisol II assay that could predict the response to a Synacthen test in patients at risk of glucocorticoid-induced adrenal insufficiency.
Methods
In a cross-sectional study, 110 prednisolone treated rheumatologic patients had a 250 µg Synacthen test performed, fasting, in the morning, starting between 0800 and 1030 h, 36–48 h after the last prednisolone dose. P-cortisol was measured before and 30 min after Synacthen injection. The locally validated assay specific cut-off for normal adrenal function was 30 min P-cortisol $\geq$420 nmol/l.
Results
Forty-six patients (42%) had an insufficient response to the Synacthen test. Baseline and 30 min P-cortisol correlated positively ($P<0.0001$, $r=0.86$). Receiver-operator curve analysis showed an area under the curve of 0.94 (95% CI: 0.90–0.98). All patients with baseline P-cortisol $<$139 nmol/l also failed the Synacthen test (positive predictive value$=$100%). All patients with baseline P-cortisol $>$310 nmol/l had a normal response to the Synacthen test (negative predictive value $=$100%). Applying these cut-off values baseline P-cortisol measurements predicted the response to the Synacthen test in 58/110 (53%) of cases; P-cortisol $>$310 nmol/l (33%); P-cortisol $<$139 nmol/l (20%).
Conclusion
We have presented assay specific baseline P-cortisol concentrations that could predict the response to a Synacthen test in half of patients at risk of glucocorticoid-induced adrenal insufficiency and potentially reduce the number of needed Synacthen tests in the worldwide many glucocorticoid treated patients. Baseline morning cortisol measurements might become a valid diagnostic screening tool in the future.

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EP41

Silent pheochromocitoma – a rare case of adrenal incidentaloma

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Introduction
Pheochromocytomas are rare tumors arising from adrenomedullary chromaffin cells. Pheochromocytomas are a serious clinical condition and undiagnosed cases are associated with increased unexpected cardiovascular mortality.
Case report
A female Caucasian patient aged 52-year-old was referred to the endocrine department of a public central hospital because of an incidental right adrenal mass first found 3 years before during the work out of non specific tiredness. Annual CT CT scans documented significant growth (34, 40 and 62 mm) of a hypodense lesion (less than 10 Housefield units). Presently the patient denied gastrointestinal or abdominal complaints and did not present clinical evidence for hypercortisolism, hyperaldosteronism, hyperandrogenism or for excessive catecolamine production. Past medical history revealed chronic gastritis treated with omeprazole daily. She reported three uneventful pregnancies 25, 20 and 19 years ago. Physical examination was unremarkable, with normal blood pressure and no orthostatic hypotension. Analytic evaluation excluded hypercortisolism and hyperaldosteronism. Urinary metanephrine and normetanephrine were high (12 and 16 times higher than the upper limit of the reference range) and dopamine 1.5 times over the upper limit. Serum calcium and calcitonin were in the reference range. ^{123}I-MIBG scintigraphy presented increased right adrenal uptake. Uneventful laparoscopic right adrenalectomy was performed after preoperative treatment with doxazosin 8 mg, 2 l normal saline ev and propranolol 30 mg daily. Histologic evaluation confirmed a 55 mm pheochromocitoma, with no signs of malignancy. No genetic study was conducted.
Discussion and conclusion
About 7% of adrenal incidentalomas are pheochromocytomas. Although rare, clinically silent pheocromocytomas are recognized. Possible mechanisms may include 1) vasodilator peptides co-secreted by pheochromocytomas such as dopamine; 2) desensitization of target organs due to high catecholamine long-term exposure, 3) low circulatory volume in these patients and 4) malignancy with undifferentiation and minimal catecholamine production. This case highlights the need to exclude catecholamine producing tumors in all adrenal incidentalomas, even if they are asymptomatic.

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EP42

LH and adrenal tumor size correlate with insulin resistance in menopausal patients with adrenal incidentalomas and (possible) autonomous cortisol secretion

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High prevalence of insulin resistance (IR) has been shown in patients with adrenal incidentalomas (AI) and it has been demonstrated that an increase in IR is related to the adrenal tumor size (ATS). Also, responsive adrenal pathologies are well documented in patients with chronically elevated LH. The aim was to investigate the association between LH and IR and ATS and IR in AI patients. The case-control study was conducted in Clinic for endocrinology, diabetes and metabolic diseases, Belgrade, Serbia. The total studied group consisted of 105 menopausal women: 75 AI patients (mean age 60.13$\pm$7.28 years, mean BMI 27.60$\pm$4.66 kg/m^2, mean menopause duration 10.86$\pm$7.79 years, mean LH 31.82$\pm$14.17 IU/l and mean ATS 31.25$\pm$10.72 mm) and 30 age, BMI, menopause duration and LH matched healthy control (HC) women. Based on level of cortisol after 1 mg-dexamethasone suppression test AI patients were divided in two groups: $<$50 nmol/L, 27 with nonfunctional AI (NAI) and $>$50 mmol/l, 48 with (possible) autonomous cortisol secretion ((P)ACS). To estimate IR we used homeostasis model assessment (HOMA-IR). There was no significant difference between AI subgroups in terms of age, BMI, menopause duration, LH and HOMA-IR. HC subjects had significantly lower HOMA-IR when compared to NAI ($P=0.017$). There was a significant positive correlation between LH and HOMA-IR in AI group ($r=0.230$; $P=0.047$) and in (P)ACS subgroup ($r=0.353$; $P=0.017$), but not in patients with NAI ($r=-0.097$, $P=0.623$). The correlation of ATS and HOMA-IR was significant in AI group ($r=0.341$; $P=0.003$) and both NAI ($P=0.018$, $r=0.445$) and (P)ACS ($P=0.012$, $r=0.362$). After adjusting for age and BMI both LH and ATS were significant predictors of HOMA-IR,

($r^2=0.196$, $P=0.004$). There was no significant correlation between LH and HOMA-IR in HC. Our data suggest that not only insulin, but also the interplay between LH and insulin may contribute to the adrenal tumorigenesis.

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EP43

A case of recurrent Cushing's disease after total bilateral adrenalectomy

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Bilateral adrenalectomy usually results in lifelong primary adrenal insufficiency. Evidence exists that up to 34% of patients with Cushing's disease (CD) have some degree of endogenous cortisol secretion after bilateral adrenalectomy due to ACTH driven hyperplasia of residual cortical tissue. We present a case of a patient with atypical corticotropinoma/carcinoma and recurrence of CD after bilateral adrenalectomy.

A 59-year-old man presented with Cushing's disease (CD) in 2010. An MRI revealed intrasellar mass 8×8 mm suggestive of a microadenoma. After the surgery pathohistological evaluation was suggestive of atypical corticotropinoma (Ki-67 proliferation index 7%, positive nuclear staining for p53). CD recurred eight months after the surgery. Total hypophysectomy led to complete remission, followed by recurrence 5 months later. We performed radiosurgical treatment of the remnant tumor mass, along with bilateral two-stage adrenalectomy. Pathohistological evaluation confirmed complete removal of the left adrenal gland, and was inconlusive about the right one. Postoperatively, patient required replacement therapy. Two years after the adrenalectomy patient was diagnosed with Nelson's syndrome due to enlargement of the pituitary mass. Fractionated radiotherapy was performed, after which ACTH slightly decreased, but UFC levels continued to increase, while taking hydrocortisone replacement. Replacement therapy was stopped, but urinary free cortisol increased to 1400 nmol/24 h 3 years after the bilateral adrenalectomy, accompanied by the recurrence of signs and symptoms of CD. Computed tomography showed 4-cm large mass in the left adrenal bed suggestive of an adrenal tissue, along with the multiple liver lesions and without the signs of another primary tumor. Patient died five years after the initial diagnosis and his family refused an autopsy.

This is the first case of a recurrent CD after bilateral adrenalectomy. This report highlights the importance of long-term monitoring of the patient and individual dosing of replacement therapy.

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EP44

Late-night salivary cortisol: cut-off definition and diagnostic value in Cushing's syndrome

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Background

The diagnosis of Cushing's syndrome (CS) remains a challenge in clinical endocrinology. Several screening tests have been proposed to establish hypercortisolism. Late-night salivary cortisol (LNSC) is used as screening tool, however, individualized cut-off levels for each population must be defined.

Methods

Three group of subjects were studied: healthy volunteers, suspected CS and proven CS. All patients collected saliva at 23.00 h using a Salivette. Salivary Cortisol was measured using an automated electrochemiluminescence assay – Elecsys 2010-Roche. The functional sensitivity of the assays is 0.018 μg/dl. Diagnostic cut-off level was defined by Receiver operating characteristic (ROC) curve and Youden's J index.

Results

We studied 127 subjects: 57 healthy volunteers, 39 patients with suspected CS and 31 with proven CS (ACTH-dependent: 22 pituitary, two ectopic; ACTH-independent: two adrenal adenoma, five adrenal carcinoma).

The 2.5th–97.5th percentile of the LNSC concentrations in normal subjects was 0.054–0.1827 μg/dl, respectively. The mean ± s.d. LNSC concentration in patients with proven CS (0.6798 ± 0.52 μg/dl) was significantly higher than those in normal subjects (0.0642 ± 0.03 μg/dl; $P<0.0001$) and suspected CS group (0.1803 ± 0.19 μg/dl; $P<0.0001$).

ROC curve analysis showed an AUC of 0.9881 ($P<0.0001$) and a cut-off point of 0.1 μg/dl provides a sensibility (S) of 96.77% (95%CI 83.3-99.92%) and specificity (E) of 91.23% (95%CI 80.7–97.09%).

There were significant correlations between LNSC and late-night serum cortisol (LNSeC) levels ($r=0.6977$; $P<0.0001$) as well as with Urinary Free Cortisol (UFC) levels ($r=0.5404$; P 0.0025) in proven CS group.

Conclusion

Our results give to LNSC an excellent accuracy and reaffirm that can be used as a highly reliable noninvasive screening tool for outpatient assessment. In our population, the LNSC reference cut-off was 0.1 μg/dl with S 96.77% and E 91.23% for CS diagnosis. Given its convenience and diagnostic accuracy, LNSC may profitably be added to traditional screening tests such as LNSeC and UFC.

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EP45

Adrenal involvement in MEN1 families

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Introduction

MEN1 is a rare autosomal dominant syndrome typically characterized by neoplastic lesions of parathyroid glands, anterior pituitary gland and endocrine pancreas. Several other tumours are associated with this syndrome, including adrenal lesions, but their prevalence and clinical characteristics (endocrine secretion and aggressiveness) are largely unknown.

Objective

To determine the prevalence, clinical characteristics and the possible genotype/phenotype association of adrenal lesions in MEN1 patients, as well as their global impact on patients' outcome.

Material and methods

We retrospectively studied 16 patients belonging to six families of individuals with MEN1. Adrenal involvement was evaluated clinically, biochemically and imagiologically based on clinical records.

Results

Adrenal lesions were identified in 9 of 16 (56.3%) patients. This group comprises seven women and two men with a mean age of 55.6 years. The mean age at diagnosis of MEN1 was 46.3 years (18–68) and adrenal involvement was detected between 0 and 16 years after the syndrome was diagnosed. Among the 16 patients evaluated, a total of nine adrenal nodules were founded, with a median of two nodules per patient. Only three patients had unilateral involvement. The mean adrenal lesion diameter at diagnosis was 17.5 mm (6–30 mm). Hormonal hypersecretion – autonomous cortisol secretion – was founded in one patient. None of the patients was submitted to adrenalectomy. Adrenal lesions were evenly distributed between the different germline mutations.

Conclusion

Adrenal tumours are a common feature of MEN1 that can affect more than half of the patients. Most of the tumours are bilateral non-functional lesions, but hormonal secretion may occur and should be promptly identified in order to reduce the morbidity/mortality of the syndrome. Adrenal evaluation should be considered in patients with MEN1.

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EP46

Differential effects of aldosterone excess on potassium homeostasis and blood pressure in Asian subjects

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Introduction
Hypokalemia is considered as a late manifestation of primary aldosteronism (PA), long preceded by hypertension. However, there have been reports of normotensive PA patients presenting with hypokalemia. This study aims to examine the relationship of hypokalemia and blood pressure in patients with hyperaldosteronism.
Methods
A retrospective review of patients who underwent saline infusion test (SIT) from 2014 to 2016 was conducted. All patients had screening plasma aldosterone concentration (PAC): plasma renin activity (PRA) ratio of >20. Postinfusion PAC level <5 ng/dl (139 pmol/l) indicated normal aldosterone suppression, PAC >10 ng/dl (277 pmol/l) confirmed PA, whereas PAC 5–10 ng/dl (139–277 pmol/l) was regarded as indeterminate. Hypokalemia was defined as serum potassium <3.5 mmol/l.
Results
Over a 3-year period, 52 patients referred for hypokalemia had non-suppressible postinfusion PAC (>5 ng/dl). They comprised of 36 men and 16 women, with a mean age of 58.4 ± 9.1 and 57.3 ± 13.2 years respectively.
In the PA group consisting of 26 men and 11 women, the mean serum potassium were 2.9 ± 0.3 mmol/l and 2.7 ± 0.5 mmol/l respectively. Eighteen (69.2%) men and 10 (90.9%) women were on ≤2 antihypertensive agents, including two women (age 48 and 51) with severe hypokalemia (<2.5 mmol/l) who were normotensive and rendered normokalemic after adrenalectomy and spironolactone treatment separately.
In the indeterminate group comprising of ten men and five women, the mean serum potassium were 3.1 ± 0.2 mmol/l and 3.0 ± 0.2 mmol/l respectively. Five (50%) men and 4 (80%) women were on ≤2 antihypertensive agents.
In all patients with moderate to severe hypokalemia (≤2.9 mmol/l), 7/11 (63.6%) men and 8/9 (88.9%) women were on ≤2 antihypertensive agents.
Conclusion
In our cohort of Asian patients, majority with hypokalemia secondary to autonomous aldosterone production required only 0–2 antihypertensive agents, even in those with more severe degree of hypokalemia. This suggests possible differential effects of aldosterone excess on potassium homeostasis and blood pressure.

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EP47

Effect of adrenal mass lateralization on diagnostic tests in patients with Cushing

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The frequency of adrenal masses is increasing in parallel with the progress of the technology. Most of these masses, which are detected by chance, are not functional, and only a part of them are exposed to an excess of hormone. The most common dysfunction in masses with hormonal activity is hypercortisolism. However, the diagnosis of Cushing's disease is based on more than one test. In this study, we intended to compare the values of screening tests to determine whether the presence of a unilateral mass or bilateral mass would help in the diagnosis.
Materials and methods
Adrenal masses were detected in our clinic and 143 patients who were followed up were evaluated. 112 of these patients have unilateral adrenal mass, 31 have bilateral adrenal masses. Twenty (17.8%) of 112 unilateral adrenal masses and 15 (51.6%) of the patients with bilateral adrenal masses were diagnosed as Cushing. The 1 mg overnight dexametasone suppression test (DST), 2 days 2 mg dexametasone suppression test (Liddle test), and 24-h urine cortisol levels used for diagnosis in these patients were compared. Averages of tests were taken multiple times.
Conclusion
The mean age of the patients with bilateral and unilateral adrenal masses was around 60. When the mean values of 1 mg DST, Liddle test and 24 h urine were compared, no statistically significant difference was found between the two groups.
Comment
In the case of Cushing's syndrome, the adrenal glands on one side or on both adrenal glands are not diagnostic in terms of diagnosis.

Table 1

Cushing's Syndrome	Unilateral mass (*n*:20)	Bilateral Masses (*n*:15)	*P*
Age	58.2 ± 2.4	63.5 ± 2.5	0.7
1 mg DST	5.9 ± 1.6 (median:3.3)	5.8 ± 1.8 (median:3.1)	0.9
Liddle test	4.8 ± 1	4.2 ± 0.7	0.2
24 h urine cortisol	138.2 ± 28.8	184 ± 26.5	0.5

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EP48

Late night salivary cortisol measurement may help in excluding Cushing's syndrome in patients with chronic kidney disease

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Objective
The diagnosis of Cushing's syndrome may be challenging, especially in cases of patients with chronic kidney disease (CKD).
Aim
The assessment of late night salivary cortisol concentration, serum and salivary concentration in overnight dexamethasone suppression test in patients with CKD stage III–V and a control group.
Patients and methods
37 patients mean age 66 ± 12 ($M=13$) with CKD stage III–V according to KDIGO and 28 controls mean age 45.3 ± 15 years ($M=6$) were enrolled to the study. Patients were recruited in the nephrology clinic during their routine control visits. Serum and salivary cortisol were measured by Roche ECLIA cortisol test (Cobas E411). Two samples of late night salivary cortisol (LNSC) from each subject were obtained from home. 1 mg dexamethasone suppression test (DST) was done in patients and controls with serum and saliva measurement at 0800 h. Serum creatinine assessment was done no longer than 1 week prior to cortisol measurement. GFR was obtained from the Cockcroft−Gault calculator.
Results
The mean GFR in patients was 33.89 ml/min (8.4–54) while in controls 125 ml/min (73–230) ($P<0.0001$). The mean serum DST cortisol in patients was 2.62 μg/dl (0.46–7.42). In 19 (51.4%) patients serum DST cortisol was >1.8 μg/dl. In all controls serum DST cortisol was <1.8 μg/dl (mean, min–max 0.70, 0.36–1.48). The mean DST salivary cortisol in patients was 0.88 μg/dl (0.11–0.88) while in controls 0.18 μg/dl (0.02–0.69) μg/dl. Although there was a significant difference between controls' and patients' salivary cortisol concentration in DST ($P=0.01$), all but one patient's salivary measurement were within control ranges. The mean LNSC in patients was 0.26 μg/dl (0.10–0.65) while in controls 0.29 μg/dl (0.04–0.80), $P=0.4$. All patients' LNSC measurements were within control ranges. In the patients' group the negative correlation between GFR and DST serum cortisol was detected, $r=-0.6$, $P=0.001$ (the higher cortisol the lower GFR).
Conclusion
LNSC may be helpful in excluding Cushing's syndrome in patients with CKD.

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EP49

The short Synacthen test revisited – reevaluation of the normal reference range using LCMSMS

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Background
The Synachten test is used to diagnose for adrenal insufficiency (AI) and non-classical congenital adrenal hyperplasia (CAH). The cut-off levels for s-cortisol and s-17-hydroxyprogesterone are derived from immunoassays that were not well standardized and are no longer in use. Introduction of liquid chromatography tandem mass spectrometry (LCMSMS) could resolve the lack of standardization of steroid hormone assays and enable increased diagnostic accuracy.
Aim
Define cut-off values for s-cortisol and s-17OH-progesterone by LCMSMS after intravenous administration of 250 µg tetracosactide acetate (Synachten).
Methods
The Synachten test was performed in healthy individuals ($n=60$) and patients referred for evaluation of adrenocortical function ($n=42$). Steroids were assayed by LCMSMS. Cut-off level for s-cortisol was defined as the 2.5% percentile in healthy subjects not using oral estrogens ($n=55$), and for 17-OH-progesterone as the 97.5% percentile in the healthy women.
Results
Cortisol cut-off levels were 415 and 493 nmol/l at 30 and 60 min, respectively. All controls had higher cortisol at 60 compared to 30 min. Applying the current cut-off of 550 nmol/l, 27 healthy controls would have had a false negative test at 30 min, and six at 60 min. For s-17-OH-progesterone the cut-off levels were 10.5 and 11.1 nmol/l at 30 and 60 min, respectively. Forty-two patients performed the test for suspected AI or non-classic CAH. Applying the new cut-offs, seven who had AI according to old criteria, now scored normal.
Conclusions
Cut-off levels for s-cortisol after Synacthen test are lower than the commonly recommended discriminating levels when cortisol is analyzed by LCMSMS. When applied, a significant proportion of patients can be re-categorized from adrenal insufficiency to healthy. We recommend using the 60 min value as standard, as cortisol increased from 30 to 60 min in all controls.

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EP50

Cushing's syndrome in pregnant woman

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Background
Pregnancy occurs rarely in Cushing's syndrome (CS), slightly over 150 cases have been reported in the literature. The risk of maternal morbidity and a poor fetal outcome is significant when CS coexists with pregnancy. CS may be difficult to detect clinically and laboratory because of the hormonal changes and pathological comorbidities associated with normal pregnancy.
Material and methods
A case of CS that was diagnosed and treated during pregnancy.
Case
Woman Y., 30y.o., since she was 18 had menstrual irregularities and since she was 28 an arterial hypertension, type 2 DM. She was on supervision of therapeutist and take metformin for her DM and hypotensive medication. Unexpected pregnancy occurs in December 2016. She was referred in our clinic in 15 weeks of her pregnancy because of uncontrolled DM and hypertension. Examination revealed increased blood pressure, fatigue, easy bruising, excessive hair growth on the face and body, swelling and rounding of the face, edema of legs and feet. Laboratory evaluation: UFC-1475.0 and 1511.0 nmol/24 h (N 138.0–524.4), serum cortisol – at 0800 h −868 nmol/l (190–650), at 2300 h −995 nmol/l (50–350)), suppressed ACTH level. HbA1c–7.7%. Insulin therapy initiated to treat DM. MRI data: adenoma in left adrenal (32×30 mm). 13.05.16.-unilateral adrenalectomy was done. Adrenal insufficiency developed post-operatively and glucocorticoid therapy was started. She was under close supervision of gynecologist. At 38 weeks gestation surgical delivery performed (boy, 1900 g, 44 cm, 7/8 Apgar score, with three degrees of fetal growth retardation and two degrees of malnutrition). Insulin was cancelled after delivery, and hydrocortisone and antihypertensive therapy cancelled 2 months postpartum.
Conclusion
High clinical suspicion of the CS during pregnancy can help for the diagnosis and leads to better outcomes for the mother and the fetus. Multidisciplinary approach needs for these patients with careful supervision during pregnancy and postpartum.

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EP51

Education sessions in patients with adrenal insufficiency

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Introduction
Adrenal insufficiency (AI) is a rare and potentially life-threatening disease. The most common causes are primary adrenal insufficiency (Addison's Disease), due to an adrenocortical disease, and secondary insufficiency, due to disorders of the pituitary gland. Chronic glucocorticoid replacement is vital and patients should be educated about how to act in acute stress situations, in order to avoid adrenal crisis. Taking this into account, we organized education sessions, aimed at patients with AI.
Discussion
We realized group sessions of about 90 minutes duration each, with maximum 8 patients with AI; the presence of a family member or caregiver was strongly advised. A multimedia presentation was performed, focusing on basic knowledge on adrenal insufficiency, management of the disease during stress situations and early recognition of signs and symptoms of an adrenal crisis. At the end of each session, patients were given an emergency hydrocortisone kit and taught how and when to use it. In addition, three brochures with written information with general information about the disease, specials situations and how to prepare and administer emergency medication were available to take home. The identification card of disease carrier (European Society of Endocrinology) was also provided to those who didn't have it. Patient adherence was 100% and a second session will be scheduled in order to access the effectiveness of the first session and to reinforce patient education.
Conclusions
AI is a chronic disease with a significant burden in both patients and its partners. A careful and repeated education is the best strategy to avoid life-threatening emergencies.

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EP52

Characteristics of aldosterone-producing adenomas: a tissue microarray study

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Background
Sporadic aldosterone-producing adenomas (APA) are relevant cause of endocrine related hypertension in Primary Aldosteronism (PA). Next generation sequencing techniques have identified somatic mutations in APA harbored in KCNJ5, ATP1A1, ATP2B3, CACNA1D, CTNNB1 and PRKACA genes. Yet, a number of APA harbor no mutations in candidate genes (designated as wild type, WT) and little is known about genotype/phenotype correlation.
Objectives
We investigated the tissue-based molecular and histopathological characteristics of 132 APAs after laparoscopic unilateral adrenalectomy in PA-patients and studied genotype/morphometry and histopathology correlation.
Methods
Tumor-DNA was screened for somatic mutations in candidate genes by targeted ($n=84$) or whole-exome ($n=48$) sequencing. Accurate characterization of 179 morphometric parameters and of immunohistochemistry (IHC) results for steroidogenic enzymes CYP11B1, CYP11B2, CYP17, HSD3B1 and HSD3B2 was performed on tumor tissue microarrays from all samples by digital image analysis.

Results
Prevalence of *WT* APA in our cohort was 34% and affected men more frequently. In 8/48 APA, non-recurrent somatic mutations (*NR*) were identified. H&E analysis demonstrated that 6 morphometric parameters correlated negatively with *WT* status whereas those same parameters correlated positively with the presence of *KCNJ5* or *NR* ($P<0.01$). The same reversed pattern between *WT* and *KCNJ5* mutated APA was found in 10 cytoplasmic parameters, including mainly color-based features ($P<0.01$). *KCNJ5* mutation status was negatively correlated with CYP11B1 and HSD3B1 expression ($P<0.01$). On the contrary, *WT*, *CACNA1D* and *NR* APA significantly correlated positively with CYP11B1. *ATP1A1* mutated APA correlated positively with CYP11B2 ($P<0.01$) and not with CYP11B1 or HSD3B2.
Conclusion
Our findings in *NR* APA point towards a *KCNJ5*-like morphometric pattern associated with a *WT*-like steroidogenic enzymes expression pattern. *WT* APA presented an opposed morphometric pattern in comparison to mutated APA, indicating that in absence of detectable somatic mutations APA cells are driven towards a different cellular fate.

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EP53

Adrenal cushing's syndrome surprisingly unveiling breast cancer

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Introduction
Cushing's syndrome is an endocrinopathy characterized by glucocorticoids excess. Adrenalectomy is the recommend treatment for unilateral adrenal Cushing's syndrome and is usually associated with resolution of the disease.
Clinical Case
A 54-year old woman with central obesity (BMI 34.3 kg/m^2), diabetes and hypertension had a left adrenal mass of 15 mm and characteristics suggestive of adenoma (Hounsfield unit of <10). On CT reevaluation, five years later, there was evidence of mass growth (28 mm) and the characteristics were suspicious of malignant lesion (Hounsfield unit of 38 and absolute contrast washout of 35%). She was then referred to our department for evaluation. Urinary catecholamines and metanephrines were normal, ACTH level was 4.2 pg/ml and the cortisol following 1 mg overnight dexamethasone suppression test was 11.0 µg/dl. The 24 h urinary-free cortisol, late-night salivary cortisol and two-day low-dose dexamethasone suppression test were consistent with ACTH-independent Cushing's syndrome. A left adrenalectomy was performed. At pathological evaluation, there was a neoplasm of solid pattern, with vascular invasion and a immunohistochemical pattern suggestive of a breast carcinoma metastasis. Mammography revealed a 15 mm nodule with spiculated contours that on breast biopsy revealed a NST (no special type) breast carcinoma. The patient was submitted to neoadjuvant chemotherapy and surgical tumorectomy. Five months after surgery she was admitted in Endocrine department for adrenal insufficiency. Ten months after the adrenalectomy, the patient presents an adrenal insufficiency (compensated with replacement therapy) and maintains follow-up on endocrinology and multidisciplinary breast cancer appointments.
Conclusion
The authors present a case of Cushing's syndrome of adrenal origin, with a concomitant metastasis of a breast carcinoma. The find of a metastasis in an adrenal mass, is consistent with a tumor-to-tumor metastasis, a rare finding in adrenal masses that, in this case, allowed the diagnosis of a previously unknown breast cancer.

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EP54

Giant adrenal tumor in a patient admitted for fever

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Introduction
Adrenal tumors are usually detected due to clinical manifestations of hormonal hypersecretion or incidental findings on imaging evaluation. Although most incidentalomas are non-functioning adenomas, it is important to appropriately evaluate such masses to exclude hormonal excess or malignancy.
Case description
An 81-year old male was admitted to our hospital for fever with 15 days of evolution. The patient also presented chills and loss of 3 kg in the last 4 weeks. Regarding past medical history, the patient had type 2 diabetes, hypertension, coronary artery disease, heart failure, cerebrovascular disease (stroke 8 years before), vertebral fractures (3 years before), deep vein thrombosis (3 months before), renal lithiasis and a right adrenal mass (3 cm in the abdominal tomography 16 months before; no functional study available). An elevated C-reactive protein (142 mg/l) was observed, with negative blood and urinary cultures and no other signs of infection. The abdominal ultrasound shown a right adrenal mass of 13 cm. On magnetic resonance, the mass was heterogenous with invasion of inferior vena cava. The patient had no stigmas of Cushing's syndrome. Plasma catecholamines, urinary catecholamines and metanephrines, and renin and aldosterone levels were normal. The midnight salivary cortisol was normal and the plasma cortisol level after 1 mg overnight dexamethasone suppression test was 3.7 µg/dl. Given the risk for a surgical approach, the fast growth of the tumor and the imaging characteristics suggestive of adrenal carcinoma, a decision to preclude biopsy was made. The patient started mitotane and two months later the mass has 15 cm and the patient is still on follow-up in outpatient setting.
Conclusions
The authors present a case of adrenal carcinoma in a patient with previous adrenal mass not completely studied at presentation. Adrenal incidentalomas are frequent. This case highlights the importance of prompt evaluation of adrenal incidentalomas to early recognize rapidly growing adrenal carcinomas.

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EP55

The relative risk of developing Addison's disease among patients with type 1 diabetes mellitus: a nationwide, matched, observational cohort study

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Background
Both prevalence and incidence of type 1 diabetes (T1DM) is increasing. T1DM is associated with other autoimmune diseases, such as Addison's disease (AD). This combination is rare, with estimated prevalence in Norway 20 per million. Having both DM & AD is associated with marked excess mortality.
Objectives
To study prevalence and incidence of AD among patients with and without T1DM.
Methods
Nationwide, observational study cross-referencing the Swedish National Diabetes Register with Inpatient Register in patients with T1DM & AD and matched controls from the general population (matched 1:5 for age, sex and country). Demographics at baseline, group proportions and time to AD diagnosis using a Cox proportional hazards model were assessed.
Results
Prevalence: Between 1987–2012, 105 subjects were diagnosed with AD among 30,685 patients with T1DM, while 32 among 153,918 controls. The odds ratio for AD in T1DM patients vs controls was therefore 16.5 (95% CI 11.1–24.5).

The prevalence of AD in patients with and without T1DM was 3400 and 200 per million, respectively. Incidence: Between 1998-2013, 67 subjects were diagnosed with AD at a mean age of 36.7 years (SD 13.1) among 36,705 patients with T1DM, while 33 were diagnosed with AD at a mean age of 43.1 (SD 15.1) among 184,304 controls. The estimated relative risk increase to develop AD in T1DM patients was therefore 10.7 (95% CI 7.0–16.2). The incidence of AD for a patient with and without T1DM was 195 and 18 per million patient-years, respectively.
Conclusion
This nationwide study shows that prevalence of AD is higher than previously reported and that the incidence of AD for a patient with T1DM is 195 per million patient-years. T1DM patients have a more than 10-fold higher risk of developing AD than matched controls and their AD develops at a younger age.

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EP56

The frequency of incidental liver and renal masses in patients with adrenal incidentalomas

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Purpose
Adrenal incidentalomas (AIs) are adrenal masses, which are found on imaging studies not performed related to an adrenal problem. Hepatic incidental masses and renal incidental masses are usually seen in abdominal imaging methods. We aim to investigate the frequency and the kind of hepatic and renal incidental masses in patients with AIs.
Methods
Retrospective evaluation of 381 (245 female and 136 male) AI patients and 285 (168 female and 117 male) controls were done. Adrenal masses were divided into two groups according to Hounsfield Units (HU) ≤ 10 and > 10, also classified as right, left and bilateral sided. The comparisons were made between hepatic and renal and both hepatic and renal incidental masses in AIs patients.
Results
Renal incidental mass and both hepatic and renal mass frequency were found higher in AIs group than controls. InAIs patients who had left sided unilateraladrenal mass HU > 10, the frequency of both hepatic and renal incidental mass was found more than left sided unilateral adrenalHU ≤ 10 group ($P = 0.001$). Also in patients who had bilateral sided adrenal mass HU > 10 the frequency of both hepatic and renal incidental mass was found more than bilateral sided unilateral adrenal HU ≤ 10 group ($P = 0.049$).
Conclusions
Increased incidence of both hepatic and renal incidental masses were detected in AIs patients which adrenal mass HU greater than 10. We consider that the physicians should carefully evaluate these cases. Large studies are needed to define the incidence and follow-up of AIs patients with hepatic and renal incidentalomas.

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EP57

Primary adrenal insufficiency: a Portuguese multicentre study by the adrenal tumour study group

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Introduction
Primary adrenal insufficiency (PAI) is a rare but severe and potentially life-threatening condition. There are no studies characterizing portuguese patients with PAI.
Aims
To characterize the clinical presentation, diagnostic workup, treatment and follow-up of patients with confirmed PAI.
Methods
A multicentre retrospective study of PAI patients followed in 12 portuguese hospitals.
Results
We investigated 278 patients with PAI (55.8% were females) with mean age of diagnosis of 33.6 ± 19.3 years, 7.3 years after the beginning of the symptom presentation. The most frequently reported symptoms and signs were asthenia (60.1%), hyperpigmentation (55.0%), weight loss (43.2%), hypotension (42.8%) and hypoglycaemia (8.6%). Hyponatremia was documented in 36.3% of cases and hyperkalaemia in 25.9%; 29.1% of patients were diagnosed in adrenal crisis. In 122 patients the diagnosis was established using morning cortisol < 5 g/dl and plasma ACTH 2-fold the upper limit of the reference range and in 39 cases by the corticotropin stimulation test. The main causes were autoimmune adrenalitis (140 cases), idiopathic (48 cases), congenital adrenal hyperplasia (27 cases) and tuberculosis (17 cases). Concerning associated autoimmune diseases, the most common were autoimmune thyroiditis (81 patients) and type 1 diabetes mellitus (25 patients). Seventy-nine percent were treated with hydrocortisone (mean dose 26.3 ± 8.3 mg/day) in three (57.5%), two (37.4%), one (3.7%) or four (0.5%) daily doses; the remainder with prednisolone (10.1%), dexamethasone (6.2%) and methylprednisolone (0.7%); 66.2% were medicated with fludrocortisone (median dose of 100 μg/day). Since diagnosis 33.5% have been hospitalized due to disease decompensation. At the last consultation, 17.2% of the patients had complaints (7.6% asthenia and 6.5% depression) and 9.7% presented changes in the ionogram.
Conclusion
This is the first multicentre Portuguese study about PAI. As described in international studies a significant number of PAI patients continue to have symptoms of over or under-substitution despite optimal steroid replacement.

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EP58

Adrenal incidentaloma: a challenging dilemma!

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The prevalence of adrenal incidentaloma on abdominal Computed Tomography (CT) is around 4.4%. This prevalence is increased in obese, diabetic, hypertensive patients, and could be as high as 10% in older patients. Unilateral adrenal masses larger than 4 cm should be considered for surgical removal to avoid missing adrenal carcinoma, particularly in younger patients.
This is the case of a 67 year old gentleman with Type 2 diabetes mellitus, known to have hypertension, hypercholesterolaemia, ischaemic heart disease with six coronary stents, and iron deficiency anaemia. He was on polypharmacy including aspirin, clopidogrel, bisoprolol, amlodipine, oral hypoglycaemic agents, insulin and iron supplementation. He presented with increased urinary frequency and pain in the right flank. Urinalysis and examination of all systems were unremarkable.
An ultrasound of kidney, ureter, and bladder (KUB) was performed showed a well-defined solid echogenic mass superior to the right kidney measuring $98 \times 76 \times 85$ mm with no vascularity. CT of the adrenals and abdomen revealed a 7 cm right adrenal mass, most likely myelolipoma, multiple bilateral small renal cysts, and an extensively calcified atherosclerotic abdominal aorta. Phaeochromocytoma and Conn's syndrome were ruled out following normal 24 hour urinary metanephrines and normal renin aldosterone ratio. It was rather unlikely for Cushing's in view of normal 24 hour urinary cortisol and lack of the clinical stigmata of excess cortisol.
Conclusion
Is it best to leave it alone, bearing in mind his multiple co morbidities or to operate in view of right flank pain, the size of tumour, and the risk of bleeding in this type of tumour?

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EP59

Assay of steroids with Liquid chromatography tandem mass spectrometry is superior to immunoassays in monitoring patients with 21-hydroxylase deficiency

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Objective
Immunoassays of steroids are still used in the diagnosis and biochemical monitoring of patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency (21 OHD). However, high levels of steroid intermediates can promote cross-reactivity between steroids giving rise to falsely elevated levels.
Design
Fifty-nine patients with classic 21OHD (38 women) were studied. Blood samples were collected in the morning after overnight medication fasting. Immunoassay and liquid chromatography-tandem mass spectrometry (LC-MS/MS) quantitation of the following steroids were performed: 17OH-progesterone (17OH), 21-deoxycortisol (21DF, an 11-hydroxylated derivative of 17OHP), 11-deoxycortisol, testosterone and androstenedione.
Results
Concentrations of testosterone, androstenedione and 17OHP were lower when measured with LC-MS/MS compared with immunoassays, with exception of testosterone levels in men. Testosterone results differed by 30.0% in females and only a small difference in men (+1.1%). The difference was even larger for androstenedione (31.3%) and 17OHP (57.0%).
The correlation between 21DF and 17OHP was good ($r=0.87$), but three patients did not have measurable 21DF which indicate that 21DF is not superior to 17OHP to monitor replacement therapy. Subjects with no enzyme activity had significantly lower mean 11-deoxycortisol concentrations compared with subjects with severe enzyme failure, analyzed by *LC*-MS/MS. Levels of other steroid hormones did not differ significantly between the genotypes and methods.
Conclusions
LC-MS/MS is superior to immunoassays in monitoring patients with 21-OHD on corticosteroid replacement therapy as they are more specific and can be multiplexed. Immunoassays seems to overestimate high levels of 17OHP and androstenedione considerably.

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EP60

Treatment of patients with primary and secondary adrenal insufficiency with hydrocortisone modified-release (Plenadren®)

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Introduction
Adrenal insufficiency is a life-threatening disease. Conventional treatment requires multiple daily doses of immediate-release hydrocortisone or cortisone acetate causing non-physiological peaks and nadir of cortisol and it has been also associated with premature mortality, high frequency of infections, reduced quality of life, altered metabolic profile and reduced bone mineral density. A modified-release hydrocortisone (Plenadren®, Shire) by combining a rapid with an extended-release of the hormone can mimic the normal circadian rhythm of cortisol and may be administered as a single daily dose. Plenadren has been also associated with a reduction of body weight and blood pressure and improvement of the glyco-metabolic parameters.
Purpose
The study objectives are: (1) to compare the area underr the curve (AUC) of cortisol under conventional therapy and Plenadren and (2) to evaluate clinical (body weight, body composition, blood pressure), glyco-metabolic (HbA1c)) and bone (T score, BMD, serum bone alkaline phosphatase (BAP) and cross laps) parameters at 3, 6 and 12 months of treatment with Plenadren.
Materals and Methods
Thirteen patients (7 M/6 F; age 53±17 (m± S.D.)) with primary adrenal insufficiency in seven subjects and secondary in six cases were prospectively enrolled in the study.
Results
Daily cortisol profiles were more physiological on Plenadren and body exposure to cortisol, calculated as area under the curve, was not statistically significant between conventional therapy and Plenadren. Currently, the median follow-up is 9 months (range 3–24 months). In one obese and diabetic patient body weight decreased as well as fat mass while lean mass increased and HbA1c improved. In one patient with osteoporosis T score improved and accordingly cross laps decreased and BAP increased. All study parameters did not show significantly changes in the remaining patients.
Conclusions
Treatment with Plenadren provides a more physiological cortisol profile and in some patients shows a beneficial effect on glucose metabolism and bone and body composition without increasing adrenal crisis and/or infections.

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EP61

Autoimmune Addison disease – data from long-term follow-up of patients from a tertiary hospital's Endocrinology Department

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Introduction
Autoimmune Addison disease requires lifelong glucocorticoid and mineralocorticoid replacement. Optimal therapy is not standardized and must balance adequate hormone substitution with prevention of treatment-related complications.
Objective
Assessment of patients followed at our department: epidemiology, associated conditions, treatment, cumulative hydrocortisone dose and comorbidities.
Methods
Review of clinical records of patients currently followed at our department, diagnosed from 1975 until 2015. Statistical analysis using SPSS v. 23.0.
Results
A total of 27 records were evaluated, 17 were women, 10 men. Mean age at diagnosis was 32±9.7 years, mean follow-up 19.7±13.8 years. Disease duration was 20 or more years in 55.6%. Mean current age 51±13 years. The most frequently associated immune system disorder was autoimmune thyroiditis (42.3%). Regarding glucocorticoid replacement, 92.6% were treated with hydrocortisone (HC), 2 patients with prednisolone. Mean daily dose of HC 31.2±10.0 mg (range 5.0–47.5 mg). Mineralocorticoid replacement with fludrocortisone, mostly 0.1 mg/d. Osteoporosis/osteopenia was found in 33.3% ($n=9$), hypertension (HT) in 25.9% ($n=7$), diabetes in 14.8% ($n=4$), treatment for depression or anxiety in 40.7% ($n=11$) and dyslipidemia in 51.9% ($n=14$). Mean cumulative HC dose was higher in patients with osteoporosis/osteopenia and in those with HT, dyslipidemia and diabetes, although not reaching statistical significance. Tendency remained when adjusted for age.
Discussion and conclusion
Our sample shows a long follow-up time, associated with lifelong need of Endocrinology assessment. A significant number of patients developed comorbidities possibly related to long-term glucocorticoid therapy (osteoporosis, HT, dyslipidemia and diabetes). All of these were related to higher cumulative HC dose. Absence of statistical significance was likely due to sample size. To reduce the risk of complications, replacement therapy in autoimmune Addison disease should be individually adjusted and overtreatment avoided.

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EP62

Effect of GH treatment on coagulation and fibrinolysis parameters in prepubertal children with growth hormone deficiency

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Background
Increased fibrinogen levels have been reported in prepubertal children and adolescents with growth hormone deficiency (GHD), which were reduced after rhGH treatment. rhGH treatment has also been shown to exert a beneficial effect on the amount of aPAI-1 in children with GHD.
Aim
Of the study was to evaluate whether prepubertal GH deficient (GHD) children showed any impairment in coagulation- and fibrinolysis-related parameters and the effect of GH therapy on these parameters.
Patients and methods
Fifteen prepubertal children (10 girls and five boys) of a mean (s.d.) age of 9.8 (0.4) years with GH deficiency were included in this hospital based prospective study. Serum levels of PT, APTT, fibrinogen, VII, VIII, AT, PC, D-dimers, Plg, and PAI-1 were measured before and after 6–12 months of GH treatment.
Results
At baseline all studied parameters were within normal ranges. A significant increase in PT values was noted after a mean (s.d.) interval of 9.3 (0.4) months of treatment: 12.46 (0.2) s vs 12.1(0.15) s, $P=0.045$. A significant decrease in PAI-1 levels (3.04 (0.1) U/ml vs 2.28 (0.3) U/ml, $P=0.018$) was noted at the same time. No significant changes in the rest of parameters were found during the study period.
Conclusion
GH replacement therapy for 6–12 months led to a significant increase in PT values, while fibrinogen levels did not change. Moreover, GH treatment reduced PAI-1 levels in GHD children, suggesting a beneficial effect of GH treatment on possible risk of future atherothrombosis. Further evaluation of the clinical significance of these changes is needed.

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EP63

Treatment with modified-release hydrocortisone for 6 months: A clinical audit in 15 patients with adrenal insufficiency

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Background
Patients with adrenal insufficiency (AI) exhibit increased morbidity, mortality and impaired quality of life (QoL) and conventional hydrocortisone replacement does not mimic the endogenous circadian pattern and may compromise adherence. A modified – release hydrocortisone formulation (Plenadren) for once-daily use is licensed in order to meet these needs.
Objective
To audit the effects of treatment change from HC to Plenadren in an out-patient, daily-life clinical setting.
Patients and methods
Fifteen consecutive patients with AI and problems with adherence and/or QoL were shifted from HC to Plenadren treatment. The effect of treatment was assessed by clinical biochemistry, DEXA scanning and QoL (AddiQol) before and after 6 months.
Results
Fifteen patients (10F/5M) were included in the audit of whom 8 had primary AI with a mean age of 49.5 years. The mean daily HC dose was 21.4 mg and the mean daily plenadren dose was 20 mg. No significant changes were recorded in fasting lipid levels, morning salivary cortisol, serum electrolytes, HbA1c, or CRP before and after plenadren treatment. Likewise, body composition and BMD were unchanged. The AddiQol questionnaire showed a trend towards improved sleep, less muscle pain and better concentration at 6 months. Fourteen of the 15 patients continued on Plenadren after 6 months.
Conclusion
Plenadren treatment for 6 months in patients with AI was well received but did not translate into detectable changes in clinical biochemistry or body composition. Longer treatment duration and a larger patient group are needed to evaluate the long term benefit of plenadren.

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EP64

Cushing's Syndrome During Pregnancy mimicking preeclampsia – case report

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Introduction
Physiological changes of pregnancy could be similar with classical presentation and biological confirmation of Cushing's Syndrome (CS). To diagnose CS in pregnancy is very difficult especially in previously healthy women. Since the hypercortisolemia in the pregnancy increase maternal and foetal morbidity it is a concern for endocrinologists, gynaecologists, and paediatricians.
Patient case report
Herein, we present young woman (23 years old) admitted to the Genecology Clinic, with uncontrolled hypertension and gestational diabetes. The pregnancy was terminated with an emergency caesarean section at 28 weeks of gestation due to sever preeclampsia. Five months after delivery hypertension, weight gain, poor glycaemic control, irregular menstrual cycles and cushingoid features persisted. She was admitted to the Endocrinology Clinic for further evaluation. Computed tomography revealed right adrenal adenoma, size 32×41 mm. Endocrine evaluation verified increased cortisol and decreased ACTH. There was no plasma cortisol suppression after low- and high-dose dexamethasone suppression tests. Vanillylmandelic acid in 24 h diuresis, plasma catecholamine and chromogranin serum level, were normal. Potassium was decreased, but other electrolytes (sodium, calcium, phosphorus, magnesium) were in normal range. After adequately preoperative preparation, right adrenalectomy was performed. The procedure and postoperative course were uneventful. The histopathological examination confirmed a benign adrenocortical adenoma.
Conclusion
Even though CS in pregnancy is very rare, it is worthy to be considered when pregnant women develop hypertension and gestational diabetes. Delayed diagnosis and treatment could lead to maternal-foetal complications.

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EP65

Potentially aggressive adrenal oncocytoma during pregnancy: about one case

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Oncocytary cells adrenal adenoma or adrenal oncocytoma is an extremely rare tumor, mainly composed by oncocytomes. The diagnosis is exclusively confirmed on histological findings. There are about 50 cases published in the scientific reviews, of which only one case described a pregnant woman.
We report an observation about a 31 years old patient, with no personal antecedent, explored in our unit for an adrenal masse, measuring $71\times58\times46$ mm discovered during an abdominal CT scan done for low back pain.
Patient did not present obvious signs of adrenal hypersecrtion at clinical exam, we noticed some sympathic signs associated to an amenorrhea, and a pregnancy of 8 weeks of amenorrhea was then diagnosed. At CT scan the adrenal masse did not match with the characteristics of an adenomatous one, having a spontaneous density of 40 HU, and an absolute washout up to 33%.
Methoxylated drift and hormonal exploration were normal.
Regarding to the size of this mass and its radiological characteristics with a strong suspicion of malignancy, Surgical management was decides, and patient was treated at 12 weeks of amenorrhea with simple post-operative issues. Histological findings concluded to an adrenal adenoma with oncocytary cells presenting malignant potential (according to BISCEGLIA criteria).
Pregnancy was leaded to its term, with birth of a healthy new-born. The patient was followed for more than one year without recurrence.
Treatment of adrenal oncocytoma should always be surgical, with an exert as large as possible.

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EP66

Primary hyperparathyroidism associated with Cushing syndrome and primary hyperaldosteronism

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Introduction
The simultaneous occurrence in the same patient of more than one endocrinological condition is rare and was described in the multiple endocrine neoplasia (MEN). Here, we report a patient with an unusual combination of primary-hyperparathyroidism, papillary thyroid microcarcinoma, primary-hyperaldosteronism and ACTH-independent Cushing's syndrome.
Case description
A 54-year-old women with a primary-hyperparathyroidism was admitted to our hospital to undergo a parathyroidectomy for a single adenoma and total thyroidectomy for suspicious nodules in which one of it was confirmed histopathologically to be a 3 mm papillary thyroid microcarcinoma. An exploration of a resistant hypertension associated with hypokalaemia was done and the co-secretion excess of aldosterone (aldosterone-renin ratio >23 ng/ng twice) and cortisol (negative overnight and low-dose Dexamethasone suppression with low ACTH level) was confirmed with an abdominal CT-scan showing a 19 mm left adrenal adenoma. The patient has also multiple lipomas.
Conclusion
The multiple endocrine hypersecretion exists and the MEN1 should be considered since there is a considerable number of atypical MEN1 syndrome thus the DNA testing is scheduled.

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EP67

Comparison of biochemical and hormonal parameters in patients with primary adrenal insufficiency of autoimmune and no-autoimmune cause

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Introduction
Primary adrenal insufficiency (PAI) can be of autoimmune origin (AI), non-autoimmune origin (bilateral adrenalectomy, acute hemorrhage, infection) (NAI) or pharmaceutical (mitotane) origin. Studies have shown that these patients develop long-term morbidities and increased mortality due to excessive glucocorticoid tissue exposure. Data about differences concerning hydrocortisone (HC) needs, cortisol hormonal levels and metabolic parameters in these patients are scarce.
Methods
This retrospective analysis included patients with PAI with follow-up more than 5 years (mean follow-up: 9 ± 6.9 years). Patients had two different day curves of cortisol (F) measurements and 24 h urinary cortisol levels (UFC) and were on oral HC replacement treatment (total mg/day).
Results
We included 12 patients with Addison disease (AD), 8 patients under therapeutic mitotane levels (>13 mg/l) and six patients with PAI of other causes (NAI). BMI increases in all groups in the follow up and it is positively correlated with daily HC substitution ($P=0.017$, $r=0.5$). Mitotane group had statistical significant higher BMI at diagnosis compared to the two other groups ($P=0.015$). This difference among groups in the BMI disappears in the follow-up thus probably due to 'Cushing effect'. NAI group had higher HC substitution compared to AD group ($P=0.01$) and higher Hb1Ac and cholesterol levels during follow up compared to AD group ($P=0.02$) and mitotane group ($P=0.05$). As expected HC substitution as well as UFC levels were significant higher in the mitotane group compared to the two other groups ($P=0.0014$, $P=0.05$ respectively). Median F levels were positively correlated with HC substitution ($P=0.027$) (mitotane group was excluded).
Conclusion
Patients with NAI had statistically higher HC substitution as well as Hb1Ac and cholesterol levels in the follow up compared to AD group. Despite the small sample of patients the over-substitution of these patients should be reconsidered regarding the consequences.

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EP68

The role of dehydroepiandrosterone sulphate (DHEAS) in the evaluation of autonomous cortisol secretion in adrenal incidentalomas

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Introduction
Subclinical hypercortisolism (SH) has been reported in 5–20% of patients with adrenal incidentalomas (AIs), with various cardiometabolic consequences. We intended to investigate the contribution of DHEAS to standard testing, as another indicator of autonomous cortisol secretion in AIs.
Materials and methods
Ninety consecutive patients ($n=90$) with AIs were included in a prospective cohort study. SH was diagnosed if ≥ 2 criteria were fulfilled: an overnight dexamethasone suppression test (DST) ≥ 1.8 μg/dl, a 24 h urinary free cortisol (UFC) above the upper limit of normal, midnight/morning serum cortisol ≥ 0.5 and plasma ACTH <10 pg/ml. Age- and sex-specific DHEAS ratios were calculated and a ratio of 1.25 was considered the cut off. Data are expressed as median (interquartile range).
Results
Ten cases of SH were found among the 90 patients (11%), harboring 112 AIs. DHEAS ratio in patients with SH was 1.55 (2.5) and 1.85 (2.67) in non-functional AIs. A DHEAS ratio ≤ 1.25 was not predictive of SH.
Conclusion
DHEAS failed to prove a useful screening tool for SH in patients with AIs in this study. Further study is needed to evaluate its potential as an adjunct to DST.

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EP69

Adrenocortical carcinoma in pregnancy

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Introduction
Adrenocortical carcinoma (ACC) is a very rare tumor. The mean age at onset is between 40 and 50 years. Patients with nonfunctioning ACC report symptoms of abdominal discomfort or back pain due to the large tumor size. Surgery for ACC should be performed by an expert surgeon.
Case
A 29-year-old patient with 25 weeks of pregnancy admitted at our clinic with right side pain. 10×11 cm solid mass on right adrenal gland was detected by ultrasonography. The lactate dehydrogenase level of the patient was 10 times higher than normal ranges. The urinary metabolits were within normal limits. Because of the increase in the size of the mass, the patient underwent operation urgently. The histopathological report indicates an adrenocortical carcinoma and tumor weighting 376 g and measuring $10\times9\times7$ cm. The patient gave birth on the 32nd gestational week. The patient was evaluated after delivery and liver, pulmonary and brain metastases were detected. One week after delivery patient was died in intensive care unit.
Conclusion
Several clinical data shown that the secretion and or proliferation of adrenocortical tumors may have be affected by the hormonal context of pregnancy. Most of patients present with excess steroid hormone or abdominal mass effects. In our patient, a mass was detected in the ultrasonography performed with the cause of side pain. In pregnancy treatment procedure was not still standardized in ACC, but ACC was an aggressive malignant tumor, so our patient

was operated urgently. Because of her pregnancy chemotheraphy was planned after birth. But one week after delivery patient was died.

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EP70

Abnormal aldosterone/renin ratio is common in patients of African compared to European origin, is associated with hypokalaemia, and left ventricular hypertrophy, but is rarely associated with abnormal adrenal imaging characteristics

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Adrenal mineralocorticoid biochemistry differs between people of African and European ancestry. The aldosterone/renin ratio (ARR) is the initial screening test for primary hyperaldosteronism (PHA), but little data exists regarding ethnic variations in this.

Following clinical observation of a high prevalence of abnormal ARR in patients of African origin, we retrospectively reviewed all ARR measurements in a single centre over 10 years. Rates of hypokalaemia and intraventricular septal thickness (IVS, by echocardiography) were studied as end-points of PHA, and adrenal imaging was reviewed. Data were analysed using Student's *t*-test, χ-square test and Mann–Whitney–Wilcoxon test as appropriate.

ARR was available in 1,473 patients, and abnormal in 374 (25.4%). Abnormal ARR occurred in 305/1473 (20.7%) of European and 69/124 (55.6%) of African patients ($P<0.001$). Among those with abnormal ARR, hypokalaemia (<3.5 mmol/l) was documented on at least one occasion in 171/305 (56.1%) European and 43/69 (62.3%) African patients. Median (range) IVS was 1.57(0.78–2.80) cm in African-origin and 1.2 (0.69–2.18) cm in European patients ($P<0.002$). Adrenal adenoma was identified in 2/69 (2.8%) African and 41/305 (13.4%) of European patients ($P<0.005$).

In summary, ARR was abnormal in 55.6% of African-origin patients screened at an Irish hospital, but only 2.8% had demonstrable adrenal pathology. Rates of hypokalaemia were similar between European-origin and African-origin patients, while cardiac hypertrophy was more marked in African-origin patients. These findings have implications for the use of current screening guidelines for ARR in African-origin patients and also for the mechanistic role of aldosterone in hypertensive complications in African-origin patients.

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EP71

Neutrophil-lymphocyte and platelet-lymphocyte ratios as biomarkers in distinguishing adrenocortical adenomas and carcinomas

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The role of systemic inflammation in promoting tumor progression has been a topic of increasing interest. Neutrophil-lymphocyte ratio (NLR) >5 and platelet-lymphocyte ratio (PLR) >190 used as indicators of inflammation have been reported to have prognostic value in numerous solid tumors. The aim of this retrospective study was to investigate NLR and PLR as biomarkers in distinguishing between adrenocortical adenomas and adrenocortical carcinomas (ACC). Nineteen patients with ACC (mean age 54 years, range 24–75; eight male, 11 female) and 22 patients with adrenal adenomas (mean age 47 years, range 28–71; six male, 16 female) were enrolled in the study. In the ACC group, only one patient presented with functional tumor (excess estradiol), whereas all the others were discovered incidentally. Eleven out of 19 patients with ACC were operated laparoscopically, while the open approach was used in eight of them. In the adenoma group, the first presentation of the disease was hyperandrogenemia in one patient, and in the rest of the group, adenoma was discovered incidentally. Open surgical approach was used in one patient with adenoma and the others were operated laparoscopically. The mean size of adenoma was 5.8 cm while the mean ACC size was 9 cm ($P<0.05$). In the ACC group, NLR>5 was found in 26.3% (5/19) patients which was higher compared to 9% (2/22) of the patients with NLR>5 in the adenoma group. PLR>190 was found in 36.8% (7/19) of ACC patients compared to 18.2% (4/22) in the adenoma group. Mean NLRs in the ACC and in the adenoma group were 3.6 and 3.1, respectively ($P=0.886$) and mean PLRs were 219.1 and 143.3, respectively ($P=0.026$). Our results indicate that in addition to tumor size, PLR might potentially serve as biomarker of malignant tumor behavior.

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EP72

Adrenal involvement of Non-Hodgkin's lymphoma: a case report

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Introduction

The involvement of certain organs such as the adrenal gland is rare in non-Hodgkin's lymphoma (NHL). Although lymphomas can involve virtually all extranodal organs, different organs show different frequency of involvement. Adrenal gland involvement is usually bilateral. We report that a rare case of unilateral adrenal involvement of diffuse large B-cell lymphoma presenting with abdominal pain.

Case

A 64-year-old-man presented with abdominal pain, weakness, weight loss. Abdominal computed tomography (CT) revealed 59×53 mm right adrenal mass, 40×25 mm paraaortic lymphadenopathy, multiple solid mass lesions in the spleen and malignant infiltrating mass lesions in the perineal vascular structures. Surgical lymph node biopsy demonstrated a diffuse large B cell lymphoma. The pathology specimens showed neoplastic infiltration of pleomorphic lymphoid cells with scanty cytoplasm, irregular nuclear contour, large nuclei, with one to three peripherally positioned nucleoli. He was treated with rituximab, cyclophosphamide, doxorubicin and vincristine (R-CHOP). The patient tolerated treatment well without significant side effects. After the six courses chemotherapy, the patient's systemic symptoms were improved.

Conclusion

Extranodal organ involvement is more common in non-Hodgkin's lymphoma than in Hodgkin's lymphoma. Systemic chemotherapy has been regarded as the best therapeutic approach for NHL involving rare extranodal sites. Adrenal involvement of systemic lymphoma should be considered when evaluated the adrenal masses.

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EP73

Challenges in differential diagnosis of adrenal incidentaloma or clinical case of multiple myeloma

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Adrenal incidentaloma (AI) in patients with cancer poses diagnostic challenge for doctors. We present clinical case of generalised metastatic bone diseases and adrenal mass.

Male 59 years old asked the second opinion about incidental adrenal mass, which was suspected for adrenal cancer by urologist. His medical anamnesis began in April of 2015 with severe generalised bone pain. The whole body MRI/CT detected multiple bone lesions, adrenal mass (57×45×56 mm, 37 HU) and prostate mass. Urologist studied PSA and carried out prostate biopsy, the results excluded prostate cancer. Basing on size and CT dencity of adrenal mass, the urologist suspected adrenal cancer and prepared to perform adrenal biopsy. First, he decided to get an endocrinologist consultation to exclude pheochromocytoma and ask the second opinion about suspected adrenal cancer. There were excluded pheochromocytoma, subclinical Cushing and adrenal insuficiency. Taking into accout the fact that adrenal cancer metastasis affect liver and lung first, which were abcent in this case, lack of rapid growth of adrenal mass, the suspected diagnosis of adrenal cancer was hardly probable. The suggestion for adrenal

biopsy was refused because of hematologic disturbances and potential hemorrhage. Also there was made an offer to perform the bone lesion biopsy, which is easier and safer to perform. The results were consistent with multiple myeloma. Patient was seen by hematologist, the appropriate treatment assigned. The interesting fact was that the hematologic, bony and urinary signs, which are typical for myeloma, were abcent. Unfortunately, patient died after second cource of chemotherapy.
This case illustrates as diagnostic as administrative issues. First, the urologist did not follow the diagnostic protocol for adrenal incidentalomas, which would have been fatal. Secondly, the management of AI in cancer or suspeceted cancer patients should be absolutely multidisciplinary. Thirdly, untypical signs of the disease requires doctors to be more educated in edjacent specialities.

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Iatrogenic Cushing syndrome and suprarenal secondary insufficiency due to interaction between fluticasone and ritonavir

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Introduction
The interaction between corticosteroids and protease inhibitors (PIs) is a clearly described drug interaction.
Case report
A 44-year-old woman diagnosed with HIV category B3 diagnosed in 1989; severe lipodystrophy. In addition , HCV genotype IA. Bronchial asthma since 2000. Treatment with fluticasone 1 inh/24 h, salbutamol on demand, darunavir 800 mg/day and ritonavir 100 mg/day. He had known lipodystrophy since 2001 and the abdominal perimeter was monitored, aiming to increase it. Likewise, it presented progressive proximal weakness in lower limbs, with increased hair, hair fragility and alopecia reason why it is referred to Endocrinology. Moderate hirsutism, muscular atrophy and in the analytical study: normal FSH and LH are objectified. Testosterone 0.05 ng/ml (0.1–0.9), ACTH 1.0 pg/ml (7.2–63.3), Cortisol am 0.65 µg/dl (4.30–22.40) urinary free cortisol 3.74 µg/24 h (36–137). A Synacten test is performed: Basal 0.52; 30 min 2.33; 60 min 2.84 with ACTH 1 and was diagnosed as having an independent iatrogenic Cushing ACTH syndrome associated with secondary adrenal insufficiency. With this diagnosis he is referred to the pulmonology department for corticosteroid replacement. Inhaled and substitution treatment was initiated with hydrocortisone and went home with a new antiretroviral regimen (raltegravir, tenofovir and abacavir)
Discussion
Fluticasone is a synthetic steroid that is cleared by the cytochrome P450 CYP3A4 enzyme, which is inhibited or potentiated by a multitude of drugs, including ritonavir. As it is not metabolized, an increase in circulating levels leads to a decrease in the secretion of ACTH and therefore a suppression of the adrenal gland with insufficiency of the same and cushing syndrome.
The options are the substitution of Fluticasone by a non-substrate of CYP3A4 such as beclomethasone and the substitution of ritonavir for another antiretroviral. Most cases resolve in about 9–12 months.

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Body composition in women with Cushing's syndrome of different etiology

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Introduction
Cortisol has important roles in the regulation of body composition and hypercortisolaemia have major impact on body fat distribution. The aim of this study was to analyze differences in adipose tissue distribution in women with Cushing's disease and Cushing's syndrome due to adrenal adenoma.
Method
We evaluated 12 women with Cushing's syndrome, six with ACTH secreting pituitary adenomas (Group A) and six with adrenal adenomas (Group B). In all subjects BMI was calculated and body composition assessed by dual energy X-ray absorptiometry. Basal values of serum cortisol, ACTH and DHEA-S were determined at admission to the hospital.
Results
Mean age was comparable between Group A and Group B (44.5 +/− 14.7 years vs. 52.7 +/− 5.6 years, $P=0.23$) while BMI was significantly higher in Group B (32.7 +/− 5.5 kg/m^2 vs. 25.6 +/− 4.3 kg/m^2, $P=0.034$). Group B had significantly higher percent of total body fat (45.4 +/− 4.3% vs. 34.5 +/− 8.4%, $P=0.021$) but borderline difference in trunk fat percentage (Group B 44.3 +/− 6.8% vs. Group A 32.6 +/− 10.7%, $P=0.055$). Main difference in adipose tissue percentage was found on arms and legs, which was higher in Group B (arms 53.6 +/− 8.8% vs. 38.5 +/− 11.9%, $P=0.037$; legs 47.6 +/− 4.4% vs. 39.0 +/− 5.9%, $P=0.022$). There was no significant difference in lean body mass or bone mineral density between these two groups. As expected, ACTH was significantly higher in group A (74.3 +/− 16.4 ng/l vs. 14.7 +/− 7.6 ng/l, $P=0.040$), but with no significant differences in morning cortisol concentrations (Group A 664.2 +/− 210.4 nmol/l vs. Group B 432.8 +/− 146 nmol/l, $P=0.060$), midnight cortisol concentrations (Group A 461.3 +/− 236.2 nmol/l vs. Group B 330.3 +/− 203.6 nmol/l, $P=0.410$) or DHEA-S concentrations (4.9 +/− 5.4 nmol/l vs. 2.8 +/− 3.8 nmol/l, $P=0.564$) between groups.
Conclusion
Our group of women with Cushing's syndrome due to adrenal adenoma had higher BMI and increased total fat adiposity. It was not determined yet if the origin of hypercortisolism, or derangements in other related hormones or metabolic pathways, could possibly influence body composition in those patients.

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Clinical course of patients with adrenal incidentaloma: retrospective analysis of a single center

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In the adrenal incidentaloma (AI) it is fundamental to determine functionality and benignity. The aim of this study was to evaluated the clinical, radiological and hormonal evolution of AI and compare the frequency of autonomous cortisol secretion (ACS) between American and European Guidelines.
Methods
Retrospective evaluation of patients with AI referred to our service in the last 5 years.
Results
140 patients were included, 50.9% were men. At diagnostic, the media of age was 66 ± 11.2 years and the median of size was 20 mm. CT detected the 95% of AI and 80% had an adenoma-like appearance (49.3% left). Hormonal evaluation revealed that 54.3% were nonfunctional (NF), 38.6% possible autonomous cortisol secretion (PACS), 5.7% ACS, 5% Cushing's syndrome (CS) and 1.4% pheochromocytoma (PCC). Considering American guidelines: 87.9% were NF, 9.3% subclinical Cushing's syndrome and 0.7% CS. The majority of patients remained stable. None developed overt CS. The 13.6% showed growth, with a median of 6 mm. Median follow-up: 30 months. There were significant statistical differences ($P<0.05$) between the group of NF and PACS/CS in terms of size and between NF and CS in terms of growth. No differences were observed in terms of sex, age or cortisol-related comorbidities. Seven patients underwent surgery: one PACS, three ACS, two PCC and one adrenal carcinoma. The 4.3% died due to unrelated adrenal disease.
Conclusions
The AI's are predominantly small, benign, nonfunctioning; stable in time, tumor size and hormonal production. The use of the diagnostic criteria for ASC according to European guidelines shows an increase in the frequency of PACS/ACS, therefore, ACTH determination should be considered in the diagnosis.

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EP77

Malignant androgen-secreting adrenocortical carcinoma with adrenal insufficiency: a case report

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Adrenocortical carcinoma (ACC) is a rare malignancy, accounting for 0.02% of all annual cancer. The majority of these tumors are benign, non-functioning adenomas that are incidentally discovered on abdominal image studies. Others are functional adenomas secreting cortisol, aldosterone, or less commonly androgens or estrogens. Pure androgen-secreting adrenal tumors are very rare.
Case report
A 34-year-old female patient presented with pain in the left upper abdomen. A multiphasique CT scan abdomen was done, which revealed large adrenal mass measuring 18×14×14 mm in dimension with central hemorrage. Patient gave history of amenorrhea since 6 months associated with increased hair growth of chest, lower abdomen, and face. Moreover the patient declare recent weight loss (11 kg in 2 months) with asthenia, anorexia, and melanoderma.
On examination, heart rate was 84/min, blood pressure 120/70 mm of Hg. Hirsutism was evaluated based on Ferriman-Gallwey score (result = 13). Biochemical screening showed a total testosterone = 8 ng/ml (0.06–0.82), DHEA sulfate = 3.27 mg/ml (0.4–2.17 mg/ml), 17-hydroxyprogesterone > 20 ng/ml (0.1–0.8 ng/ml), LH = 0.83 mUI/l and FSH = 0.1 mUI/l. The diagnosis of Addison's disease was confirmed by basal serum ACTH = 125.82 ng/l and serum cortisol = 135 µg/l after ACTH test; serum aldosterone and 24 h urinary VMA were normal. A diagnosis of androgen-secreting adrenocortical cancer with adrenal insufficiency was made.
Patient underwent exploratory laparotomy with excision of large adrenal tumor without any complication. The histopathological examination described a mass 21×18×12 mm with microscopique features of tumor cells sharing mild nuclear atypia and rare mitotic figures: histological and immunohistochmical aspect of adrenocortical carcinoma (Weiss score = 3, Ki67 = 10).
On follow-up after 6 months, patient was comfortable, and no longer had amenorrhea or hursitism. Total testosterone was 0.03 ng/ml (0.06–0.82), DHEA-sulfate was 0.174 µg/ml (0.4–2.17 µg/dl) and CT scan abdomen was normale.

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EP78

Hyperaldosteronism screening in Hypertensiologists experience - epidemiological review of over 800 cases

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Primary aldosteronism (PHA) is one of the most common cause of secondary hypertension. It can possibly concern over 10% of hypertensive patients, but often is being under-recognised. The basic tool of case PHA detection is aldosterone to renin ratio (ARR). Appropriate cutoff value of ARR is still under discussion.
We review occurrence of CT/MRI detectable adrenal gland laesions according to assigned ARR cutoff value. Retrospective data from 833 consecutive hypertensive patients of average age 39.85 (S.D.: +/− 15), 449 men and 384 women was analized. ARR > 20, 30, 40 concerned respectively: 12.7%, 7.6%, 4.7%. CT/MRI was performed respectively in patients with ARR > 20, 30, 40 in 55.7%, 66.7%, 69.2%. Laesions in adrenal glands in groups of ARR > 20, 30, 40 concerned respectively: 47%, 52.4%, 56%. The most common CT/MRI findings were adenomas: respectively: 37.3%, 42.9%, 44.4% in groups of ARR > 20, 30 and 40. Less common was nodular hypertrophia: respectively: 10.2%, 9.5%, 14.8% in groups > 20, 30, and 40. The average potassium level in a group of ARR > 20 was 4.05 (mmol/l) (S.D.: +/− 0.46), > 30 3.94 (S.D.: +/− 0.50), > 40 3.93 (S.D.: +/− 0.55).
Average concentration of urine aldosterone in a group > 20 was 14.36 (µg/24 h) (reference value 2.1–18.0 µg/24 h) (S.D.: +/− 10.88), > 30 15.72 (S.D.: +/− 12.33), > 40 17.71 (S.D.: +/− 14.08).
Adrenal lesions in enlarged ARR group were notably more often than adrenal incidentalomas occurrence reported in population (47% vs 2–3%). Higher cutoff ARR value is more specific and allows to reduce costs of confirmative tests. If the ARR over > 40 group we miss 16.95%, in ARR > 30 group we miss 6.78% in compare to ARR > 20. Can we afford missing them considering its' increased cardiovascular risk?
In everyday PHA diagnostics practice there is still lack of "game changer" bringing the final conclusion for diagnostic and profilactic strategies for the whole hypertensive population.

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Clinical, laboratorial and densitometric evaluation of adult women with congenital adrenal hyperplasia

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Introduction
There is paucity of data comparing bone densitometry and body composition in adult women with congenital adrenal hyperplasia (CAH) treated with glucocorticoids since childhood and the same parameters in healthy women of the same age and BMI.
Methods
20 women with classical CAH (35% simple virilizing, 65% salt losing), aged 16–45 years, had anthropometric, laboratorial and densitometry exam (DXA) for bone mineral density (BMD) (L1–L4, total femur and femoral neck). Laboratory determinations during follow-up were recorded and expressed as average levels. 18 control women of the same age and BMI as patients realized densitometric evaluation for mineral density and body composition.
Results
BMI ranged from16 to 41 kg/m^2 (average 26.3; 25% overweight and 30% obese), whereas height varied from136 to167 cm (average 151 cm). During follow-up, 35% patients were treated with prednisone as the sole glucocorticoid type, 50% used prednisone and dexamethasone and 15% other combinations. Average daily dose of prednisone was 7.5 mg (hydrocortisone equivalent dose 37 mg/day) and 70% used fludrocortisone (average 0.1 mg/day). Combined oral contraceptives were taken by 65% women. Half of women were not controlled based on average testosterone and androstenedione levels, 40% presented altered glycemic status, 26% elevated LDL cholesterol, 21% elevated triglycerides, 68% low HDL-cholesterol levels. No patient presented low BMD according to Z-score and compared to control group. Fat-free mass was considerably lower in patients than controls (33.726 vs 40.637 kg) and it correlated positively with testosterone levels (R 0.52, *P* 0.027). Women using fludrocortisone had lower body fat mass than women who used only glucocorticoids (34.3 + 12.3% vs 44.9 + 3.8%).
Conclusion
Adult women treated for classical congenital adrenal hyperplasia had important metabolic disturbances and alterations in body composition. Nevertheless bone mass was preserved, possibly because hyperandrogenism was not controlled most of the time.

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EP80

The effect of subclinical hypercortisolism on bone mineral density in female patients with adrenal incidentalomas

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To investigate the prevalence of SH and osteoporosis in female patients with unilateral AIs (UAIs) and bilateral AIs (BAIs).
We enrolled 106 female patients, 68 (64.2%) with UAIs and 47 (35.8%) with BAIs. SH was diagnosed in the presence of serum cortisol levels after 2-day low-dose dexamethasone suppression test (LDDST) > 50 nmol/l with at least one of the following parameter (midnight serum cortisol > 208 nmol/L, 24-h urinary free cortisol > 245 nmol/24 h, or ACTH < 10 ng/l). BMD was measured with dual-energy X-ray absorptiometry at lumbar spine (LS), femoral neck (FN), and total skeleton.
No difference was noted in age, BMI, percent of postmenopausal women and years since menopause. The overall prevalence of SH was 20.2%, and was more prevalent in BAIs than UAIs patients (36.1% vs 11.8%, respectively, $P = 0.003$). The largest tumor diameter was similar in patients with UAI and BAI ($P = 0.254$).

After adjustment for BMI, waist, and presence of BAIs, SH were associated with adrenal mass size (odds ratio (OR) = 1.101, 95% CI 1.041–1.166, $P = 0.001$) and age (OR = 1.086, 95% CI 1.021–1.155, $P = 0.009$). LS-BMD and total-BMD were lower in BAIs than in UAIs patients (0.94 ± 0.13 vs 0.86 ± 0.17, $P = 0.015$, and 1.08 ± 0.18 vs 1.02 ± 0.14, $P = 0.029$). There were no differences in FN-BMD. Patients with BAIs had an increased frequency of osteoporosis (46.41% vs 23.5%, respectively, $P = 0.036$). The presence of osteoporosis was associated with SH (OR = 5.775, 95%CI 1.423–23.426, $P = 0.014$) and lower BMI (OR = 1.226, 95%CI 1.071–1.405, $P = 0.003$), after adjusting for age, menopause and vitamin-D.

This study suggests significantly higher prevalence of SH in patients with BAIs than in patients with UAIs. Tumor mass could be of importance for the amount of autonomous cortisol production. The prevalence of osteoporosis was higher in patients with BAIs due to SH.

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EP81

Long term follow up of patients with adrenal incidentaloma and 'autonomous cortisol secretion'

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The aim of this study was to compare the long-term co-morbidities and biochemical data between patients with adrenal incidentaloma and 'autonomous cortisol secretion' who were treated surgically and conservatively.

Methods

The research of the database of the patients with adrenal incidentaloma diagnosed between 2007 and 2014 was performed. Among them, 43 patients with 'autonomous cortisol secretion' were identified and invited for a follow-up visit. Diagnostic criteria for 'autonomous cortisol secretion' were: cortisol- > 83 nmol/l after 1 mg dexamethasone suppression test plus one additional criteria (suppressed ACTH secretion or elevated urinary free cortisol). At follow-up visit the anthropometric as well as biochemical data were collected (blood glucose, lipid panel test, HOMA index, cortisol after 1 mg dexamethasone, urinary free cortisol, and ACTH). All patients were evaluated for hypertension, dyslipidemia, osteoporosis and diabetes mellitus/impaired glucose tolerance.

Results

Of the 43 invited patients, 26 patients performed follow up visit (4 males). Among them, 17 patients were treated surgically and 9 were treated conservatively. Median follow-up was 6 years (range 2–16), median age at follow-up was 62 years (range 41–76). There was no difference in BMI at baseline and at follow up in both groups. In the group of surgically treated patients, during follow-up period one patient was diagnosed with arterial hypertension, 4 with hyperlipidemia, and one with diabetes mellitus. Nevertheless, nine out of 12 patients with hypertension in the surgical group reported improvement/disappearance of arterial hypertension at the follow-up visit. Among conservatively treated patients, six out of nine patients had no difference in co-morbidities, one was newly diagnosed with osteoporosis, one with arterial hypertension and one with renal insufficiency. Conclusion: Patient who underwent surgery for 'autonomous cortisol secretion' experienced improvement in the regulation of hypertension after medium follow-up of 6 years. No other significant differences were found in the prevalence of comorbidities between conservatively versus surgically treated patients.

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Adrenocortical carcinoma - casuistic analysis

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Introduction

Adrenocortical carcinomas are rare neoplasms with an incidence of 0.7 to 1.5 per million/year. Diagnosis often requires a multidisciplinary approach. When the disease is confined to the adrenal gland, absolute criteria defining malignancy, do not exist, however a score of Weiss> or =a 3 is considered diagnosis. The prognosis is usually reserved and conventional chemotherapy is not curative.

Material and Methods

Retrospective analysis of the clinical and demographic characteristics, review of the anatomopathological and therapeutic criteria of patients with adrenocortical carcinoma treated at our Institution between 1999 and 2015.

Results

Twenty-two patients with a mean age of 56 years were evaluated, 50% of cases were male. The majority of patients (63.6%) were symptomatic and pain was the most frequent symptom (57.1%). All patients underwent surgical treatment. Multiorgan resection was performed in 5 cases (22.6%). The surgery was R0 in 72.7%. After histological examination, 72.7% presented Weiss score> 2. Adjuvant therapy was performed in 5 patients (22.6%). Considering the revision of the Weiss score, TNM staging and margins status, 50% of the patients would had indication for adjuvant treatments. In this series, the relapse rate (local or distance) was 38.1% (8 cases) and the overall survival at 5 years was 62%; which compares favorably with that described in the literature.

Conclusions

The rarity of this pathology makes diagnosis and therapeutic orientation difficult. A rigorous and standardized histological evaluation is imperative to ensure the most appropriate adjuvant treatment. The referral of this patients to centers of expertise is essential, with the hope that new target therapies will lead to better results.

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EP83

A near miss on blaming the heart: a rare case of Adrenocortical carcinoma with thrombus extension into right atrium and Cushing syndrome

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A 39 year old female patient presented with one week history of Shortness of breathing. Over the last four months she noted bilateral leg swelling, which failed to improve on diuretic. Examination revealed no other evidence of fluid overload or heart failure. An element of right heart strain rather than failure was raised on cardiologists review. Subsequently, an echo showed a friable mass extending form inferior vena cava to right atrium into proximal left ventricle. The nature of which was revealed to be a tumor thombus extending from the upper pole of right kidney with resultant pulmonary emboli. To this end, an impression of invasive renal carcinoma was made. Until endocrinology review for erratic hyperglycemia, when the patient reported irritability, 6 weeks amenorrhea, change in weight distribution and facial hirsutism in addition to abdominal striae on examination. Hence,the diagnosis shifted to Adrenocortical carcinoma with Cushing. Tertiary center was consulted. In the meantime, Mitotane was started gradually, alongside Hydrocortison. It was a difficult time for the patient who preferred palliative support at home. Unfortunately, few days after discharge she was readmitted with hypoglycemiia, metabolic acidosis and liver impairment. She was treated as Addison crises, though cortisol levels came normal later. Liver involvement was not confirmed to be Mitotane related toxicity or ischemic injury with progression of malignancy.

Unfortunately, she did not survive his well-known aggressive tumor. ACC are tumors are rare tumors and presentation with such vascular invasion is an additional rarity. As clinician on medical take, there is tendency to overclaim heart failure. Having high index of suspicion for patients with Cushing syndrome is central, although not all tumors are functional. The definitive management of ACC is surgical which is not always feasible, particularly with such vascular extension. Wider scale clinical studies pave the management of ACC and optimize Mitotatne therapy.

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EP84

Congenital Adrenal Hyperplasia due to 11β-Hydroxilase Deficiency: clinical and molecular studies of two novel families with variable phenotypes

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11β-hydroxylase deficiency is the second most frequent cause of congenital adrenal hyperplasia (CAH), corresponding to approximately 5% of cases., and caused by inactivating mutations in the *CYP11B1* gene. We aimed to describe four new cases from two different families with a clinical diagnosis of 11β-hydroxylase deficiency. Family 1: Two siblings born from consanguineous parents. A 31-year-old (yo) woman presented at 5 yo with genital ambiguity (Prader II), high blood pressure (HBP) and precocious pubarche (PP). She lost follow and returned after 3 full term normal pregnancies while using prednisone. 4 years after last gestation, she remained normotensive without any treatment. Her 24 yo brother presented at age 7 yo with PP, hypokalemia and HBP, when glucocorticoids and anti-hypertensives were started. He had low treatment adherence and evolved with persistent hypertension and left ventricular hypertrophy. Family 2: A 2.9 yo boy presented with PP and high BP, managed with hydrocortisone and anti-hypertensives. His sister presented at 21 days of life with genital ambiguity and salt wasting, managed with hydrocortisone and oral sodium. A detailed steroid profile was performed in all subjects, which confirmed the diagnosis. The CYP11B1 coding region of the patients' and their parents' was automatically sequenced. In the two siblings from Family 1, a homozygous splice site point mutation, IVS4 ds-1 G>A, was identified in exon 4 (g.3132G> A). In Family 2, both siblings harbored a nonsense mutation in exon 6 (c.1066 C> T), which generates a truncated protein (p.Q356X). The mutations presented herein were associated with a highly variable phenotype, from a mildly virilizing phenotype to a high degree of virilization with hypertension and with salt wasting, which is unexpected. Further studies of variants in other genes associated with hypertension, in compensatory pathways of steroid synthesis and metabolism, or the verification of chimeric CYP11B genes are needed to clarify the phenotypic heterogeneity.

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EP85

'Record-breaking hyponatraemia' with Addison's disease

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Addisons disease is a rare but potentially life threatening endocrine disorder. It is well-known for disguising as a variety of presentations before diagnosis. Here we present a case report of Addison's disease presenting with very severe hyponatraemia. A 35 year old lady was admitted with lethargy, low mood, weight loss and feeling generally unwell for the last 3 months. Six weeks prior to her admission, her GP arranged some routine investigations including U&E which were normal with a Na of 137. He later prescribed her Mirtazapine for her low mood and anxiety which she took for 4 days. This made her feel more unwell and triggered the hospital admission. She looked tanned but there was no buccal or palmar pigmentation. She was alert with normal cognition.

Admission blood results showed a plasma Sodium of 94 mmol/l, K 5.7 and normal urea/creatinine. Further investigations showed: Serum Osmolality 252, Urine osmolality 192, Urine Na 27, TSH 3.2 and random cortisol 290. She was monitored on ITU and was given normal saline and IV Hydrocortisone for a presumed diagnosis of Addison's disease. Her Sodium level slowly came up to 114 and then to 118 over the next few days. The short synacthen test showed a flat response with the following Cortisol values: 0 min 240, 30 min 242 and 60 min 260. She denied taking exogenous steroids in any form. Later her ACTH came back very high (>2000) with positive anti-adrenal antibodies confirming primary adrenal insufficiency. The Renin/Aldosterone results are still awaited. She transiently developed behavioral disturbance with strange affect raising the suspicion of osmotic demyelination. Fortunately this resolved with reducing the dose of Hydrocortisone suggesting 'steroid psychosis' as cause of the behavioral symptoms. The sodium level stabilized in the low 120's but increased further slowly with addition of Fludrocortisone.

This case demonstrates the unusual presentation of Addisons disease with very severe hyponatraemia with surprisingly few neurological signs or symptoms. It also highlights theproblem of antidepressants potentially exacerbating hyponatraemia in these patients.

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EP86

24 hour ambulatory blood pressure levels according to adrenal adenoma size

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Aim

The etiology and underlying pathology of non-functional adrenal adenoma has not been clearly defined, yet. Blood pressure levels according to adrenal adenoma size has not been evaluated, yet. Therefore, we evaluated 24 hour ambulatory blood pressure levels in patients with non functional adrenal adenoma.

Materials & Methods

We studied thirty newly diagnosed adrenal adenoma patients in a tertiary health-care center. They grouped in two categories according to adenoma size. Cut-off size was taken 23 mm. 24 hour ambulatory blood pressures were evaluated in all participants. Delta blood pressure was found by calculating the difference between maximum and minimum blood pressure values.

Results

There were 17 patients with lower adenomas size, which was smaller than 23 mm, the remaining 13 patient's adenomas size was equal or higher than 23 mm. Patients with higher adenomas size had statistically higher systolic delta levels compared to lower size group (70.84 ± 34.9 to 51.29 ± 18.0, $P=0.004$). Additionally; the maximume systolic (165.6 ± 28.7 to 152.0 ± 23.1) and maximum diastolic blood pressure (115.1 ± 37.8 to 100.2 ± 14.9) were higher and also minimum systolic (94.76 ± 11.05 to 100.70 ± 18.60) and minimum diastolic blood pressure (60.69 ± 9.01 to 62.41 ± 12.62) were lower in this group. However; the differences did not reach statistically significance.

Conclusion

Delta systolic blood pressure has been found toe higher in higher adenomas size group. Further studies are necessary to better clarify the association between blood pressure and non functional adrenal adenoma.

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Adrenal Medulla

EP87

Coexisting Graves's disease and pheochromocytoma

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Introduction

Although Graves' disease is often accompanied by other autoimmune diseases, only a few cases of Graves' disease accompanied by pheochromocytoma have been described.

Herein we report a rare case of coexisting Graves' disease and pheochromocytoma.

Observation

A 50-year-old male patient was referred to our department for the evaluation of right adrenal incidentaloma of 80*66 mm. He had a history of coronary disease and he presented with heat intolerance, diaphoresis, palpitations, intense headaches, excessive nervousness, mood disturbances as well as a rapid weight loss of 30 kg during the last one year.

On physical examination, he had a body weight of 53 kg, a body mass index of 16.5 kg/m^2 and a blood pressure (BP) of 120/75 mm Hg in supine position and 95/60 in standing position.

However his blood profile showed paroxysmal hypertension with peaks of 160/110 mm Hg. The pulse rate was 132 beats per minute (bpm). He had neither goiter nor exophthalmos. Electrocardiogram (ECG) showed a regular sinus tachycardia at 138 bpm with signs of left ventricular hypertrophy.

Laboratory tests indicated diabetes mellitus with a fasting blood sugar of 2.86 g/l and a glycated hemoglobin of 7.9%, hyperthyroidism with a low TSH of 0.05 µIU/ml, an elevated free T4 of 1.96 ng/dl and urinary metanephrines and normetanephrines were greater than 20 time normal values. TSH receptors antibodies were positive.

Thyroid scintigraphy showed homogeneous increased uptake involving the whole thyroid gland.

The diagnosis of coexisting Graves' disease and pheochromocytoma was established. Treatment with prazosin, benzylthiouracil and insulin was then initiated. Propranolol was added progressively. The patient was planned for right adrenalectomy after achieving euthyroid state.

Conclusion
Pheochromocytoma and Graves' disease are known by their similar clinical features making their differential diagnosis difficult. In our case, adrenal incidentaloma evaluation had revealed the pheochromocytoma. Otherwise, a meticulous physical examination and detailed laboratory investigations are needed in order to make a precise diagnosis.

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EP88

Pheochromocytoma in neurofibromatosis type 1

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Background
Individuals with neurofibromatosis type-1 (NF1) carry an increased risk of pheochromocytoma (PHEO). Detection strategy is unknown but most experts recommend screening if hypertension develops.
Objective
Report the characteristics of PHEO in patients with NF1 (NF1 group) and compare them with non-NF1-associated PHEO (non-NF1 group).
Methods
Retrospective cohort study of patients undergoing PHEO resection in two Spanish tertiary hospitals, from 1980–2016.
Results
Of 78 patients undergoing PHEO resection, 5 (6.4%) had NF1. NF1 patients were younger than those with non-NF1 (mean age 41.8 vs 52.5 yr, $P=0.068$). Males comprised 60% versus 40% of the NF-1 group and non-NF1 group, respectively. PHEO was incidentally diagnosed in 3 of 5 (60%) from NF1 group and only in 29 of 73 (39.7%) from non-NF1 group ($P=0.395$). Remaining NF1 cases were diagnosed by screening (hypertension, $n=1$) and compatible adrenergic clinic ($n=1$). Hypertension was present in 2 (40%) NF1 patients and in 33 (45%) non-NF1 patients. Urinary and/or plasma catecholamines were elevated in all NF1 patients and in 55 (88%) of non-NF-1 group. There was no significantly difference ($P=0.207$) in tumor size between both groups of patients (median 4.6 cm vs 5.6 cm in NF1 and non-NF1 patients, respectively).
Conclusion
In our series, age at diagnosis and gender were similar in NF1 and non-NF1 PHEO patients. NF1-associated PHEO is diagnosed incidentally in more than half of the patients. Although all NF1-PHEO tumors were functioning, only two of five patients had hypertension. It is necessary to keep in mind the possibility of developing PHEO in NF1 patients even in those non-hypertensive patients. On the contrary, in all patients with PHEO is advisable to search clinical criteria used to diagnose NF1, and thus confirming an often-delayed diagnosis.

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EP89

Should all patients with Neurofibromatosis type 1 undergo biochemical screening for Pheocromocytoma?

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Pheocromocytomas (PHEO) are catecholamine secreting tumours which can occur sporadically or as part of other hereditary/familial syndromes including Neurofibromotosis 1 (NF-1). Unlike the case with other genetic syndromes, the current neurofibromatosis guidelines do not recommend a routine hormonal screening strategy for PHEO in the absence of hypertension or other symptoms. In this paper we describe 2 asymptomatic and normotensive patients with NF-1 where secretory PHEO were incidentally diagnosed. The first patient is 61- year old female with a history of NF-1 who received a diagnosis of takotsubo cardiomyopathy and was found to have an incidental adrenal mass of 2.4 cm where subsequent investigations confirmed a diagnosis of secretory PHEO.The second patient is a 44 - year old female with also a background of NF-1 who was found to have a $7.8 \times 7.0 \times 5.8$ cm adrenal adenoma where further work up confirmed PHEO. Both patients underwent adrenalectomy and the histology confirmed the diagnosis and their catecholamines level normalised eventually. Undiagnosed PHEO will put patients at unnecessary risk from having an adrenergic crisis and even death. These cases highlight the importance of considering routine biochemical screening for a catecholamine secreting tumour in all patients with NF-1 to prevent the development of catastrophic events in the future.

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EP90

Pheochromocytoma in pregnancy

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Introduction
Pheochromocytoma is a tumor originating from the chromaffin cells. These tumors secrete catecholamines which act on target organs and cause hypertensive crises. They are rare during pregnancy, and a differential diagnosis must be carried out mainly with pregnancy-induced hypertension.
Case
A 27-year-old patient in week 17 of pregnancy admitted to our clinic with hypertension and 45×55 mm heterogeneous nodular lesion in left surrenal. The hospitalized patient had tachycardia and hypertensive episodes despite the treatment. Urinary catecholamine and metanephrine collections revealed elevated norepinephrine and normetanephrine. Magnetic resonance imaging identified a adrenal adenoma. After subsequent pharmacological treatment with alpha and beta blockers, a left adrenalectomy was performed laparoscopically. The histopathological report indicates pheochromocytoma (Pheochromocytoma of the Adrenal gland Scaled Score: 6) and tumor weighing 70 g and measuring $6.5 \times 5.5 \times 3.5$ cm. After the surgery urinary catecholamine and metanephrine collections was normal. Postoperatively the patient with 24 weeks gestation had no antihypertensive need.
Conclusion
Pheochromocytoma in pregnancy can cause the death of both the fetus and the mother. This issue should be remembered in hypertensive pregnancies. The approach to the biochemical diagnosis is the same as for the nonpregnant patient. MRI (without gadolinium enhancement) is the preferred imaging modality, and ^{123}I-MIBG is contraindicated. Adrenal pheochromocytomas should be removed promptly if diagnosed during the first or second trimester of pregnancy. In our case, its recognized with new onset hypertention and adrenal tumor was removed in the 2nd trimester.

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EP91

The role of p27 in pheochromocytoma development

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Defective p27 function predisposes mice and rats to pheochromocytomas (PCC), and reduction of p27 repression is a feature of human PCCs. These findings suggest that p27 plays a role in PCC tumorigenesis. Recently, it was reported that p27 indirectly regulates gene transcription by associating with transcription factors (TF) and inhibiting gene transcription at specific promoters.
We hypothesized that defective p27 promotes tumor formation in adrenomedullary cells because of aberrant gene expression. To address this hypothesis, we used normal adrenomedullary tissue from wild-type rats or human individuals and performed chromatin immunoprecipitation-sequencing (ChIP-Seq). DNA sequences bound by p27-contaning protein complexes were immunoprecipitated from rat and human tissue extracts using an anti-p27 antibody coupled with magnetic beads. DNA sequences were identified by quantitative next generation sequencing (NGS).

We successfully pulled down DNA sequences with the anti-p27 antibody, indicating that p27, together with unknown transcription factors or co-factors binds the chromatin in adrenomedullary cells. DNA sequences bound by the p27-containing complexes were mapped on the rat/human genome and analyzed using both Genomatix and MEME suite software to identify the most enriched TFs and TF binding sites (Tcf19, Tcf4, Znf423, Runx1, Ascl2, Lhx4). The binding between p27 and these selected TFs is being verified by immunoprecipitation. The association of p27-containing complexes to specific promoters of these identified genes is currently being validated. The p27-dependent regulation of the expression of selected target genes will be verified by modulating p27 levels in PCC cell lines. The significance of the p27-dependent gene expression will also be obtained by analyzing the expression of these target genes in normal adrenal medulla and PCC of MENX-affected rats (with loss of functional p27).
In conclusion, the observation that p27 may regulate gene transcription will give insight into the pathomechanisms associated with reduced p27 function specifically in adrenomedullary cells.

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EP92

Role of microenvironment on metabolic control of murine pheochromocytoma SDHB silenced cells

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Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors. About 30–40% of Pheo/PGLs are due to a germ-line mutation in one of the 13 main susceptibility genes which include the genes encoding the four subunits of the succinate dehydrogenase (SDH - mitochondrial complex II). In PHEO/PGL due to SDHB mutations up to 80% of affected patients develop metastatic disease and no successful cure is at present available. Tumor microenvironment plays a pivotal role in modifying the metabolism and the functional characteristics of tumor cells, becoming a potential therapeutic target. To obtain an experimental model resembling the in vivo conditions of the SDHB-mutated PHEO, we evaluated the effects of SDHB silencing and microenvironment on metabolism in the mouse tumor tissue-derived cell line (MTT), cultured alone or in association with mouse primary fibroblasts (here representing the tumor microenvironment). SDHB silenced cells showed a significant increase of both glucose and lactate uptake, and an increase of intracellular lactate compared with control. This increase was even more evident when SDHB silenced cells was co-cultured with mouse primary fibroblasts. The expression levels of monocarboxilase transporter 4 (MCT4), responsible for the transport of lactate from the intracellular to the extracellular space, was found upregulated in fibroblasts in co-culture with tumor cells. Consequently, in co-cultures, primary fibroblasts showed an increase of extracellular lactate. Surprisingly, SDHB silenced cells in co-culture showed a reduction of ATP levels compared to SDHB cultured alone and control cells in co-cultures. Our data demonstrate that SDHB silencing strongly affects tumor metabolism, and these changes are more evident in co-cultures. The comprehension of the mechanisms driving these changes in tumor metabolism may suggest new therapeutic targets.

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EP93

Role of microenvironment on proliferation and migration of an SDHB silenced murine Pheochromocytoma cell line

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Paragangliomas are rare neuroendocrine tumors derived from neural crest cells: if localized in the adrenal medulla they are called Pheocromocytomas (Pheo).The 30–40% of Pheo are mutated in one of the susceptibility genes among which there are genes encoding for the four subunits of the succinate dehydrogenase (SDH). Germ line mutations of SDHB are metastatic in about 80% of the cases. Surgery is the current therapy, but in presence of metastasis there is no effective treatment. Using shRNA, we stably silenced for SDHB a Pheo murine cell line (MTT). The proliferative growth of non-silenced cells (CN) was higher than that of the silenced ones (B-). However, in co-culture with fibroblasts, the proliferation of B-was higher than that of the CN cultivated in the same conditions.
When cultured in fetal-bovine-serum (FBS), B- cells tended to aggregate more than the CN. When FBS was not present, both the cells lines lost this characteristic. When cultured in conditioned medium from activated murine fibroblasts (CAF), the aggregating effect disappeared, the cells assumed a longer shape and started migrating.
To understand whether this change corresponds to an epithelial to mesenchimal transition (EMT), we are evaluating the EMT markers and the expression of metalloproteases either secreted in the medium or expressed on membranes. To understand if the cross talk between fibroblasts and tumor cells was due to a signal mediated by receptors, we evaluated the phosphorylation of mTOR, Akt and ERK in B- and CN cells without detecting any difference.
These preliminary data suggest that the microenvironment, here represented by fibroblasts, affects the behaviour of cancer cells and studies on this interaction are needed to identify new therapeutic targets in SDHB mutated tumors.

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EP94

Pheochromocytoma: a clinical and pathological study

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Objective
To assess clinical features, diagnosis, treatment and outcome in patients with pheochromocytoma surgically treated in the past 3 decades in two tertiary referral hospitals.
Methods
A retrospective study on clinical and pathological characteristics, treatment, and outcome in patients with pheochromocytoma followed up in specialized neuroendocrinology units who underwent surgery in the period 1981–2016 was performed.
Results
81 patients (45 women (56%); age 51 ± 15 year (range, 13–76)) were studied. The tumor was sporadic in 68 patients (84%) and familial in 13 patients, more frequently in the context of a MEN type 2 ($n=6$).10% of the pheochromocytoma were bilateral. Most of the patients (66%) were symptomatic. The main complains were the classic triad (27%), and hypertensive crisis (27%). 40% of the pheochromocytoma were incidentally discovered on imaging investigations. 47% of patients were hypertense at diagnosis. 24-h urinary catecholamines excretion was determined in 80% of patients, being elevated in 75% of cases. Fractionated urinary metanephrines were only determined in 23% of patients, and were elevated in 84%. Abdominal CT was the most used imaging technique (87%, $n=68$), followed by ^{123}I-MIBG scintigraphy (54%, $n=42$) which detected 88% of those tumors ($n=37$). MRI was performed in 50% of the patients, 87% of those tumors were hyperintense in T2. 89% ($n=65$) patients had a preoperative alpha-adrenergic blockage. 17 patients (22%) had a complication during surgery, being hypertensive crisis the most common complication (12.5%, $n=10$). Median tumor diameter was 5.9 ± 2.8 cm (range, 1.5–13). 15% of pheochromocytomas had vascular invasion, 15% had capsular invasion and 23% presented necrosis. Only 6% presented ganglionar or distant metastasis. 68 patients were followed in our two centers, 55 patients (81%) were cured, 4 of them (6%) had persistent disease and 9 (13%) had recurrence after surgery.
Conclusion
Pheochromocytoma in our series is generally a large, symptomatic and sporadic tumor. Incidentally discovered pheochromocytoma is common. Abdominal CT is the preferred imaging technique for localization. Surgical complications are common. Despite the high rate of vascular invasion in the histopathological study, ganglionar and distant metastasis are rare. The presence of cases with persistent and recurrent disease after surgery requires a long term follow-up. these tumors.

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EP95

Biochemical testing for pheochromocytoma

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Introduction
Biochemical testing for Paraganglioma/Pheochromocytoma (PGL/PHEO) is recommended in patients with classical symptoms, in those harbouring an adrenal incidentaloma and in patients who have a hereditary risk for developing a PGL/PHEO. Measurements of plasma free metanephrines and/or urinary fractionated metanephrines provide a highly sensitive test for diagnosis but false-positive results remain a problem.
Aim
Comparative analysis of plasma and urinary metanephrines results in a group of individuals suspected of having PGL/PHEO.
Subjects and methods
Retrospective analysis of tests performed at a tertiary hospital during the year 2015 (January 1st-December 31th) and correlation with imaging studies and clinical data.
Results
686 measurements of urinary and/or plasma metanephrines, ordered by physicians of different medical specialties, were performed. From the analysis of these results, we identified 124 patients with both measurements; they were 77 women and 47 men with a mean age of 47.3 years (range 6–82). The main reason for testing was therapy-resistant or paroxismal hypertension ($n=68$; 54.8%) followed by the presence of an adrenal incidentaloma ($n=13$,10.4%). Abnormal high values were observed in 56 patients: in 44 (45.2%) only abnormal urine values, in 6 (4.8%) both urine and plasma abnormal values and in 6 (4.8%) only abnormal plasma values. 3/6 patients who presented elevation of urinary and plasma metanephrines had histologically proven disease (2 PHEO, 1 abdominal PGL). Among the patients with normal plasma metanephrines and high urinary metanephrines only one (2.3%) had a bilateral pheochromocytoma in the context of a MEN2A syndrome. None of the 6 patients with normal urinary metanephrines and increased plasma metanephrines had disease.
Conclusion
In the present series, all patients with a histologic diagnosis of PGL/PHEO had elevated urinary metanephrines regardless, in one case, normal plasma metanephrines. On the other hand, the frequency of increased urinary metanephrines without a positive imaging was very frequent.

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EP96

Paraganglioma and Fallot Tetralogy: case report

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Introduction
Catecholamine secreting tumors are rare neoplasias. About 15% are paragangliomas. If untreated, they are almost invariably lethal. Surgery is the only curative therapy.
Case report
A female caucasian patient aged 32 was evaluated in the endocrine department. She had a dramatic medical history: Fallot's Tetralogy was diagnosed soon after birth but was not corrected. Only a Blalock-Taussing shunt was performed after three isquemic strokes due to endocarditis, when patient was 22. She suffered from sequelar right-side hemiparesis and epilepsy. She had also glucose-6-phosphate desidrogenase deficiency. At 32 she was assisted at the emergency department because of recent vomiting, headache and arterial hypertension. She had a recent weight loss with a BMI of 16 kg/m^2. Examination revealed depressed mood, orthostatic hypotension, holosystolic aortic bruit and chronic hypoxia signs. Several hypertensive paroxysms (maximum value: 240/140 mmHg) with diaphoresis were documented. Urinary normetanephrine and metanephrine were very high (227 and 58 times higher than the upper limit of the reference range) with a paradoxal increase in clonidine test. The CT scan revealed a solid hypervascular right paramedian retroperitoneal tumor with 49 mm of diameter at the level of the superior mesenteric artery with strong uptake in I^{123}-MIBG scintigraphy. Surgery was uneventful after careful pre-operatory preparation with α- and β-blockers and volume expansion. Five months later the patient recovered weight and was normotensive without antihypertensive drugs. Succinate dehydrogenase mutations (SDHA, SDHB and SDHC) were not found.
Conclusion
We report a challenging situation, life-threatening without surgical treatment, but with a high surgical risk due to the severe comorbidities. A positive outcome was strongly dependent on the multidisciplinary collaboration of different departments.

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EP97

Retrospective audit at a UK teaching hospital of phaeochromocytomas and paragangliomas against the 2016 guidelines

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Introduction
In this audit we explored the treatment and follow up of pre-2016 cases against the 2016 European Society of Endocrinology (ESE) guidelines on PPGL follow-up.
Results
Demographics of the patients revealed 50% were male with median age (45 ± 5), 82% of patients underwent surgery of which 73% were diagnosed with adrenal phaeochromocytomas & 27% with paragangliomas. Only 64% of surgical cases were followed up in clinic in the last year. Of all surgical cases only 73% had evidence of undergoing genetic testing. In the first year post surgery the following appropriate biochemistry screening was performed: Chromogranin A = 36.5%, (27% unknown), Urinary MN or catecholamines = 64% (27% unknown), Calcium = 64% (27% unknown), PTH = 56%, (unknown in 27%), Calcitonin = 46% (27% unknown), CEA = 0% (27% unknown). In the first year post surgery between 9% and 27% of patients underwent USS/CT/MRI/MIBG/PET scan of neck or abdomen appropriately.
Discussion
The recommendations made in these guidelines have been implemented locally and a local registry of cases is in development to improve follow up of cases (see poster for further details).

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EP98

Pheochromocytoma – surgical outcomes

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Objective
To retrospectively evaluate the results of the pheochromocytoma surgery in our institution assessing the surgical complications, perioperative hemodynamic instability and oncologic outcomes.
Methods
The medical records of patients admitted for pathologically confirmed pheochromocytoma between 2000 and 2015 were reviewed. Patients with paragangliomas were excluded.
Results
We identified 40 patients with 43 resected pheochromocytomas. The mean age was 47 years with an equal distribution between genders. Twelve cases (30%) had a syndrome known to have an increased incidence of pheochromocytoma. The mean tumor size was 7 cm (range of 1.5–17.2 cm). Most of the lesions were functional (95%) and preoperative alpha-blockade has been instituted in 93% of the patients, with 48% having a beta blocker simultaneously. Fourteen cases (30%) underwent a minimal invasive approach. The mean operative time was 150 min and the median of intraoperative blood loss was 150 ml. More than a half of the patients (54%) had a hypertensive crisis at some point during surgery, almost always associated with manipulation of the lesion. Ten patients (25%) required vasopressor support after adrenal gland removal. Two patients (4.6%) had CTCAE 3/4 complications. There were no cases of mortality and the median length of stay was seven days. Two (5%) cases were defined as malignant: one secondary to metastatic disease to distant organs (recurrence at 30 months of follow-up in the form of multiple lung metastasis) and other to lymph nodes who is alive and disease-free. Three patients were diagnosed with contralateral pheochromocytoma during the follow-up, admitted as a new primary lesion, in context of a known genetic syndrome.

Conclusion
The results of our retrospective study show that adrenalectomy is a safe, effective and a low morbidity procedure. However, the organization of surgical, anesthetic and medical teams experienced in this type of pathology is fundamental for perioperative management.

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EP99

Role of urinary fractionated metanephrines and catecholaminas in the diagnosis of pheochromocytoma/paraganglioma

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Introduction
Paragangliomas/pheochromocytomas present frequently with vague symptomatology which makes its diagnosis difficult and challenging. Cuantification of fractionated metanephrines and fractionated catecholamines in 24 h urine sample are used for diagnosis. There are situationes that can produce false positive results such as stress, drugs or smoking that must be taken into account.
Patients and methods
Retrospective study on the requests made for the diagnosis of pheochromocytoma/paraganglioma to the laboratory with the determinations of fractionated catecholamines and metanephrines during 10 months. Determinations were analysed by HPLC with electrochemical detector (Teknochroma®).
Results
During this period 260 determinatios (of 218 patients) were analysed. 10 of these patients were diagnosed of pheochromocytoma, nine of extraadrenal paraganglioma and 199 patients did not present either of the pathologies. Patients with paraganglioma were excluded (Table 1).

Table 1 Sensitivity and specificity of fractionated catecholamines and metanephrines.

	Sensitivity	CI 95%	Specificity	CI 95%
Catecholamines	0.9	0.71–1.09	0.88	0.83–0.92
Metanephrines	0.9	0.71–1.09	0.89	0.85–0.93

Of the patients who did not present pheochromocytoma (199), 35 had elevated catecholamines and/or fractionated metanephrines (18% false positive), 17 were due to antihypertensive or antidepressant drugs, 11 had other adrenal pathologies and seven others.
Conclusions
1. Urinary fractionated metanephrines have a higher specificity than catecholamines. Both of them present the same sensitivity in our patients.
2. The rate of false positive results surpasses those of true positive, especially those produced by drugs, as published in literature.

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EP100

Lung adenocarcinoma in a 34-year-old female SDHB asynptomatic mutation carrier – case report

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Introduction
Patients with germline mutations in one of the succinate dehydrogenase (SDH) genes are at substantially increased risk of developing paragangliomas (PGL) and pheochromocytomas (PCC). Mutations in SDHB are the most commonly found gene mutations in PC/PGL and are associated with younger ages at presentation, higher rates of metastases and poorer prognosis. Although familial PGL syndromes were initially thought to predispose only for PCC and PGL, other tumor types such as gastrointestinal stromal tumors (GISTs), renal cell carcinomas (RCCs), and pituitary adenomas (PAs) have expanded the SDHx-associated tumor spectrum.
Case Report
A 34-year-old female patient, with a history of mild asthma, non-smoker, was referred to the Endocrinology Department as an asymptomatic carrier of a pathogenic heterozygous germline SDHB mutation (c.1-?_72+?del). Her paternal-uncle died from metastatic bladder paraganglioma by the age of …She had also family history of breast cancer (paternal-aunt) and prostate cancer (paternal-grandparent). Twenty-four-hour urinary excretion of fractionated catecholamines and metanephrines were in the normal range. Screening computed tomography (CT) scan showed a 3 cm mass in the lower lobe of the right lung. CT guided transthoracic lung biopsy revealed adenocarcinoma of probable primary lung origin. Staging positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (^{18}F-FDG PET/CT) showed, besides malignant right lung involvement, moderate left paratracheal FDG uptake. She underwent inferior right lobectomy with mediastinal lymph node ressection and histologic examine confirmed lung adenocarcinoma pT2a N0 M0 R0, stage I B. The patient is under surveillance.
Discussion
Questions still remain unresolved concerning non PCC/PGL tumors in patients with germline pathogenic SDHx mutations with regard to their pathogenesis, clinicopathological phenotype, and possible causal relation to the aforementioned mutations.

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EP101

Pheochromositoma in childhood

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Introduction
Feochromositoma is a rare neuroendocrine tumor derived from chrommaffin cells of adrenal medulla. The most characteristic clinical symptoms are headache, perspiration, palpitation, and paroxysismal hypertension. Childhood feochromositoma is generally genetic while it is mostly sporadic in adults. Here we report three feochromositoma cases in whom two had von Hippel Lindau syndrome (VHLs).
Case 1
10 years old girl with admitted with fever. Her physical examination revealed hyperthermia and hypertension. Urine VMA level was increased and ultrasound examination showed left adrenal mass, diagnosis of pheochromositoma was confirmed after resection. In the second year of her follow-up GA-68 Octreotide scintigraphy determined accumulations in right adrenal and pancreas, pathological diagnosis were feochromositoma and neuroendocrine carcinom respectively after resection. Two disorederes together suggested VHLs and heterozygous p.L129P mutation in VHL gene was detected.
Case 2
11-years-old boy admitted with perspiration and palpitation in whom hypertension was determined. Urine VMA level was increased, and bilateral adrenal mass was determined in ultrasonography. Diagnosis of pheochromositoma was confirmed after resection. In his 5 years of follow-up he admitted with headache. Cranial MRI showed frontal, adrenal ultrasound showed right adrenal masses, after resection hemangioblastoma and pheochromositoma were diagnosed respectively. Associaton of two disorders suggested VHLs and heterozygous p.R161Q mutation in VHL gene was determined.
Case 3
9-years-old boy admitted with perspiratation and palpitation in whom hypertension was determined. His family history was significant with pheochromositoma in his father and grandmother. His urine VMA levels were high and adrenal ultrasound revealed bilateral adrenal masses. Diagnosis of pheochromositoma was confirmed after resection of both masses. No mutation in VHL gene was detected.

Conclusion
Although rare pheochromositoma should be thought in children with hypertension. In children pheochromositoma is mostly genetic in which VHLs is most frequent. Genetic tests should be performed in all children after diagnosis.

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EP102

A case of silent pheochromocytoma presenting with clinical and radiological findings suggesting metastatic adrenal lesion

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Case
A 75-year-old male patient was treated for lung adenocarcinoma 12 years ago. During the routine imaging studies of the patient who was followed without treatment after curing, a suspicious, non-adenomatous lesion in the right adrenal gland, 16×9 mm in size was detected by thoracic computed tomography. Serum aldosterone/renin ratio and urine catecholamine tests were normal with no complaints of suspicion for pheochromocytoma. F18FDG PET-CT showed an increase in metabolic activity (SUVmax:4,8) in the right hilar region. The cytological examination was benign with bronchoscopy. Laparoscopic right adrenalectomy was performed because no other lesions were detected. Histopathologic examination revealed non-invasive pheochromocytoma showing positive staining with synaptophysin and chromogranin.
Discussion
Pheochromocytoma is very rare in adrenal incidentalomas, however, can be asymptomatic at rates up to 10%, as they can manifest with attack symptoms or less with persistent hypertension. It is suggested that catecholamine synthesis is defective in these tumors. In some reports it is specified that, this phenomenon may be seen in some mutations in the succinate dehydrogenase gene. In some reports, however, about 10–20% of silent pheochromocytomas were reported to be due to laboratory error. On the other hand, non-adenomatous lesions in the adrenal glands in a patient known as primer malignancy are generally considered as metastases. In our case, the patient was referred to a similar presentation and it was initially thought that the lesion may be a metastatic lesion. However, the fact that the primary malignancy has been in control for more than 10 years has been questioned about metastasis. One of the methods that can be applied in such a case is biopsy but pheochromocytoma should be firstly excluded. In this case report, we have demonstrated that; in non-adenomatous adrenal lesions, the absence of clinical signs and normal catecholamine levels do not exclude pheochromocytoma.

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EP103

The storm before the calm: a phaeochromocytoma

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We report a case of a male patient aged 45 years who presented with a history of intermittent back discomfort over a year, but more persistent over the previous 2–3 months. His general practitioner (GP) referred him for an ultrasound of the spine for a possible encapsulated lipoma but the findings were unremarkable. He was then referred to a consultant gastroenterologist for further assessment. He had normal endoscopic examinations, however the MRI had shown a right adrenal lesion which led to a referral to the endocrine team.
On further history he reported episodes of perspiration and bursts of aggression, for the past few years. Investigations revealed a normal cortisol response following overnight dexamethasone suppression and a normal renin aldosterone ratio.
He had elevated 24-h urinary normetanephrines 6360 nmol/24 h and metanephrines 2530 nmol/24 h (normal <2129 and <1622 respectively), in keeping with phaeochromocytoma. Subsequent meta-iodobenzylguanidine (MIBG) scan showed prominent activity in the region of the right adrenal gland. The patient was initially commenced on an alpha blocker doxazosin, and the dose was incremented to the maximum of 16 mg BD. He was subsequently commenced on beta blocker bisoprolol, and his blood pressure dropped from average of 150/100 mmHg (no history of hypertension) to around 110/70 mmHg.
This patient had a right adrenalectomy, made an uneventful recovery and was discharged with no medication. His BP remained at around 130/85 mmHg at his post-operative consultations. Phaeochromocytoma presents with various forms of signs and symptoms. In our case, the history of episodes of intermittent perspiration, back pain and severe aggression were uncommon symptoms emphasising the importance of comprehensive history taking.
Since surgery the patient has no longer experienced any of the above, and he describes himself to be calmer than ever.

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EP104

Improvement of insulin secretion and oral glucose tolerance after pheochromocytoma removal: a case report

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Introduction/case report
Diabetes mellitus is an important clinical manifestation of catecholamine excess in patients with pheochromocytoma, and glucose control is usually better after tumour removal. Both impaired insulin secretion and increased insulin resistance have been implicated as underlying causes. We describe the case of a 38-year-old male patient diagnosed with left adrenal pheochromocytoma and personal history of diabetes mellitus diagnosed at age 36, under treatment with metformin, saxagliptin and gliclazide, with a preoperative HbA1c of 7.2%. BMI of the patient was 23 kg/m^2. After successful pheochromocytoma removal, the anti-diabetic medication was immediately stopped with remission of diabetes mellitus (HbA1c 3-months-postoperative 5.7%).
Methods
We performed oral glucose (75 g) tolerance tests and measured venous plasma glucose and serum insulin levels at the time of diagnosis and three months after successful surgery, to derive the insulinogenic index (IGI) as proposed by Wareham, and whole body insulin sensitivity index (ISI) as proposed by Matsuda and DeFronzo.
Results
Plasma glucose and serum insulin levels are shown in the table 1.

Table 1

Time (min)	−15	0	30	60	90	120
Preop glucose (mmol/l)	9.8	9.5	10.9	12.7	15.8	16.1
Postop glucose (mmol/l)	5.3	5.3	8.0	10.7	10.9	7.0
Preop insulin (pmol/l)	28	42	104	161	248	181
Postop insulin (pmol/l)	74	47	316	461	613	354

Improved glucose levels were associated with increased insulin levels and an increase in IGI, from a preoperative value of 5.7–33.6 pM/mM, while the ISI remained unchanged.
Conclusion/discussion
Remission of diabetes mellitus in our patient was associated with marked improvement of insulin secretion and oral glucose tolerance after removal of pheochromocytoma. Adrenergic alpha2A receptors on pancreatic beta cells play an important role in mediating inhibitory effects of catecholamines on insulin release, according to recent genetic association and pharmacological intervention studies. In our case, impaired insulin secretion could be corrected by surgery.

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EP105

Ephedrine/caffeine toxicity masquerading as phaeochromocytoma in a vigorexic male with paroxysmal hypertension and headache

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Clinical case
A 19-year-old male came to the Emergency Department complaining about a holocraneal nonpulsatile headache growing in intensity for the last 3 h, unresponsive to common analgesics. He had been suffering anxiety sleep deprivation, nervousness, tremor and heart palpitations for the last week. Family history was irrelevant, and the patient had no history of hypertension, dyslipidaemia, diabetes or smoking or medication use; he reported moderate alcohol, coffee and energy drink consumption but no cocaine nor amphetamines. He was on a high-protein diet with casein-based supplements, maintained a very high level of physical exercise and lately had been consuming a 'fat-burner' obtained from a local gym, but ignored its composition. The patient was fully conscious and did not have chest pain, fever or dyspnoea. His BP was 219/126 mmHg and HR 129 bpm, with sinus tachycardia in the EKG. He was treated with diazepam and diltiazem, discharged with BP 154/87 and HR 98 and referred to our Endocrinology Clinic for phaeochromocytoma screening. He brought the 'fat-burner' pills containing ephedrine 50, ASA 100 and caffeine 150 mg; he had been taking 1–2 daily during the week before the hypertensive episode. He was asymptomatic, with athletic constitution, weight 87 kg, height 173 cm, BMI 29 kg/m^2, waist 88 cm, impedanciometry 19% fat mass, BP 119/76, HR 75. Physical exam was otherwise unremarkable. Lab tests including metanephrines, aldosterone, PRA, TSH and microalbuminuria; chest X-ray and 24 h. ABPM were normal.
Diagnosis
Paroxysmal hypertensive episode caused by ephedrine/caffeine toxicity, with no target-organ damage. Vigorexia. Phaeochromocytoma/paraganglioma were ruled out.
Commentary
Ephedrine is a sympathomimetic amine with no legitimate medical indications at present, but widely used as doping or to trim subcutaneous fat. Its use has been linked with major cardiovascular and renal events, including ictus and sudden death, and must be discouraged.

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EP106

Loss diagnosis of pheochromocytoma in the initial evaluation

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Introduction
In most cases, adrenal masses are non-functioning adrenocortical adenomas. On '*Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline*' published in 2016, the experts 'suggest against repeated hormonal work-up in patients with a normal hormonal work-up at initial evaluation unless new clinical signs of endocrine activity appear or there is worsening of comorbidities'.
Case report
A 59-year-old male patient was referred to endocrinology with a right adrenal mass of 17 mm compatible with adenoma, discovered in difficult-to-control hypertension study. The patient had no symptoms apart from hypertension, that was controlled with three classes of antihypertensive drugs. Initial hormonal evaluation revealed normal urinary fractionated metanephrines, normal aldosterone/renin ratio (with interfering drugs suspension), intermediate hyperglycaemia and subclinical hypercortisolism (1 mg overnight dexamethasone 2.1 μg/dl). One year later, adrenal mass was stable and hormonal study highlighted elevation of total and fractionated urinary metanephrines (total metanephrines 1921 μg/24 h (329–1263), fractionated metanephrine 956 μg/24 h (64–302) and normetanephrine 636 μg/24 h (162–527) with normal 3-methoxytyramine. The repetition of metanephrines, with adequate preparation, confirmed these results: urinary total metanephrines 2005 μg/24 h (329–1263), urinary fractionated metanephrine 1094 μg/24 h (64–302) and normetanephrine 545 μg/24 h (162–527) with normal 3-methoxytyramine. The patient kept lack of symptoms such as headache, palpitations, diaphoresis or tremors. ^{123}I-MIBG scintigraphy revealed focus of hyperactivity located on projection of the right adrenal gland suggesting the presence of pheochromocytoma. We sent this patient to multidisciplinary expert team. Plasma-free metanephrines were measured with elevated results: 125 pg/ml (<65) and he will undergo unilateral adrenalectomy soon.
Discussion
This case illustrates the possibility of false negative results in hormonal evaluation of adrenal masses. These misleading results can happen, for example, by an inadequate urine sampling. If we had not repeated the measurement of metanephrines, the diagnosis of pheochromocytoma had not be done at this time.

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EP107

Unexplained resistant hypertension in a young male with recurrent transient ischemic attacks, resembling endocrine hypertension

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A 27-year-old male without relevant familial or personal history had three TIAs in the last year, lasting for about 20 min with partial right palsy and aphasia. By the time he was cared for in the Emergency Department. he had already recovered; his lab tests, chest X-ray and EKG were normal but his BP was high (PAS 170–190 mmHg, PAD 105–120 mmHg). He had no chest pain, headache or neurovegetative symptoms. On discharge the patient was treated with manidipine and ASA and referred to the Neurology Clinic and to our Hypertension Clinic for phaeochromocitoma/paraganglioma screening and diagnostic workup.

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Cardiovascular Endocrinology and Lipid Metabolism

EP108

Stress cardiomyopathy in pheochromocytoma

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Introduction
Rare cases of pheochromocytoma are associated with stress induced Takotsubo cardiomyopathy explained by high catecholamine exposure causing microvascular spasm and direct myocardial impact.
Case report
A 49-year-old female with a history of poorly controlled hypertension, with paroxysmal elevations in blood pressure and rare supraventricular extrasystoles, lipothymic events, was firstly assessed in the cardiologic department. She presented with resistant hypertension, associated with acute pulmonary oedema and cardiogenic shock. Echocardiography revealed new mid LV segment motion abnormality with apical ballooning, ECG – acute ST-segment elevation in the anterior leads and a rise of cardiac biomarkers. The coronary angiography excluded any coronary artery lesion. Thoraco-abdominal CT imaging revealed an 86/85/68 mm left adrenal mass, suggestive for pheochromocytoma. Laboratory evaluation for 24-h urine and plasma catecholamine metabolites disclosed intermediary-low elevated values (plasmatic MN = 10/11 pg/ml; plasmatic NMN = 59/41 pg/ml, urinary MN = 114/881 μg/24 h; urinary NMN = 632/1121 μg/24 h), despite high cardiac impact of the spells. She was submitted to 12 days of alpha adrenergic blockade followed by beta blockers, during which control of blood pressure and spells was achieved. Improvement of systolic function (EKG and echocardiography) could be noticed. Laparoscopic adrenalectomy was safely performed without hemodynamic events during surgery or immediately afterwards. Metanephrines and normetanephrines levels normalised with good residual adrenal function. Long term systolic function as well as high blood pressure returned to normal.
Conclusions
Takotsubo cardiomyopathy is associated with reversible LV-ballooning. In this observation, we report a case of stress cardiomyopathy caused by

pheochromocytoma; a rare medical condition which is easily confused with acute coronary syndrome due to clinical and biochemical resemblance, especially in our case where plasma and urinary catecholamines were only slightly elevated.

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Clinical Case Reports – Pituitary/Adrenal

EP109

Prolonged zona glomerulosa insuffiency with hyperkalemia in primary hyperaldosteronism after adrenalectomy

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Introduction
Hyperkalemia due to zona glomerulosa (ZG) insufficiency is generally transient and mild for patients with aldosterone-producing adenoma (APA) after adrenalectomy. We report here a case with prolonged ZG insuffiency requiring long-term mineralocorticoid replacement (MR) therapy.
Case report
A 45-years-old female with hypertension and hypokalemia admitted to outpatient clinic with incidentally detected right adrenal adenoma (3 cm) showing signal loss on opposed-phase images of MRI. Laboratory tests revealed high plasma aldosterone concentration (PAC) (72 ng/dl, *N*: 7–30 ng/dl), supressed plasma direct renin concentrations (DRC) (5.25 ng/l, *N*: 5.41–34.53 ng/l) and high PAC/DRC ratio (13.71). PAC after saline infusion test was 30.7 ng/dl. After confirmation with adrenal venous sampling (AVS), right adrenalectomy was performed laporoscopically. Serum urea, creatinine, sodium, PAC (19.6 ng/dl) and DRC (13.6 ng/l) were in normal limits on postoperative 20th day; but serum potassium was markedly increased (5.9 mmol/l). The causes of pseudohyperkalemia and hyperkalemia were excluded. Because of low suppression index in the contralateral adrenal during AVS, hypoaldosteronism was thought to be the etiology as PAC did not increase while serum potassium level was higher than 5 mmol/l. Patient was followed-up with high-sodium, low-potassium diet on polystyrene sulfonate therapy. On the second month postoperatively, serum potassium was still high (5.6 mmol/l). MR therapy with fludrocortisone 0.1 mg/day was started for persistent hyperkalemia. Treatment continued for eight months until PAC and DRC raised up to 23.27 and 20.8 ng/l, respectively. After then, serum potassium concentration remained at the upper limit of normal range (5 mmol/l) with normal renal function tests, PAC (10.8 ng/dl) and DRC (8.1 ng/l) without replacement.
Conclusion
Suppression of contralateral ZG function by supressed plasma renin level in APA can lead to ZG insufficiency and hypoaldosteronism after adrenalectomy. Hypoaldosteronism cause impairment of renal potassium clearance and hyperkalemia. MR therapy may be essential in case of prolonged hyperkalemia.

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EP110

Mature ganglioneuroma of the adrenal gland

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Introduction
Ganglioneuroma is an extremely rarely seen tumour in the adrenal gland, which originates from neural crest cells. Clinically, they generally have a silent course and in laboratory tests, the hormone levels expressed from the adrenal gland are within the normal range.
Case
A 46-year old male patient, for whom a mass in the adrenal gland was diagnosed incidentally on abdominal ultrasonography and MRI. The physical examination, laboratory tests and hormonal tests were within normal limits. As the appearance on dynamic adrenal CT was compatible with an adenomatous lesion, a biopsy was applied to the left adrenal gland. In the histopathological examination, findings were determined of neuroblastic tumour and ganglioneuroma, so adrenalectomy was applied and adrenal ganglioneuroma (mature type) was reported in the pathology examination.
Conclusion
Ganglioneuroma is rarely seen in adults and diagnosis is difficult as it is asymptomatic. As the masses are asymptomatic, they are not usually determined before reaching large dimensions. With increased availability of high-resolution tomography and MRI, an increase has been seen in the frequency of these types of masses. In recent years, ganglioneuroma have been separated into two sub-types as mature or maturing ganglioneuroma. In mature ganglioneuroma, the tumour is completely formed of a ganglioneuromatous component. Diagnosis is made histopathologically and it should be kept in mind as a rare tumour in adrenal masses.

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EP111

Primary adrenal insufficiency and pregnancy – a case report

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Primary adrenal insufficiency (PAI) is uncommon in pregnancy. Women with PAI have reduced fertility and parity. If unrecognized or untreated during pregnancy PAI increases risk for maternal and foetal morbiditiy and mortality. Majority of women diagnosed before conception and appropriately treated, have uneventful pregnancies, with increased risk of cesarean section (CS) and preterm delivery.
We report a 38-year-old woman with PAI during first spontaneus pregnancy.
The patient was diagnosed with Addison's disease at the age of 17, and hyperthyroidism 14 years later. Her family history revealed hyperthyroidism in mother. She had regular menstrual pattern and no pregnancy during 5 years of marriage. Gynecological investigation was unremarkable, but she had addisonian crisis during hysterosalpingography 6 months before conception. At that time she was taking 30 mg hydrocortisone, 0.1 mg fludrocortisone and 50 mcg levothyroxine/daily. At 8 weeks of pregnancy she started to complain of fatigue, dizziness and palpitations, with no nausea or vomiting. Physical examination was unremarkable, BP 100/70 mmHg, with no orthostasis or discolouration of skin/mucous membranes. Oral progesterone was started because of spotty vaginal bleeding and in 2 weeks she developed mild hyponatraemia. We recommended to split hydrocortisone in four doses, and increased fludrocortisone to 0.125 mg. During second trimester she was stable, plasma electrolytes and thyroid function test were normal, with no foetal or placental abnormalities on ultrasonography. In the middle of the third trimester hydrocortisone and fludrocortisone doses were further ajusted to 35 mg and 0.15 mcg respectively. She underwent CS at the 39th gestational week and a healthy baby girl weighing 3250 g was delivered. During the 15-month follow-up period mother and baby were in good condition.
We presented a case of women with autoimmune polyglandular syndrome (APS 2) and succesful pregnancy outcome. Women with PAI should be monitored by a multidisciplinary team throughout pregnancy to ensure maternal and foetal health.

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EP112

Paraganglioma (PG) and cyanotic congenital heart disease (CCHD): the role of tisular hypoxia

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Introduction
CCHD comprises a number of different congenital heart defects associated with elevated pulmonary artery pressure and pulmonary vascular resistance, resulting in a reversed or bidirectional shunt (Eisenmenger syndrome). These entities develop systemic hypoxia. Pheochromocytoma and paraganglioma (PHEO/PG)

are neuroendocrine tumours. Several inheritance genetic alterations have been reported in PHEO/PG syndromes. A pathogenic association between these entities is proposed.
Case report
A 41-year-old female diagnosed of a CCHD in the new-born period, on stable medical treatment, as surgery was rejected. She presented with symptoms suggesting exacerbation of heart failure. Catecholamine hypersecretion was suspected; 24 hour urine metanephrine: 215 μg/24 h (NV < 341) and normetanephrine (NM): 2491 μg/24 h (NV < 444). Abdominal CT showed a retroperitoneal lesion consistent with a PG. Functional imaging with Iodine^{123}MIBG showed a pathological uptake area at the same localization. No other pathological images were observed. Genetic testing was performed and no mutations in SDHD, SDHC, SDHB, VHL, SDHAF2, MAX and TMEM127 genes were found. She underwent surgery after alpha blockade. Pathological examination confirmed the diagnosis of a PG. NM became normal after surgery and patient symptoms improved.
Discussion
Several hypoxemic phenomenon have been related to be implicated in the pathogenesis of PHEO/PG, as it is known that some of the genetic alterations (SDHx, VHL, HIF2) lead to enhanced production of hypoxia inducible factors, which induce an increase in angiogenic factors leading to the development of tumours. The patient had an evolved heart disease with significant cyanosis. Chronic exposure to hypoxia in patients with CCHD could increase the risk for developing PHEO/PG. In addition, the noradrenergic biochemical phenotype found agrees with that observed in some of the PHEO/PG syndromes. In patients with CCHD the diagnosis of PHEO/PG can be difficult to suspect because symptoms may be confounding, nevertheless catecholamine excess may be dangerous. Therefore we consider that the existence of a PHEO/PG should be ruled out in patients with CCHD and aggravation of the previous heart function.
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EP113

Von Hippel Lindau disease in two Turkish families with different mutations

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Von Hippel-Lindau (VHL) disease is an inherited, autosomal dominant syndrome manifested by a variety of benign and malignant tumors. Herein we describe, two families who had VHL. A 21-year-old man (index case 1) presented with bilateral adrenal mass, serendipitously discovered by radiologic examination. He had newly diagnosed arterial hypertension. His family history was significant for his mother who had operated for pheochromocytoma, his two uncles who had experienced cerebral tumors and his mother's cousin who had bilateral pheochromocytoma. After the diagnosis of bilateral pheochromocytoma, bilateral adrenalectomy was performed. Histopathological data correlated with pheochromocytoma. A genetic test was carried out. A germline mutation p.R167Q (c.500G > A) was detected in the patient confirming VHL. A further genetic test was prescribed in other family members. His mother had a history of cystic astrocytoma, meningioma, hemangioblastoma and right adrenalectomy for pheochromocytoma. A germline mutation p.R167Q (c.500G > A) was detected, too. Index case 1's brother had a history of arterial hypertension and the germline mutation p.R167Q (c.500G > A) was detected, too. Index case 1's mother's cousin had a 24-year history of hypertension. He had experienced right adrenalectomy 24 years ago and left adrenalectomy 4 years ago with the diagnosis of pheochromocytoma. The germline mutation p.R167Q (c.500G > A) was detected, too. A 43-year-old woman (index case 2) was referred from the cardiology department to our outpatient clinic to examine the etiology of endocrine-induced arterial hypertension (150/90 mmhg). After the diagnosis of pheochromocytoma, the right adrenalectomy was performed. 5 years after the operation she had operated for the pancreatic neuroendocrine tumor and 15 years after the operation she was diagnosed as hemangioblastoma. A genetic test was carried out. A germline mutation p.L118R was detected in the patient. A genetic test was prescribed to the other members of the family. Her two boy's genetic tests were detected the same mutation. All patients with pheochromocytomas should be screened for the genetic syndromes for example MEN 2 and VHL. It is important for averting the further morbidity and mortality in the patients and their families. Family screening is crucial in patients who are diagnosed with the disease.
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EP114

Large adrenal adenoma presenting as a clinically inapparent Cushing syndrome, a trap diagnosis

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Adrenal incidentalomas (prevalence between 0.4 and 7%) have become a very common clinical problem, the major concern being the risk of malignancy and hormone overproduction.
A 57-year-old woman was admitted for asthenia and uncontrolled hypertension. The only relevant clinical signs were abdominal obesity (BMI = 31.1 kg/m^2) and hypertension. Abdominal ultrasonography showed a voluminous left adrenal solid mass of 10/9 cm, with well-defined sharp borders, hypoechoic with necrotic areas and hyperechogenic foci of scars and calcifications. The differential diagnosis of an atypical adenoma and pheochromocytoma or adrenocarcinoma was difficult.
Laboratory assays revealed hypercortisolism, indicated by the loss of the circadian rhythm of cortisol secretion: cortisol value at 8 a.m. of 7.84 μg/dl and at midnight of 11.2 μg/dl, elevated free 24 h urinary cortisol of 731.4 μg/24 h (normal range: 50–190 μg/24 h), no suppression at overnight dexamethasone suppression test (cortisol of 5.46 μg/dl), low ACTH level of < 1 pg/ml and decreased cortisol level < 50% at the high dose dexamethasone test. Plasmatic metanephrines, normetanephrines, renine and aldosterone were normal. Abdominal CT scan indicated a tumoral left adrenal mass of 10/8.5/8.5 cm, well defined, inhomogeneous, with microcalcifications, < 10 HU, induced caudal displacement of the left kidney, no lymphadenopathy or other visceral involvement. She underwent left laparoscopic adrenalectomy. The histopathological evaluation indicated Ki67 < 1% and chromogranin, synaptophysin, calretin, protein S100, inhibin were isolated low positive; PanCK, EMA were negative; CD31 showed the capillary network, without emboli; vimentin was positive; suggesting an atypical adenoma and excluding an adrenocarcinoma, a kidney and liver tumor, but also a pheochromocytoma. Two weeks after surgery, a large ischemic vascular attack occurred, with poor prognosis. We should keep in mind that voluminous cortisol-producing adrenal adenomas could have clinically inapparent features, but with hidden vascular damages and increased cardiovascular risk.
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EP115

NK/T lymphoma adrenal presenting as adrenal insufficiency and cranial nerves neuropathies-a case report

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Adrenal Lymphoma is extremely rare with fewer than 200 cases reported. The most common subtype is the diffuse large B cell lymphoma. Malignant lymphoma arising in the endocrine glands represents only 3% of extranodal malignant lymphomas and is usually confined to the thyroid gland. NK/T-cell lymphoma presents primarily in the nasopharynx and sinuses. Although involvement of the adrenal glands can be seen in disseminated disease, primary presentation with adrenal masses and adrenal insufficiency is extremely rare. We report a case of 34 years old gentleman presenting with prolonged fever, constitutional symptoms and symptoms and signs of adrenal insufficiency. He was treated as adrenal crisis in the district hospital with hypotension, hyponatremia, and hyperkalemia. He appeared cachexic, with no hyperpigmentation or palpable lymph nodes. His lactate dehydrogenase enzymes (LDH) was elevated. Cortisol taken during this stressful period was deemed too low. This was confirmed by an inadequate response to the Synacthen test. CT Adrenal was performed and reported as bilateral enlarged adrenal, likely hyperplasia. He developed multiple cranial nerves neuropathies that progressively worsened. CT Brain was normal. Lumbar puncture revealed high opening pressure and CSF biochemistry revealed no cells and negative for tuberculosis. With the possibility of disseminated tuberculosis, empirical anti-tuberculosis medications were started but failed to abate his

symptoms. Laparoscopic left adrenal excision biopsy was performed and histology features are in keeping with high grade NK/T cell lymphoma. His condition deteriorated fast and he succumbed to his illness. This case illustrates the need to include Primary Adrenal Lymphoma in the differential diagnosis of adrenal masses especially when adrenal contour is preserved on imaging, hypoadrenalism and high LDH.

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EP116

Primary hyperparathyroidism and primary hyperaldosteronism – cause or coincidence in arterial hypertension – case report

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Introduction
30% of the adult population has high blood pressure. About 6% of the hypertension may be caused by primary aldosteronism and very rare by primary hyperparathyroidism. The combination of these two causes is very rare.
Case report
Our patient is women (age 50) with a 21 year long history of uncontrolled hypertension. Treatment of hypertension consist of a beta-blocker, calcium channel blockers, angiotensin converting enzyme inhibitor, loop diuretics and thiazide diuretics. Laboratory tests confirmed the presence of hypercalcemia (ionized calcium 1.42 mmol/l), and hypokalemia (3.4 mmol/l). After correction of medical therapy results shows elevated levels of parathyroid hormone (221.7 pg/ml) and aldosterone/renin ratio (A/R > 30), normal value of metanephrines and normetanefrine, normal ACTH and cortisol levels and diurnal rithm of secretion. CT of the abdomen showed adenoma like enlargement of left adrenal gland of 2 cm. Scintigraphy and ultrasound confirmed the presence of hyperplasia/adenoma of the lower left parathyroid gland. Bone mineral density indicates osteoporosis and ultrasound of abdomen described nephrolithiasis in the left kidney. Due to hypercalcemia, first we have decided to operate the parathyroid glands. Surgery leads to normalization of calcium. The pressure is regulated without both the diuretics at a reduced dose of a calcium channel blockers. After recovering from surgery, in a hospital setting we discontinued therapy and dynamic testing was conducted (volume loading test and postural stimulation test) that indicate adrenal hyperplasia as a cause of primary hyperaldosteronism. Patient started with spironolactone therapy that even in small doses leads to normalization of potassium and reduce the need for other antihypertensive agents.
Conclusion
More endocrine disorders can simultaneously affect arterial hypertension. Treatment of hyperparathyroidism may lead to better control of hypertension. Despite the existence of left adrenal enlargement that looks like an adenoma, adrenal hyperplasia is a possible cause of primary hyperaldosteronism.

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EP117

Endocrine masses displayed as incidentalomas in patients with unilateral nephrectomy

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Introduction
Menopausal adrenal tumours may be elements of a complex panel of co-morbidities. Some of these are represented by the presence of a second pathology requiring surgery at the kidney level.
Aim
We aim to introduce a series of two cases involving menopausal women who were referred for specific endocrine assays after they had a unilateral nephrectomy (UN).
Method
This is a cases series observational study. The patients gave their consent. They were followed in different medical and surgical centres from Romania.
Results
A 61-year woman was admitted for a right adrenal and a thyroid incidentaloma after left UN for renal cancer with clear cells, Fuhrman Nuclear Grade of 2 (pT3N0Mx). Post-operatory endocrine panel of investigations were consistent for non-secretor low risk lesion. A fine needle aspiration biopsy at thyroid excluded a second malignancy. A 56-year old female had left UN 14 years ago for a benign condition. One year after surgery a right adrenal tumour of 1.2 cm was discovered at CT (computer tomography) scan. After 13 years, the subject became hypertensive and experienced hot flushes in association with secondary amenorrhea so an endocrine evaluation was considered. Non-secretor adrenal profile and high Follicle Stimulant Hormone consistent for physiological menopause was associated with stationary CT aspects for right adrenal tumor but also a left adrenal tumor of 1.3 cm was identified. Nevertheless, abdominal CT scan performed 1 year later showed similar aspects. Further serial imaging was recommended.
Discussion
Adrenal incidentaloma discovered in menopausal patients with UN requires a complex differential diagnosis including the fact that they need to be differentiated from metastases arising from kidney cancer. Also, serial imaging assessments after kidney removal may lead to the discovery of different solid masses as thyroid incidentaloma or nodules.

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EP118

Case with metastatic lung cancer who developed adrenal insufficiency

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Adrenal metastasis is common (35%) among the patients with lung cancer, while less than 3% of the patients develop bilateral adrenal metastasis. Adrenal metastases are generally small and clinically asymptomatic. Adrenal insufficiency is rare despite the presence of adrenal metastasis. Lam et al. reported this ratio as 0.7%. We aimed to present a case with lung cancer and bilateral adrenal metastasis who developed adrenal insufficiency.
A 63-year old male patient was presented with cough. Chest X-ray revealed a mass lesion in the upper zone of left lung. PET/CT examination was performed and demonstrated increased FDG uptake in upper lobe mass lesion of left lung, mediastinal lymph nodes, bilateral surrenal glands (9 mm at the right and 5.5 × 2 cm at the left),liver and bones. Following bronchoscopy, the patient was diagnosed with non-small cell lung cancer. Pathologic examination of surrenal biopsy material revealed surrenal metastasis. The patient had no signs of adrenal insufficiency and electrolyte imbalance at the time of diagnosis. He was scheduled for cisplatin + gemcitabine chemotherapy. Although lung and adrenal gland lesions were stable within 6 months after treatment, the patient developed hypoglycemia, hypovolemia, hyponatremia and hyperkalemia. Laboratory examination revelaed ACTH:1250 pg/ml (normal: 0–46), and cortisol 4.43 µg/dl (n:5–29). The patient was given prednisolone and fludrocortisone treatment with the diagnosis of adrenal insufficiency. Symptoms of the patient were subsided after treatment. Post-treatment laboratory examination revealed Na:138 mEq/l (normal:135–145), K: 4 mEq/L/normal:3.5–5.5) and ACTH:37 pg/ml.
It should be considered that patients with lung cancer and adrenal metastasis may later develop adrenal insufficiency despite the absence of adrenal insufficiency at the time of diagnosis. Although fatigue, nausea, hypotension and hyponatremia may also be seen in the patients with cancer, these may also be the signs of adrenal insufficiency.

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EP119

Adrenal haemorrhage: from Urology to Endocrinology

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Background
Bilateral adrenal haemorrhage (Waterhouse–Friderichsen syndrome) is a rare consequence of sepsis (usually a result of meningococcal infection), with an

estimated 15% mortality. Despite the predominant association with meningococcal infection, there are other recognised aetiologies: sepsis resulting from other organisms, and non-infectious causes, such as anticoagulant treatment, trauma and postoperative adrenal haemorrhage.
Case report
A 53-year-old man was admitted in the Urology department, to undergo a retropubic radical prostatectomy (prostatic adenocarcinoma). Other medical history: thromboangiitis obliterans, managed with warfarin and acetylsalicylic acid. No complications on the postoperative period; prophylactic antibiotherapy was started with ceftriaxone. On the 7th postoperative-day, the patient had a lipothymia episode, with a decrease of consciousness level (Glasgow 9), hypotensive and subfebrile condition. Blood evaluation consistent with sepsis: leukopenia, thrombocytopenia, raised transaminases, C-protein reactive and troponin, and severe hyposmolar hyponatremia (113 mEq/l). No anomalies detected on neurologic evaluation or cranial computerized-tomography (CT). Antibiotherapy was changed to Piperacillin-Tazobactam. A random ACTH, cortisol and TSH were performed as workup for hyponatremia: ACTH 141 pg/ml (0–46), cortisol 2.5 ug/dl (4.3–23), normal TSH. Abdominal CT scanning was performed: grossly abnormal adrenal glands bilaterally, with masses compatible with hematomas. On the 8th day he began intravenous hydrocortisone in high doses, with recovery of natremia and consciousness level. Blood and urine cultures results were negative (probably "decapitated"). When discharged, the patient was asymptomatic, with normal blood evaluation, and taking long-term hydrocortisone and fludrocortisone. So far, the patient has been asymptomatic and is being monitored by the Endocrinology department.
Conclusions
This case highlights the importance of awareness for symptoms/signs and electrolyte variation when assessing surgical patients post-operatively. The early recognition of this disease allowed immediate treatment, avoiding a worse outcome and leading to a quick recovery. There are risk factors, as anticoagulation therapy, predisposing the development of this rare, but serious, disease.

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EP120

Hemangioma a rare adrenal tumors: report of two cases

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Introduction
Dramatically with increased use of computed tomography (CT) and magnetic resonance imaging (MRI), more and more uncommon adrenal masses have been detected at abdominal examinations. Adrenal cavernous hemangiomas (ACH) are rare vascular tumor. The first case report was published in 195 by Johnson and Jeppesen. Approximately less than 70 cases were reported in the literature to date. ACH are nonfunctioning benign tumors that is often discovered incidentally. They are more frequent in women in the 5th or 7th decade. Their differential diagnosis preoperatively is rather challenging.
These tumors are unilateral lesions in general large and most usually cavernous. All cases reported were treated with surgery.
Case report
We describe two cases of ACH in a 66 years old woman and a 36 years old men. In the first case ACH was discovered as incidentaloma and in the second it was revealed by flank pain.
The diagnostic was performed on ultrasonography. Because of the impossibility of ruling out the presence of malignancy (CT, MRI), surgical adrenalectomy was performed. The patients did well postoperatively. Pathological examination revealed that the adrenal masse corresponded to an ACH.
Discussion
ACH is an uncommon benign vascular tumor. These rare tumors usually localized in the liver and the skin. Adrenal site is extremely rare occurring only in 0.01% of cases and accounts for 63 reported cases in the literature.
ACH are often discovered as incidentalomas either by imaging studies or histologic examination.
The indications for resection of this neoplasm particularly in tumours more than 3 cm in diameter are to relieve the mass-effect-type symptoms, to exclude malignancy, and to treat complications such as haemorrhage, necrosis and thrombosis.

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EP121

A rare case: adrenal lymphangioma

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Adrenal lymphangioma is a rare benign tumors of the adrenal gland. Because of the increased use of imaging methods in recent times, the diagnosis is usually made incidentally. It is usually due to malformation between the lymphatic and the venous system. Those with small indiameters are generally asymptomatic and can be evacuated by needlea spiration. However, surgery is recommended for cysts over 6 cm in diameter due to risk of infection, bleeding, compression of neighboring organs, and perforation. A 45-year-old male patient was admitted due to left abdominal pain and swelling for 2 months. There was no chronic disease or drug use in hisstory. Blood pressure: 130/80 mm/hg, pulse rate was 94/min. Ultrasonography revealed a grade II hepatosteatosis in the liver and a 70 mm multilocular cystic lesion in the left suprarenal region. A mass lesion with multilocule cystic components was observed in the abdominal MRI was T_1 hypointense, T_2 hyperintense in the left adrenal gland and 75 mm in diameter. There were no blood pressure attacks, flushing and palpitations. In laboratory tests: sodium 138 mmol/l (n:135–145), potassium 4.3 mmol/l (n:3.5–5.5), ACTH 27.4 pg/ml (n:0–46), basal cortisol 15.83 μg/dl (n:5–29), 1 mg dexamethasone supression test 0.83 μg/dl (<1.8) was detected. Plasma aldosterone-to-renin ratio was <10, metanephrine and normetanephrine were normal in 24 hour urine.
Laparoscopic left surrenalectomy was performed for the hormone inactive mass. Pathologic examination revealed D2.40 positive, CD34 positive, MelanA on cystwall as local positive lymphangioma. The patient was asymptomatic for 8 months. We aimed to present the rare case of adrenal lymphangioma in ourcase.

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EP122

A rare case of a patient with MEN 4 phenotype and associated pheochromocytoma

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Introduction
MEN4 syndrome is a recently described form of MEN in patients with parathyroid and anterior pituitary tumors, which may also develop bronchial, gastric and pancreatic neuroendocrine tumors. In general, the patients present with clinical signs of primary hyperparathyroidism and simptoms caused by pituitary hormones hypersecretion or due to the tumor mass. However, clinical cases with the coexistence of pituitary tumors and pheochromocytoma are very rare described.
Case presentation
We present a young male patient of 44 years old, who presented in our department for endocrinological pre-operative assessment of a pituitary macroadenoma. The brain MRI indicated a macroadenoma (31/30/21 mm) with supra- and para-sellar extension, compressing the optic chiasm, optic tract and the 3rd cranial nerve on the right side. The patient accused acute right blindness starting 2 weeks ago, denying other simptoms. On clinical examination, the patient was obese (BMI = 36 kg/m^2) and hypertensive (BP = 170/100 mmHg). In addition, personal and family medical history were not significant, excepting personal arterial hypertension debut at 36 years old. Endocrinological evaluations showed normal levels of pituitary, thyroid, mineralocorticoid and glucocorticoid hormones. However, there were detected elevated values of parathyroid hormone (110 pg/ml), plasmatic and urinary normetanephrines (250 pg/ml and 900 ug/24 h) and plasmatic chromogranin A (230 ng/ml). Furthermore, abdominal computed tomography have identified a left adrenal nodule of 1.02/1.14 cm with no other lesions. Thus, in the first instance, the patient underwent laparoscopic left adrenalectomy and afterwards transsphenoidal pituitary surgery, after which he regained visual acuity of the right eye and also it was obtained normalized blood pressure values. Adrenal histopathology confirmed the presence of pheochromocytoma. Blood samples were collected for genetic testing.

Conclusion
We present the case of a young patient with pituitary non-functioning macroadenoma and hyperparathyroidism (MEN4syndrome), also associating left pheochromocytoma.
Keywords: MEN 4 phenotype; pheochromocytoma.
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EP123

The difficulty in predicting aggressive tumour behaviour of phaeochromocytomas
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Phaeochromocytoma and paragangliomas (PH/PG) are rare neuroendocrine tumours. Prediction of aggressive tumour behaviour remains a major challenge. The Phaeochromocytoma of the Adrenal gland Scaled Score (PASS) is used to separate benign from malignant lesions with a score $>$ 4 showing potential for biologically aggressive behaviour. Pre-operatively, MIBG together with CT/MRI remain the diagnostic radiological gold standard.
We report a 68-year-old female who was found to have a locally arising colonic adenocarcinoma on biopsies. Staging also identified a 10.7 cm right adrenal lesion and work-up revealed markedly raised urinary metanephrines and positive MIBG imaging. The MDT decision was to first remove the colonic cancer with appropriate alpha blockade. It was felt that a combined laparoscopic approach would not be appropriate given the adrenal lesion size, which might require an open procedure. Histology confirmed a stage III Duke's C tumour and adjuvant chemotherapy commenced. Although adrenal surgery had been planned once she completed chemotherapy, she did not tolerate chemotherapy and it had to be discontinued. An open adrenalectomy was undertaken. Histology was consistent with a phaeochromocytoma with a PASS score of eight. 2 months after adrenal surgery, she reported intermittent tingling and numbness in the left arm with thoracic back pain. An MRI confirmed a soft tissue mass at T_2 extending into the spinal cord. Urinary metanephrines confirmed persistently elevated normeta-drenaline levels. She underwent bilateral laminectomy under alpha-blockade. Histology confirmed a metastatic phaeochromocytoma. She is currently awaiting Ga^{68}-DOTATATE PET-CT imaging to guide further management.
Ga^{68}-DOTATATE PET-CT has been shown to be the most sensitive imaging modality for detection of metastatic PH/PG and would potentially have identified metastatic lesion(s) not seen on MIBG scanning. We therefore propose that Ga^{68}-DOTATATE PET-CT – where available – should be used for initial staging and MIBG should be reserved for those patients only for whom MIBG therapy is being considered.
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EP124

An unusual cause of unilateral adrenal haemorrhage
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A 24 year old man was admitted by the Surgeons with left sided abdominal pain. He was febrile and tachycardic and found to have raised inflammatory markers. Abdominal CT scan revealed a 6 cm left adrenal haemorrhage with no evidence of an underlying lesion. Initial endocrine investigations were unremarkable for Cushings, Conn's and adrenal insufficiency. Norepinephrine levels were high but settled subsequently. He had a coagulopathy and evidence of reactivation of EB virus. He had a past history of Multiple sclerosis treated eighteen months previously with Alemtuzumab.
He remained febrile and developed acute kidney injury. His symptoms and signs fitted the criteria for haemophagocytic lymphohistiocytosis (HLH), confirmed on bone marrow biopsy. His coagulopathy was due to antibodies to factor VIII (acquired haemophilia) and he developed autoimmune thyroiditis requiring Thyroxine replacement. His HLH was successfully treated with steroids and Rituximab.
We think Alemtuzumab treatment had induced the autoimmune disorders (his coagulopathy and thyroid disease), as well as reactivating EB virus. The combination of coagulopathy and EB viral infection may have caused his adrenal haemorrhage. Endocrinologists should be aware of the wide spectrum of autoimmune disorders that can be precipitated by monoclonal antibody treatment.
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EP125

Incidentaloma as a first manifestation of lymphoma
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Introduction
Incidentally discovered adrenal masses (incidentalomas) are common and in some cases differential diagnosis could be a challenge.
Case report
A 55-years old woman presented with an incidental left adrenal mass of 36mm discovered on an abdominal ultrasound. As sole background she underwent resective surgery of an ovarian serous cyst. She denied symptoms like flushing, headache, diaphoresis or palpitations. Physical examination was irrelevant. BP: 130/76 mmHg; CF:78 bpm.
Fractionated metanephrines and catecholamines in a 24-hour urine specimen, sodium and potassium levels, 24-hour urinary free cortisol, adrenocorticotropic hormone, aldosterone/plasma renin plasma ratio and dehydroepiandrosterone sulfate were normal.
Abdominal computed tomography showed an heterogeneous left adrenal gland and multiple nodes in locations such as subdiaphragmatic region, celiac trunk, gastrohepatic ligament, splenic hilum and retroperitoneal area, most of them with the presence of central necrosis.
Additionally axillary and paratracheal nodes were found, and also lungs nodules less than 5mm in diameter were described. PET F-18 FDG scan identified an hypodense centrum area suggestive of necrosis into the left adrenal. A tomography guided biopsy only detected necrotic cells. Finally a left adrenalectomy was performed and histopathological study revealed a diffuse large B-Cell non-Hodgkin's lymphoma. The patient was started on chemotherapy with a successful response.
Conclusion
Biopsy could be necessary in the differential diagnosis of necrotic adrenal masses even when lymph nodes are present.
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EP126

Clinical case of aldosterone-producing adrenocortical carcinoma
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Aldosterone-secreting adrenocortical carcinoma (ACC) is rare neoplasm, which detected in 2.5% of active ACCs.
Clinical case
A 58 years old female, was admitted to our clinic with complaints of high blood pressure, back pain, weakness, convulsions. Biochemical evaluation confirmed primary hyperaldosteronism (serum aldosterone 1012 pg\ml, serum renin concentration 0.5 mkME\ml, aldosterone-renin ratio 202.4, hypokalemia 1.2 mmol\l). There was no evidence of cortisol co-secretion on standart low-dose dexamethasone test. The level of metanephrine and normetanephrine in urine were in normal range. A CT scan with contrast-enhanced identified right adrenal tumor 8*6*9 cm with heterogeneous structure. Native density of tumor was 38 Hounsfield units (HU). In arterial and venous phase tumor density was 70 HU, delayed - 55 HU. Dynamics of growth was $+5$ cm in 6 months. Surgical treatment was performed: in the right retroperitoneal there was tumor about 15 cm in diameter, comressed the inferior vena cava, right renal artery, and renal veins. Adrenalectomy with a tumor and lymph node dissection was performed. Histological examination revealed adrenocortical cancer. Ki-67 expression was up to 75% in 'hot spots'. Number of Weiss score - 6. A 1.5 month follow-up CT–scan was no evidence of local reccurence. Serum aldosterone level was in normal range.
Although rare, this case demonstrates the ability of this pathology, and therefore requires caution against the ACC at the small size of the tumor. As a method of follow-up screening can be a controlling level of aldosterone and potassium in the blood and monitoring blood pressure. To improve the results of treatment these patients it is necessary to conduct studies with larger numbers of patients, as well as development of new diagnostic and prognostic criteria allowing to improving diagnosis ACC before and after surgery.
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EP127

The case of adrenal incidentaloma due to unrecognized nonclassic congenital adrenal hyperplasia

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Introduction
A rare cause of adrenal incidentaloma is congenital adrenal hyperplasia (CAH). Nonclassic CAH is one of the most frequent autosomal recessive disorders. Most cases of nonclassic CAH are never diagnosed due to very mild symptoms.
Case report
A 62-year-old woman admitted at our Department for right adrenal incidentaloma sized 39×34×38 mm confirmed by MRI. She was asymptomatic. Her past medical history included stabile hypertension, euthyroid Hashimoto thyroiditis, uterine leiomyoma, varicose vein surgery and pulmonary embolism. Menarche occured at the age of 18, and the monthly menstrual cycle continued until the menopause at the age of 51. She had a miscarriage and three failed *in vitro* fertilisation attempts. Upon physical examination clitoromegaly was present. Endocrine assessment for excess of cortisol, catecholamine and aldosterone concluded that the adrenal mass was hormonally non-functioning. ACTH level was normal. 17- hydroxyprogesterone, total testosterone, androstenedione and progesterone were elevated: 26 nmol/l, 3.4 nmol/l, 8.5 ng/ml, 16.2 nmol/l, respectively. A 0.25-mg intravenous ACTH-stimulation level of cortisol (341/347/402) and 17- hydroxyprogesterone (29/51) showed partial cortisol insufficiency and nonclasssic CAH. After informed consent molecular genetic study for CAH was conducted. Our patient was found to be a heterozygote with two mutations in the CYP21A2 gene: p.P30L i I2G, that verified the diagnosis of CAH. In order to prevent adrenal insufficiency Hydrocortisone was advised in a case of surgical procedures or illness. During the 2 year follow-ups there were changes in either clinical and biochemical presentations or in repeated abdominal MRI examinations.
Conclusion
Undiagnosed nonclassic CAH is the cause of miscarriage, infertility and adrenal incidentaloma in our patient. 17- hydroxyprogesterone would be determined in all patients with infertility or adrenal incidentaloma.

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EP128

DOC secreting adrenal adenoma, a rare cause of hypertension

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Secondary endocrine hypertension affects around 10% of all hypertensive population, most frequently primary aldosteronism (PA). Less frequent forms of adrenal hypertension include pheochromocytomas and other causes of mineralocorticoid excess than PA, featuring suppressed renin without excess of aldosterone. Featuring. We present a 29-year-old woman with difficult to control hypertension diagnosed two years before and poor response to ACEI and ARA II treatment. She was referred for study and treatment. She had a normal appearance, without Cushing's stigmata, overweight nor clinical suspect of pheochromocytomas. She had not noticed hirsutism and maintained regular menstrual cycles. Biochemical study was normal except for slightly lower potassium (3.48 mmol/l). Hormonal study showed suppressed renin activity (<0.2 ng/ml per h), with normal to low aldosterone (7.3 ng/dl), normal urinary metanephrines and normal plasma ACTH (34.5 pg/ml). Abdominal CT revealed a well-defined heterogeneous and much vascularized right adrenal mass of 6 cm in diameter. Deoxycorticosterone (DOC) measured in previous stored sample was 237.9 ng/dl (normal < 15 ng/dl) with normal deoxycortisol (4.5 ng/ml; NV < 7.2), testosterone, DHEAs and plasmatic and urinary cortisol. Open right adrenalectomy was performed due to the size and suspicion of malignancy. On light microscopic examination, the tumour was an adenoma of 6.5 cm not encapsulated, composed of cells with clear and eosinophilic cytoplasm and large nuclei without mitosis nor necrosis. Weiss's criteria classified it as adrenocortical adenoma. Postoperatively, DOC level fell to 7.1 ng/dl and blood pressure and potassium normalized.
Conclusion
DOCA-producing adrenal neoplasm are exceptionally reported, and they are usually malignant tumours. They should be suspected in the presence of adrenal tumours with supressed renin but inappropriate low aldosterone, not suggesting PA. Early diagnosis can be very important because malignancy is the rule in this peculiar pathology.

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EP129

Aldosterone-producing adrenocortical carcinoma and alteration of secretion pattern on recurrence: a case report

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Introduction
Adrenocortical carcinoma (ACC) is a rare neoplasm with a variable but overall poor prognosis. The presentation is heterogeneous usually with mass effect and less often with evidence of hormonal secretion. About half of cases the tumors are hormonally active most commonly with cortisol secretion followed by sexual hormones production, being rare the aldosterone secretion.
Case report
A 41-year-old male presented with hypertensive crisis and marked hypokalemia. A primary hyperaldosteronism was diagnosed and Computed Tomography (CT) showed a 9 cm suspicious adrenal mass. The patient started on spironolactone and underwent open adrenalectomy. A total resection was done (R0) and it was a 10 cm adrenal carcinoma, Weiss score 5, Ki67 30% and stage II ENSAT. There was clinical and biochemical normalization and at 9 months CT didn't show any recurrence. Due to high risk carcinoma therapy with mitotane was proposed, however the patient refused and left follow-up. 30 months after surgery, he was admitted to the Emergency Department for adrenal carcinoma relapse and disseminated metastatic disease with simultaneous secretion of aldosterone and cortisol. He started on chemotherapy with EDP-M (etoposide, doxorubicin, cisplatin and mitotane). Despite initial favorable course, the patient got worse with disease progression, culminating in death 44 months after the diagnosis.
Discussion
The management of ACC is challenging. Surgery is crucial for treatment and mitotane is important as an adjuvant therapy, as a chemotherapeutic agent and also to control the hormonal secretion. We report a case of an aldosterone-producing ACC, an extremely rare cause of primary hyperaldosteronism. Even rarer was the change on secretion profile throughout disease evolution with multiple steroid production. The hormonal profile should be carefully investigated in an ACC and the possibility of multiple combined hormonal secretion or the shift of the profile secretion should be considered.

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EP130

Congenital adrenal hyperplasia: hazards of non-compliance with treatment!

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A 30-year-old male presented to emergency with history of palpitations for 6 months. At birth he was diagnosed with salt-losing congenital adrenal hyperplasia (female pseudohermaphrodite) and commenced on steroid therapy. He also underwent corrective surgery. He needed both fludrocortisone and hydrocortisone. At age 17, he visited urology because of bilateral testicular enlargement. On examination he had normal secondary sexual features, but his testicles felt hard and four times the normal size. His serum testosterone level was 50.4 nmol/l (10–38 nmol/l), 17-OH-progesterone 142 nmol/l (<13 nmol/l) and ACTH (corticotrophin) of 139 ng/l (0–50 ng/l), clearly indicating non-compliance. He had bilateral orchidectomy. Upon pathologic review, these lesions were most consistent with testicular tumors of the adrenogenital syndrome. Patient continued to default at clinic appointments. At age 26, he presented to the surgeon with increasing abdominal girth and abdominal pain. CT of the abdomen demonstrated very low-density adrenal masses (18×11 cm on the left side and 8×4.5 cm on the right side). Blood work up showed high 17-OH- progesterone indicating inadequate suppression with glucorticoids partly due to non-compliance. As these adenomas was new onset and there was a possibility of adrenocortical cancer the patient underwent laparoscopic bilateral adrenelectomy. The final histology to be consistent with adrenal myelolipomas. Hydrocortisone dose

was doubled and fludrocortisone 100 mcg/day was started. Now at age 30, he presented with history of palpitations and dizziness. He had sinus tachycardia In ECG (HR120/min). Blood work up: Na 130 mmol/l (135–145 mmol/l) K 5.33 mmol/l (3.5–5.1 mmol/l) Plasma renin 100 μIU/ml (<40 μIU/ml). This indicated under replacement. He was clearly tachycardic because of volume depletion. His compliance was enforced. Within 6 weeks his heart rate normalised with normalisation of renin levels. Persons with CAH are at increased risk of developing adrenal myelolipomas, testicular adrenal rest tumours particularly if their CAH is poorly controlled.

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EP131

Adrenal insufficiency due to both hemorrhage and thrombosis related with primary antiphospholipid syndrome

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Background
Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis and/or an adverse pregnancy outcome in the presence of persistent laboratory evidence of antiphospholipid antibodies. Loss of adrenal function due to bilateral adrenal vein thrombosis, resulting in hemorrhagic infarction, may occur in association with APS.
Case presentation
We present the case of a 45-year-old woman with APS diagnosis since she was 37, with history of multiple thrombotic events (deep vein thrombosis, sigmoid sinus thrombosis, spontaneous abortion, adrenal hematoma and pulmonary embolism). She was hospitalized for adrenal hematoma under anticoagulant therapy with warfarin. The basal adrenal function tests revealed morning serum cortisol 0.7 μg/dl (reference range 3.7–19.4) and ACTH 345 pg/ml (5–46). Abdominal CT showed nodular lesion with 55 HU density (29×27 mm) suggestive of adrenal hematoma in the left adrenal gland; right gland is thickenned. Adrenal insufficiency was associated with both hematoma in the left adrenal gland and thrombosis in the right gland. The patient was discharged under corticosteroid treatment and low molecule weight heparin (LMWH). After being discharged, warfarin was started again and she was admitted in the emergency department with dyspnea and pleuritic chest pain. Initial analytical study revealed INR (2.26), hypoxemia (PO2:64 mm/Hg) and hypocapnia (32 mm/Hg). She was restarted on therapy with LMWH. Further study showed deep vein thrombosis in right lower extremity. The patient was discharged after vena cava filter replacement.
Discussion
The recurrence rate of thrombotic events among patients with APS is highly variable among studies, with an annual recurrent thrombosis risk ranging from 5 to 12%. However adrenal involvement has been reported in 13% of cases of catastrophic APS. In patients with antiphospholipid antibody syndrome, adrenal insufficiency is often seen with bilateral adrenal thrombosis, although rarely in some patients an adrenal gland hemorrhage may occur with other adrenal gland hematomas.

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EP132

In spite of long-term symptoms, a pheochromocytoma diagnosed in pregnancy results in fetal loss despite proper approach

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A 27-year-old woman with had sweating flushing attacks for three years prior to pregnancy, but did not follow with any medical examination. At 12th gestational week, hypertension was detected and alpha-methyldopa was started, no abnormal findings were found in the routine examinations, in the 24-h holter study, blood pressure values (using alpha-methyldopa) were found to be higher than 144/99 (general), 147/101 (awake) and 134/92 mmHg (sleep). 24-hour urinary levels of catecholamine and metabolites were significantly higher than normal ranges; noradrenaline was 787.99 μg/24 h, dopamine 3635.43 μg/24 h, normetanephrine 1605.31 μg/24 h. MR imaging revelaed a heterogeneous lesion (49×37 mm) in the left adrenal gland. Because of the early stage of pregnancy laparoscopic surrenalectomy was performed. Histopathologic examination revealed a tumor consistent with pheochromocytoma. In the follow-up, there was no maternal problem except hypotensive state but unfortunately, because of anhydramnios and intrauterine growth retardation, medical abortion was applied at the 27th gestational-week. Pheochromocytoma is a very rare cause of hypertension in pregnancy however, early detection are crucial because of the increased risk of maternal-fetal mortality. Therefore, in cases of high blood pressure which can not be explained by gestational hypertension, it is necessary to carefully evaluate other secondary causes such as pheochromocytoma. The most suitable period for the operation is the second-trimester. Surgical approach was used and no complication related to the operation occurred in our case. However, it was thought that the outcome of fetal loss due to developmental delay was related to the adverse effects of circulatory factors due to long-term illness in the patient. The fact that the patient could not be examined in the pre-pregnancy period and probably the prolongation of the duration of the illness resulted in a negative result. Especially in women of childbearing age, the importance of hypertension in terms of maternal and fetal outcomes is emphasized by this case report.

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EP133

POEMS: a rare cause of adrenal insufficiency in a young male

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POEMS syndrome characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes is a rare disease that usually presents in the 6th decade. We report a case of a young male in whom the presenting manifestations were mandibular mass, adrenal insufficiency and peripheral polyneuropathy. Clinical case: A thirty-three year old man from Guinea-Bissau was admitted to our hospital with asthenia, weight loss, decreased tactile sensibility with pain and muscle weakness in upper and lower limbs. Bedridden for 2 years, after surgery of mandibular mass with nondiagnostic histological examination. Physical examination revealed mandibular deformity, unilateral gynecomastia, bilateral axillary lymphadenopathy, sensorial motor peripherial polyneuropathy, edema of lower limbs. Lab. evaluation: normochromic, normocytic anemia, thrombocytosis, hyperkalemia, normal renal/liver function and protein electrophoresis, immunofixation: monoclonal protein negative, urine: increased kappa/lambda chains, Bence Jones protein neg., morning cortisol 8.3 ug/dl, ACTH 129 pg/ml. Laboratory workup confirmed adrenal insufficiency, subclinical primary hypothyroidism and primary hypogonadism. Thoracic-abdominal CT: hepatosplenomegaly, multiple sclerotic lesions in thoracic vertebras and ribs. Gluco- mineralocorticoid substitution and levothyroxine therapy were started with clinical improvement. Bone marrow biopsy revealed plasma cell dyscrasia and confirmed POEMS syndrome. Axillary lymphadenopathy biopsy: Castleman disease. The patient had several community-acquired, nosocomial pneumonias and an episode of pulmonary edema. Autologous hematopoietic cell transplantation (HCT) was planned, cyclophosphamide induction started. Meanwhile he suffered two ischemic strokes which resulted in motor aphasia and hemiparesis. Cerebral angiography revealed vascular lesions compatible with vasculitis and stenosis of two cerebral arteries. Comments: In this case, although serum immunofixation was negative for monoclonal protein, bone marrow biopsy confirmed POEMS syndrome. There is no standard therapy, however patients with disseminated bone marrow involvement are treated with chemotherapy with or without HCT. In this patient despite the young age, the disease was already advanced and resulted in severe complications, which led to resignation from chemotherapy and HCT complications, which led to resignation from chemotherapy and HCT.

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EP134

Recurrent phaeochromocytoma – Iatrogenic

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Phaeochromocytoma is a common endocrinological diagnosis with an incidence of 1–2 per 10 000 people. Prompt evaluation and treatment leads to an excellent prognosis. Recurrence has been documented rarely (with literature reporting possibility of up to 8 years delay) and causes are generally attributed to inherited mutations, seeding during surgery or malignancy. Malignancy rates have been variable from 10% depending on site and mutations. In addition, the definition of malignant pheochromocytoma/paraganglioma is not always clear as there is no combination of clinical, histopathologic, or biochemical features to reliably predict biologic behaviour. In general; pathologic evaluations provide little prognostic insight to predict risk of recurrences or metastases reliably. We present a case that demonstrates relapse as a result of possible seeding from original laparoscopic adrenalectomy as one of the factors. Thus, pre-operative features that potentially make the tumour a high risk for recurrence should be identified and aid in creating an individualised management plan. Aspects that have been recognised to be directly related to outcome such as the size of tumour, underlying conditions such as MEN 2A/B and neurofibromatosis, the site of the tumour and anatomical ease of surgical intervention. This case highlights the importance of the recognition of such factors & multi-disciplinary team input, to prevent recurrences which have a significant effect on long-term cure and prognosis.

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EP135

An association of adrenal ganglioneuroma, Addison's disease and Mediterranean fever: a case report

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Introduction
Ganglioneuroma is a rare benign tumour arising from neural crest sympathogonia. It is usually asymptomatic and non functional. An association between ganglioeneuroma and genetic or autoimmune diseases such as Addison's disease or Mediterranean fever has never been described.
Case description
We report the case of a 24-year-old woman presenting with paroxysmal abdominal pain with loss of weight and no fever. Physical examination along with biological and hormonal explorations were normal. CT scan showed a solid tumour of the right adrenal gland, measuring 50×31 mm, with no sign of malignancy and a moderate ascites, so the patient underwent adrenalectomy. Anatomopathological examination of the adrenal gland confirmed the presence of a ganglioneuroma, and the patient presented an adrenal insufficiency 4 days after the surgery. Addison's disease was confirmed with positive anti- adrenal antibodies, with anti-21-hydroxylase at 2866.9 U/ml and she received corticosteroid replacement therapy. The patient continued to have recurrent abdominal pain, fever and ascites. A Mediterranean fever was suspected, and she was put on colchicine 1 mg per day, with improvement of paroxysmal abdominal pain. Genetic confirmation is underway.
Conclusion
We report for the first time an association between ganglioneuroma, Addison's disease and Mediterranean fever whose clinical features can be confused. A possible underlying genetic mechanism can be suspected rather than just a random association.

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EP136

Adrenal carcinoma after ovariectomy. Report of a case

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Adrenocortical tumorigenesis has been observed in mice. It is speculated to be gonadotropin dependent. In particular LH receptors appear to be found within such adrenal tumors in high density and elevated LH levels may be related to adrenal tumorigenesis. The aim was to describe the case of a patient who after ovariectomy developed a large malignant adrenal tumor. A patient, female, aged 42 presented with uterine leiomyomas. She was treated by surgical excision of the uterus along with ovariectomy. Subsequently, she refused to be treated with estrogens, developing however severe postmenopausal symptoms. At the age of 50 she presented with musculoskeletal symptoms affecting the spine, both knees and the left shoulder. A CT scan of the abdomen was performed showing a large mass originating from the left adrenal gland. An MRI was performed and the patient was treated by left adrenalectomy. The adrenal tumor was malignant, measuring 6×6×5 cm, androgen receptor positive and progesterone receptor positive in some areas. The patient recovered. On follow up 6 months later she was free of any malignant disease. She developed Hashimoto's thyroiditis, antithyroglobulin antibodies being 425 IU/ml (normal values <115 IU/ml) and antimicrosomal antibodies being 213 IU/ml (normal values <34 IU/ml), while TSH was 3.9 IU/L (0.3–4.2 IU/L). In conclusion, the case of a patient is presented who developed a large adrenal tumor following ovariectomy. Adrenal tumorigenesis has been observed in mice following ovariectomy. It is believed to be related to LH stimulation by elevated LH levels, LH receptors having been observed within the adrenal tumors. In mice tumorigenesis may be prevented by the administration of agents lowering gonadotropin levels (Rahman et al, Reprod Biol 2001). It may be that in such cases of premature ovarian failure following surgical ovariectomy, thought should be given to possible treatment aiming at low gonadotropin levels.

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EP137

ACTH-independent Cushing syndrome with concomitant parathyroid carcinoma

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Introduction
The incidence of parathyroid carcinoma in primary hyperparathyroidism is less than 1% and the association with ACTH-independent Cushing syndrome is very rare.
Case report
A 40-year-old female was admitted for weight gain and reddish-purple striae. One month earlier she had a ¾ parathyroidectomy for primary hyperparathyroidism with histopathological examination showing a parathyroid carcinoma and two parathyroid adenomas. She also had a history of deep vein thrombosis. She had no family history of endocrinopathies. The physical exam revealed a positive Chvostek sign, facio-troncular obesity, reddish-purple striae and grade I hypertension. Biochemical assessment revealed hypocalcaemia (5.75 mg/dl) and diabetes mellitus. Hormonal assessment revealed hypoparathyroidism (PTH = 12.45 pg/ml), no catecholamine excess, normal prolactin level. High levels of urine free cortisol (415.91 µg/dl) and positive long low dose DST(2mg/day×2 days) (12.29 µg/dl) confirmed the clinical suspicion of Cushing syndrome. ACTH levels were suppressed. Chromogranin A levels were normal. We performed a pituitary MRI and a CT of the neck, thorax and abdomen that showed bilateral adrenal macronodular hyperplasia with no other suspicious masses including pituitary adenomas. DXA evaluation showed osteoporosis for which she later received bisphosphonate therapy. A bilateral adrenalectomy was performed and subsequent mineralocorticoid and glucocorticoid replacement therapy was initiated. Genetic test for MEN1 syndrome is pending. The hyperparathyroidism relapsed 18 months after the parathyroidectomy. Calcium levels remained in the high normal range during monitoring with normal renal function and the last scintigraphy and CT scan showed an adenoma of the remaining parathyroid with no sign of local recurrence of the parathyroid carcinoma. Periodic follow-up also revealed a pituitary microadenoma with minimally raised prolactin and a thymic lesion that were stationary over the last 7 years of monitoring.

Conclusion
In patients with primary hyperparathyroidism special attention should be given to signs of other endocrinopathies as hyperparathyroidism could be the first manifestation of a MEN syndrome.

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EP138

Incidental adrenal cyst: a case report

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Introduction
Cystic adrenal lesions (CAL) are a rare diseases representing 5.4–6.0% of all pathological changes affecting adrenal glands. In about one-third of the cases, lesions are detected incidentally; in the remaining two-thirds cysts lesions are symptomatic, which is typically related to their large size or rapid growth. Although CAL are usually benign, since malignancy is reported in up to 7% of all CAL. Management algorithms for CAL vary and are controversial because of the overall rarity of such lesions.
Case report
We describe a case of a 29-year-old man who presented with abdominal pain. The computed tomography of the upper abdomen revealing the presence of a 4-cm simple cyst originating from the left adrenal. All serological and hormonal secretion tests were negative. So the final diagnosis was a simple left adrenal cyst; 8 months later, abdominal ultrasound follow-up revealed adequate cyst shrinkage down to 2.8×6.9 cm. The patient remains symptom free to date.
Discussion
Surgical excision of adrenal cysts is indicated by the presence of symptoms, suspicion of malignancy, or the detection of a functioning adrenal cyst. Cysts may coexist with primary and metastatic adrenal tumours. Malignancy of the cyst is found in 7% of all affected patients. Adrenocortical and adrenomedullar hyperfunction is accompanied by adrenal cysts in ca. 15% of cases. What is more, adrenal cysts accompany approximately 7% of primary and metastatic cancerous processes, and in 0.5% of cases they are of parasitic origin and their clinical management remains controversial. However, surgical intervention is not recommended for asymptomatic patients with incidental cysts, for the fact that the pathological data of our series revealed no malignant cases. Patients after surgical resection should be followed up closely especially in functional cysts and when histopathology showed cystic tumor.

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EP139

Gynecomastia in men: A rare case of adrenal feminizing tumors

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Estrogen-producing adrenal gland tumors (EPAGT) are extremely rare, accounting for only 1–2% of all adrenal tumors. They are most commonly observed in men or in children, and are unusual in women. They are almost always malignant even if they seem benign at presentation, and most of them have a poor prognosis. We present a case of a 71-year-old man with painful bilateral gynecomastia, without galactorrhea, over 4 months. Markedly elevated plasma estradiol levels were found (161.7 ng/l; normal 15.5–63.3) with low LH and FSH values. All other parameters were within normal range (b-HCG, PRL, TSH, FT4, total testosterone, SHBG, cortisol, ACTH, DHEA SO4, delta-4-androstenedione, 17OHPRG, fractionated metanephrines, cromogranine-A). Echographic images and mammography showed bilateral mammary gland hypertrophy excluding any nodules. CT abdominal scan indicated a large retroperitoneal mass measuring 14×8 cm with posterior and inferior deviation of the left kidney, with heterogeneus contrast uptake. It appeared to be a retroperitoneal tumor independent of any other retroperitoneal organ. To clarify its etiology, a biopsy was performed. The histology suggested an adrenal cortex tumor. It displayed cell proliferation with abnormal nuclei. Immunohystochemistry was positive for melan A, HMB45, INHA and focal AE1/AE3. The Ki-67 was around 15%. While it was impossible to distinguish between adenoma and carcinoma, the images were suggestive of malignancy. Although there were no signs of metastasis in toraco-abdomino-pelvic-CT, a PET-scan is arranged to exclude some other lesions. Gynecomastia in adult males is usually related with drugs and systemic or endocrine diseases. However, it is less often related with rare conditions, such as the testicular tumor of Leydig cells and the rarest adrenal feminizing tumor. Surgery is the main option for EPAGT, nevertheless the prognosis is very poor.

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EP140

Virilization – a non-negligible manifestation of an adrenal tumor

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Introduction
Adrenocortical carcinoma (ACC) is a rare and aggressive endocrine malignancy with a poor prognosis. Hormone-secreting ACC appear with manifestations of virilization, feminization or Cushing syndrome.
Case Report
A 63-year-old woman with no pathological history of relief was referred to Endocrinology evaluation with an history of deepening of the voice since 1-year ago, as well as hair loss and facial and abdominal hirsutism with 6-month evolution. The analytical study revealed the following results: total testosterone 6.03 (Normal Range (NR) 0.06–0.82) ng/ml, delta-4 androstenedione >10.00 (NR 0.30–2.99) ng/ml, DHEA-S 545.8 (NR 18.9–205) µg/dl, 17-OH-Progesterone 6.32 ng/ml, SHBG 71.4 (NR 14.1–68.9) nmol/l, FSH 7.96 ng/ml, LH 5.96 ng/ml Estradiol 123.8 pg/ml; normal urinary catecholamines and metanephrines; normal renin and aldosterone values; ACTH 2.1 ng/l (NR <63.3), urinary free cortisol 353.6 (NR 36–137) µg/day, late-night salivary cortisol 0.499 (NR <0.32) µg/dl and plasma cortisol after 1-mg overnight dexamethasone suppression test 13.3 µg/dl (NR<1.8). She performed an abdominal MRI with documentation of a massive solid tumor lesion with heterogeneous contrast uptake, well delimited and measuring about 13.4 cm in diameter, which was admitted to be dependent on the left adrenal gland. Were identified several hepatic and lung nodularities suggestive of secondary lesions. In a multidisciplinary evaluation, it was decided to perform left adrenalectomy by laparotomy. No ascites or signs of peritoneal carcinomatosis were present. The anatomopathological examination revealed an ACC ENSAT stage IV, pT2NxMx, with a modified Weiss score of five and a classic Weiss score of seven. The patient is now proposed for adjuvant chemotherapy with mitotane.
Conclusions
We report a case of an ACC combining hyperandrogenism with Cushing's syndrome. Hormonal hypersecretion, particularly hypercortisolism, is associated with a worst outcome. Complete tumor removal remains the only potentially curative treatment.

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Clinical Case Reports - Thyroid/Others

EP141

The ovarian origin of hiperandrogenism in the postmenopausal woman with the adrenal adenoma – a case report

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Hyperandrogenism is a clinical condition characterized by excessive secretion of male sex hormones. An excess amount of androgens in women is manifested by

symptoms of defeminization and masculinization. Hormonally active adrenal and ovarian tumors and non-tumor causes must be considered in the differential diagnosis. The authors describe the case of a 77-year-old patient who had hirsutism and reduction of the timbre of the voice. At the beginning she was suspected to have adrenal hyperandrogenism because of the tumor in the adrenal gland. Then adrenalectomy was conducted but it did not lead to alleviate symptoms. A MRI of the pelvis revealed a change of appendages projection and the patient underwent the total hysterectomy. The normalization of testosterone levels as well as reduction of the symptoms was observed after the operation. Finally, the ovary etiology of hyperandrogenism was confirmed. This case report is an example of difficulties in recognition the etiology of hyperandrogenism.

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EP142

Secondary autonomic neuropathy in patient with polyglandular autoimmune syndrome III and type 1 gastric neuroendocrine tumor: a case report

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The polyglandular autoimmune syndromes (PAS) are rare disorders characterized as multiple autoimmune-mediated organ failure. PAS III includes chronic autoimmune thyroiditis with type 1 diabetes mellitus or pernicious anemia and/or vitiligo or alopecia and many other organ-specific autoimmune diseases, but never involves adrenal cortex. Several patients with PAS III and associated type 1 gastric neuroendocrine tumor (NET) have already been reported. We report probably the first case of PAS III, type 1 gastric NET and concomitant secondary autonomic failure as the main clinical manifestation. A 65-years-old woman with severe postural and postprandial orthostatic hypotension admitted to the hospital. The orthostasis has been debilitating and gradually has worsened in the past year. She has lost about 25 kg due to postprandial sickness and consequent dietary restrictions. The patient has a history of mild type 2 diabetes mellitus. She has been treated with metformin and her HbA1c has been $< 6\%$ during the last 8 years. Diabetes has resolved due to weight loss and the patient has had a good glycemic control without any treatment for the past year. The patient has a history of primary hypothyroidism due to chronic autoimmune thyroiditis. Besides that she has suffered from hair loss with global alopecia over the last decades of life. Initial B12 vitamin deficiency without anemia has been detected. Upper endoscopy was performed, showing multiple gastric polyps. Histological examination revealed chronic atrophic gastritis, hyperplasia of endocrine cells and gastric NET G1, Ki-67 = 1%. Numerous gastric polyps have been removed during endoscopy. The patient has been treated with intramuscular B12 vitamin injections with a gradual positive effect on the autonomic dysfunction. Annual endoscopic follow-up and lanreotide injections are recommended to prevent progression and dissemination of the gastric NET.

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EP143

MEN 1 Syndrome- a case with recurrence of neuroendocrine tumor and hyperparathyroidism after 9 years of follow up

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Introduction
Life expectancy is decreased in MEN1 patients due to multiple tumors that may be larger, more aggressive, resistant to treatment and with a higher risk of recurrence.
Case report
We report a 59-year-old male patient with family history of endocrine tumors (father- pituitary adenoma, son- primary hyperparathyroidism, daughter-microprolactinoma, primary hyperparathyroidism). He was first referred to our Clinic in 2007 after being incidendally diagnosed with well differentiated pancreatic neuroendocrine tumor (CT-scan performed for nephrolithiasis and repeated renal colic revealed a pancreatic mass that was surgically removed). In 2009 the patient was diagnosed with primary hyperparathyroidism and multinodular goiter for which subtotal parathyroidectomy and total thyroidectomy were performed. He also presented MEN1 associated tumors such as non-functioning left adrenal adenoma, bilateral asymmetric lipomastia and multiple subcutaneous lipomas and conditions associated with calcium disorders: nephrolithiasis, nephrocalcinosis, secondary osteoporosis. Regarding these findings, the patient was diagnosed with MEN1 syndrome and started undergoing periodical follow-up. Between 2009 and 2016, at the anual reevaluation, no clinical or paraclinical evidence of tumor recurrence was found. In October 2016 he presented a mild elevation of calcium and PTH levels and the sestamibi parathyroid scan revealed the presence of parathyroid adenoma. The CT-scan showed two pancreatic masses, immunohistochemistry tests from the biopsy supported the diagnosis of neuroendocrine tumor NET G1 and the patient started treatment with somatostatin analogues. Further assessment of the possibility of tumor resection and parathyroidectomy is considered.
Conclusion
Considering the high risk of tumor recurrence in MEN1 patients, regular follow-up is crucial in detecting and treating the relapses. Our patient developed both recurrence of neuroendocrine tumor and hyperparathyroidism.

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EP144

Insulinoma- from diagnosis to full recovery. Case study

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Introduction
Insulinoma is a rare form of a functional neuroendocrine tumor with an estimated incidence at 1–2 new cases per million persons per year. This infrequent endocrinopathy, frequently escaping standard disease course, constitutes a diagnostic challenge for every endocrinologist. Successful surgical resection of the lesion is the only available method that ensures patient's full recovery.
Case study
53 years old patient with complaints about recurring episodes of hypoglycemia, without accompanying adrenergic symptoms though, was admitted to Department and Clinic of Endocrinology, Medical University of Lublin. During diagnostic procedures: low glucose levels (ranging from 1.94–3.56 mmol/l) with corresponding inadequately high insulin levels were observed in a prolonged glucose tolerance test, where glucose and insulin concentrations measurements had been carried out every hour. Afterwards supervised 72-h fast was introduced, only to be terminated after just 24 h, due to symptomatic hypoglycemia (2.28 mmol/l). Insulin levels at the end of fasting remained disproportionately elevated (10.7 mU/l). Based on follow up diagnostic tests we were able to exclude other potential causes of hypoglycemia in the form of adrenal insufficiency and hypothyroidism. Abdomen CT scan didn't reveal any lesions in pancreas whereas abdomen MRI unveiled presence of the tumor, 2 cm in diameter, located in the tail of pancreas. On the 1st of September 2016 patient underwent surgical resection of the pancreas mass. Histologic evaluation confirmed the diagnosis of insulinoma (pNET: G2 insulinoma). Octreoscan and abdomen MRI didn't indicate a diffuse process. Currently all of the symptoms subsided, the patient doesn't require any additional treatment.
Conclusions
Insulinomas are neuroendocrine tumors of rare occurrence. The readily available imaging methods rarely allow for a location confirmed diagnosis because of borderline small size of lesions. Persistent hypoglycemia being the most characteristic symptom facilitates the diagnosis and introduction of proper treatment.

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EP145

Insulinoma masquerading as neurologic disease

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Introduction
Insulinomas are the most frequent cause of hypoglycemia and the most common functional endocrine pancreatic tumors. Whipple triad is often present and should alert to the diagnosis.
Case report
A 36-year-old male was admitted in the emergency room with loss of consciousness, diaphoresis and blurred vision, and hypoglycemia (50 mg/dl). The patient recalled recurrent symptoms of diaphoresis, tremors and palpitations, sometimes with loss of consciousness and incontinence of urinary sphincters, for the past 4 months, having been diagnosed with epilepsy and medicated with anticonvulsive drugs. This symptoms were associated with weight gain, occurred before meals and were relieved with eating carbon hydrates. He had no family history of endocrine disease. Prolonged supervised fasting test was applied and led to symptomatic hypoglycemia with hyperinsulinemia (blood glucose 40 mg/dl, plasma insulin 68.7 μIU/ml and C-peptide 7.07 ng/ml). Other hormonal studies were normal, rejecting the diagnosis of multiple endocrine neoplasia. He maintained severe hypoglycemia despite glucose fluid administration and nutritional adequate plan, and medical treatment was necessary with octreotide 300 mg/day and diaxozide 900 mg/day. Abdominal magnetic resonance demonstrated a well-defined enhanced lesion in the tail of the pancreas measuring 14 mm. Nodule enucleation was performed by laparoscopy and pathological examination revealed an encapsulated pancreatic mass measuring $17\times14\times15$ mm. Mitotic index was <2 per 10 CGA and proliferation index ki-67 was estimated $<2\%$. Immunohistochemically, tumor cells showed a positive staining for insulin, synaptophysin and cromogranine. Shortly after surgical treatment, glucose level increased to normal range. The patient was discharged without any hypoglycemic symptoms after 7 days.
Conclusion
The diagnosis of insulinoma may be challenging due to its rarity and variable presentation. Other diseases, such as neurologic, may be considered first, but it's important to contemplate the diagnosis since chronic and severe hypoglycemia can be fatal and the surgery is usually curative.

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Endocrine Tumours and Neoplasia

EP146

Glucose metabolism abnormalities and insulin resistance are frequent in well diferentiated digestive NETs

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Introduction
Incidence of Digestive NETs (DNETs) has increased in the last 40 years. Visceral obesity, metabolic syndrome (MetS) and insulin resistance (IR) have been associated with several types of cancer.
Aim
To evaluate possible associations of obesity, hyperinsulinemia and IR with well-differentiated (WD) DNETs through a case control study.
Materials and methods
Ninety-six patients with gastrointestinal (75.0%) and pNET (22.9%) WD DNETs were recruited from Endocrine Tumours Clinic of IPO Porto and cross-matched with a control group ($n=96$) from PORMETS, a nationwide epidemiological study designed to evaluate the MetS prevalence in the general population, pair-matched by age, gender and place of birth. Hyperinsulinemia and IR were defined according to Mattews's classification. WD DNETs were classified according to primary tumour localization, hormonal secretion, TNM stage and WHO grading.
Results
MetS was present in 45.8% of WD DNETs. According to grading, 66.7% were G1 and 27.1% were G2 tumours. The disease was localized in 31.3%, locoregional in 16.7% and disseminated in 43.8%. Both patients and controls had high mean body weight (26.9 vs 27.2 kg/m^2, $P=0.645$). No significant differences were found between the two groups for waist circumference, Fasting Plasma Insulin (FPI) and HOMA-IR ($P=0.236$; $P=0.372$ and $P=0.274$, respectively). Median Fasting Plasma Glucose (FPG) and Impaired Fasting Glucose (IFG) frequency were higher in WD DNETs ($P<0.001$ and $P=0.013$, respectively). FPG $\geq$ 100 mg/dl and HOMA-RI ≥ 5 were associated with a higher risk for WD DNETs (OR 4.3 (95%CI 2.3–8.2, $P<0.001$); OR 4.1 (95%CI 1.2–13.5, $P=0.014$), respectively). When anthropometric and metabolic parameters are compared, there was no difference between somatostatin analogues users and no-users.
Conclusion
Association of glucose metabolism abnormalities and IR with WD DNETs confirmation can open new perspectives for prevention and treatment, through modifying lifestyle and insulin sensitizers use.

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EP147

Clinical and hormonal characteristics of adrenal incidentalomas

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Introduction
Widespread use of abdominal imaging has led to the identification of an increasing number of adrenal incidentalomas (AI) in the last decades. Causes of these adrenal masses are multiple.
Aim
The aim of this study was to investigate the clinical and hormonal characteristics of AI.
Materials and methods
The study was a retrospective monocentric analysis of 44 patients with AI who underwent radiographic and endocrine evaluations.
Results
The mean age was 59.25 ± 10.3 years and the sex ratio (F/M) was 1.3. Arterial hypertension was diagnosed in 27 patients (61.4%), obesity or overweight in 84%, diabetes in 18 patients (40.9%), dyslipidemia in 7 patients (15.9%). Five patients had an extra-adrenal tumor (11.4%). First diagnostic procedure was computed tomography (CT) in 63.6%, abdominal ultrasonography in 31.8% and magnetic resonance imaging in 4.5%. Regarding the location of the masses: 36.4% were in right side, 34.1% were in left side and 29.5% were bilateral. The Cause of radiologic imaging was kidney problems in 50%, liver disorders in 20.4%, epigastralgia in 13.6%, thorax pathology in 6.8%, rheumatologic causes in 6.8% and an inflammatory syndrome in 2.3% of cases. The average diameter of tumors was 26.6 ± 15.9 mm. The mass was single in 65.9%, well limited in 95.5% and homogeneous in 81.8%. Patients with functioning tumors had larger tumor diameters than those with non-functioning tumors ($P<0.05$). Final diagnosis was: non-functioning adenomas in 68.2%, pheochromocytoma in 6.8%, Cushing's syndrome in 6.8%, primary aldosteronism in 4.5%, subclinical Cushing's syndrome associated to phéochromocytoma in 2.3%, hematoma in 2.3%, tuberculosis in 2.3% and metastasis in 6.8%. Patients with functioning tumors had larger tumor diameters than those with non-functioning tumors ($P<0.05$). Two patients were diagnosed with adrenal insufficiency.
Conclusion
Our study showed that AI occurred more frequently in overweight or obese women with diabetes and hypertension. Its most common diagnostic procedure was CT and etiologies were dominated by nonfunctioning adenomas.

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Pituitary insufficiency, the beginning of a diagnostic journey

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Introduction
We report a case of a pituitary insufficiency apparently resistant to treatment.
Case report
A 74 year old patient was admitted through the ER in our department for a recently discovered pituitary macroadenoma. His general condition was poor in spite of the initiation of corticotherapy. Evaluation: Smoker, with no significant medical history, the BP: 100/60 mmHg, no orthostatic hypotension, disoriented, confused, with moderately altered general state and no visual deficit. Biologically: normal ionogram, TSH: 0.076 mcIU/ml, fT_4: 0.767 ng/dl, total T_3 <40 ng/dl, prolactin: 21.5 ng/dl, IGF1: 84.8 ng/ (low). He had leukocytosis, high neutrophils, but normal markers of inflammation. No causes of infection were found, but the clinical condition worsened in the next 2 days despite an i.v. with Hydrocortisone and oral Levothyroxine. Additional imaging studies showed an adenoma of 3.4/2.8/3.8 cm, with a mass effect on the optic chiasm, multiple secondary lesions in the upper and infratentorial regions at the cerebral MRI. During the neck ultrasound we found a multinodular goiter with a large nodule of 1.53/1.33 cm with multiple large pathological laterocervical adenopathies. The thoraco-abdomino-pelvic CT found a large pulmonary mass of 45/49 mm in the left lung, some osteholytic lesions in the right ribs and body of L5, a large cephalic pancreatic lesion of 35/24 mm and bilateral adrenal metastatic lesions. At that moment we thought that the pituitary macroadenoma was highly probable to be a metastatic lesion with multiple options regarding the origin of the primary neoplasia. The biopsy of an excised cervical adenopathy showed an aggressive neuroendocrine tumour as the probable cause, diagnosis which was unfortunately sustained by the lethal outcome of the patient.
Conclusion
The pituitary insufficiency in normally a benign condition which responds to treatment and has a favourable outcome; if this is not the case we must search for additional causes of poor responders.

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EP149

Thyroid carcinoma in multiple endocrine neoplasia type 1

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Introduction
Multiple endocrine neoplasia type 1 (MEN1) is a cancer syndrome characterized by the development of neuroendocrine tumors of the pituitary gland, parathyroid and pancreas, and other neoplasms such as adrenocortical tumors and carcinoid.
Observation
We report the case of a 70-year-old women with acromegaly that diagnosed 15 years ago, in relation with pituitary macroadenoma (30×25 mm) invading the left cavernous sinus and in contact with the third ventricle without endocrine or ophthalmological repercussions. The impact of acromegaly is diabetes mellitus treated with insulin complicated by retinopathy. The visceral assessment revealed a hypertension with cardiomegaly and a multinodular goiter diagnosed 2 years after the discovery of the acromegaly. Refusing pituitary surgery and radio-therapy, the patient remains uncontrolled with maximal dose of somatostatin analogues and dopaminergic agonists, the Gh level is 70 and IGF1 is 638 ng/ml. Exploration of the goiter finds 3 nodules (20 to 30 mm of diameter) benign in fine needle aspiration biopsy, operated 10 years later and the pathological examination finds papillary carcinoma of the thyroid, patient is treated by iodine 131 under recombinant TSH, It is currently in remission, her thyroglobulin level is under 0.20 ng/ml. During evolution, the patient presents bilateral renal lithiasis repeatedly, the balance allowed the discovery of a primary hyperparathyroidism with high serum calcium and PTH around 150 pg/ml due to a right inferior parathyroid adenoma, complicated with osteoporosis for which the patient refused surgery. In this clinical context, the genetic studies to search presence of mutation in *MEN1* gene encoding the menin protein was performed and confirm multiple endocrine neoplasia type1.
Conclusion
The hypersecretion of Gh induces an organomegaly, and the development of multinodular goiter is very frequent but discovery of thyroid carcinoma is rare, the prevalence of this association remains to be determined.

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EP150

Small pancreatic neuroendocrine incidentalomas: an observational prospective study

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Background
Diagnosis of small pancreatic neuroendocrine incidentalomas (PNETs-I) is increasing during last years and often their management remains unclear.
Objective
To describe our experience with patients with PNETs-I in our institution.
Methods
Since March 2000, patients with non functioning PNETs-I ≤30 mm were evaluated in our center, prospectively. A descriptive analysis of all patients and a comparative study between observational group (OG) vs resection group (RG) was made.
Results
Forty-six patients were evaluated: 36 in OG and 10 in RG. Median follow up (months) was 35.9 in OG and 76.6 in RG. Most of patients (69.9%) were diagnosed in the last 6 years. Mean age (years): 69.5 in OG and 57 in RG ($P<0.003$). Gender: 56.5% women. Mean tumor size (mm) was 12.5 (11 in OG vs 18.7in RG $P<0.005$). PNETs-I were multiple in 17.4% cases. At diagnosis, all PNETs-I's size were ≤20 mm in OG, without metastases. In RG, 8 patients (80%) had surgery complications, mostly mild to moderate without deaths. Diagnosis was made by imaging procedures in 91.6% of OG. In our series, 82% had a CgA assessment at diagnosis. Median CgA value was 179 µg/l (72–304). At the end of follow up, 88% in OG of patients had no change in tumor size, the rest had tumor growth <20%; In OG no PNETs-I resection were needed, and none of the patients metastasized or died because of PNETs-I in this group.
Conclusions
Non functioning PNETs-I is increasing in incidence in our center. After almost 36 months of follow up, no patients had significant growth, developed metastases and neither of them died from PNETs-I. In OG, active surveillance is safe in selected PNETs-I patients. We need prospective multicentric studies to confirm our results.

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EP151

Potential inhibitory effect of progesterone on breast cancer metastasis via the regulation on protein expression of apoptosis- and EMT-related genes

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Breast cancers that are estrogen receptor (ER)/progesterone receptor (PR)-positive are more likely to respond to hormone-related treatments than tumors that are ER/PR-negative. The present study investigated the effect of progesterone (P4) on 17β-estradiol (E2)-induced cell proliferation, apoptosis, EMT, and migratory and invasive features of MCF-7 clonal varient (CV) breast cancer cells that are ER/PR-positive. Preferentially, E2 was verified to induce breast cancer progression by stimulating cell proliferation, EMT, and migration of MCF-7 CV breast cancer cells. On the other hand, P4 reduced E2-induced MCF-7 CV cell proliferation by down-regulating the protein expression of cyclin D1 and E1 and induced apoptosis of MCF-7 CV cells by up-regulating Bax and p53 and by

down-regulating Bcl-2. Also, P4 appeared to inhibit E2-induced EMT process by increasing mRNA and protein expression of E-cadherin, a crucial epithelial marker, as well as by reducing the expression of mesenchymal markers such as N-cadherin and vimentin and EMT-associated transcription factors such as snail and slug. Eventually, E2-induced migration and invasion ability of MCF-7 CV cells and the protein expression of proteolytic enzymes such as MMP-9 and cathepsin B were reduced by P4 treatment. Co-treatment of RU486, a PR inhibitor, restored the inhibited cellular migration and invasion and the reduced expression of proteases by P4 to the control levels, suggesting the involvement of PR in P4-induced inhibition on migration and invasion of MCF-7 CV cells. Taken together, P4 treatment may be suggested as an effective tool for suppression of human breast cancer progression and metastasis. (This work was supported by a grant from the Next-Generation BioGreen 21 Program (no. PJ011355-2015), Rural Development Administration, Republic of Korea.)

Keywords: Progesterone; breast cancer cells; epithelial-mesenchymal transition; metastasis; migration.

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EP152

Incidental paraganglioma, diagnosis and follow-up – case report

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Paragangliomas and Pheochromocytomas are tumors originated from chromaffin cells (Pheochromocytomas (PHEO): adrenal glands; Paragangliomas (PGL): paravertebral thoracic, abdominal, and/or pelvic sympathetic ganglia, and glossopharyngeal and vagal neck and skull base parasympathetic ganglia). Catecholamine hypersecretion predominates in PHEO, while PGL are oligosymptomatic with compression-related symptoms. The authors report the case of a 33-year-old male with an incidental retroperitoneal PGL, detected during an investigation for urinary lithiasis (abdominal pain that shifted to different location, varying in intensity), without clinical evidence of catecholamine hypersecretion. The abdominal ultrasound identified a well-defined 5.0×4.5 cm hypoechoic nodular area at the right retroperitoneal region, above the renal pelvis, dislocating the renal vein anteriorly. The image was confirmed by CT (a 5.6×4.5×4.1 cm nodular area anterior to the right adrenal gland without a cleavage line with the inferior cava vein), MRA (a 5.4×3.5×4.6 cm nodular area anterior to the right adrenal gland), and PET/TC with FDG (a right retroperitoneal 5.2×3.8 cm mass that dislocated the inferior cava vein at the confluence of the renal veins; SUVmax =29.7). *^{123}I-MIBG* scintigraphy showed a discrete tumoral uptake. Ultrasound-guided biopsy: the patient presented a hypertensive peak during this procedure and was successfully medicated. He did not present arterial hypertension during the follow-up. Histopathology: suggestive of paraganglioma and neuroendocrine tumor.chemical investigation for catecholamines and plasmatic metanephrines hypersecretion: negative. Surgery: anterior laparotomy (without pharmacological preparation, since the tumor was non-secreting) without complications. Histopathology: paraganglioma/neuroendocrine tumor. Post-op follow-up: normal levels of metanephrines/catecholamines. I^{123} MIBG scintigraphy without evidence of the previously described lesion in the right lumbar region. No recurrence or clinical evidence of disease after a 5-year period.

Conclusion

Despite the tumour dimensions, there were no symptomatology previously to the diagnosis and no recurrence at a 5-year follow-up.

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EP153

Primary hepatic neuroendocrine tumor with multiple liver metastases treated with somatostatin analogues: case report

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Introduction

Somatostatin analogues (SSA) have been used as first line treatment to control the symtoms in hormonally active neuroendocrine tumors (NET), for over three decades. Primary hepatic neuroendocrine tumors (PHNETs) are rare neoplasms. Despite increased incidence of PHNETs over time, these tumors remain a rarity. According to the previously reported cases, primary neuroendocrine carcinoma of the liver is usually multicentric, often mimicking liver metastases. The demonstration of the hepatic origin of a neuroendocrine carcinoma is often arduous.

Case presentation

A 59-year-old woman underwent ultrasound examination 3 years ago, that revealed two liver nodular tumors (the largest having approximately 4 cm), with a complex structure. Abdominal IRM images confirmed multiple liver nodular tumors with intense vascularization, suggesting liver metastases. The patient was asymptomatic. In order to determinate the primary site of the tumor, the patient underwent multiple imagistic investigations and endoscopies. Among the blood tests (5-hydroxy **indole acetic acid**, carcinoembryonic antigen, chromogranin A, serotonin), only chromogranin A presented significantly high values. Further, a liver aspiration biopsy was performed. The histopathological examination result completed with the immunohistochemistry techniques suggested a well differentiated neuroendocrine carcinoma of an intermediary stage, with a proliferation marker ki67 of 4%, most likely a metastasis. For a full diagnosis, Octreoscan (11In-pantreotide scintigraphy) was performed. The whole body scintigraphy at 10 minutes completed with the SPECT/CT at 4 hours established a primary liver site with secondary spleen metastases, along with liver and renal adenopathies. Treatment with somatostatin analogues (SANDOSTATIN LAR 30 mg/month), was commenced, with favourable outcome. After 18 months of treatment, serum chromogranin values are still normal, while the volume of the tumors decreased significantly (by repeated MRI).

Conclusion

Despite that the liver represents the common site for metastases from other gastrointestinal neuroendocrine carcinomas or other tumors, primary hepatic neuroendocrine tumors are rare, but can occur. The diagnosis of primary neuroendocrine tumors of the liver is difficult, as radiological appearances on ultrasound, CT scan and MRI can mimic other pathologies.

Keywords: Neuroendocrine tumors; liver metastases.

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EP154

Development of an everolimus-resistant BON1 cell line with altered cell cycle and c-Met activity

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Introduction

Pancreatic neuroendocrine tumors (panNETs) are often inoperable at diagnosis. The mTORC1 inhibitor everolimus is approved for the treatment of advanced NETs. Unfortunately, the development of resistance against everolimus limits its clinical efficacy.

Aim

Our aim was to establish an everolimus-resistant panNET cell line to find common mechanisms of resistance.

Methods

Pancreatic neuroendocrine tumor cells (BON1) were treated for 24 weeks with 10 nM everolimus (Novartis). Medium supplemented with 10 nM everolimus was changed every 3 days. Two independent everolimus resistant BON1 cell lines were established (RR1 and RR2). Resistance was defined with an at least 2-fold higher IC_{50}, compared to the parental/control cell line.

Results

After 24 weeks of permanent exposure to everolimus both cell lines (RR1 and RR2) showed morphologic changes when compared to the control cell line. The control cell line showed sensitivity to everolimus with cellular survival declining to 54.70% (IC_{50}=34 nM) at 144 h treatment, whereas RR1 and RR2 showed resistance with cellular survival rates of 96.70% (IC_{50}=5200 nM) and 92.30% (IC_{50}=2500 nM), respectively. Western blot analysis showed different adaptive changes of the protein expression level in RR1 and RR2, but two prominent mutual features: The cell cycle component CDK1 (cdc2), which orchestrates the G1-S and G2-M progression was remarkably downregulated and the tyrosine kinase c-Met responsible for tumor cell motility, invasion and metastasis formation was upregulated. Consequently, flow cytometric analysis showed a significant cell cycle shift to G1 phase in RR1 and RR2 cells as well as a higher migration potential than control cells after everolimus treatment.

Conclusion
Everolimus resistance might be acquired by permanently altering the cell cycle and the migration potential. Combinatory treatment approaches to overcome resistance will be subject of further studies.

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EP155

False positive findings on 6-[18F]fluor-L-3,4-dihydroxyphenylalanine Positron Emission Tomography (^{18}F-FDOPA-PET) performed for imaging of neuroendocrine tumors

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Background/Aim
Neuroendocrine tumors (NETs) are rare tumors arising from neuroendocrine cells throughout the body. Positron Emission Tomography (PET) scanning with 6-[18F]fluor-L-3,4-dihydroxyphenylalanine (^{18}F-FDOPA) has been shown to be a valuable technique for the imaging of NETs. While the sensitivity has been assessed numerously, studies systematically describing false positive results, other than physiological variants, are lacking. Our aim was to systematically examine, in a large series of ^{18}F-FDOPA PET scans, false-positive results and determine which other tumor types have the potential of ^{18}F-FDOPA uptake.
Patients and methods
A single-center study was conducted among patients, aged 18 years or older, who underwent a ^{18}F-FDOPA-PET scan for the clinical suspicion or follow-up of a NET between January 2004 and December 2014. Clinical data were retrieved from medical charts. We compared the original ^{18}F-FDOPA PET scan report with the pathology report of the ^{18}F-FDOPA PET-positive lesion. In case this was inconsistent with the diagnosis of a NET, both the scan and the pathology slides were reassessed. Non- NET tissues were immunohistochemically stained for aromatic-L-aminoacid decarboxylase (AADC), Chromogranin A and Synaptophysin.
Results
1070 ^{18}F-FDOPA PET scans from 705 patients were evaluated. Focal or multiple ^{18}F-FDOPA avid lesions were described in 709 ^{18}F-FDOPA PET scans (66%). Histology of these ^{18}F-FDOPA PET positive lesions was present for 508 (72%) scans. In eight cases the original pathology report and revision was not compatible with a NET but showed a squamous cell carcinoma of the cervix and larynx, a multiple myeloma (in two cases), a hepatocellular carcinoma, a schwannoma, an adrenocortical carcinoma and a skeletal myxoid chondrosarcoma, with positive immunohistochemical staining for AADC in four out of the seven stained tumor tissues.
Conclusions
Pathological uptake of ^{18}F-FDOPA does not always indicate the presence of a NET. The possibilty of ^{18}F-FDOPA uptake by tumor types other than NETs should be considered.

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Imaging follow-up of non-functioning adrenal masses at Vilnius University Hospital Santariskiu Klinikos: 2010–2016

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Background
Current guidelines suggest against further imaging follow-up (FU) of patients with non-functioning adrenal masses with clear benign features on imaging studies.
Aim
To analyse the data of patients with non-functioning adrenal masses who had FU at Vilnius University Hospital Santariskiu Klinikos (VUHSK) from 2010 to 2016.
Methods
Cases coded as D35.0; D44.1; C74.1; C74.9; E26.0; E27,8; E24,8 according to ICD-10 classification were retrieved from database. Electronic data capture system was used to extract CT scans and biochemical testing data retrospectively.
Results
There were 714 subjects assessed for adrenal masses from 2010 to 2016 at VUHSK. At least one FU and non-functioning adrenal masses with obvious benign features on CT scan had 216 subjects and thus were included into further analysis. They were 61.6 ± 11.2 years of age (184 female) with tumour size at baseline of 22.8 ± 12.8 mm. Average FU time was 4.1 ± 1.4 years (from 2 to 7), during which tumour size increased in 84 (39%), decreased in 48 (22%), did not change in 84 (39%) cases. Significant increase (by $>$ 20% in addition to at least 5 mm increase in maximum diameter) was observed in 19 (8.8%) cases. Average size of 19 significantly enlarged tumours changed from 19.37 ± 7.60 mm to 30.58 ± 13.68 mm in 2.7 ± 1.4 years. All these tumours were associated with female gender. Despite tumour size enlargement, none of them became functioning during observation time.
Conclusions
Our study showed, that the significant enlargement of non-secreting initially benign adrenal masses during follow up of about 2.7 years occurred in 8.8% of cases and was associated with female gender. Further larger studies with longer follow up are needed to suggest time-frame for imaging follow up in order not to miss the enlargement of the adrenal masses that could require surgery and also to estimate possible enlargement prediction factors.

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Medullary thyroid carcinoma and pheochromocytoma in multiple endocrine neoplasia type 2A – a reversed order diagnosis

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Introduction
RET germline mutation in codon 634 of exon 11 is one of the most frequent mutations of classical multiple endocrine neoplasia type 2A (MEN2A). Virtually all patients with classical MEN2A develop medullary thyroid carcinoma (MTC), which is often the first manifestation of the disease and usually occurs early in life. Pheochromocytomas (PHEOs) tend to be diagnosed several years later or simultaneously with the MTC.
Case report
The patient, a 45 year-old man, was referred to the Endocrinology outpatient department following a bilateral adrenalectomy, performed 2 months before, (Pheochromocytoma of the Adrenal gland Scaled Score: left $=0$, right $=4$) and the finding of a thyroid micro nodule in a neck ultrasonography. There was no familiar history of MEN2 neither of its components. The physical examination did not disclose particular signs namely skin alterations in the interscapular region. Laboratory tests revealed elevated calcitonin (63.47 pg/ml, $n < 2$). CEA, calcium, phosphorus, parathyroid hormone and plasmatic metanephrines were within the normal range. Thyroid, ultrasound guided, fine needle aspiration cytology of a 7 mm nodule in the left lobe was negative. Genetic testing of the RET proto-oncogene identified the heterozigous pathogenic variant c.1901G$>$A (p.Cys634Tyr) in the exon 11. The patient was submitted to total thyroidectomy with bilateral central neck dissection. The histology revealed multifocal and bilateral MTC (biggest diameter - 10 mm).
Discussion
Although less common the PHEO can be the first manifestation of MEN2A. Moreover, MTC is not always the most aggressive component of the syndrome.

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Bilateral pheochromocytomas, asyptomatic medullary thyroid carcinoma associated with left side thyroid hemiagenesis in a patient with MEN2A: diagnostic correlations

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Multiple endocrine neoplasia 2A (MEN2A), an autosomal dominant genetic syndrome caused by germline mutation in RET proto-oncogene, associates medullary thyroid carcinoma (MTC), pheochromocytoma (PHEO) and primary hyperparathyroidism (HPT). Thyroid hemiagenesis (TH), the absence of one lobe, is a rare congenital abnormality (300 cases are reported in literature). Most cases of TH are diagnosed when patients present a lesion in the functioning lobe. TH was observed among members of the same family and genetic causes have been evoked. The present case is a 35 year-old-female patient with family history of MEN2A (the pedigree was studied). Genetic testing of the patient's cousin and nephew indicated heterozygosity for the same mutation at codon 634. Plasma metanephrines, normethanephrines, parathormone (PTH) and calcitonin (CT) levels were increased. Serum ionized calcium was normal. Abdominal computed tomography provided the bilateral heterogeneous adrenal masses measuring 30×21 mm on the right and 20×16 mm on the left with an intense enhancement after contrast infusion. Neck ultrasound examination described 2 hypo-echoic, heterogeneous thyroid micro-nodules in the right thyroid lobe, with micro-calcifications inside, which measure 78×58, respectively 45×47 mm. In the left side, hemiagenesis of the thyroid lobe was observed. No parathyroid adenoma or lymphadenopathy were found. The patient had underwent a bilateral laparoscopic adrenalectomy for PHEO followed by total right thyroidectomy. Microscopic examinations established the diagnosis of multicentric PHEO and synchronicity of C-cell hyperplasia with medullary thyroid microcarcinoma. Although the identified RET mutation has hight risk, suggesting a possible aggressive evolution, in this case the CMT development was gentle, with a good prognosis (lesion $<$ 1 cm diameter, without distant metastases, preoperative basal calcitonin $<$ 150 pg/ml). In conclusion our patient is a rare case of association of an anatomic thyroid abnormality and MTC in the context of a complex genetic disease.

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Follow-up of adrenal incidentalomas after the initial approach

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Aim
To describe the follow-up of adrenal incidentalomas (AI) classified as non-functioning and no suspicious for malignancy in the first approach.
Patients and methods
Observational retrospective study of a cohort of patients who consulted in the Endocrinology service between 2005 and 2015 because of an AI. Statistical analysis performed with SPSS 19th version.
Results
Two hundred and one patients with IA were firstly evaluated. Thirty two of them (15.92%) underwent surgery after the initial evaluation. One hundred and twenty four patients out of the 169 who didn't undergo surgery (73.37%) were followed: 97 unilateral AI and 27 bilateral AI. Age: 58.48±11.84 years. Size: 26.36±14.14 mm. 57.3% Women. Repeated measurement of plasma metanephrines in 26 patients (20.97%): 21 unilateral AI (21.65%) and five bilateral AI (18.52%). No catecholamine production in any AI. Median follow-up: 4.12±3.44 years. Ninety eight patients (79.03%) underwent a 1 mg dexamethasone suppression test to screen the cortisol autonomous production: 76 unilateral AI (78.35%) and 22 (81.48%) bilateral AI. Follow-up: 2.83±2.67 years. 10 patients (10.20%) diagnosed with subclinical Cushing not present in the first evaluation. The rest of them showed no autonomous cortisol production. A follow-up imaging study was performed in 103 patients (83.06%): 80 with unilateral AI (82.47%) and 23 with bilateral AI (85.19%). Median follow-up: 2.77±2.70 years. In four patients (5%) with unilateral AI there was a significant growth (28.85±15.63 mm), so they underwent surgery to remove them. None of them were malignant.
Conclusions
There wasn't any patient with new cathecolamine production in the follow-up. In 10.20% of patients we discovered a subclinical Cushing. Our findings agree with previously published studies. There was a significant AI growth in 5% of the patients so they were operated upon. Pathological diagnosis didn't show malignancy in any case, which is consistent with the available scientific evidence.

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A case of silent pancreatic neuroendocrine tumour of carcinoid variety masquerading as an insulinoma

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Objective
To highlight an unusual cause of hyperinsulinaemic hypoglycemia
Methods: Case Report
Results or Case Presentation
A previously healthy and fit 52 year old gentleman of Asian descent presented with recurrent severe neuroglycopenic hyperinsulinemic hypoglycemic symptoms, suggestive of insulinoma. On several occasions he was confirmed to have severe hypoglcaemia with venous blood glucose values ranging between 1.5 and 2.7 mmol/l with inappropriate high level of insulin and C-peptide of 32 mc/unit per ml (N. 2–23) & 4.5 ng/ml (N. 0.78–5.19) respectively. Other hormonal assessment including pituitary hormones, chromogranin A, urinary 5-HIAA, and cortisol were all normal. CT imaging picked up a 4×4 cm well circumscribed lesion in the tail of the pancreas, with no lesion elsewhere. Endoscopic ultrasonography confirmed the mass to be avascular and within the pancreas. He underwent laparoscopic distal pancreatectomy uneventfully in February 2016. Histology of the tumour showed a well differentiated neuroendocrine tumour of a carcinoid variety, grade 2, with positive staining for chromogranin A, and Synaptophysin CK. Following surgery, the patient had no further hypoglycemia and remained symptom free up to 9 month of follow up. Postoperative PET scan and CT scanning of chest, abdomen and pelvis showed no recurrence of the tumour, and no lesion elsewhere.
Discussion
Non-islet cell tumours induced hypoglycemia is generally caused by big IGF-II molecules secretion. Rarely carcinoid tumours were reported to secrete insulin but this is usually in the context of carcinoid syndrome and has been reported to arise from tumours in the lungs, appendix and the liver. For a silent pancreatic carcinoid tumour to cause hyperinsulinaemic hypoglycemia is rather unusual. Plausible mechanisms include processing and secretion of insulin from tumour cells. Alternatively secretion of insulin from adjacent islet cells may have been caused by paracrine effects. The exact mechanism in our case, however, only remains speculative.
Conclusion
Tumours of the pancreas causing hypoglcemia may not necessarily be insulinoma. Silent neuroendocrine tumour of the carcinoid (Argantafinoma) variety may be the culprit.

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CYP2W1*6 polymorphism as a potential predictive marker of sensitivity to mitotane treatment in adrenocortical carcinoma.

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Mitotane is the only approved drug for the treatment of advanced adrenocortical carcinoma (ACC) and we recently demonstrated that a high expression of cytochrome P450 2W1 (CYP2W1) correlated with response to mitotane. The association between CYP2W1 alleles and a generally increased cancer risk is under debate. Aim of the study was to evaluate the frequency of CYP2W1 polymorphisms and its correlation with the response to mitotane treatment in ACC patients.
Methods
DNA was isolated from whole blood of 108 Caucasian ACC patients (F/M = 68/40) treated with mitotane monotherapy in adjuvant (ns = 66) or palliative (n = 42) setting. Three CYP2W1 polymorphisms were genotyped by PCR and sequenced: CYP2W1*2 (p.A181T), CYP2W1*5 (p.Q482H) and CYP2W1*6 (p.P448L). The response to therapy was evaluated by time to progression (TTP).
Results
The allele frequencies for CYP2W1*2 and CYP2W1*6 were 8 and 18%, respectively, and are comparable to those found in the European population (1000 Genomes Project Phase 3 allele frequencies, ENSEMBLE, 5% for CYP2W1*2 and 17% for CYP2W1*6). For CYP2W1*6 there were slightly more homozygotes than expected (P = 0.1). Both variant alleles were in the Hardy-Weinberg equilibrium. CYP2W1*5, which is only reported in non-Causasian population, was not found. We did not find any correlation between CYP2W1*2 allele and clinical outcomes. Whereas, we observed that patients with advanced disease who have CYP2W1*6 allele have a worse response to therapy (median TTP 3.0 vs 5.5 months, P = 0.03, HR 1.83). Among these patients, 86% who have CYP2W1*6 allele did not reach the therapeutic range of mitotane plasma level (14–20 mg/l) in comparison to 61% of those without CYP2W1*6 allele (P = 0.09, chi-squared = 2.7). No relevant impact of CYP2W1*6 was observed in patients treated with adjuvant mitotane.
Conclusion
This study further suggests that CYP2W1 might be involved on mitotane metabolism and that CYP2W1*6 allele might correlate with a worse sensitivity to mitotane palliative treatment.

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Abstract unavailable.

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Ectopic ACTH-syndrome – 31 consecutive patients from the Helsinki University Hospital

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Background
Ectopic ACTH syndrome (EAS) is rare and published series are scarce.
Aim
To increase the understanding of EAS we describe 31 consecutive cases in years 1997–2016.
Results
Of the 31 patients, 65% (20/31) were women and 35% (11/31) men. Median follow-up was 23 months (0–217). Median age at diagnosis was 62 years (21–78), with peak incidences in age groups 30–39 and 60–69 years. Most patients presented with hypokalemia (87%), muscle weakness (77%), ankle edema (74%), hypertension (71%), psychiatric manifestations (58%), changes in body fat distribution (58%), and bruises (51%). Median (range) cortisol, ACTH and 24 h urinary free cortisol were 1467 nmol/l (121–4380), 155 ng/l (16–4700), 8221 nmol/l (568–69038), and median (range) cortisol after 1 mg DST 1103 nmol/l (74–3390), respectively. Thirteen (42%) underwent CRH-testing, which was accurate (< 50% increase in ACTH and < 20% in cortisol) in 9/13 (69%) patients. Underlying tumours: pancreatic NET (n = 6), pulmonary NET (n = 6), pulmonary small cell carcinoma (n = 6), unknown primary (n = 4; no tumour detected n = 2, disseminated disease n = 2), medullary thyroid carcinoma (n = 3), thymic NET (n = 2), and, ileum NET, prostate carcinoma, poorly differentiated pulmonary NEC, poorly differentiated pulmonary LCC (n = 1 for each). Median overall survival was 23 month (0–217). At the end of follow-up, 12/31 (39%) patients were alive. Four patients initially cured recurred at 2, 6, 6 and 10, and 12 years, respectively. Surgery of the primary tumour was possible in 10/31 (32%) patients, nine (90%) of whom were alive at the end of follow-up. Bilateral adrenalectomy was performed in 10/31 (32%) patients, three (30%) of whom were alive at the end of follow-up. Outcome was best in thymic and pulmonary NETs.
Conclusion
EAS affects women in 65% of cases. Incidence peaks in age groups 30–39 and 60–69 years. Recurrences are possible > 10 years later. Overall survival is poor.

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Ectopic Cushing's syndrome caused by a pulmonary adrenocorticotropic hormone secreting tumour: a case report

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Introduction
Ectopic adrenocorticotropic hormone (ACTH) production by the pulmonary neuroendocrine tumour (p-NET) is rare, and is considered an aggressive variant of carcinoid tumours with poor prognosis.
Case presentation
59-year-old male with fast progressing generalized fatigue, abdominal discomfort, and diarrhea was hospitalized in gastroenterology unit of Hospital of Lithuanian University of Health Sciences, Kauno klinikos (HLUHS KK). Digestive tract diseases were ruled out. Persistent hypokalaemia (up to 2.2 mmol/l) was observed and endocrine pathology changes were considered. Examinations revealed markedly elevated plasma ACTH (44.4 pmol/l) and cortisol (> 1665 nmol/l) levels, diabetes, osteoporosis. No suppression of serum cortisol level with high-dose dexamethasone test was found, confirming ACTH dependent Cushing syndrome. The treatment with Metirapone was started. Pituitary and abdominal magnetic resonance imaging (MRI), abdominal computer tomography (CT) scans were normal. Thoracic CT scan showed nodules in the S2, S3, S6 of the left lung. No cytologic changes were found in repetitive bronchial leachates through endoscopic bronchoscopy. There were two episodes of pneumonia (Pseudomonas aeruginosa) and two episodes of sepsis (Staphylococcus aureus and Enterococcus faecium). Suspected fungal infection, intended antifungal treatment. Single nodule in S3 of the left lung with no changes in size was found in repeated chest CT. ^{99M}Tc-tectrotyd SPECT-CT showed left lung S3 neuroendocrine tumour. The radical surgery (bilobectomia superior sinistri) was performed. Histological result was well-differentiated p-NET (pT1a N0 R0 G1). No radiochemotherapy was suggested. On the follow up visit after three months normal glycaemia, potassium and cortisol were found.
Conclusion
We present ectopic ACTH secreting neuroendocrine lung carcinoma with likely good prognosis. No clearly defined guidelines of follow up exist.

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Could alcohol ablation become the standard of care for benign insulinomas?

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Introduction
Surgical resection is currently considered the standard treatment for symptomatic insulinomas; however, its morbidity is high (> 10%) and it is restricted to suitable candidates. In recent years, alternative minimally invasive therapies, such as endoscopic ultrasound (EUS)-guided ethanol ablation (EA), have emerged as new therapeutic options, especially for small lesions or poor surgical candidates. We report two cases of insulinoma ablated with EA.
Cases report
We report two cases of recurrent hypoglycaemia due to benign insulinoma: a 75-year- old man, with a 9 mm hypoechoic lesion in the neck of the pancreas, unfit for surgery because of comorbidities (case 1); and a 71-year- old man with a 19×14 mm hypoechoic lesion in the pancreas head, who refused surgery treatment (case 2). EUS fine needle aspiration (EUS-FNA) confirmed neuroendocrine tumor with a Ki67 <5% in both of them. They were admitted to our department for EA. Insulinomas were punctured under EUS guidance with a 22 G needle. A total volume of 0.8 ml (case 1) and 13 ml (case 2) ethanol 98% was injected. After each injection a whitish halo was observed inside the lesion, and no extravasation of alcohol was detected. There were no perioperative or postoperative complications. In case 1, hypoglycaemia was not reported along the two years follow-up period. Case 2 presented occasional mild hypoglycaemia 1 year after treatment, so we considered repeating EA, but the patient refused it.
Conclusion
EUS-guided ethanol ablation of a single small insulinoma is an effective, minimally invasive, and safe therapeutic modality. Currently, it is considered when surgery cannot be an option. However, this new technique should be applied to a wider range of potential candidates. A multicentric study seems necessary to establish the indications of EA in insulinomas.

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Clinical characteristics and survival of patients with paraganglioma: a single center experience

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Paragangliomas (PGLs) and pheochromocytomas (PCCs) are rare neuroendocrine tumors that derived from pluripotent neural crest stem cells. PCCs are derived from the adrenal medulla, while PGLs are histologically identical tumors derived from ganglia outside the adrenal gland. Even though the majority of tumors are benign, they are associated with high morbidity rates caused by excessive catecholamine secretion. We retrospectively analyzed 71 patients (36 female and 35 males) with PGLs between January 2002 and December 2016. Twenty three patients were lost to follow up. Kaplan-Meier curve was used as the univariate version of survival analysis. The median age at diagnosis was 47.0 years (11–75) and the mean tumor size was 53 mm (26–170 mm). PGLs in our group were mostly distributed in abdomen (60%), head and neck (26.2%), rarely in spine (9.2%) and chest (4.6%). Hereditary form of disease was present in 22.5% of patients. The most common mutation was in SDHB gene (10/16), hereafter in VHL gene (3/16); two patients had mutation in SDHD gene and one in SDHC. Multiple PGLs were identified in six patients. Hormonally secreting tumors were present in 28%; 16/30 patients had positive finding on I-123 MIBG scintigraphy. Surgical resection was performed in 79% of patients, tumor embolization in 11%. At 22 patients the median proliferation index Ki67 was 1.8% (0.1–18%) and median PASS score 3(1–6). Metastatic disease was present in 18.8% of patient at the time of diagnosis and five patients had acquired metastasis. These patients were treated with PRRT (6/14), chemotherapy (3/14) and sutent (3/14). Median overall survival (OS) was 284 months (95%CI 251–318) with 10-year OS 88%. Mean disease free survival was estimated 20 months (95%CI 8–31). We presented clinical characteristics, genetic profile, treatment options and survival of our patients with PGLs, our experience as single tertiary center.

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Corticotroph deficiency in patients with insulinoma

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Introduction
The metabolic stressor, hypoglycemia, elicits integrated counterregulatory responses, including activation of the hypothalamic–pituitary–adrenal axis. However, it is suggested that recurring insulin-induced hypoglycemia can impair this counter-regulation. Here we report three cases of patients with isulinoma and corticotroph deficiency.
Case reports
The first case, 38-year-old man *was referred* because of recurrent episodes of *hypoglycemia*. Hormonal investigations were in favour of dissociated anterior pituitary failure, with growth hormone and corticotroph deficiency. The hypothalamic-pituitary MRI was normal. The fasting test argued in favour of a hyperinsulinemic hypoglycemia. The abdominal scan and the endoscopic ultrasound showed a mass within the tail of the pancreas. Distal pancreatectomy was performed. Histology disclosed an insulinoma. On follow up, no hypoglycemic episodes recurred and cortisol and GH response to induced hypoglycemia was normal. The second case, 68 years old man referred for investigation of hypoglycemic episodes. He was diagnosed with corticotroph deficiency and hypergonadotropic hypogonadism with negative investigations. The hypothalamic-pituitary MRI was normal. After treatment with glucocorticoids, hypoglycemic episodes were significantly improved. After 6 years, he presented severe hypoglycemia and investigations revealed a 1.5 cm tumor in the head of the pancreas with hepatic and pulmonary metastases. The third case, 38 years old woman with a history of primary hypothyroidism for 6 years, presented with symptomatic hypoglycemia and a history of weight gain. Laboratory investigations argued in favour of a hyperinsulinemic hypoglycemia and the abdominal scan showed a mass within the tail of the pancreas. Furthermore, she was diagnosed with corticotroph deficiency. The hypothalamic-pituitary MRI was normal.
Conclusions
Our clinical cases show that hyperinsulinemia and hypoglycemia in patients with insulinoma can give rise to functional corticotrophin deficiency. The pathophysiological mechanism of this defective counter-regulation remains to be clarified; some studies suggest it could be related to hyperinsulinemia-induced decreased in CRF secretion.

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Hyperinsulinemic hypoglycemia in a 71-year-old patient with a suspected case of β-cells hyperplasia of pancreatic body and tail- case report

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B-pancreatic cells are programmed to react to plasma glucose level with insulin secretion. Insulin secretion is precisely regulated and in the physiological conditions fasting glucose levels are maintained in the range 3.5–5.5 mmol/l. In hyperinsulinemic hypoglycemia, a disorder of the regulation of insulin secretion, insulin secretion continues at low concentrations of plasma glucose. In adults hyperinsulinemic hypoglycemia is the cause of 0.5 to 5.0% of hypoglicaemias and are result of eather β-cell tumor (insulinoma), or β-cell hyperplasia. Rapid diagnosis and treatment is essential in the prevention of acute and chronic complications of hypoglycaemia, especially in central nervous system.
We are presenting the 71-year-old patient who had been previously diagnostic evaluated at the primary health care level due to frequent episodes of unconsciousness and weakness periodically in period of 3 years prior to admission. After established refractory hypoglycemia patient was sent to our department where endogenous hyperinsulinism after 72-hour test of hunger was found. After endoscopic ultrasound showed probable β-cells hyperplasia of the body and tail of the pancreas. I-131 ocreotid scintigraphy of somatostatin receptors was negative. Calcium artery stimulation of the pancreas with insulin sampling from vein lienalis showed a clear gradient of insulin and distal pancreatectomy was suggested which patient refused. inhibitor of potassium channels-diazoxide was introduced in the therapy which led to reduction in subjective symptoms and no registered hypoglycaemas.

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EP169

Respiratory symtoms lead to a diagnosis of pheochromocytoma: An unusual presentation

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Introduction
Pheochromocytoma is one of the major secondary causes of hypertension. The classic triad of pheochromocytoma symptoms of headache, sweating and tachycardia is not present in a high percentage of patients and is sometimes diagnosed as incidentaloma or atypical presentations.
Case report
The authors present a 56-year-old man, with no known diseases, referred to Endocrinology evaluation by incidentaloma of the right adrenal gland, from the Pneumology appoitment, where he was followed by persistent cough, after an episode of bronchospasm. From the complementary study, a 32 mm nodule in the right adrenal gland was observed on thoracic computed tomography and confirmed by MRI. Bronchofibroscopy with bronchoalveolar lavage and functional respiratory tests were also performed, which were normal. Patient didn't refer any symtoms, however, he maintained a sustained hypertension in the ambulatory monitorization. Analytically, there was a significant increase in the urinary normetanephrines (2585 ug/24 h for a reference value <390) and urinary metanephrines (1551 ug/24 h, for a reference value <320), as well as plasma noradrenaline (1107 pg/ml for a reference value <750) and plasma adrenaline (137 pg/ml, for a reference value <110). Remaining study was without alterations, namely renin-angiotensin-aldosterone axis, thyroid function and urinary free cortisol. Patient started alpha-adrenergic blockade with phenoxybenzamine and laparoscopic adrenalectomy was performed 3 weeks later. Pathological anatomy confirmed diagnosis of pheochromocytoma.
Conclusion
Authors present a case of atypical presentation of pheochromocytoma. The respiratory airways are sensitive to the effects of catecholamines. Although they have mainly beta-adrenergic receptors, there are also alpha receptors that may explain the patient's clinical condition (bronchospasm).
Given the existence of multiple presentations, detection of a pheochromocytoma might be difficult but is mandatory, not only for the potential cure of the hypertension but also to avoid the potentially lethal effects of the unrecognized tumor.

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EP170

A rare cause of secondary endocrine hypertension in a young woman with hypokaliemia and recurrent transient ischemic attacks

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Clinical Case
A 39-year-old woman was referred to our Hypertension Clinic for workup after three episodes of TIA with SBP >180 mmHg in the last 6 months. Diagnosed and treated of hypertension and hypokaliemia since she was 15 years old, no secondary cause had been searched. She was treated with Telmisartan/Amlodipine/Hydrochlorothiazide 80/10/25 mg plus Carvedilol 12.5 mg BID and potassium supplements. She had no history of diabetes or dyslipidemia and did not smoke. Height was 168 cm, weight 63 kg, IMC 22.3 kg/m^2, office BP 142/88 mmHg, HR 72 bpm. The physical exam was otherwise normal.
Treatment was changed to Diltiazem/Doxazosin for 3 weeks. Lab: normal including TSH and metanephrines, except venous pH 7.51, Cr 1.23 mg/dl, CKD-EPI eGFR 57 ml/min/1.73 m^2, albuminuria 139 mg/g Cr, aldosterone 792 ng/ml, PRA 58 ng/ml per h, normal ratio (13.7).
Funduscopy: stage 2 hypertensive retinopathy, brain RMN: scattered white matter microinfarctions, heart US: normal function, mild LVH (LVMI 92 g/m^2). Chest X-ray and abdominal US: normal.
AngioCT excluded renal artery sclerosis, but showed a 12 mm subcapsular mass in the right kidney. The adrenals were normal.
Renal venous sampling for renin: Peripheral 628 U/l (normal <42), Left renal vein 645 right renal vein 3120 U/l; right/left ratio 4.8. Laparoscopic nodulectomy was performed; a encapsulated 14 mm adenoma with clean margins was obtained. It tested positive for renin.
Diagnosis
Secondary aldosteronism due to reninoma, resistant hypertension and target-organ damage (retinopathy, brain microinfarctions and TIAs, stage IIA CKD with microalbuminuria, LVH). Two months after surgery the patient is normotensive with manidipine 10mg/day: aldosterone, ARP, K^+, venous pH and albuminuria are normal.
Commentary
Reninoma is rare but probably infradiagnosed, and a long diagnostic delay is not unusual. Even with well-controlled BP, it may cause severe organ damage due to hyperaldosteronism. Thus, it should be included in the workup of secondary hypertension.

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EP171

Atypical symptoms of hypoglycemia, hiding a diagnosis of insulinoma: a case report

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Introduction
Insulinoma is a rare pancreatic tumor, typically sporadic, solitary and benign. However, nonspecific symptoms of hypoglycemia, negative laboratory investigations and small size of these tumors can retard the diagnosis, and symptoms may be misattributed to psychiatric, cardiac, neurological disorders.
Case presentation
A 35-year-old male had history of night time seizures with hallucinations, delirium and spasms, lasting from 10 minutes to 1.5 hours for about 2 years. These seizures were always resolving spontaneously. Due to recurrent seizures he was consulted by phychiatrist and diagnosed with depression and conversion disorder and treated with psychotropic medications. As the spasms remained, he was referred to neurologists. During examination early in the morning while performing electroencephalography typical dyscognitive seizures occured. Plasma glucose analysis was performed for the first time and hypoglycemia of 1.4 mmol/l was found. Symptoms disappeared after intravenous glucose infusion.

Management and outcome
The patient was hospitalized due to suspected insulinoma and supervised 72-hour fast test was performed. Plasma glucose was 3.5 mmol/l, plasma insulin - 49.3 pmol/l (43–210 pmol/l) and C-peptide - 780 pmol/l (260–1730 pmol/l) at the baseline. The test was ended after 16 hours with plasma glucose of 1.7 mmol/l, plasma insulin - 29.7 pmol/l, C-peptide - 521 pmol/l. These results confirmed the diagnosis of insulinoma. Abdominal computed tomography scan with contrast demonstrated a well-defined hypervascular lesion involving the head of pancreas measuring 10×15 mm in diameter, typical of neuroendocrine tumor. The patient underwent laparoscopic extirpation of the pancreatic mass. Histopathological evaluation revealed a pancreatic well-differentiated (G1) neuroendocrine tumor – benign insulinoma. The patient gradually discontinued all psychotropic medications following the operation. Currently he is feeling well, without any seizures and normal plasma glucose for about 1.5 years.
Conclusion
We recommend to check plasma glucose for all patients with seizures of unknown origin, although they are not typical to hypoglycemia.

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EP172

A nomogram consisted of routine biochemical tests may increase the diagnostic accuracy of chromogranin A in detecting patients with neuroendocrine tumors

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Introduction
Falsely elevated serum chromogranin A (CgA) is associated with the use of proton pump inhibitors, the presence of renal impairment and systemic inflammation. We aimed to investigate which laboratory parameters are independently associated with increased CgA and to develop a nomogram, in order to improve the diagnostic accuracy of CgA in detecting patients with neuroendocrine tumors (NET).
Methods
Our retrospective study included 155 subjects (controls) and 55 treatment naïve patients with NET, with available data on CgA, other laboratory tests, medical history and antropomethric parameters. Nomogram was developed in a form of scoring system, based on z-score obtained from receiver operating curve analysis for each parameter that was independently associated with CgA.
Results
CgA was positively associated with erythrocyte sedimentation rate, red cell distribution width, serum creatinin, glucose, urine leukocyte casts and the use of proton pump inhibitors. The combination of all these parameters was associated with increased CgA with an area under the curve of 0.771 ($P<0.001$). Overall, CgA level of 189 had a sensitivity of 56.4% (42.3–69.7) and a specificity of 76.8% (69.3–83.2) in detecting patients with NET (area under the curve 0.656, $P<0.001$). In subjects with a score of <6, CgA level of 150 ng/ml had a sensitivity of 68.2% (45.1–86.1) and specificity of 89.4% (80.8–95.0), (AUC 0.767, $P<0.001$). In subjects with a score ≥ 6, AUC decreased to 0.534 ($P=0.538$).
Conclusion
CgA should not be used as a biomarker for NET in patients with laboratory signs of inflammation and renal impairment. Our study suggests the possibility to adjust CgA in these patients in order to increase its diagnostic accuracy.

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EP173

Concentration of dehydroepiandrosterone sulphate in 109 males and 54 females with adrenal tumors

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Relation of dehydroepiandrosterone sulphate (DHEAS) concentration and adrenal tumors (AT) has never been investigated systematically. After promising Terzolo group (1995, 1996, 2000) investigations, there was made a recommendation in the last clinical guidelines for adrenal incidentaloma (2016) to assess concentration of DHEAS in special clinical situations. Here we present the first systemic study of DHEAS in adrenal tumors.
The aim was to analyse the clinical and laboratory characteristics (including DHEAS) of 109 males and 54 females with AT.
Methods
During 2014–2016 years concentration of DHEAS was determined in 5133 patients. Out of those case records of 590 females and 450 males were randomly selected for a detailed retrospective analysis. The relation between presence or absence of AT and DHEAS was established. Age and gender adjusted maximal values (R max) and minimal values (R min) of DHEAS concentration were used to express the results.
Results
AT were detected in 109 males and in 54 females. R max ≤ 0.4 was found in 64.81% of females starting from 45 years-old and in 67% of males starting from 60 years-old. R max value >1 was found in 11 cases of females (20.4%) and only in one case of males (0.92%). R min <1 value was detected in 13 cases of males (11.92%) and in two cases (3.7%) of females.
Conclusions
Out of all 163 cases of adrenal tumors, high level of DHEAS was found more frequently in females (7.36%), otherwise, low level of DHEAS was found more frequently in males (7.97%).

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EP174

Jejunum/ ileum Neuroendocrine Tumours: results of a multicentric retrospective study

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Introduction
The Neuroendocrine Tumors Study Group of the Portuguese Endocrine Society (SPEDM) performed the first observational study between November 2012 and July 2014 too assess the profile of Gastroenteropancreatic Neuroendocrine Tumours (GEP-NET) patients (pts) followed at the main Portuguese hospitals. Several demographic and clinical data were collected
Objective
Characterize the clinicopathological features and treatment of patients with NET originating in the jejunum and ileum.
Material and methods
Included 71 pts with ≥ 18 years and a confirmed diagnosis of jejunum /ileum NET based on histopathology/cytology findings.
Results
Mean age was 57.2 (32–83) years, 61% ($n=43$) males. Most tumors 89% ($n=63$) were located at the ileum; two were multifocal. Ki67 was available in 86% of pts, 64% G1. At diagnosis 91% (51/56) had lymph node metastases and 70% (43/61) distant metastases.
The most common symptom, available in 59 pts, was abdominal pain in 49% (29/59). Serum Chromogranin A (Crg A) was available in 65% (46/71) and was $2\times \geq$ upper limit of normal in 61%(28/46). Urinary 5HIAA checked in 61% (43/71) was elevated in 56%(24/43), 86% of these with distant metastases. CT scan was the preferred radiologic procedure in 87% of pts. Nuclear medicine imaging, either octreotide scan or ^{68} Ga-DOTA-NOC Pet Scan was used in 75%(53/71) of pts Tumor size known in 58 pts was 24 ± 14.7 mm. Primary tumor surgery was performed in 90 and 32% did surgery of hepatic metastases. 62% of the pts received somatostatin analogues(SA), two were treated with SA and interferon and two with systemic chemotherapy. 11 cases were submitted to hepatic transarterial embolization. Peptide Receptor Radionuclide Therapy with ^{177}Lu was done in 9%.

Conclusions
This paper reveals important information regarding clinical practice. Most of our pts presented with well differentiated tumors but in an advanced stage. Regarding therapy there was an extensive use of surgery and systemic treatment mainly with SA.

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EP175

Follow-up in neuroendocrine tumors: is chromogranin A the confounder?

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Introduction
Chromogranin A continues to be one of the most valuable markers for neuroendocrine tumors (NETs) **however,** it has several limitations, including its reduced specificity.
Methods
The authors present the case of a patient diagnosed with a midgut NET, during follow-up.
Results
Male patient, 61 years old, with chronic renal disease (CRD), underwent right hemicolectomy owing to ileo-cecal valve lesion; histological result consistent with NET. Pre-operatory staging: without metastatic disease on thoracic-abdominal CT; octreoscan with elevated expression of somatostatin receptors on ileo-cecal valve topography; CgA 32 nmol/l (<6.0), NSE 14 ng/ml (<15.0). Anatomopathological examination of surgical specimen: well-differentiated G1 NET; mesenteric infiltration and metastization in 1 of 20 lymph nodes (T3N1Mx; AJCC-IIB; R0). After 3 years of stable disease, the patient presented CgA of 1173.8 ng/ml (<85), with impaired CRD (Cr 4.42 mg/dl), on dyalisis. 3 months later: CgA 1619.0 pg/ml and Calcitonin 26 pg/ml (<10). In additional investigation, cervical-thoracic-abdominal CT and 68 Ga-PET rated negative for relapse. Total colonoscopy, including evaluation of ileocolonic anastomosis, didn't demonstrate alterations. The patient maintained follow-up with clinical stability, showing in the last evaluation CgA 272.3 ng/ml, Calcitonin 38 pg/ml, NSE 12 ng/ml (<15) and Cr 6.88 mg/dl.
Conclusions
Evaluation of CgA in end stage renal disease is not reliable. Although it's postulated that higher the degree of renal failure, higher the CgA concentration, it wasn't verified such correlation. In NET patients, renal function should be carefully evaluated and ruled out the potential impact on the concentration of CgA.

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EP176

Large intestinal metaplasia is a precancerous lesion present in patients with gastric neuroendocrine neoplasms type 1

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Background
Intestinal metaplasia (IM) of the gastric mucosa is a relatively frequent precancerous lesion. The aim of the study was to assess the prevalence and the kind of IM and also to find parameters that could predict the presence of IM in gastric neuroendocrine neoplasms type 1 (GNEN1).
Methods
Fifty-nine (45 females) patients with GNEN1 were retrospectively studied. All patients included in the study had positive parietal-cell antibodies. All patients underwent a gastroscopy with multiple biopsies. Chromogranin A, gastrin, vitamin B12, folate and ferritin levels were also assessed.
Results
The mean age and follow up were 54.14±13.62 years and 67.66±48.9 months, respectively. At diagnosis, chromogranin A, gastrin, vitamin B12, folate and ferritin levels were: 277.54±173.54 ng/ml (<98), 896.18±818.98 pg/ml (<110), 395.43±488.18 pg/ml (300–960), 12±11.36 ng/ml (2–20) and 58.02±75.08 ng/ml (20–350), respectively. Intestinal metaplasia appeared in 48 patients (81.35%) with GNEN1; 41 (85.5%) had large IM, 1 (2%) had small and 6 (12.5%) had both small and large IM. In univariate regression analysis, only mean follow-up from the parameters studied (age at diagnosis, gender, biochemical markers) predicted the presence of intestinal metaplasia (OR: 0.979; 95%CI: 0.961–0.997, $P=0.021$).
Conclusion
Our study showed a high prevalence of large IM in GNEN1. Mean follow up predicted IM presence. Further clinical studies are required to determine which parameters predict the presence of IM in patients with GNEN1.

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EP177

Pancreatic neuroendocrine tumors (PNETs) in patients with MEN1 syndrome

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PNETs represent the leading cause of mortality in MEN1 patients. Yet, their characteristics, behaviour, and therefore management, are still uncertain.
The aim of this study was to describe the main clinical characteristics of NETs in MEN1, and to compare them with sporadic NETs.
We investigated 164 patients with PNETs retrospectively, treated in one centre from 2004–2016. We identified 15 (9.1%) patients with MEN1. All patients had germline mutations in *MEN1* gene, except one who had sporadic MEN1. There was no gender difference among the groups. No difference in age at onset between the groups was noted (48±16.1 in MEN1 vs 53.8±13.5 years in sporadic, $P>0.05$). According to WHO classification, well-differentiated tumors were the most frequent in MEN1, in contrast to sporadic PNETs where well-differentiated carcinomas prevailed ($P<0,01$). Functioning PNETs were more frequent in MEN1 group (60 vs 30%, $P<0.05$). Among functioning tumors, insulinoma and gastrinoma were the most frequent in both groups ($P>0.05$). MEN1 patients had multiple tumors more frequently (33.3 vs 5%, $P<0.05$). Metastatic disease as initial presentation had 17% of MEN1, and 26% of sporadic patients ($P>0.05$). Surgery was performed in 70% of MEN1, and 92% of sporadic patients. Tumor size did not correlate with the presence of metastases at surgery in any of the groups. Median OS was 149 months (95%CI 71–226) with no difference between the groups ($X^2=2.049$, $P>0.05$). Mean time to tumor progression (TTP) was estimated to 41 months (95%CI 10–75). However, no difference was found regarding the MEN1 status ($X^2=0.22$, $P>0.05$). TTP negatively correlated to Ki-67, local invasiveness and stage of the disease in all patients, but not to size or functionality. These data suggest that MEN1 PNETs share similar clinical behaviour as sporadic PNETs. Therefore, close tumor surveillance and early surgery are advocated, irrespective of the tumor size or functionality.

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EP178

Dysregulation of the components of the splicing machinery in neuroendocrine tumors and its association with malignancy and aggressiveness

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Dysregulation of the splicing machinery is emerging as a novel cancer hallmark due to its association with multiple dysfunctions in tumor cells. An inappropriate function of the components of this machinery (spliceosome) could be primarily linked with the generation of tumor-associated aberrant splicing variants. In line with this, we have previously reported that overexpression of aberrantly spliced variants of somatostatin receptor 5 (sst5TMD4) and ghrelin (In1-ghrelin) is directly associated to malignancy features in gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Therefore, in this study we aimed to characterize, for the first time, the pattern of expression of a selected set of components of the splicing machinery in GEP-NETs samples, compared to adjacent non-tumoral control-tissues, and to determine its relationship with the aggressiveness of these tumors. Accordingly, we designed a PCR-based array to determine the expression levels of components of the major ($n=13$) and minor spliceosome ($n=4$) and associated splicing factors ($n=28$) using a microfluidic technology in 20 pancreatic NET-samples (47% G1, 47% G2 and 6% G3) and control-tissues. The results showed that the expression of several splicing factors and spliceosome components was altered in tumor tissues compared to non-tumoral adjacent tissues. Remarkably, important splicing factors (e.g. CELF4, NOVA1, SNW1, and RAVER1) and components of spliceosome (e.g. PRP8) were clearly overexpressed in NET-samples, wherein they were correlated with some malignancy features. Furthermore, *in vitro* assays using NETs cellular models (i.e. BON-I/QGP-I-cells) demonstrated that CELF4 and NOVA1 overexpression induced an increase on cell-proliferation, while their silencing (using specific siRNAs) caused a marked decrease on cell-proliferation, suggesting a role in the aggressiveness of these tumors and their putative suitability as therapeutic targets in pancreatic NETs. Hence, our results demonstrate an alteration of splicing machinery in pancreatic NETs and unveil its putative relevance in NETs development/progression, where it could provide novel diagnostic biomarkers and therapeutic tools for this pathology.

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EP179

Serum succinate: investigation of its putative role as a new biomarker in malignant *SDH-x* mutated pheochromocytoma-paraganglioma patients?

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Introduction
Malignant paraganglioma/pheochromocytoma (MPP) are very rare neuroendocrine tumors with heterogeneous prognostic and no gold-standard treatment. MPP can be associated with germline mutations at *SDH-x* genes which encode for the succinate dehydrogenase that catalyzes the oxidation of succinate to fumarate. *SDH-x* mutations lead to inactivation of the enzyme and thus accumulation of succinate.
Aim
This project aims to evaluate succinate as a potential early serum biomarker in *SDH-x* MPP patients.
Material & Methods
A fully validated LC-MS/MS method has been developed to quantify succinate serum levels. A prospective collection of MPP patients 'serum has been initiated.
Results
Succinate has been quantified in 108 serum samples collected from 47 MPP patients. Among them 25 presented a *SDH-B* mutation, 4 a *SDH-D* mutation and 15 were *SDH* wild-type (WT). Succinate levels were statistically higher in the *SDH-B* group (mean $=25$ µM, min-max: ~3–106 µM) compared to the WT group (mean $=7$ µM, min-max: 4–11 µM) ($P=0.01$).
Conclusion
These results suggest a role of succinate as serum biomarker in *SDH-x* patients. TNM adjustment is ongoing to determine cut-off value that may differentiate mutated *vs* WT patients. Quantification of serum succinate levels after treatment is in progress and aims to evaluate succinate as a biomarker of response in *SDH-x* MPP patients.

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EP180

Survival analysis of patients with gastroenteropancreatic neuroendocrine tumors

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Introduction
One of the main difficulties in the study of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) is their wide heterogeneity and variable outcome. Several potential influencing factors on patient survival have been recently identified. These factors could help predict patients' prognosis.
Objectives
Analysis of long-term survival of our GEP-NETs cohort according to the presence of metastatic disease, tumor grade, age, sex, tumor functionality and tumor origin.
Materials and methods
Ambispective study of patients with GEP-NETs in Hospital Universitario La Princesa (Madrid, Spain) from 1995 to the present. Survival analysis and factors involved were assessed by Kaplan-Meier method and Cox regression analysis using STATA v12.0.
Results
One hundred and four patients were evaluated (55 women, age 61 ± 16 years). Primary origin was pancreatic in 39, intestinal in 69 and unknown in 6 cases. Histological tumor grade was G1 in 51%, G2 in 39% and G3 in 10% of cases. 68% patients had metastatic disease and 33 died during follow-up. Median survival time was 5261 days (CI 3247 to not reached). Grade G3 multiplied the risk of mortality by 26 (CI 6 – 112); metastatic disease doubled the risk (CI 1.3 – 5.1); every 10-year increase in age multiplied the risk by 1.6 (CI 1.2 – 2.2); and if the tumor had unknown primary origin, the risk was multiplied by 2.5 (IC 0.9 – 7.4). Sex and tumor functionality did not significantly affect survival.
Conclusions
Several factors influence the heterogeneity and clinical outcome of patients with NETs. Median survival is reduced in patients with G3, metastasis, and primary tumors of unknown origin. Knowing these factors guides the therapeutic approach of this rare disease.

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EP181

Insulinoma – clinical features and outcome of patients diagnosed at a central hospital

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Insulinoma, a rare neuroendocrine tumor (NET), is benign in more than 90% of cases. We present a review of patients diagnosed with insulinoma at our Department.
Methods
Retrospective review of clinical records of patients diagnosed with insulinoma between 2011 and 2016.
Results
Six female patients were diagnosed with insulinoma (age at presentation 30–66, follow-up: 0.25–3.25 years). Episodes of sweating, palpitations, tremor, confusion, visual disturbances and weight gain were present in five patients from 2 months to 5 years before diagnosis. There was no familial history or

clinical findings of hereditary tumor syndromes. The 72-h fast test confirmed endogenous hyperinsulinism at 4–12 h of fast. Abdominal CT: pancreatic lesion in four patients (14–25 mm). Endoscopic ultrasound done in four patients revealed pancreatic nodule; three performed cytology/biopsy compatible with pancreatic neuroendocrine tumor (pNET). Five patients underwent surgery: two tumor enucleation, three central and distal pancreatectomy with left hepatectomy and splenectomy in 1 of these. Histopathology: well differentiated pNET G1(two patients) and G2 (three patients). Two patients had lymph node involvement and one of them liver metastases. Among five surgically treated patients: four did not have recurrence of hypoglycemia and the one with liver metastases was treated with octreotide and deceased 2 years after diagnosis. The sixth patient had undergone central and distal pancreatectomy with splenectomy 5 years earlier due to pNET without diagnosis of insulinoma at that time and presented us with large hepatic metastases and hypoglycemia. Octreotide and peptide receptor radionucleide therapy (DOTA-TATE) were started due to hepatic hyperfixation in PET-68Ga-DOTANOC.

Discussion

In this group there was a high prevalence of malignancy, which is unusual. Time elapsed from onset of symptoms to diagnosis was highly variable. The natural history of malignant insulinoma is difficult to predict, however uncontrolled hypoglycemia, liver tumor burden exceeding 30% of liver volume, morphologic progression and Ki67 $>$10–20% are factors of poor prognosis.

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EP182

Effects of ketoconazole on ACTH-producing and non ACTH-producing neuroendocrine tumor cells

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Prolonged spontaneous remission of hypercortisolemia in ectopic ACTH syndrome after long-term treatment with steroidogenesis inhibitors has been described. Direct drug effect on the adrenal glands, effects on tumoral ACTH secretion and/or *POMC* gene expression have been suggested. Medical treatment could be used for symptoms, but also for disease control.

Materials and methods

In human BON-1 and DMS-79 cells, we have evaluated the effects of ketoconazole on cell growth, apoptosis, cell cycle, LDH production, POMC/-chromogranin-A mRNA expression and ACTH/serotonin secretion.

Results

In the BON-1 cells, ketoconazole significantly suppressed cell growth in a dose and time-dependent manner. Maximal inhibitory effects by 10 μM ketoconazole were 41 and 95% after 3 and 7 days ($P<0.0001$); the ratio LDH/DNA after 3 days was increased. The IC_{50} value of growth inhibition was 7.8 μM after 7 days of treatment. Ketoconazole also induced a significant G1-phase arrest accompanied by a decrease in S-phase and G2-phase, as well as a significant increase in early and late apoptosis ($P<0,01$), confirmed using an ELISA method. Ketoconazole (up to 10 μM) did not significantly affect the chromogranin-A expression or serotonin secretion (corrected for cell number). DMS-79 cells are less sensitive to ketoconazole, with maximally inhibitory effects by 50 μM ketoconazole of 44 and 94% after 3 and 7 days of treatment ($P<0.0001$). The IC_{50} value of the growth inhibitory effect was 15 μM after 7 days of treatment. The highest ketoconazole concentration (50 μM) tested induced a significant G1-phase arrest ($P<0.001$), increased number of dead cells ($P<0,001$) without significant effect on early/late apoptosis, increased total apoptosis (ELISA; $P<0.0001$), as well as the LDH/DNA ($P<0.001$). Ketoconazole up to 10 μM suppressed ACTH secretion ($P<0.01$). POMC expression did not show significant changes.

Conclusions

These results suggest a potential direct effect of ketoconazole on cell proliferation, apoptosis and cell cycle in ACTH- and non-ACTH producing NET cells. Additional studies are required to confirm and extend these results.

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EP183

Treatment with (177Lu)-DOTATATE in patients with advanced metastatic somatostatin receptor-positive tumors

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Introduction

The NETTER 1 trial resulted in markedly longer progression-free survival (PFS), with preliminary evidence of an overall survival benefit. We report the results of PFS and safety of (177Lu)-DOTATATE in patients treated in our hospital between 2014 and 2016.

Methods

Transversal and descriptive study of seven patients with advanced, progressive, somatostatin receptor-positive tumors who had received previous treatments. All of them were treated in progressive disease with (177Lu)-DOTATATE. Results are expressed in average (s.d.) or percentage(%). SPSS version 2.2 was used for statistical analysis.

Results

71.4% (5) were women, with an average age of 46.4 (16.2). Histological classification was: 4 (57%) well-moderate differentiated neuroendocrine tumors (three pancreatic, one ileal), 2 (28.6%) paragangliomas and 1 (14.3%) follicular thyroid carcinoma. At the time of administration of (177Lu)-DOTATATE, all tumors were in metastatic stage. The localization of the metastasis was: bone 85.7% (6), liver 57.1% (4), lymph nodes 42.8% (3) and lungs 14.3% (1). All patients had received previous treatments: two underwent surgery exclusively, five of them several systemic therapies: one with somatostatin analogues (SA) and surgery, two only SA, one surgery, SA, temsirolimus and sunitinib, and one patient with diagnosis of metastatic follicular thyroid carcinoma, received: surgery, radioiodine, sorafenib, sunitinib, everolimus, adryamicine, and SA. 177Lu-DOTATE was infused every eight weeks in four doses, except in two patients who have received only three. At the data-cutoff date PFS was of 20.29 (7.13) months. Two patients had adverse events related to the treatment: one hematologic events (mild-moderate thrombocytopenia and anemia), and one self-limited nausea and vomiting. Death occurred in one patient after 15 months of stable disease.

Conclusions

In real world practice treatment with (177Lu)-DOTATATE not only shows benefit in advanced intestinal NETS but also in other patients with metastatic disease, previous treatments, and positive somatostatin-receptor expression it seems to have favorable results attending to PFS and safety.

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EP184

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) followed in the endocrinology and nutrition service's monographic outpatient clinics of neuroendocrine tumors in hospital clínico san carlos (HCSC). Description of its characteristics and evolution

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Introduction

The multidisciplinary approach of the patients with GEP-NETs is very important, having a fundamental role the participation of the endocrinologist.

Methods

Description of cases of GEP-NETs followed in the Service of Endocrinology of the SCCH from 1990 to 2016.

Results

95 patients were included, 53.7% were males, age 61.2 years (IR: 50.5–73.5). The diagnosis was incidental in 53.8%. 27.6% presented clinical secretion, from them the most frequent was carcinoid (13.8%). The median primary tumor size was 3 cm (IR: 2–4). The most frequent location was pancreas (43.2%) followed by small intestine (20%). The initial stage was 49.5% I and 39.6% IV (72% hepatic metastases). Clinic as a cause of diagnosis was significantly associated with staging (Cramer's V (V) 0.72, $P<0.05$). Chromogranin A (CrA) was high in 30% and 5-Hydroxyindolacetic in 18.7% (only 73.7 and 58.4%, respectively) were

studied. 9.4% of the patients had history of familiar syndrome. Degree of differentiation (DD) 1 and 2 (63 and 30.3%) predominated. The follow-up was 6.63 years (IR: 4.6–9.3). During that period, 30.2% of the cases were lost, with mortality rate of 17.9% of the remaining group, due to progression in 83.3% of the patients. The most frequently used treatment was surgery (39.1%). From stage IV patients 20.8% received only somatostatin analogues and 45% received more than one treatment (surgery, chemotherapy, antiangiogenic drugs, somatostatin analogues or everolimus) There was significant association between mortality and stage (V 0.42, *P* 0.04), CrA (V 0.38, *P* 0.012), presence of symptoms at diagnosis (V 0.32, *P* 0.017) and DD (V 0.41, *P* 0.02).

Conclusion

Patients followed in the endocrinology outpatients clinic are more frequently stages I and DD1 and DD2 that have been incidentally diagnosed. More than 50% of the cases were treated only with surgery or somatostatin analogues. One third of the patients had secretion.

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EP185

Descriptive and survival study of 142 cases of gastroenteropancreatic neuroendocrine tumor (GEP-NETs) diagnosed at the Hospital Clínico San Carlos (HCSC)

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Introduction

Neuroendocrine tumors (NETs) constitute a very heterogeneous group of rare neoplasms, although their incidence has increased in recent years. We describe its evolution and survival.

Methods

Retrospective study. All patients with histopathological diagnosis of GEP-NETs performed at the HCSC between 2000 and 2016 were selected, data from the medical history were included. Statistical analysis were done with SPSS.

Results

One hundred and forty-two patients, 54.9% male, mean age 60.2 years (s.d. 19.7). The median follow-up time was 3.3 years (IR: 0.78–6.33). The most frequent locations were pancreatic (28.2%) and rectal (16.2%). The tumor stage was: I 47.2%, II 4.9%, III 13.4%, IV 34.5%. The initial stage (IS) presented positive correlation with the degree of differentiation (DD) (Cramer's V 0.46, $P < 0.05$) and with levels of Chromogranin A (Cramer's V 0.37, $P < 0.05$). 12% had progression and 64% died during follow-up (72% due to tumor). Overall survival at 5 years was 69 and 53% at 10 years. There were significant differences in survival according to location, with gallbladder and colon being the lowest (0 and 38% at 5 years, respectively). DD, IS and sex were also associated with survival (at 10 years: G1 95% vs G3 14.3% $P < 0.01$, stage I 91% vs IV 28% $P < 0.01$, median males 7.5 years vs 16.9 in females *P* 0.018). These differences were maintained after multivariate analysis in the case of DD and IS.

In stage IV survival was modified according to surgical treatment (operated median 5.9 years vs non-operated 0.64 years, $P < 0.01$).

Conclusion

In our sample the overall mortality was high, despite having a low rate of progression. DD and IS were determinants of survival. In advanced stages surgical treatment improves survival significantly.

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EP186

Nonfunctional adrenal incidentaloma affects central blood pressures and arterial stiffness parameters

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Introduction

In recent years, it is thought that cardiovascular risk is increased in patients with nonfunctional adrenal insidentaloma (NFAI). There are not enough studies in the literature that evaluating this condition in patients with NFAI who don't have traditional cardiovascular risk factors. The aim of our study is to determine peripheral and central blood pressures and arterial stiffness in patients with NFAI who don't have traditional risk factors and autonomous cortisol release with pulse wave analysis (PWA) measurement.

Material and methods

In our cross-sectional study, we evaluated 70 participants (35 patients with NFAI and 35 healthy volunteers) without traditional cardiovascular risk factors. All participants were similar in terms of gender, age and body mass index. Measurements of peripheral and central blood pressures and PWA were made with Mobil-O-Graph PWA/ABPM device (I.E.M. GmBH, Stolberg, Germany). Radiological and biochemical data were obtained retrospectively in the NFAI group.

Results

In the NFAI group, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central SBP, central DBP, peripheral vascular resistance, augmentation pressure (AP), augmentation index that corrected based on pulse rate of 75 bpm (Aix@75) and pulse wave velocity (PWV) were significantly higher than control group. We also found that PWA measurements are affected by age and the time from diagnosis to PWA measurement. There was no significant correlations between biochemical parameters and central blood pressures and arterial stiffness parameters in NFAI group.

Conclusion

In patients without traditional cardiovascular risk factors who have NFAI that known as cardiometabolically innocent, both peripheral and central blood pressures and arterial stiffness parameters are affected negatively. These patients are at risk for cardiovascular diseases.

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EP187

Landscape of sporadic adrenal tumours from surgical unit – histopathological audit of 101 cases from a single centre in Poland

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Laparoscopic surgery of adrenal tumours is widely used because of its high effectiveness, patients safety and relatively low cost. Current indications to adrenalectomy of oncological and endocrinological origin are highly accepted. However there is still lack of perfect clinical tool identifying malignant lesions. In everyday practice clinicians rely on low specific features, especially considering larger nonsecretory lesions to surgery.

To show the landscape of sporadic adrenal tumours we analysed retrospectively histopathological findings from 101 consecutive adrenalectomies performed in our centre in 71 women and 30 men of average age 57.7 years (s.d. 13.5), between 2009 and 2016 years.

There were 53 (52.47%) adenomas found; 7 (6.93%) of them secreting: 4 (3.96%)-cortisol, 3 (2.97%)-aldosterone. Pheochromocytoma occurrence was notably often-14 cases (13,86%). Adrenal cancer was found in two cases (1.98%), metastatic lesions from lung, kidney and urinary bladder in three cases (2.97%); and 1(0.99%) malignant peripherial nerve seath tumor (MPNST) derived from ganglioneuroma of adrenal gland was found. Thirteen cases (12.87%) of adrenal hyperplasia were found. In 16 cases (15.84%) the histopathological findings were classified as "various" in detail consisting of: 3 myelolipomas, 1 angiomyolipoma, 2 cysts, 6 pseudocysts or secondary posthaemorrhagic/inflammatory lesions, 1 normal adrenal tissue, 1 fatty tissue, 1 mesenteric cyst and 1 teratoma. In two cases benign adrenal lesions coincided with unilateral kidney cancer. Seventeen patients (16,83%) had previous oncological anamnesis positive, while patients with adrenal cancer had negative previous oncological anamnesis.

We observe that adrenalectomy of oncological indications is prevalent: adrenal lesions with positive previous cancer history; lesions suspected of

malignancy because of the CT morphological features. In the audit almost half of them occur benign incydentalomas. Are we overtreating, then? We conclude there is a great need of new specific clinical tools to identify malignancy in adrenal glands in everyday practice.

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EP188

An elevated chromogranin A: is it always a tumor progression?-case report

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Introduction

Pancreatic neuroendocrine tumors (PNET) are rare, with an incidence of 1/100,000/year. Chromogranin A (CgA) is the most valuable marker in the diagnosis and monitoring of PNET. One of the disadvantages is its low specificity and the existence of a number of processes leading to an increase in its concentration, which often results in confusion and diagnostic difficulties.

Case report

We present a 44-years-old female patient with a history of PNET-pT3NxMx-G3 surgically excised in 2007, chemotreated with 6 cycles of Gemcitabine and Capecitabine. In 2009, a left thoracotomy for lung metastasis was performed, followed by 10 cycles of chemotherapy and in 2015 the patient was diagnosed with a recurrence of PNET which required atypical pancreatectomy. Immunohistochemistry revealed intense positive markers: NSE, chromogranin, synaptophysin CD56 and ki67 = 3%. The subsequent evaluations showed normal biological (CgA, serotonin, 5HIAA) and morphological (thoraco-abdominal CT) parameters until 2016, when CgA level was 7-fold higher that the upper normal value (545 ng/ml vs 76 ng/ml) but with normal thorax and abdomino-pelvic CT. As the patient took moderate doses (40 mg/day) of Omeprazole 6 months for gastroesophageal reflux disease, iatrogenic elevation of CgA was suspected. After cessation of proton pump inhibitors (PPIs) therapy for 1 week, serum CgA level rapidly decreased to 66 μg/l ($N < 100$ μg/l).

Conclusions

In this case, the elevated CgA raised the suspicion of a new recurrence which required further investigations. PPIs may cause serious differential diagnostic problems with elevation of serum CgA especially in suspected neuroendocrine tumors. An interesting phenomenon highlighted by this case is the report of rapid normalization of CgA after withdrawal of PPI. Giving particular attention to the use of PPIs as a possible cause for elevated CgA levels might help to prevent the need for further diagnostic procedures.

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EP189

An unknown giant neuroendocrine tumor

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Introduction

Neuroendocrine tumors may develop in almost any organ. These types of tumors may present with giant and asymptomatic mass. We describe a case of a large non functional neuroendocrine tumor reported in the department of endocrinology and diabetology of Hedi Chaker hospital in Sfax-Tunisia in 2016.

Presentation of case

A 28 years old male presented with asthenia, gastric heaviness and epigastric pain. Further computerized tomography, a large mass (20 cm) near the stomach in the coeliomesenteric region has been demonstrated. Magnetic Resonance Imaging has showed the presence of a voluminous encapsulated mass with abundant vascularization and central necroses, measuring 18.5 cm × 14.5 cm compressing the vascular structures. The dosage of methoxylated plasma derivatives was negative. The dosage of NSE was returned positive at 30.5 ng/l. The biopsy of the mass showed a histological and immunohistochemical aspect of a neuroendocrine tumor. The therapeutic decision was to start with exploratory laparotomy and tumor excision if possible. Because of the vascularized character and significant bleeding during the intervention, a surgical abstention was decided. The patient had two chemoembolization sessions with good tumor response. It is being evaluated for possible re-intervention.

Conclusion

The incidence of neuroendocrine tumors has been increasing during the last decade, underscoring the need to improve our understanding of their biology and behavior especially.

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EP190

A challenging case of metastatic paraganglioma and metastatic melanoma and prolactinoma

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Background

Paragangliomas are extremely rare endocrine tumours and can cause diagnostic difficulty, especially with a coexistent metastatic malignancy.

Case

A 78-year-old man with diagnosed metastatic melanoma underwent a PET scan for staging of the malignancy. It showed a left upper quadrant mass with multiple skeletal deposits and a lesion in the pituitary all with intense focal uptake. The mass was unusual for a metastatic lesion from melanoma although other lesions, including pituitary could be explained by metastatic melanoma. A biopsy of the abdominal mass showed histological features of a paraganglioma; 24-h urinary catecholamines showed raised noradrenaline 1474 nmol/24 h (70–550 nmol/24 h), dopamine 6277 nmol/24 h (400–3000 nmol/24 h) and a normal adrenaline < 21 nmol/24 h (0–190 nmol/24 h) confirming a functional paraganglioma. The diagnosis of the skeletal lesions was unclear, and a 123-MIBG scan showed increased activity at the skeletal lesions but no avidity at pituitary confirming skeletal metastases from the paraganglioma with no definite explanation for the pituitary lesion. An MRI pituitary showed diffuse enlargement of pituitary gland with fossa expansion indicating chronicity and suggestive of prolactinoma rather than metastasis as his prolactin was 9400 mU/l and rest of his pituitary function was normal. He had no symptoms of diabetes insipidus. Resection of the paraganglioma was performed after preoperative alpha and beta blockade. His post-operative catecholamines normalised and post operative PET scan has shown stable appearance of skeletal lesions. He was started on Cabergoline for his prolactinoma and referred for chemotherapy for the metastatic skeletal lesions.

Conclusion

Metastatic paragangliomas in patients with a separate existing metastatic malignancy provides a diagnostic and management challenge. With a structured approach to investigation and management the clinical picture can be clarified, which then facilitates appropriate intervention.

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EP191

Biology and differential diagnosis of calcitonin secreting neuroendocrine tumors

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Introduction
Calcitonin secreting neuroendocrine tumors (NET) are rare and not well recognized. Due to many similarities, it is sometimes difficult to differentiate them from medullary thyroid carcinoma (MTC), which can hamper choice of proper therapy. We investigated our group of patients with this type of NET in terms of diagnosis and biology.
Patients and Methods
We analyzed 38 patients with calcitonin secreting NET (5% of all our patients with NET). In addition to standard work up, calcium-stimulation test for calcitonin was performed in 15 of them, and results compared to 34 patients with MTC, and 21 control subjects with elevated calcitonin level and thyroid pathology other than MTC. Statistical analysis was done with SPSS software.
Results
Primary localization of NET was lung (16), pancreas (12), unknown primary (8) and intestine (2), with majority (54.1%) being grade G3, and high majority being metastatic (94.7%). Majority (55.6%) had goiter and 26.3% concomitant TPOAb, while 28.9% co-secreted another hormone (ADH, insulin, serotonin, PTHrP). Patients with NET had significantly higher basal calcitonin levels compared to controls (P(0.01), but with no significant difference compared to patients with MTC ($P=0.427$). Unlike this, patients with NET achieved significantly lower calcitonin levels after calcium stimulation compared to patients with MTC (P(0.01), but no different compared to controls ($P=0.102$). There was no significant correlation between basal calcitonin level and presence of TPOAb ($P=0.816$) or goiter ($P=0.670$) in these patients. Their median overall survival was 24.0 months (95% CI 10.9–37.1).
Conclusion
Patients with calcitonin secreting NET can secrete very high calcitonin levels, but can be differentiated from patients with MTC by absence of significant response to stimulation with calcium. Survival of these patients is poor, but influence of calcitonin on survival is yet to be determined.

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EP192

Cancerous neuroendocrine vs endocrine tumours: broad commonalities and differences

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Endocrine cancers are defined, by European Taskforce on Endocrine Cancer, as malignant tumours arising from endocrine organs including thyroid, adrenal, parathyroid, pituitary, as well as neuroendocrine tumours in general. Cancerous neuroendocrine tumours arise from neuroendocrine cells which can be found within the endocrine system: in the pituitary, pineal, parathyroid and (medulla of the) adrenal gland, or more scantily within the thyroid, pancreas, ovaries and testicles, or more diffusely throughout the body, being present in respiratory, urinary and digestive tracts, as well as breast, skin, prostate and gynaecological structures.
Neuroendocrine and most endocrine cancers are considered both rare and complex.
Commonalities exist in terms of gross classification, that is, designation by site, cell type and whether they are associated with excess hormone/peptide secretion – differences are revealed as this broad definition narrows.
For example: within the adrenal gland:
Endocrine – adrenocorticol carcinoma (ACC) arises within the cortex, and may be associated with excess secretion of steroidal hormones. TNM staging.
Neuroendocrine – pheochromocytoma arises within the medulla, and may be associated with the overproduction of catecholamines. No standardised staging and malignancy designation may be withheld in the absence of metastatic disease, though presentation, family history and proliferation rate will influence treatment planning and follow-up.
Both may be associated with inherited disorders such as multiple endocrine neoplasia, therefore careful history taking and consideration of genetic counselling (Table & diagram of sites, cell type and associated hormone).
Accurate identification of disease site, cell type and associated hormone secretion is paramount in delivering optimal clinical care – evidence based guidelines are available for most neuro/endocrine tumours - but consideration should also be given to meeting the psychosocial and informational needs of the individual diagnosed with one of these rare cancers.
1. http://www.endocrinecancer.eu/en/pages/statement.
2. http://www.ese-hormones.org/guidelines/index.aspx.
3. http://www.enets.org/current_guidelines.html

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EP193

Short-term contralateral recurrence of a Litynski–Conn adenoma

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Clinical Case
A hypertensive 60-year-old woman with nephroangiosclerotic stage IV chronic renal failure (eGFR 23.44 ml/min/1.73 m^2) was referred to our hypertension clinic after the CT finding of a 26-mm left adrenal mass with adenoma density during hypertension workup, with normal right adrenal. Physical exam was unremarkable except for BP 167/98 mmHg. Plasma aldosterone was 353 ng/ml, PRA 1.3 ng/ml/h, ratio 90.2, K^+ 3.1 mEq/l, and metanephrines were normal. Primary aldosteronism was confirmed by standard captopril test. Adrenal vein sampling showed full left lateralization of aldosterone secretion. The patient underwent laparoscopic adrenectomy, and a 21-g left adrenal -including a 4-cm adenoma with clean margins- was removed. One month after surgery, K^+, aldosterone and ARP were normal, and BP was controlled with manidipine 20 mg.
One year later, BP and plasma K^+ were still controlled but the patient showed again a pattern of primary aldosteronism with aldosterone 747 ng/ml, PRA 0.9 ng/ml/h, ratio 83.0. A new CT showed absent left adrenal, and a 17×11 mm mass in the right adrenal, with adenoma density. Low-dose (12.5 mg) spironolactone was added to the treatment, but surgery was deferred.
Diagnosis
Primary aldosteronism caused by aldosterone-producing adenoma (Litynski–Conn syndrome), with contralateral recurrence after one year. Secondary hypertension with nephroangiosclerotic stage IV chronic renal failure.
Commentary
Contralateral recurrence of an aldosterone-producing adenoma in a previously normal adrenal after a complete surgical removal is exceedingly rare, particularly after such a short follow-up. The differential diagnosis would include familial type II aldosteronism (as types I and III usually cause severe hypertension in the pediatric age and associate normal or bilaterally hyperplastic adrenals but not adenomas, while type II may associate adenomas in adult patients) but as there is no known genetic marker for this condition, confirmation is not possible at this point.

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EP194

Acinic cell adenocarcinoma of the parotid gland associated with paraneoplastic Cushing's syndrome – a rare clinical case

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Introduction
Primary acinic cell carcinoma (ACC) is an uncommon salivary gland (SG) tumor, making up 1–3% of all SG neoplasms, more frequent in women, at 40–60 year old. The cause is still unknown and the only well-established risk factor is

ionizing radiation. ACC metastasize in 10–15% of the cases, 35% tends to recur and the rate of disease-associated death is about 16%. Surgical resection is the mainstay treatment, but radiation therapy may be used in some cases and, more rarely, chemotherapy in advanced ACC.
Case Report
We describe a case of a 46-year-old man referred by paresthesias, general malaise and hypokalemia of 2.5 mEq/l. The patient had a history of pericentimetric nodule in the left submandibular gland diagnosed 1 year before, hypertension and dyslipidemia diagnosed 4 months before and also new-onset diabetes mellitus (DM) diagnosed in the previous month. Ambulatory analysis showed endogenous hypercortisolism, and he was admitted to the endocrinology department for further investigation. Hormonal study revealed: ACTH 206.8 (<63.3) ng/l, cortisol 30.1(6.2–19.4) μg/dl; cortisoluria, 24-hour salivary cortisol and low-dose dexamethasone suppression test confirmed Cushing's syndrome(CS); high-dose dexamethasone suppression test was compatible with ectopic CS. Initial imaging study found several hepatic nodular lesions, suggestive of secondary lesions by neoplastic process. Investigation was continued, with imaging and cytological documentation of probable primary parotid malignancy with hepatic metastasis. Octreoscan revealed increased uptake in the parotid gland and mild expression in hepatic metastasis. No uptake was observed in PET-Gallium. The patient underwent right parotidectomy, with the histological diagnosis of ACC, pT3NxR1, with no neuroendocrine differentiation, Ki67 70%. Imaging reevaluation revealed disease progression, with pulmonary and bone metastasis, and the patient started chemotherapy. Meanwhile, hypercortisolism was controlled with metyrapone (3 g/day), ketoconazole (400 mg/day) and lanreotide (120 mg/month).
Conclusion
The authors present a very rare case of ACC, with paraneoplastic CS and aggressive behavior, presenting significant diagnostic and management challenges.

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EP195

Malignant pheochromocytoma – a challenging diagnosis with nonconsensual management

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Introduction
Pheochromocytomas and extra-adrenal paragangliomas are rare neuroendocrine tumors, with a peak incidence between the 3rd–5th decades of life and about 10% are malignant. Although they have the same radiographic and histologic characteristics of their benign counterpart, malignant pheochromocytomas are diagnosed by the presence of local invasion or metastatic tumor in the non-chromaffin tissues, and offer a poorer prognosis. Treatment is typically extirpative surgery, although MIBG-radiotherapy and chemotherapy have been offered in nonsurgical cases.
Case Report
An 83-year-old man with history of diabetes mellitus and hypertension presented abdominal pain, anorexia and weight loss. An abdominal CT revealed a large, hypocaptant and heterogenous neoformative lesion of left adrenal gland, 48× 58 mm, and adjacent metastatic adenomegaly with 18 mm. He was then referred to our Endocrine Department. Imaging study was repeated and revealed an additionally left renal mass, on the posterior face, exophytic, with 40×13× 38 mm, suspected for metastasis. Biochemical diagnosis of pheochromocytoma was established by a marked increase of urinary catecholamines and fractionated metanephrines: norepinephrine 1222 (<97) μg/24 h, epinephrine 106 (<27) μg/24 h and dopamine 1166 (<500) μg/24 h; normetanephrines 3711 (<390) μg/24 h and metanephrines 1226 (<320) μg/24 h; vanillylmandelic acid (VMA) was 29.3 (1.4–6.5) mg/24 h. ^{123}I-MIBG scintigraphy was performed and evidenced left adrenal gland lesion compatible with pheochromocytoma, without uptake on left renal mass. The patient started alpha-adrenergic blockade with phenoxybenzamine (10+10 mg/day) and 6 weeks later underwent exploratory laparotomy surgery, with left adrenalectomy and nefrectomy. Histological examination confirmed malignant pheochromocytoma diagnosis and the patient maintains close surveillance.
Conclusion
Malignant pheochromocytomas present clinicians with three major challenges: scarcity, complexity of characterization, and heterogeneous behavior and prognosis.

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Neuroendocrinology

EP196

Identification of molecular targets of Sunitinib in pancreatic neuroendocrine tumours

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Pancreatic neuroendocrine tumours (pNETs) are rare neoplasms arising from the endocrine pancreas. The fist line treatment is surgery that is often not curative in the presence of metastatic disease. Therefore, there is an increasing need for medical therapy. Sunitinib is a multi-target receptor tyrosine-kinase (RTK) inhibitor, described as having as main target VEGF receptor, with antitumor and antiangiogenic effects, approved for pNETs medical treatment. This study is aimed at evaluating Sunitinib effects in the human pNET cell line, BON1, in order to identify tissue-specific molecular targets that might predict the efficacy of the treatment. We tested BON1 cell viability and proliferation by means of Proliferation Assay and Luminescent Cell Viability Assay after treatment with Sunitinib (0.25–7.5 μM) and found an IC50=5 μM. Western blot analysis confirmed that BON1 cells express VEGF, IGF1 and EGF receptors, therefore we tested the effects of VEGF 50 ng/ml, IGF1 100 nM and EGF 15 nM alone or each in combination with Sunitinib 5 μM. We found that BON1 cell viability is not affected by VEGF and EGF, while it is significantly enhanced by IGF1 (+20%; $P<0.05$), that was capable of blocking the antiproliferative action of Sunitinib, suggesting that the main target of this drug is IGF1 receptor. Therefore, we tested Linsitinib, a specific IGF1 receptor inhibitor, and found that it significantly reduces BON1 cell viability (−25%; $P<0.05$) and blocks the proliferative effects of IGF-1. These data indicate that IGF1 receptor represents the main molecular target of Sunitinib in BON1 cells and that it may play a crucial role in pNET cell proliferation control, suggesting that Linsitinib might be an effective medical treatment.

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EP197

Study of different *in vitro* systems for the evalutation of Sunitinib effects in pancreatic neuroendocrine tumour cells

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Finding new preclinical models to study the effects of anticancer drugs is one of the aims of biomedical research. Indeed, testing different *in vitro* systems can lead to a better understanding of the molecular pathways regulating tumor development and growth, and help to find new therapeutic approaches. This is crucial especially in the settings of pancreatic neuroendocrine tumours (pNET), where one of the main drugs approved for medical treatment is Sunitinib, a multi-targeted receptor kinase inhibitor. Clarifying the effects of this drug may be important to develop more effective medical treatment, therefore we tested Sunitinib on the human pNET cell line, BON1, grown in two different *in vitro* systems, monolayer and spheroid, in order to understand the different effects of the drug in 2D and 3D settings.

BON1 cells were grown in monolayer and treated with Sunitinib at increasing concentrations (0.25–5 μM). Cell Proliferation Assay and Luminescent Cell Viability Assay were employed to test Sunitinib antiproliferative effects. We found that Sunitinib 5 μM significantly reduced BON1 cell viability by 30% ($P<0.01$ vs control) after 3 days. Similarly, Sunitinib 5 μM significantly reduced BON1 cell proliferation by 50% ($P<0.05$ vs control) after 3 days and by 90% ($P<0.05$ vs control) after 7 days.
Then, BON1 cells were grown in spheroids with Sunitinib at increasing concentrations (0.25–5 μM). Spheroids size was analyzed with ImageJ software after 3 and 7 days. We found that Sunitinib does not affect spheroid size, but induces spheroid disgregation after 7 days of treatment at 5 μM.
These results indicate that measuring spheroid diameter in a 3D system is not the optimal system to assess the antiproliferative effects of Sunitinib on BON1 cells. On the other hand, the differences observed between the employed models could reflect the variations in drug response depending on cell aggregation state.

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EP198

Von Hippel–Lindau syndrome: *in vivo* portrait with 68Ga-DOTANOC PET-CT

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Introduction
Von Hippel–Lindau syndrome (VHL) is an autosomal dominantly inherited neoplastic disorder with marked phenotypic variability, characterized by a broad spectrum of clinical manifestations in central nervous system (CNS) and viscera. Specific gene mutation can be demonstrated; however imaging plays an important role in diagnosis. 68Ga-labelled somatostatin analog (68Ga-DOTANOC) PET-CT is routinely employed for somatostatin receptor (SSTR) imaging, mainly for neuroendocrine tumors evaluation, but could be an optimal whole body imaging method for screening and follow-up VHL patients.
Purpose
To present 68Ga-DOTANOC-PET-CT findings in three VHL female patients (58, 58 and 65 years old), demonstrating both CNS and visceral tumors.
Material and Methods
68Ga-DOTANOC-PET/CT scan was acquired 45 min after intravenous administration of 100–200MBq 68Ga-DOTANOC in three patients with VHL referred for pancreatic neuroendocrine tumor (PNET) evaluation. Abnormal findings were correlated with histopathology or other imaging modalities (CT, MR, ophthalmoscopy).
Results
68Ga-DOTANOC-PET/CT showed, in all patients, other lesions than PNET, which proved to be related to VHL. Retinal and spinal cord hemangioblastomas were detected in two patients. Endolymphatic sac tumor was demonstrated in one. Lung hemangioblastoma was suspected in one. Liver and lymph node metastasis were present in one patient. Two patients had a pheocromocytoma previously removed by surgery.
Discussion
In VHL diagnosis a multidisciplinary approach is mandatory. Although genetic testing is available, imaging plays a key role in the identification of abnormalities, their follow-up and in the screening of asymptomatic gene carriers. Several analytic and imaging modalities are needed for diagnosis and follow-up. Screening is essential because the lesions in VHL disease are treatable. Early detection enables more conservative therapy and may enhance the patient's length and quality of life. In these three VHL patients, 68Ga-DOTANOC-PET-CT has demonstrated to be a promising whole-body screening high-resolution imaging method for evaluation of the entire picture of this disease.

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EP199

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs): clinico-pathological characteristics and disease outcome of 110 patients treated at single referral medical center

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Introduction
GEP-NETs incidence increased markedly over the past decades probably due to increased imaging. GEP-NETs are generally indolent but often have unpredictable biological behavior and aggressive clinical course.
Aims
To collect information regarding demographics, presentation, pathology characteristics, treatment and outcome of GEP-NETs.
Methods
Following approval of our institutional ethical board, pathology and clinical records of all GEP-NETs patients diagnosed and treated at our institution during 2005–2015 were reviewed.
Results
We identified 110 patients with GEP-NETs distributed by site as pancreatic 32 (F=45.1%, age 61.2±6.8), gastric 19 (F=50%, age 66.2±11), duodenum 9 (F=33.3%, age 66.3±12), small bowel 13 (F=25%, age 60±12), appendix 34 (F=55.8%, age 36±19) and colorectal 3. The pNETs presented with abdominal pain (45.1%) incidentally (25.8%) or syndromatic (21.8%); including two insulinomas, one gastrinoma and four MEN1 patients. Mean size was 31±23 mm and grading was G1 39.2, G2 42.8, G3 17.8%. Distant metastases (DM) were seen in five patients (M1=3). Surgery was performed in 61.3%, additional treatment given to 32.2% (re-op, somatostatin analogue, TKI, chemotherapy). The gNETs presented mostly during work-up for anemia or GI bleeding (70.6%). Mean size was 15 mm and the majority (82.3%) were GCT1 and there were no DM. The dNETs presented with anemia (43%), abdominal pain (43%) or incidentally. None was syndromatic. Mean size was 11.2 mm, 50% were G1, and 2 had DM at presentation. Surgery was performed in 33.3% patients. The sbNETs presented with bowel obstruction (27%), abdominal pain (36%) or incidentally. None were syndromatic. Only 15% were G1, 6 had DM (M1=5), and 77% had surgery. Excluding aNETs, the overall mortality at last visit was 23.7% (7.9% disease related) at mean follow-up of 34.5 months.
Conclusion
GEP-NETs are associated with significant morbidity and mortality. The primary site of the tumor has clinical implication for disease management.

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EP200

Insulinoma: diagnostic features and treatment management

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Backgraund
Insulinoma is the most common functional pancreatic neuroendocrine tumor originating from β-cells, with unregulated insulin production and rarely associated with MEN-I syndrome. Diagnosis and treatment of insulinoma are a challenge in the practice of endocrinologist.
Aim
To determine on the basis of retrospective analysis the optimal approaches to the management of patients with organic hyperinsulinism.
Materials and methods
Medical records of 72 patients admitted with suspected organic hyperinsulinism had been screened and medical histories of patients with a confirmed diagnosis of organic hyperinsulinism were included into the analysis. Anamnesis, results of objective, laboratory and instrumental examinations, methods and results of the treatment were analyzed.
Results
The diagnosis of insulinoma was confirmed in thirty two cases. Hypoglycemia was achieved within the first 48 h after the start of the 72-h fasting test in 100% of cases. Study results showed that in 50% of cases the size of the pancreatic neoplasm was more than 1.4 cm. Inverse correlation between tumor size and plasma glucose concentration at the time of hypoglycemia was found ($r=-0.45$,

$P=0.02$). Surgical treatment was carried out in thirty out of 32 patients. Surgical enucleation of insulinoma was performed in 12 (40%) cases, distal pancreatectomy – in 18(60%). Insulinoma was confirmed in 27 cases, while in three patients diagnosis of non-insulinoma pancreatogenous hypoglycemia ('nesidioblastosis') was established according to histological findings. Positive clinical result was achieved after all surgeries. In postoperative period patients were discharged within 11–30 days. Patients without post-operative complications were discharged 13.0 ± 1.4 days after surgery. Twelve (40%) patients developed post-operative complications. The duration of hospital stay in these cases was significantly longer 20.1 ± 1.9 ($P<0.01$).

Conclusions

Obtained data confirmed that comprehensive approach including 72-h fasting test, use of modern imaging techniques and application of high-tech treatment methods, is crucial for successful diagnosis and treatment of insulinoma.

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EP201

A rare case: non-islet cell tumor hypoglycemia with adrenal insufficiency

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Non-islet cell tumor hypoglycemia (NICTH) is a rare paraneoplastic syndrome and is the second most common cause of tumor-related hypoglycemia following insulinoma. Its prevalence is not known and is likely that many cases would go undiagnosed. In here, we describe a patient with PNET who presented with severe hypoglycemia.

A 37-year-old male with known metastatic Pancreatic neuroendocrine tumors (PNET) presented with weight loss, sweating, and tremor, episodic altered sensorium. He had documented blood glucose values below 35 mg/dl during those episodes. He received two cycles of lutetium therapy and was referred to our institute. At blood glucose of 33 mg/dl, he had undetectable plasma insulin ($\leq$0.19 mU/l), low C-peptide 0.159 ng/ml (normal: 0.8–4), cortisol: 5.6 µg/dl (n:5–29), GH: <0.05 ng/ml and low IGF1 <25 ng/ml (normal: 109–284 ng/ml). ACTH: 60 pg/ml (normal: 0–46), Na: 136 mmol/l (normal: 132–146), K: 4.2 mmol/l (normal:3.5–5.5), TSH 1.274 uIU/ml (n: 0.35–4.94), FT_4: 1.47 ng/dl (n:0.7–1.48), FT_3: 2.6 pg/ml (n: 1.71–3.81), prolactin: 8.28 ng/ml (n:2.1–17.7), LH: 5.08 IU/l (1.5–9.3), FSH: 10.22 IU/l (n:1.4–18.1), testosterone: 405.78 ng/dl (n:241–2270). Magnetic resonance imaging of pituitary gland was normal. We were started prednisolone 30 mg/day with which his symptoms abated. After prednisolone treatment, there was no recurrence of hypoglycemia on follow-up. In NICTH patients, the serum levels of insulin, C-peptide, and IGF1 are usually decreased or undetectable; however, the circulating level of total IGF2 as determined by conventional immunometric or receptor assays may be increased, decreased, or normal. In the absence of IGF2 assays, low serum insulin in combination with low IGF1 levels at the time of hypoglycemia is a strong biochemical evidence of NICTH. High-dose glucocorticoid therapy has immediate beneficial effect on symptomatic hypoglycemia.

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EP202

Late manifestation of a mixed adenoneuroendocrine carcinoma of the cecum

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Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) is a rare tumor of the gastrointestinal tract that consists of a dual adenocarcinomatous and neuroendocrine differentiation. The clinical behavior seems to be influenced by the neuroendocrine component. We report a patient with mixed adenoneuroendocrine carcinoma of cecum who presented 18 years after her initial diagnosis and treatment.

Case report

A 59-year-old woman presented with a 3-month history of episodic hypotension, tachycardia and face and upper trunk flushes. She had a history of cecum tumor resection 18 years ago. It was a poorly differentiated mixed adenoneuroendocrine carcinoma. The tumor extended in the pericolic adipose tissue with perineural and lymphonodular invasion. It was TNM stage IIIB (T3N1M0). Postoperatively, she received interferon and 5-fluoracil chemotherapy for 6 months.

The patient was asymptomatic for 18 years until symptoms of carcinoid syndrome (CS) appeared. Serum chromogranin A and 24-h urine 5-hydroxy-indole-acetic-acid (5-HIAA) were abnormally high. An abdominal magnetic resonance imaging revealed multiple metastatic liver lesions confirmed by biopsy. In111-pentetreotide scintigraphy detected the lesions in the liver and others in the left shoulder and the right sternum-clavicle joint. Bone lesions were also demonstrated by Tc-99m DTP scan. Octreotide LAR 30 mg per month was initiated and resulted in amelioration of symptoms. Chromogranin A and 5-HIAA decreased but remained above normal range. The symptoms of CS reappeared after 2 years and the patient received 9 cycles of targeted radiotherapy (177Lu-Dotatate), which finally resulted in clinical and imaging improvement.

Conclusion

We report a rare case of a patient with a mixed adenoneuroendocrine carcinoma of the cecum who presented with metastatic disease and carcinoid syndrome 18 years postoperatively. Due to the rarity of these tumours and the unknown natural history, lifelong follow up is required.

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EP203

Quality of life in patients with neuroendocrine tumors treated with 177Lu-[DOTA^0,Tyr^3]-octreotate: a Single Tertiary Care Portuguese Center Experience

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Introduction and purpose

177Lu-[DOTA^0,Tyr^3]octreotate (177Lu-DOTA-TATE) is a radiopharmaceutical frequently used in peptide receptor radionuclide therapy (PRRT), which is a promising treatment modality in patients with metastasized neuroendocrine tumors (NETs). We purpose to evaluate the quality of life (QoL) in patients with somatostatin receptor positive inoperable or metastatic NETs throughout the three cycle's (with three months intervals) protocol used in our hospital.

Patients and methods

We included 24 patients, 16 men and 8 women (age: mean = 67 years; range = 29–81). The majority (13/24 cases; 54.2%) were gastroenteropancreatic NETs. Patients were treated with a mean cumulative 177Lu-DOTA-TATE activity of 614 mCi (range: 303–1177 mCi).

Patients were invited to self-report QoL during PRRT cycles. We analyzed the overall QoL and specific domains of QoL according to the Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) scoring manual.

Results

From 24 patients, 15 completed at least 2 copies of the EORTC QLQ-C30 at different time-points (during the 1st or 2nd cycle and during the 3rd). Twelve patients had progressive disease, eleven had stable disease and one had notable lesions regression during PRRT.

Regardless the treatment outcome, Global Health Status/QoL (GHS/QoL) and all the functional scales (except social status) improved significantly in all group ($P<0.05$). On GHS/QoL, we found an improvement on scores superior to 10 points before vs after therapy ($\Delta +10.56$; $P=0.003$).

Besides GHS and functional scales, we observed also a favorable impact on disease-related symptoms as fatigue ($P=0.00003$), insomnia ($P=0.0003$), appetite loss ($P=0.0003$), constipation ($P=0.033$) and diarrhea ($P=0.014$).

Conclusions

A better health-related QoL in cancer patients with incurable disease is an important outcome of cancer therapy, especially when survival is prolonged. Therapy with 177Lu-DOTA-TATE significantly improved QoL regarding to several functions and had favorable impact on global health status even on those with progressive disease.

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EP204

Triple tumors in a patient with insulinoma

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Introduction
Hypoglycemia is a rare clinical problem in patients not being treated for diabetes mellitus and requires further evaluation and management if Whipple's triad is present. Insulinoma commonly presents with fasting hypoglycemia. Insulinoma is rarely associated with type 1 multiple endocrine neoplasia, when tumors are usually multiple and more frequently malignant. The diagnosis of insulinoma is established by demonstrating inappropriately high serum insulin concentrations during a spontaneous or induced episode of hypoglycemia, e.g. 72-h fast.
Patient
46-years old female was referred to our department for evaluation of spontaneous fasting hypoglycemia. She had multiple episodes of temporary probably neurohypoglycemic symptoms (confusion, unusual behaviour) and gained a lot of weight in 2016 (+20 kg). Before the beginning of 72-h fast her serum glucose was 1.8 mmol/l, insulin concentration 20.6 mcU/ml, C-peptide 1.2 nmol/l. Testing was stopped after 6 h due to very low glucose levels (1.5 mmol/l) but without any obvious symptoms of hypoglycemia, insulin was high. After glucagone 1 mg i.v. glucose increased for 1.5 mmol/l. Her serum calcium, iPTH, prolactin and IGF-1 were normal. CT showed 1.8 cm lesion in the pancreatic neck and also unusual lesion in proximal jejunum that appeared to be a neuroendocrine tumor. There was also typical teratoma in left ovary (maximal size 6.6 cm), also seen on US. The patient underwent operation – partial pancreatectomy, proximal jejunal resection with anastomosis and left ovariectomy. Based on patohistology and imaging results benign insulinoma was confirmed, in jejunum there was ectopic pancreatic tissue, and there was mature teratoma of left ovary. We have not performed genetic testing for MEN1 since we thought it was unlikely. After operation, the patient was asymptomatic and normoglycemic.
Conclusions
We found three different tumors, including insulinoma, in a single patient. This combination has not yet been described to coincide and is not due to multiple endocrine neoplasia.

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Paediatric Endocrinology

EP205

An analysis of R356W and Q318X mutations and 8 bp deletion in 21-hydroxylase gene CYP21A2 in causing pseudo-precocious puberty in patients with congenital adrenal hyperplasia in Pakistani children

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The first signs of puberty are visible around the age of 8 years in girls and 9 years in boys. If signs of puberty appear before the designated ages in girls and boys, puberty is viewed as precocious. In peripheral precocious puberty, androgens concentrations increase due to testicular tumours or congenital adrenal hyperplasia (CAH). Two mutations, R356W and Q318X, and one 8 bp deletion in CYP21A2 gene, causing CAH type of precocious puberty were examined. Blood samples were obtained from 42 CAH patients (30 boys and 12 girls) exhibiting higher 17-OH progesterone concentrations and 42 normal healthy controls. DNA was extracted, primers of exons of CYP21A2 splice sites were designed and PCR-RFLP method was employed. The PCR product of CYP21A2 digested by enzyme Fnu4HI for R356W mutation gave bands of AA (~106, 110, 229 and 37 bp). The frequency of this genotype was 100% in both groups indicating absence of R356W mutation in both groups. For Q318X, the restriction enzyme, PstI gave bands of 3 different genotypes, GG (161 and 329 bp segments) in 18 patients, GC (490, 329 and 161 bp segments) in 21 patients and CC (segment of 490 bp) in 3 patients (2 boys and 1 girl). For 8 bp deletion, PCR amplification with allele specific primers yielded a segment of ~710 bp; 8 bp deletion was not found in any patient but 3 control subjects were heterozygous for it. The frequency of homozygous wild type (NN) was 1 in patients and 0.85 in controls; the frequency of homozygous mutants (DD) was 0 in both groups, whereas the frequency of heterozygous (DN) was 0 in patients and 0.15 in controls. The frequency of allele D was 0 in patients and 0.075 in controls. The frequency of allele N was 1 and 0.925 in patients and controls respectively.

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EP206

Congenital adrenal hyperplasia: impact of therapy on growth and sexual maturation – a 5-year retrospective study of a Tertiary Pediatric Endocrinology Center

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Objective
To evaluate the comparative effects of different glucocorticoid treatments on growth and sexual maturation in patients with congenital adrenal hyperplasia.
Patients and methods
We conducted a retrospective observational cohort study in 78 patients (60 girls, 18 boys) diagnosed with congenital adrenal hyperplasia (CAH), followed-up for a period of 5 years. The majority had 21-hydroxylase deficiency (75 patients), 2 had 11-β hydroxylase deficiency and 1 patient had 3-β hydroxysteroid dehydrogenase deficiency. Patients received either Prednisone (PDN), Hydrocortisone (HC) or Hydrocortisone plus Dexamethasone (DEX). Data on growth, bone maturation, puberty onset, predicted adult height, and parental height were collected. Height gain was calculated as the difference between parentally determined target height and final or predicted height at the last evaluation.
Results
Height gain with therapy was 0.42 S.D. over the initial estimated height deficit. Height gain correlated with the clinical form of CAH, with better outcome in non-classical vs classic forms ($P<0.01$). There were no significantly differences between groups in regard to type of therapy ($P=0.164$). There was no difference in change of body mass index regarding the type of treatment ($P=0.99$). Girls over 12 years of age treated with HC had higher rates of spontaneous menarche versus PDN treated girls ($P=0.006$). Twelve children developed precocious puberty, which correlated with older age at treatment initiation ($P=0.048$).
Conclusions
The type of therapy did not influenced height gain. HC facilitated spontaneous menarche onset in normal age range. Late diagnosis and therapy led to higher rates of precocious puberty in children with CAH.

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Pituitary – Clinical

EP207

The risk of hypotension, evaluated by ambulatory blood pressure monitoring, during fasting and outside fasting in patients with adrenal insufficiency

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The risk of hypotension during Ramadan fasting in patients with adrenal insufficiency is unknown. The aim of our study was to evaluate objectively this risk.
Methods
It is a prospective case-crossover study on 28 patients with known and treated AI. Patients had no hypertension and were regular fasters. All patients underwent a clinical examination and a 24-hours blood pressure monitoring during Ramadan fasting then outside fasting.

Results
There were 23 women. The mean age was 37 ± 14 years. It was a central adrenal insufficiency in 26 patients. The mean duration of the disease was 9 ± 8 years. The mean daily dose of hydrocortisone was 19 ± 3 mg. Systolic hypotension (<90 mmHg) did not occur during fasting and occurred in two cases outside fasting. Diastolic hypotension (<60 mmHg) occurred in 12 cases during fasting and in 13 cases outside fasting without a significant difference. All cases of hypotension were asymptomatic. The levels of systolic and diastolic blood pressure during the 24 h and during the fasting period (from pre dawn to sunset) did not significantly differ between the fasting day and the non-fasting day.
Conclusion
Blood pressure levels during fasting were comparable to those outside fasting and there was not an increased risk of hypotension during fasting.

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Steroid Metabolism + Action

EP208

Steroid metabolome changes in the 1 mg dexamethasone suppression test

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Introduction
Dexamethasone induced negative feedback on CRH, ACTH and cortisol secretion is one of the key principles in the diagnostic workup of hypercortisolism. Cortisol secretion has been studied extensively, but changes of other steroids remained apart. Our aim was to establish steroid profile changes in 1 mg dexamethasone test.
Methods
The Steroid profile consisting of 103 steroids and their metabolites from the serum of 9 male and 8 healthy female controls was measured before and in the morning at 0800 hours after 1 mg dexamethasone administered at 1100 hours. Samples were analyzed using GCMS/MS for the measurement of most of the steroids. Only a few were measured by RIA.
Results
Dexamethasone administration suppressed the most the levels of corticosterone (29×), cortisol (20×), 11-OH-androstenedione (12×), 11β-Hydroxy-androsterone (13×), 11β-Hydroxy-etiocholanolone (13×), 11β-Hydroxy-epiandrosterone (6×), 17-Hydroxypregnenolone (5×). Other steroids like DHEA (3×), Androstenedione (2×), Pregnenolone (2×) were suppressed at much lower rate than their 11β-hydroxylated metabolites. As expected, none of the measured steroids increased after dexamethasone.
Conclusions
Inhibition of ACTH secretion leads to a strong suppression of the whole adrenal steroidogenesis including androgen production.
The most prominent changes were observed in corticosterone, cortisol, and interestingly 11-OH-androstenedione and their 5-β/α-reduced metabolites, which all decrease more than 10 times in comparison with the basal levels.
This clearly demonstrates the key role of 11β-hydroxylase being the most influenced enzyme by the adrenocortical axis suppression.

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Thyroid Cancer

EP209

Clinical relevance of RET proto-oncogene variants L769L and S836S (exon 11, 13, 14, and 15) in patients with sporadic medullary thyroid carcinoma

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Background
Medullary thyroid cancer (MTC) makes up to 5–10% of all cases of thyroid malignancies. The clinical course of MTC varies from an extremely indolent tumour to an aggressive variant that is associated with a high mortality rate. RET proto-oncogene germline mutations are crucial for the onset and the progression of MTC. The aim of this study was to evaluate the L769L (subgroup L) and S836S (subgroup S) allele frequencies in patients with sporadic MTC (group A, $n=89$) compared to healthy subjects (group B, $n=83$) and to determine if these polymorphisms have influence the clinical presentation and the course of MTC.
Methods
A non-isotopic polymerase chain reaction based single strand confirmation polymorphism analysis and heteroduplex gel electrophoresis method was used to screen tumour DNA extracted from 89 formaldehyde fixed and paraffin embedded MTC specimens. We also analysed relevant clinical data in the group of patients with MTC. The study was conducted according to the Declaration of Helsinki, the protocol was reviewed and approved by the institutional independent ethics committee. All patients were provided with written informed consent.
Results
Mean age was 51.6 ± 9.2 years for the patients with MTC (range, 42.4–60.8) vs 45.4 ± 7.1 (range 38.3–52.5) for the group of healthy subjects. The allele frequencies showed a similar level of the L769L and S836S variants in both subgroups of examinees (group L, 52.5% vs group S, 47.5%; $P>0.001$). Lymph node metastases were found in all patients with MTC (subgroup L, $n=42$ vs subgroup S, $n=47$; $P>0.001$), and distant metastases in nine patients (subgroup L, $n=5$ vs subgroup S, $n=4$; $P>0.001$). Postoperatively, 52% of patients in subgroup L vs 55% of patients in subgroup S were biochemically cure ($P>0.001$). In the subgroup L, pT-category was: T0, $n=23$; T1, $n=14$; and T2, $n=5$. In the subgroup S, pT-category was: T0, $n=21$; T1, $n=16$; and T2, $n=10$.
Conclusion
We did not find any statistically significant difference in representation of the L769L and S836S gene variants. The RET L769L and S836S (exon 11, 13, 14, and 15) gene variants are not contributing factor in the development of sporadic MTC and are not promoting factor for development of metastatic MTC.

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Eposter Presentations: Calcium and Bone

Bone & Osteoporosis

EP210

Abstract withdrawn.

EP211

Bisphosphonate related osteonecrosis of the jaw: risk factors: a case report

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Introduction
Bisphosphonates (BP) have been employed for many years and have demonstrated an excellent safety profile. Nevertheless, severe osteonecrosis of the jaw (ONJ) have been described in patients with bone metastases that were treated with BP for many years.
Case
A 72 year old female with breast cancer and bone metastases treated with quadrantectomy, axillary lymph node dissection, radiotherapy, tamoxifen and pamidronate 90 mg/month. Two years later, the patient suffered from pain in the right body of the jaw one month after the extraction of low dental pieces. She had an extended intraoral ulcer, which leaved exposed part of the body of the jaw and loss of dental pieces. The patient had not received radiotherapy in the jaw. X ray revealed osteolysis and CT scan showed lesions in bone and soft parts of the jaw. Biopsy confirmed necrosis. Irrigation with chlorhexidine gluconate 0,12% and extraction of dental pieces were performed. In spite of the conservative treatment, she presented severe pain and suppuration. The right side of the jaw was removed. Pamidronate treatment was discontinued. The patient had cancer progression and died some months later.
Conclusion
The aim of this presentation is to emphasize the importance of taking into account the risk factors of ONJ at the moment of performing an invasive procedure. The estimated incidence of ONJ in patients with malignancy who receive BP seems to range between 1 and 10%. The risk factors of ONJ are related to BP, local, systemic and demographic factors. The use of less traumatic techniques available and adequate antibiotic treatment is mandatory in the presence of risk factors of ONJ. BP treatment should be interrupted after surgery until the wound is fully healed.

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EP212

Salmon calcitonin affects thyroid endocrine cells and trabecular bone in a rat model of male osteoporosis

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Calcitonin (CT) is a hypocalcemic hormone produced by thyroid C-cells that acts as an bone antiresorptive agent. The other endocrine cell population in thyroid, called follicular cells produce thyroid hormones (TH) which also affect bone turnover. In this study, we evaluated the effects of salmon CT administration on structure and function of both CT and TH producing thyroid cells as well as trabecular bone microarchitecture in orchidectomized (Orx) middle-aged rats. Fifteen-month-old male Wistar rats were either Orx or sham-operated (SO). One group of Orx animals were injected subcutaneously with synthetic salmon CT (Orx + CT; 100 IU/kg b.w.) every second day for 6 weeks. The rats from SO and second Orx group received the same volume of vehicle alone by the same schedule. The peroxidase–antiperoxidase method was applied for localization of CT in C-cells. CT-immunopositive thyroid C-cells, thyroid follicular epithelium, interstitium and colloid were evaluated morphometrically. An ImageJ public domain image processing program was used to measure bone histomorphometric parameters of the proximal tibial specimens. Blood serum samples were analyzed for CT, osteocalcin (OC) and thyroxine (T_4), and urine samples fot calcium (Ca^{2+}) concentration. We found a significant decrease in the Vc and Vv of thyroid C-cells after CT treatment compared to both SO and Orx. The Vv of the colloid was higher, while V_V of the follicular epithelium was lower after CT treatment compared to Orx. Analysis of trabecular microarchitecture showed that salmon CT administration significantly increases of cancellous bone area (B.Ar), trabecular thickness (Tb.Th), and trabecular number (Tb.N) whereas trabecular separation (Tb.Sp) was significantly decreased. CT treatment markedly elevated serum CT, but serum OC, T_4 and urinary Ca^{2+} concentrations were lower than in the Orx group. These findings indicate that administration of salmon CT inhibited calcitonin-producing thyroid C-cells and changes the structure of the thyroid gland indicating hypoactivity.

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EP213

Primary hyperparathyroidism: hormonal profile and risk of complications

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Background
Vitamin D deficiency is frequently associated with primary hyperparathyroidism, but the impact of this association on disease evolution and complications is ill defined. Aims: to assess the role of vitamin D status on the metabolic profile and spectrum of complications at patients with primary hyperparathyroidism.
Materials and methods
Transversal study involving 42 patients with primary hyperparathyroidism submitted to parathyroidectomy. We evaluated serum calcium, phosphate, serum PTH and 25OHD3, bone mineral density by DXA (Hologic) and anamnestic episodes of bone fractures and kidney lithiasis. Fifteen patients had episodes of kidney lithiasis, whereas 27 patients did not develop this complication. Twenty patients were diagnosed with osteoporosis whereas 22 patients had bone mass in the range of normal or osteopenia. Data between groups were compared using the t test and were considered significant at P values < 0.05.
Results
Twenty-nine of the 42 patients had 25OHD3 in the range of deficiency (lower than 20 ng/ml) and 20 had severe 25OHD3 deficiency (lower than 10 ng/ml). Serum calcium and phosphate were similar irrespective of the presence or absence of complications. No differences were found between mean PTH and 25OHD3 levels of patients with or without osteoporosis. Patients with kidney lithiasis had, however, higher PTH ($390 +/- 90$ pg/ml vs $209 +/- 64$ pg/ml, $P<0.001$) and lower 25OHD3 levels ($12.8 +/- 6$ ng/ml vs $19.2 +/- 7.8$ ng/ml, $P<0.05$) than patients without kidney lithiasis.
Conclusions
D hypovitaminosis accompanies frequently primary hyperparathyroidism. Patients with higher risk of kidney lithiasis seem to have higher PTH and lower 25OHD3 levels.

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EP214

Efficacy and safety of bisphosphonate discontinuation in postmenopausal osteoporosis: a systematic review

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Introduction
The maximum period of bisphosphonate use has not been determined, as their long-term appliance has been associated with adverse effects, such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFF).
The aim of this study was to systematically present existent data regarding the effect of bisphosphonate discontinuation on fracture risk and bone mineral density (BMD).
Methods/design
MEDLINE, Scopus, EMBASE and Cochrane databases were searched (up to December 2016) for randomized placebo-controlled trials.
Results
Regarding alendronate, five studies fulfilled eligibility criteria ("drug holiday": two-five years). Extending alendronate (5–10 mg/d) use to five years, after continuous treatment for five years, reduced clinical vertebral fracture risk by 55%, without difference in morphometric vertebral or non-vertebral fractures (one study). Lumbar BMD remained higher than pre-treatment levels in the discontinuation group, although lower compared with the extension group. Hip BMD decreased or remained unchanged.
Regarding zoledronic acid, two studies fulfilled eligibility criteria. After three annual infusions (5 mg/y), extending treatment to six years reduced risk of new morphometric vertebral fractures by 49%, without benefit in clinical vertebral or other types of fractures. Lumbar BMD remained above pre-treatment values in the discontinuation group, but reduced in hip sites. Extending treatment to nine years provided no additional benefit.
Regarding risedronate, one study fulfilled eligibility criteria. Discontinuation for one year (after 5 mg/d for three years) did not increase non-vertebral fracture risk, but continued to confer a reduced risk in vertebral fractures (46%). Lumbar BMD remained higher, whereas femoral neck BMD decreased, compared with pretreatment levels. No increased risk of ONJ or AFF was shown in these studies.
Conclusions
A "bisphosphonate holiday" may be considered after five years of treatment with alendronate, three with risedronate and three with zoledronic acid for up to five, one and three years, respectively. However, this decision should be individualized.

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EP215

Osteopetrosis vs Osteogenesis Imperfecta-is that so hard to distinquish? Case report

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Osteopetrosis and O.I. are both bone metabolic disorders with opposite features in terms of the metabolic turnover: while osteopetrozis has a low turnover and increased BMD due to the failure of osteoclasts to resorb bone, O.I. is well known as a high turnover disease with low BMD caused bt mutations in the COL1A1 and col COL1A2 genes that encode type 1 procollagen; yet, both condition, in spite of different mechanism, end up with increased ftracure prevalence. We report the case of a 46 year old women who presented for clinical and biological evaluation with a prior diagnisis of osteopetrosis. The anamnesis revealed that the diagnosis of osteopetrozis was set when the patient was 2 year old based on radiologycal features and multiple nontraumatic fractures suffered in childwhood; last fracture she recalls was at 20 year old and. Also she claims a familial history of osteogenesis imperfecta (maternal grandfather). The clinical examination revealed: Hight-125 cm; Weight-50 kg; BMI-32 kg/sm; blue sclerae, left leg orthosis, with unequal inferior limbs accompanied by difuze joint pain. Lab tests highlighted mild hypercholesterolemia, 25OHVitD insufficiency, low beta-crosslaps level, normal PTH, normal TSH and fT4. Near normal BMD. Dorsal and lombar spine X-ray:rarefaction of trabecular bone structure, suggesting a medium grade of demineralization.
Our O.I. final diagnosis proved to be quite difficult, taking into account the prior one of osteopetrosis, the history of pubertal fractures, familial history of O.I., growth impairment, lack of decreased BMD and increased bone turnover, mild VitD insufficiency. However, the importance of establishing the diagnosis, in our case, consists in choosing the optimal treatment; bisphosfonates are used in O.I. but not indicated in osteopetrosis. Our approach was to treat her with activ vit.D products since her actual fracture risk was not cinsidered increased.

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EP216

Osteonecrosis of the jaw and bilateral atypical femoral fracture both occurring during treatment of osteoporosis

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Background
Osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) are rare potential adverse effects of bisphosphonates and RANK-L inhibitor, occurring in 1 and 2 per 100,000 person-years, respectively. The pathogenic mechanisms of both conditions are known to be independent of each other. Here, we report both conditions sequentially occurring in the same patient.
Clinical case
An 81-year old, obese, diabetic, female was admitted due to hypertensive urgency and persistent jaw pain after tooth extraction. The patient has postmenopausal osteoporosis for fourteen years and was on intermittent unsupervised treatment with alendronate, denosumab and ibandronate. She had suffered sequential fracture of both femurs during the eighth and eleventh year of treatment. Both fractures were transverse, non-comminuted, at the proximal femoral shaft, which occurred after a minor trauma, and were managed with open reduction and internal fixation.
Upon presentation, the patient was noted with tenderness intraorally of tooth number 35 periapical region, no pus, no mandibular swelling. There was peripheral leukocytosis, elevated erythrocyte sedimentation rate, C-reactive protein. Panoramic with periapical view radiograph showed presence of bony sclerosis which represent a sequestrum compatible to chronic osteomyelitis in the molar area of the left hemi-mandible. Antibiotic infusion and excision and debridement of left posterior mandible were done. Necrotic bone with histopathologic finding of acute and chronic osteomyelitis with bacterial colonies was removed consistent with a diagnosis of osteonecrosis of the jaw. The patient was discharged on the fourth post-operative day and was placed on drug holiday.
Conclusion
ONJ and AFF can occur both in the same patient during prolonged treatment with bisphosphonates and RANK-L inhibitor and may suggest a common pathogenic mechanism. This case further emphasized that to avoid these grave consequences, bisphosphonates should be given in a limited period—five years, as recommended by experts.

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EP217

Clinical manifestations and treatment approach in osteogenesis imperfecta

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Objectives
Osteogenesis imperfecta (OI) is a group of genetic disorders that mainly affects the bones. The underlying mechanism is usually a disorder of connective tissue due to lack of type I collagen. Usually, the disease is due to mutations in the COL1A1 or COL1A2 genes. The disease is inherited in an autosomal dominant manner or occurs via a de novo mutation. There are eight types of the disease. Type I is the most common and the least sever type and is due to mutation in COL1A1 gene. We evaluated the clinical, laboratory and radiological profile of a woman with OI Type I who was treated over a 3-years period in our clinic.

Methods
A 61-year old female patient with family history of OI (son and sister) was treated in our clinic. She had history of multiple repeated fractures since 18 years old, short stature (138 cm), discoloration of the sclera, dental abnormalities, poor muscle tone in arms and legs, triangular face and skeletal deformities such as osteoporosis, spinal canal stenosis and kyphoscoliosis. Bone densitometry found severe osteoporosis. Treatment included zoledronic acid IV, vitamin D and calcium carbonate per os.
Results
After treatment with zoledronic acid the patient reported reduced bone pain and had stable bone mass (0.547 g/cm^2 before treatment and 0.535 g/cm^2 (femoral neck) after treatment) and increased T-score (femoral neck) (-3.3 SD before treatment and -2.88 SD after treatment, 3 years later).
Conclusion
Osteogenesis imperfecta is a heterogeneous disease and may have an indolent course. The diagnosis may be brought forward late in adulthood. The management includes the replacement of a calcium and vitamin D deficit and biphosphonates. Bisphosphonates remain effective and can increase bone mass, reduce bone pain and fractures.

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EP218

Special features of body composition and bone mineral metabolism in children with primary nephrotic syndrome

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Objective
To learn characteristics of biochemical markers of bone metabolism, parameters of bone mineral density (BMD) and fat component of body composition for early diagnosis of bone disorders in children with primary nephrotic syndrome (NS).
Material and methods
We compared data of laboratory investigations (phosphorus (P), total calcium (Ca), parathyroid hormone (PTH), and alkaline phosphatase (ALP)), protocols of dual-energy X-ray absorbtiometry of the axial skeleton and total body of 27 children with NS (group 1 – G1, age 9.71 ± 4.23 yrs) and 13 children of control group (G2, age 10.84 ± 3.84 yrs, $P = 0.48$). Group 1 was divided in subgroups G1a (relapse of NS, $n = 12$) and G1b (remission of NS, $n = 15$). Results were processed using SPSS17.
Results
G1 showed significantly lower age-matched z-score of BMD of lumbal spine (L1-4) (-0.71 ± 0.96) compared with G2 (0.08 ± 1.13, P = 0.036). One child of G1 had low bone density of lumbal spine with z-score -2.9. Total BMD was similar in the groups ($0.88 +/- 0.12$ g/cm^2 in G1 vs $0.91 +/- 0.19$ g/cm^2 in G2, $P = 0.39$). Fat component of body composition was increased in G1 ($38.33 \pm 11.30\%$) compared with G2 ($27.52 \pm 6.59\%$, $P = 0.0001$). Android/gynoid fat ratio was higher in G1 (0.90 ± 0.18) than in G2 ($0.70 +/- 0.20$, $P = 0.013$). Children of G1a showed lower level of Ca than control (2.24 ± 0.18 mmol/l vs 2.37 ± 0.07 mmol/l, $P = 0.009$). Concentration of Ca in G1b was similar to G2 ($2.37 \pm 0.07 +/-$ 0.13 vs 2.44 ± 0.15 mmol/l, $P = 0.71$) We didn't reveal significant difference in of PTH, P and ALP levels in the groups ($P > 0.05$).
Conclusions
Most children with NS showed normal BMD of lumbal spine, though it was lower than in healthy controls. Patients with NS had higher fat component of body composition with increased android type of its distribution.

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EP219

Bone densitometry of type 2 diabetics (about 290 patients)

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Introduction
The improvement of the survival of diabetics is accompanied by the emergence of bone fragility which can directly affect, at various levels, the various components of the bone tissue leading to quantitative and qualitative anomalies. The effects of type 2 diabetes on bone are complex because they are associated with the sometimes associated disorders of nutrition, weight and age. Densitometric studies in this context are quite contradictory. We proposed to study the bone status of type 2 diabetics.
Patients and methods
We carried out a cross-sectional study of 290 type 2 diabetics. These patients benefited from a measurement of bone mineral density (BMD) associated with PTH, vitamin D and calcemia.
The results
The average age of our population was 62.5 years. 38% of our patients were treated with insulin with a predominantly mixed regimen (basal insulin combined with oral treatments), with an average HBA1C of 7.05% for an average duration of diabetes of 8 years. Mean calcium in the general population was 2.33 mmol/l, with 2.36 mmol/l in males and 2.27 mmol/l in females, with no significant relationship between the two sexes ($P = 0.1370$).
5 patients had secondary hyperparathyroidism (> 65 pg/ml), the mean PTH in the study population was 46.82 ng/ml, higher in women than in men. 75.6% of patients had normal BMD, 23.3% had osteopenia, 24.3% were women, and 21% were men. The mean concentration of vitamin D is 13.93 ng/ml, with a maximum of 35 ng/ml and a minimum of 3 ng/ml. The mean concentration in males was 15, 14 ng/ml, significantly higher than that of females in the order of 11.91 ng/ml ($P < 0.1 = P = 0.0018$). A negative and significant correlation was found between the serum levels of 25OHD3 and those of PTH. This correlation persisted after adjusting for age and BMI. Our study did not find any significant relationship between PTH levels and BMD scores with ($P = 0.6091$).
Conclusion
According to data from the literature and despite normal BMD in patients with type 2 diabetes, it should be borne in mind that BMD alone is insufficient to assess bone status, management of other factors such as Diet rich in vitamin D and sufficient calcium intake is required.

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EP220

Effects of acromegaly on bone tissue mRNA levels relevant to bone metabolism

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Molecular basis of the bone disorders in patients with acromegaly are largely unknown.
Objective
To investigate gene expression profiles that regulate bone metabolism in bone tissue samples from patients with acromegaly.
Materials and Methods
Patients with clinically evident and biochemically proven active acromegaly and patients with hormonally inactive pituitary adenoma matched by age, sex and BMI were invited to participate. Bone samples were taken during transsphenoidal adenomectomy from the base of the sella-turcica, immediately placed in lysis buffer (QIAzol) and subjected to homogenization. Insulin-like growth factor 1 (IGF-1) was measured by an electrochemiluminescence assay on a Liaison. Total RNA isolation from bone tissue with on-cjlumn digestion of the genomic DNA was carried out with miRNeasy Mini Kit on the automatic station 'QIAcube'. Reverse transcription was carried out using a High-Capacity RNA-to-cDNA Kit. Gene expression analysis was performed by Real-Time PCR on StepOnePlus instrument with Custom TaqMan Array 48 Plus plates, TaqMan Advanced miRNA Assays.
Results
We enrolled 21 subjects (12 patients with acromegaly and 9 with hormonally inactive pituitary adenomas); 13 females and 8 males, the mean age was 38 years (confident interval (CI) 95% 33–43) mean BMI – 28 (CI95% 25–31) kg/m^2. There

were no significant difference within the groups. Mean IGF-1 in subjects with acromegaly – 785 (CI95% 527–1042) ng/ml. The expression of SOST 5,7 (CI95% 1,01–10,44, $P=0.022$), DKK1 7,97 (CI95% 4,4–11,54, $P<0.001$), BGLAP 1,51 (CI95% 0.82–2,19, $P<0.001$) was increased in subjects with acromegaly as compared to inactive pituitary adenoma. miRNA 199a-5p 0,37 (CI95% 0.06–0,68, $P=0.023$) was suppressed.

Conclusion

In spite of increased expression of Wnt signaling antagonist, bone formation is not suppressed in subjects with acromegaly. The suppression of miRNA might explain the predominant differentiation to the cartilage tissue.

Disclosures

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EP221

Osteoporosis and fractures in the real world setting

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Osteoporosis is a bone disease predisposing to bone fragility. Nowadays, the population is screened for osteoporosis and measures are taken for fracture prevention. Additionally, people are urged to have a diet rich in calcium, are given calcium supplements and are being treated for vitamin D deficiency. Moreover, osteoporosis treatment is administered. Therefore, the relationship between osteoporosis and fractures in the real world setting is very interesting.

The aim was to study the prevalence of fragility fractures in a cohort of patients being followed up and treated for osteoporosis in a center of excellence for the management of osteoporosis in Athens.

A cohort of 91 patients, 82 female and 9 male, aged 69.71 ± 1.09 years, who were followed up and treated as needed for osteoporosis in a center of excellence was studied. Bone mineral density was measured in the spine and the hip. The number of fractures having occurred in the cohort studied was recorded.

Bone mineral density in the spine as assessed by T score was -1.9 ± 0.11 (mean $\pm$ SEM) and in the left hip -2.6 ± 0.11. In the cohort of patients studied 19 patients (20.88%), 15 female and 4 male, suffered a fracture. The fractures recorded were 8 vertebral, 7 distal radius, 2 tarsal joint, 2 rib fractures and 1 fracture of the calcaneus. Within the cohort studied 2 patients had suffered two fractures, a distal radius and a vertebral and a rib and a vertebral fracture, respectively.

It appears that in the modern real world setting despite the measures taken for osteoporosis prevention and management in a cohort of patients being followed up within a center of excellence in Athens, fractures tend to occur especially in the female population. However, interestingly, within the cohort studied many patients with osteoporosis remained free of fracture at the point of time of the study.

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EP222

Is osteoporosis a curable disease?

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Osteoporosis may be a disease of unknown etiology, or a degenerative disorder in the context of aging. Nowadays, the availability of multiple forms of effective drug treatment for osteoporosis have raised the hypothesis that osteoporosis may be not only a treatable but moreover a curable disease.

The aim was to describe the case of a patient with osteoporosis who after treatment with alendronate for 6 years had osteopenia and remains in the state of osteopenia for a long period after drug cessation.

A patient, female, aged 65 years, postmenopausal, presented with osteoporosis, T score in the spine being -3.2. Alendronate 70 mg once weekly was administered along with calcium and vitamin D. The patient also had hypothyroidism on treatment with L-thyroxine, TSH levels being within the normal range.

Bone mineral density measurement was performed yearly while the patient was on treatment with alendronate, calcium and vitamin D. Six years later bone mineral density measurement in both the spine and the hip revealed osteopenia, T score being -1.3 and -1.1 in the spine and the hip, respectively. Alendronate was discontinued, while calcium and vitamin D were administered to the patient. The patient is being followed for her osteopenia yearly, T score in the hip being -1.1 five years after treatment cessation.

In the case presented alendronate appears to have had a long lasting beneficial effect on the bone in a patient with osteoporosis. The state of osteopenia appears to be stable in the presented patient. This case of persistent improvement of osteoporosis after long lasting treatment with alendronate raises the question of whether osteoporosis may be a curable disease, not being merely a manifestation of aging. This case raises the hopeful hypothesis that osteoporosis with the emergence of novel effective forms of therapy may be cured.

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Fractures at post-partum and lactation: common presentation of different clinical entities

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Introduction

Osteoporosis of pregnancy and postpartum is a rare clinical entity, which usually presents with back pain, due to spine fractures. We aimed to describe four different cases presenting with back pain and fractures post-partum, in who, with diverse underlying pathophysiology, recovery time and treatments used.

Case 1

A 32-year-old patient presented with intense back pain and difficulty in standing and walking, 2 weeks after delivery. She had hypercalcaemia, hyperphosphatemia and multiple vertebral fractures. Breast examination and mammography were inconclusive due to lactation. The diagnosis of metastatic breast cancer was made after a bone lesion biopsy. The patient received zolendronic acid and was referred to an oncologist.

Case 2

A 35 year-old patient, several weeks after a singleton pregnancy, presented with acute back pain**.** Imaging studies revealed an L2 fracture and laboratory assessment showed increased bone turnover markers and vitamin D deficiency. She received zolendronic acid and was started on vitamin D3 substitution. Her clinical course was uneventful.

Case 3

A 41 year-old lady was diagnosed with T12 and L3 vertebral fractures, while still breast-feeding. No secondary causes of osteoporosis were found. She received an 18-month course of teriparatide and Vitamin D3 supplementation. Six months after teriparatide discontinuation she presented with urinary tract lithiasis complicated by upper urinary tract infection.

Case 4

A 32-year-old patient presented with lumbar spine bone mineral density Z-score of -2.8, but no fractures, after her first pregnancy. She was treated with intranasal calcitonin and VitD3 supplementation. An improved BMD (Z-score $=-2.1$) was measured after 2 years. Her second pregnancy was uneventful.

Conclusions

Post-partum osteoporosis is a rare cause of bone pain during the puerperium. Fractures should be diagnosed early in order to avoid permanent incapacity. It is mandatory to look for and exclude secondary causes of osteoporosis including breast cancer and vitamin D deficiency.

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EP224

A multidisciplinary clinic for bone metabolism diseases; descriptive analysis of our experience in quiron salud malaga hospital

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Introduction
A multidisciplinary clinic has been developed to optimize the diagnosis and treatment of bone metabolism diseases. Initiated in March 2013, it is carried out simultaneously, once a week by an Endocrinologist and a Rheumatologist.
Objective
To describe the experience of this unit in the last 12 months.
Material and methods
Cross-sectional observational study. 235 patients were attended from December 2015 to December 2016. In the first visit, we carried out a medical record using a checklist form and impedancemetry. We requested a blood test with bone remodeling markers (CTX-I and P1NP), vitamin D, PTH, sex hormones and 24-hour urine with calciuria and phosphaturia, densitometry and dorsum-lumbar spine x-rays. In the following visit the results were evaluated and the team formed by both specialists agreed the protocol of action. Subsequently we studied treatment tolerance and analytical, radiographic and densitometric changes.
Results
97% were women with a mean age of 60 ± 9.7 years. Weight 66.3 ± 12.7 kg, height 158.2 ± 5.8 cm, BMI 26.6 ± 4.9 kg/m^2. Impedancemetry showed mean lean mass was 43.0 ± 5.9 kg and mean fat mass 23.3 ± 10.1 kg. 36.2% and 20% of the patients had a personal and family history of fracture, respectively. 15.2% patients had taken previous corticoid treatment; 9.5% had more than 2 falls in the last year. 5.7% were active smokers. 87.4% had menopause; early menopause in 13.4% and surgical menopause in 10.7%. 60% practiced more than 3 days of physical activity per week, 78.8% sunbathed more than 10 minutes a day and 36.2% took adequate dairy milk consumption. Among the digestive antecedents, 39% had gastroesophageal reflux and 16.2% hiatus hernia. 17.5% have had a vertebral fracture. In the densitometric data according to T-score they had osteoporosis 55.06%; Osteopenia 42.76% and normal 2.24%. The FRAX index was 4.3% for major fracture and 0.9% for hip fracture. Among the treatments received prior to the first consultation, 29.5% took bisphosphonates, 9.5% denosumab, 2.9% PTH. 37.5% calcium plus vitamin D.
Conclusions
A high percentage of patients received treatment before coming to the clinic. The most used was bisphosphonates. The aggregate management by two specialists in the multidisciplinary clinic is beneficial and improves the quality of care in our patients.

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EP225

Spontaneous recovery of BMD after surgical cure of Cushing's syndrome due to an adrenocortical adenoma: a 9-years follow-up

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A 33-year-old Belgian woman was referred in June 2006 to our Metabolic Bone Diseases Clinic for recent vertebral fractures. X-Rays showed a 3-level severe compression fractures with collapse of the superior endplates of D11, D12 and L1. DXA showed significantly decreased lumbar spine (LS) and femoral neck (FN) Z-scores, at -3.1 and -2.5, respectively.
She was complaining of severe back pain, muscle weakness, cognitive dysfunction, anxiety and irritability. Physical examination revealed moon-shaped face, ecchymosis, purple stretch marks on the breasts, arms, abdomen and thighs. Morning cortisol was normal but ACTH level was suppressed. Urinary free cortisol was elevated. A late-night salivary cortisol also elevated. Standard 2-day 2-mg dexamethasone suppression test showed no cortisol suppression. A loss of diurnal variation in ACTH and cortisol levels was also demonstrated. Cushing's syndrome was confirmed. Abdominal MRI showed a 3 cm left adrenal mass.
Osteoporosis was considered secondary to this endogenous hypercortisolism. Bone turnover markers (BTMs) and 24h urinary calcium excretion were elevated. Successful laparoscopic left adrenalectomy was performed in October 2006. Spontaneous BMD increase (LS Z-score -2.4) was observed already 2 months after surgery. Except for calcium and vitamin D supplementation, no bisphosphonate therapy was prescribed, given this impressive increase of BMD and because she was still premenopausal. X-Rays did not show any new vertebral fracture. BMD continued to increase. 24 months after surgery, densitometry showed 40% absolute increase in LS BMD and 16% in FN BMD, vs baseline. She reached normal BMD values at all sites 3 years following surgery.
After a 9-years follow-up (DXA and BTMs, yearly), complete spontaneous BMD recovery was confirmed (LS T-score $+1.2$ and FN T-score -0.3) with normal and stable BTMs.
Our case suggests no need for any antiresorptive therapy in severe osteoporosis due to cortisol-secreting adrenal adenoma after successful surgery, at least in premenopausal women.

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EP226

Cinacalcet for control of primary hyperparathyroidism: a single centre experience

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Although primary hyperparathyroidism (PHPT) is usually cured by surgery, some individuals are unable to undergo parathyroidectomy and are refractory to standard calcium lowering medical therapy. In such cases, targeted therapy with cinacalcet may be useful.
The aim of this study was to access the short-term efficacy of cinacalcet in lowering calcium (Ca^{2+}) levels in patients with PHPT unable to undergo parathyroidectomy and refractory to standard medical therapy.
Methods
Patients with PHPT refractory to standard medical treatment were treated with cinacalcet. Statistical analysis was carried out using the Wilcoxon test.
Results
Five patients (all female) with a median age of 76 years were included. The known duration of the PHPT was 60 months. The median follow-up of cinacalcet treatment was 12 months. Hypercalcemia related comorbidities were mental changes in 4, osteoporosis in 3 and kidney stones in 2 patients. Before medical treatment, baseline median (quartile 1 (Q1), Q3) serum PTH was 252 (159, 614) pg/ml (reference range 15–65) and serum Ca^{2+} was 11.7 (11.6, 12.65) mg/dl (reference range 8.1–10.2). After standard medical treatment, baseline median (quartile 1 (Q1), Q3) serum PTH was 222 (149, 304) pg/ml and serum Ca^{2+} was 11.9 (11.2, 12.6) mg/dl ($P > 0.05$). After the last stable dose of cinacalcet, median (quartile 1 (Q1), Q3) serum PTH was 190 (139, 361) pg/ml and serum Ca^{2+} was 10.1 (9.7, 12) mg/dl ($P = 0{,}005$). Serum Ca^{2+} normalized in 60% of patients. The median decrease of Ca^{2+} was 15.1% ($P = 0{,}005$) and of PTH was 14.4% ($P = 0{,}174$). Only one patient developed side effects (muscle spasms) without the need to stop cinacalcet.
Conclusions
These results demonstrate the efficacy and safety of cinacalcet in controlling hypercalcemia refractory to standard medical therapy.

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Bone remodeling markers predict bone loss in premenopausal women

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Aim
Bone turnover markers (BTMs) predict more rapid rates of bone loss. However, most of these studies have been carried out in postmenopausal women. Few prospective studies have examined the degradation marker C-terminal telopeptide of type I collagen (CTX) and the bone formation marker N-aminoterminal propeptide of type I collagen (P1NP) measured during the menopausal transition to predict the subsequent bone loss.
Methods
We performed a prospective cohort study including 72 healthy premenopausal women from de Endocrinology service at the Clinica Universidad de Navarra. Six women were lost in the follow-up and two were excluded because of treatment that affects bone. We measure demographic variables, CTX, P1NP and bone mineral density at baseline and five years later. SPSS 20.0 was used for statistical analysis. Differences between study groups were evaluated by Student's t test for normally and Mann-Whitney-U test for non-normally distributed variables.
Results
Mean age at baseline was 49.2 ± 0.3. After 5 years, there were no significant changes in baseline demographic characteristics (percentage of smokers, coffee intake, sun exposure and physical activity) although there was a significant increase in BMI ($P = 0.027$).
Five years later, 69% became menopausal, 48.4% (31) had normal bone, and 51.6% (33) had pathological bone (below the expected range for age and/or osteoporosis). There was a significant decrease in BMD at 5 years of follow-up compared to baseline (femoral neck 0.92 ± 0.1vs 0.87 ± 0.1 ($P = 0.000$), lumbar spine 1.17 ± 0.19 vs 1.08 ± 0.1 ($P = 0.000$) and a significant increase in BTMs P1NP (ng/ml) 37.22 ± 10 vs 52.23 ± 21 ($P = 0.000$) and CTX (ng/ml) 0.245 ± 0.125 vs 0.441 ± 0.233 ($P = 0.000$). Increased levels of P1NP and s-CTX in the premenopausal group at baseline associated with pathological bone five years later ($P < 0.001$ and $P < 0.001$, respectively).
Conclusion
Our data suggest that measurement of CTX and P1NP in premenopausal women detects those patients who will suffer bone loss five years later.

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Bone mineral density in hospital male physicians over the age of 65

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Background
Hospital physicians are indoor workers, with higher prevalence of vitamin D deficiency as compared to community-based physicians. The correlation between vitamin D deficiency and osteoporosis later in life has not been fully studied, and bone mineral density (BMD) in elderly hospital physicians has not been systematically examined.
Methods
A cross-sectional study measuring BMD in hospital male physicians aged 65 and older was carried out. BMD was measured at the hip, spine and distal forearm. FRAX analysis with BMD was performed, using the IOF recommended FRAX cut-offs for treatment (10-year probability of hip fracture ≥3% and 10-year probability of major osteoporotic fracture ≥20%).
Results
51 male physicians, employees and pensioners, participated in our study. The mean age was 71 years (median 69 years; range 65–86), all of them naive to specific treatment for osteoporosis. 14/51(27%) had osteoporosis, 7 of them defined only by distal forearm examination. 29 (56%) had osteopenia, 4 of them defined only by distal forearm examination. According to their FRAX score, 9 of the osteopenic examinees had high risk of major osteoporotic fracture and/or hip fracture.
Conclusion
In elderly hospital-based male physicians, the prevalence of osteoporosis is higher than expected. After adding the FRAX score results, 45% of the physicians would require specific treatment for fracture prevention, according to customary international clinical guidelines. Using only hip and spine BMD, 31% would require treatment. Based on our data we suggest screening elderly physicians for osteoporosis.

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Association between bone mineral density and muscle strength in patients with Turner syndrome, after consideration of selected hormonal and metabolic parameters

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Turner syndrome (TS), resulting from complete or partial loss of X chromosome, occurs in 1 per 2000-2500 liveborn female neonates. Most patients with TS, especially those untreated with growth hormone, present with osteoporosis or osteopenia, and are at increased risk of bone fractures. Available evidence suggests that depletion of bone mass may be associated with inadequate level of physical activity, and consequently, with too low muscle mass and strength. The aim of the study was to analyse an association between muscle strength and bone mineral density in patients with TS, after consideration of selected hormonal and metabolic factors. The study included 52 subjects (age 28–45 years), among them 32 women with TS (45,X karyotype; Group A) and 20 controls (Group K). The list of analysed variables included body height, body weight, BMI, bone mineral density (BMD L1-4 and BMD Total), total body fat (BF) and visceral adipose tissue (VAT) volumes determined by means of DXA, hand grip strength measured with a manual dynamometer, and laboratory parameters: TSH, FT4, FSH, oestradiol, testosterone, DHEA-SO4, ACTH, cortisol, PTH, vitamin D3 concentrations, lipidogram, levels of glucose and insulin during OGTT. Patients from Group A presented with significantly lower left ($P = 0.001$) and right handgrip strength ($P < 0.000$), lower BMD ($P < 0.000$), lower concentrations of testosterone ($P < 0.000$) and DHEA-SO4 ($P = 0.006$), larger VAT volumes ($P = 0.005$), higher BMI ($P = 0.05$), higher levels of insulin ($P = 0.026$) and FSH ($P = 0.000$). The study groups did not differ in terms of their TSH, fT4, ACTH and cortisol concentrations, and the only significant difference in lipidogram pertained to triglyceride level, higher in Group A ($P = 0.032$). Right handgrip strength in Group A correlated significantly with BMD L1-4 ($r = 0.1318$, $P = 0.0486$), VAT volume ($r = 0.1478$, $P = 0.0360$) and BMD Total ($r = 0.1921$, $P = 0.0154$). These findings suggest that handgrip strength may constitute a predictor of osteoporosis in patients with TS.

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Volumes of visceral adipose tissue, gynoid and android fat as predictors of reduced bone mineral density in women with menstrual disorders

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Disorders of bone mineralization observed in women with ovarian insufficiency are unlikely a simple function of decreased concentration of oestrogens. Published evidence suggests that adipose tissue is a central component within the complex system of metabolic and hormonal interactions responsible for adequate mineralization of the bone. However, to the best of our knowledge, the composite effects of specific substances synthesized within adipose tissue from various anatomical compartments, ovarian hormones and insulin on bone turnover, have not been a subject of a complex analysis in women with menstrual disorders. Therefore, the aim of this retrospective study was to verify if volume and distribution of adipose tissue may predict bone loss in this group. The study included 293 Caucasian women (mean age 26.7 ± 4.4 years) with at least 6-month history of secondary amenorrhea. Based on T-score values for bone mineral density (BMD) in lumbar spine, the study subjects were divided into two groups, with T-scores below −0.5 and at least 0.5. Univariate logistic regression analysis showed that lower bone mineral density (as shown by T-score below −0.5) was associated with larger volumes of gynoid (odds ratio, OR = 7.45), android (OR = 3.03) and visceral adipose tissue (OR = 1.55), as well as with higher values of body mass index (BMI, OR = 1.17), fasting concentration of insulin (OR = 1.08) and body weight (OR = 1.06). However, none of these variables turned out to be an independent predictor of BMD deficiency on multivariate analysis. These findings imply that excessive volume of adipose tissue, irrespective of distribution thereof, is a strong determinant of reduced BMD in women with ovarian insufficiency. The lack of region-specific effects of adipose tissue volume on BMD is probably associated with the influence of ovarian insufficiency on

systemic metabolism and endocrine processes, in particular with the development of insulin resistance.

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Effect of chronic atrophic gastritis on bone mineral density of Korean women

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Hydrochloric acid has been demonstrated to be important for the absorption of calcium and the bone loss is often seen in human after total gastrectomy. The aim of our study was to document the change of calcium and bone metabolism in the patients with decreased capacity of gastric acid secretion like chronic atrophic gastritis.

The study sample consisted of chronic atrophic gastritis group and control group. Chronic atrophic gastritis group was 20 post-menopausal females (age: 60.3 ± 5.1 yr) who was confirmed by gastroscopic biopsy, demonstrating atrophic change of gastric mucosal secretory tissue. Control group had 21 healthy females (age: 58.7 ± 6.5 yr) with normal gastroscopic biopsy results. Gastric pH, serum levels of calcium, phosphorus, total alkaline phosphatase, intact PTH, and bone mineral density (Delphi, Hologic, USA) were monitored in all the patients in both group before medication. There were no significant differences of gastric pH (3.9 ± 0.6 vs 3.3 ± 1.0, $P > 0.05$), calcium (8.9 ± 0.9 vs 8.8 ± 1.4 mg/dl, $P > 0.05$), phosphorus (3.2 ± 1.5 vs 3.5 ± 0.9 mg/dl, $P > 0.05$), total alkaline phosphatase (72.5 ± 24.5 vs 60.3 ± 22.4 U/l, $P > 0.05$) and intact PTH (29.3 ± 5.1 vs 27.2 ± 3.8 pg/ml, $P > 0.05$) between chronic atrophic gastritis group and control group. Bone mineral density showed decreased average value in atrophic gastritis group comparing control group (0.78 ± 0.27 vs 0.85 ± 0.31 g/cm^2, $P = 0.09$).

In conclusion, chronic atrophic gastritis which have lower capacity of gastric acid secretion may cause decrease of bone mineral density. And this mechanism may be one of the pathogenesis of senile osteoporosis.

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May serotonin metabolism polymorphisms 5HTTVNTR and 5HT$_{2A}$ have a clinical impact in osteoporosis development?

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Objectives

To study the association of serotonin transporter gene (SLC6A4) polymorphism 5HTTVNTR and serotonin receptor 2A polymorphism 5HT2A_T102C with bone mineral density and metabolic parameters of bone remodelling.

Materials and methods

BMD (g/cm2) was measured by DEXA in 105 post-menopausal women: 35 with normal BMD (age = 58.30 ± 1.33 years; BMI = 28.18 [19.13-39.87] kg/m^2) and 70 with osteoporosis (age = 68.30 ± 1.09 years; BMI = 28.90 [20.78-43.86] kg/m^2). Metabolic bone remodelling parameters were analysed: LDL, HDL, total cholesterol, $HOMA_{IR}$, insulin, glycaemia, alkaline phosphatase, osteocalcin and parathormone. It was determined the platelet and plasma serotonin concentrations by ELISA. 5HTTVNTR was evaluated by PCR and the 5HT$_{2A}$_T102C by PCR-RFLP. Statistical analysis by SPSS 21.0.

Results

In osteoporosis, we found increased osteocalcin ($P = 0.030$) and plasma 5HT concentration ($P = 0.012$) and decreased insulin ($P = 0.023$) and total cholesterol ($P = 0.027$). In women with normal BMD, we found an association between genotype 10/10 of 5HTTVNTR and decreased osteocalcin ($P = 0.035$). and between genotype CC of 5HT$_{2A}$ and decreased HDL ($P = 0.029$). Within this group, we also found inverse correlations between HDL and alkaline phosphatase ($P = 0.030$) and $HOMA_{IR}$ ($P = 0.018$). In women with osteoporosis, we found direct correlations between glycaemia and osteocalcin ($P = 0.017$) and HDL ($P = 0.049$).

Conclusion

In normal BMD, 5HTTVNTR and 5HT2A_T102C polymorphisms appear to modulate directly or indirectly some metabolic parameters associated with bone remodelling. These polymorphisms seem to have no effect in women with osteoporosis suggesting that they may play a relevant role in the susceptibility to osteoporosis development by modulating metabolic bone remodelling parameters.

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The effect of mechanical assisted squat exercise on pulmonary function, muscle mass and function with or without sarcopenia

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Introduction

Sarcopenia is a geriatric syndrome that causes age-related changes to muscle mass and function. Lung function is reduced in elderly patients with sarcopenia. We explored whether a mechanically assisted squat exercise improved muscle function and mass and pulmonary function in community-dwelling elderly women with or without sarcopenia.

Methods

Participants were recruited via posters or the websites of regional health centers. In total, 76 community-dwelling elderly subjects (aged >60 years) were screened. We finally included 47 subjects in this prospective study. They were randomly assigned to exercise or non-exercise group as a ratio of 2:1. We measured lung function, knee extensor strength, hand grip strength, and the body composition before and after 6 weeks of mechanically assisted squat exercises (3 days a week, 30 min per day).

Results

Subjects with sarcopenia had poor hand grip strength and knee extensor strength. Their lung function parameters [including vital capacity, forced expiratory volume in 1 s (FEV1), and forced vital capacity (FVC)] were lower than those of controls. After 6 weeks of squat exercises, the hand grip strength and knee extensor strength increased significantly in both the sarcopenia and control groups. Appendicular skeletal muscle mass was increased in exercise group only in without sarcopenia group ($P = 0.013$). Leg fat mass was significantly decreased in both sarcopenia and non-sarcopenic group. However, leg lean mass was significantly increased only in non-sarcopenic group after exercise. The FVC (L) and FVC (%) increased significantly only in the sarcopenia group ($P = 0.019$ and $P = 0.041$, respectively), but not in the control group.

Conclusion

Squat exercises improved not only lower extremity functionality, but also upper extremity functionality, including hand grip strength. Muscle mass was significantly increased in without sarcopenia after exercise. The FVC increased in the sarcopenia group. Thus, squat exercises may improve lung function in patients with sarcopenia.

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Beta-2 adrenergic receptor (ADRB2) gene polymorphism Arg16Gly as risk factor for osteoporosis

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Objectives
To study the association of Beta-2 adrenergic receptor (ADRB2) gene polymorphism Arg16Gly with bone mineral density and metabolic parameters of bone remodelling.
Materials and methods
BMD (g/cm^2) was measured by DEXA in 105 post-menopausal women: 35 with normal BMD (age = 58.30 ± 1.33 years; BMI = 28.18 [19.13-39.87] kg/m^2) and 70 with osteoporosis (age = 68.30 ± 1.09 years; BMI = 28.90 [20.78-43.86] kg/m^2). Metabolic bone remodelling parameters were analysed: LDL, HDL, total cholesterol, $HOMA_{IR}$, insulin, glycaemia, alkaline phosphatase, osteocalcin and parathormone. Arg16Gly polymorphism was evaluated by PCR-RFLP. Statistical analysis by SPSS 21.0. Statistical significance for $P < 0.05$.
Results
We found association between Arg16Gly polymorphism and osteoporosis with an increase of homozygous Gly/Gly in women with osteoporosis ($P = 0.009$). They showed a higher risk for the development of osteoporosis (OR = 6.517; CI95% [1.663-25.539]). In osteoporosis, we found increased osteocalcin ($P = 0.030$) and decreased insulin ($P = 0.023$) and total cholesterol ($P = 0.027$). In women with normal BMD, we found an association between genotype carriers of allele Arg (Arg/Arg + Arg/Gly) and decreased total cholesterol ($P = 0.018$). We also found an association between carriers of allele Gly (Arg/Gly + Gly/Gly) and decreased of glycaemia ($P = 0.010$). Within women with normal BMD, we also found inverse correlations between HDL and alkaline phosphatase ($P = 0.030$) and $HOMA_{IR}$ ($P = 0.018$). In women with osteoporosis, we found direct correlations between glycaemia and osteocalcin ($P = 0.017$) and HDL ($P = 0.049$).
Conclusion
Arg6Gly polymorphism of ADRB2 gene is associated with a higher risk for the development of osteoporosis. This polymorphism also appears to modulate directly or indirectly some metabolic parameters associated with bone remodelling.

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EP235

Bone histomorphometry and bone marrow adipocytes in premenopausal women with type 2 diabetes

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Few studies have evaluated bone histomorphometry in type 2 diabetic patients (DM2) and none has established if the disease control plays a role on bone morphology and bone marrow adipocytes. The aim of this study is to present preliminary data on bone microstructure, bone formation rate and bone marrow adipocytes in premenopausal women with DM2 with different levels of glucose control. Bone biopsy, followed by tetracycline labelling, was obtained for analysis of static and dynamic parameters of bone histomorphometry and volume of bone marrow adipocytes. To date, 12 bone biopsies and 6 histomorphometry analysis were performed in a group of women with mean age of 40.9 ± 6.0 yrs, mean duration of DM2 of 6.8 ± 2.6 years and median glycosylated haemoglobin of 8,1% (range 6.5–12.3). Initial results have shown a normal bone volume, reduced bone formation and an increase in adipocytes content in comparison to normal premenopausal women values at the literature. Our preliminary results suggest that bone morphology and bone marrow adipocytes content is altered in premenopausal women with DM2.

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Differences in bone strength and metabolic parameters according to the presence of hyperadiponectinemia and obesity in Korean adults: The KoGES- ARIRANG study

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Adiponectin has been thought to exert important influences in energy homeostasis and insulin signalling pathway. Some obese individuals showed paradoxical hyperadiponectine-mia (HA), however, the effect of HA on bone metabolism has not been fully clarified.
This study aimed to evaluate bone strength and metabolic parameters according to the presence of HA and obesity in Korean adults. A total of 9,172 adults (59.4% women) aged 40–70 years assessed in the Korean Genomic Rural Cohort Study from 2005 to 2008 were examined. HA was defined as the levels of higher than or equal to the upper tertile among metabolically healthy subjects with a bone mass index (BMI) less than 23 kg/m^2.
Moreover, obesity was defined as a BMI of more than or equal to 25 kg/m^2. The serum con-centrations of adiponecti-n were measured by radioimmunoassay. In addition, bone status was assessed using the calcaneal quantitative ultrasound method. Obese subjects and those who have HA accounted for 40.3% and 15.7%, respectively; about twenty percent of the non-obese and 9.5% of the obese had HA. Although most of metabolic parameters such as fasting glucose and lipid profiles were significantly better in the HA group compared with the non-HA group, bone stiffness index (BSI) in the former was lower in the latter. In both the non-obese and obese groups, individuals with HA had lower waist circumference and BSI. Moreover, obese subjects without HA showed the highest BSI levels among the group-s, which was especially prominent in women. Our results suggest that bone strength in obese individuals may be more negatively affected by high adiponectin levels. Further studies are necessary to confirm the effects of adiponectin on bone health in subjects with obesity.

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EP237

Do the surgical outcomes change if the surgeon accompanies the endocrinologist during the preoperative ultrasonography examination?

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Introduction
Parathyroid surgical therapy differs because the glands are small and of variable number and location. Although localization studies have improved greatly, we may not reliably determine the number and location of all diseased glands preoperatively. Ultrasonography (US) is the most widely used imaging method. In this study, we aimed to demonstrate how the surgical outcomes change when the surgeon accompanies the endocrinologist during preoperative ultrasonography examination.
Methods
This prospective study included 50 patients with primary hyperparathyroidism (PHPT) who underwent a minimally invasive parathyroid adenomectomy under local anaesthesia at our institution from January 2014 to December 2015. The patients were divided in two groups. In group A, all patients underwent neck US performed by an experienced endocrinologist and the surgeon on the day of operation and the location of the lesion was specified by the surgeon. Group B patients were operated according to the previous US performed by the endocrinologist only.
Results
There were 25 patients in Group A and 25 patients in Group B. The two groups were similar in regard to demographical features, biochemical and hormonal parameters. Postoperative parathyroid hormone (PTH), calcium and phosphorus levels didn't differ between the groups. In group A operation duration was significantly shorter compared to Group B (25.7 min vs 45 min, $P = 0.00$).

Conclusion
Preoperative detection of hyperactive parathyroid glands is useful for minimizing the extent of surgical intervention, reducing operation time and decreasing the risk of perioperative complication.

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EP238

Teriparatide discontinuation in a patient with post surgical hypoparathyroidism: a clinical challenge

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Context
Teriparatide may represent a possible treatment for hypoparathyroidism when oral supplementation with calcium and calcitriol fail to maintain adequate serum calcium level (SCL). The switch from teriparitide to oral calcium and calcitriol could be challenging and there is no consensus for clinical management.
Case presentation
A 50-year-old man was admitted at our Department for teriparatide discontinuation. Three years before admission, the patient underwent total thyroidectomy for a multinodular goiter. Three months after thyroidectomy, the patient was admitted to the intensive care unit for the onset of symptomatic hypocalcemia. Laboratory exams were consistent with hypocalcemia related to post-surgical hypoparathyroidism. The patient was discharged with calcium carbonate and calcitriol therapy but in the following months the patient was re-admitted several times to the E.R. for the recurrence of symptomatic hypocalcemia. Therefore in addition to the oral therapy, teriparatide was introduced. After two years of treatment, teriparatide has been discontinued in accordance to the national drug administration (AIFA) authorizing regulations. At the admission, the physical examination was normal. Laboratory exams were notable for low SCL and an elevated serum TSH level despite high dose of Levothyroxine supplementation (250 mcg/d). After teriparatide discontinuation SCL progressively decreased (6,5 mg/dl) with the onset symptoms of hypocalcemia, despite high doses of calcium carbonate and calcitriol. Further investigations revealed an atrophic autoimmune gastritis, confirmed at gastroscopy. It was decided to switch from calcium carbonate to calcium citrate and to modify patient's diet. SCL slowly increased up to 8,6 mg/dl so that the patient could be discharged. In six months, no symptomatic hypocalcemia occurred and the SCL were stable with oral therapy.
Conclusions
Teriparatide discontinuation in patients treated for hypoparathyroidism is challenging and clinically does not differ from "hungry bone syndrome" after parathyroidectomy. Furthermore calcium citrate could be an alternative to calcium carbonate in patients with achlorhydria.

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EP239

Endocrine disorders in treatment-naïve male patients with HIV infection

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Objective
To investigate endocrine disorders concerning bone metabolism, thyroid and gonadal axis in treatment–naïve HIV-infected male patients.
Subjects and methods
We studied 70 male, treatment-naïve patients (stage A = 60, stage B = 10) from the Infectious Diseases Unit of our Hospital. Anthropometric indices were measured and BMI was calculated for each participant. Blood samples were obtained after an overnight fasting for the evaluation of thyroid hormones, 25OHD3, gonadotropins, total testosterone, sex hormone binding globulin (SHBG) levels. Free Androgen Index (FAI) and bioavailable testosterone (BAT) were calculated. Bone mineral density (BMD) in the lumbar spine and adipose tissue percentage (FMR) was measured with DEXA. SPSS 16.0 was used for statistical data processing.
Results
Patients were 33.7 ± 8.9 years old (mean $\pm$ S.D.), BMI was 24.6 ± 5.2 kg/m^2, CD4+ were 475 c/μl (24–1,476) and viral load was 38 600 cp/ml (927–422 000). Four patients (6%) presented with low testosterone levels (hypogonadotropic hypogonadism) and one with newly diagnosed subclinical hypothyroidism requiring therapy. Significant reduction of BMD was observed in 26 patients (37%) from which 22 had osteopenia (Z score -1 to -2.5) and four had osteoporosis (Z score < -2.5). Reduced BMD correlated positively with low BMI ($P < 0.01$), while no correlation was found with viral load, CD4+, smoking, 25OHD3 and gonadal hormones' concentrations ($P > 0.05$).
Conclusion
In treatment – naïve HIV-infected male patients, the most frequently observed endocrine disorder is reduced BMD, which does not seem to correlate with HIV infection markers. In patients with low BMI, measurement of BMD would be helpful for early diagnosis of reduced bone mass and the prevention of further loss by using the most suitable antiretroviral therapy.

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EP240

Trabecular bone score is negatively associated with bone resorbtion markers in patients with primary hyperparathyroidism

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Objectives
Mean TBS (Trabecular Bone Score) values are generally lower in PHPT (primary hyperparathyroidism) patients than controls. The aim of this study was to assess TBS from spine DXA images in patients with PHPT and look at its correlates.
Methods
This was a cross-sectional study conducted in an osteoporosis referral center. One hundred and thirty six patients with PHPT were selected from our database (2010–2016) if they had a valid LS DXA scan. The patients were both females (20% premenopausal) and males (12%), mean age 59.4 yrs (range 16–83), with both asymptomatic and symptomatic PHPT (mean PTH 226 pg/ml, mean serum calcium 11.3 mg/dl); a third of the patients were severely vitamin D deficient (< 10 ng/ml). TBS indices were derived from LS-DXA images and cutoff points used in term of fracture risk were those previously reported.
Results
Mean TBS values of the group was 1.26 ± 0.12. TBS Z-score was negatively and significantly correlated with serum PTH, serum Calcium, Osteocalcin ($r = -0.275$, $P = 0.005$) and mostly C-telopeptide ($r = -0.314$, $P = 0.001$). Actually TBS values and both T and Z scores correlated negatively and significantly with serum C-telopeptide. TBS was in the partially degraded range but did not differ by vitamin D status, even when compared with severely deficient patients (35 pts, mean TBS 1.25). PTH correlated negatively with 25OHD and TBS correlated strongly ($r = 0.536$) with aBMD.
Conclusion
We observed a good and negative correlation between TBS and serum C-telopeptide which favor the notion that TBS might reflect degraded microarchitecture.

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EP241

Normocalcemic primary hyperparathyroidism (NPH)

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Normocalcemic primary hyperparathyroidism (NPH) is characterized by normal total and ionized serum calcium concentrations and consistently elevated PTH levels. These patients have no obvious causes for secondary elevations of PTH, such as renal disease, vitamin D deficiency or malnutrition. The group consisted

of 22 postmenopausal women, six premenopausal women, and two men, aged 58 ± 2 years (range 31–77) investigated between 2011 and 2016.
Results
All subjects had normal renal function and 25-hydroxyvitamin D levels > 20 ng/ml (80% had levels > 30 ng/ml); none used thiazide diuretics or lithium or demonstrated significant hypercalciuria. The reasons for referral included elevated PTH discovered during the evaluation of low bone mass ($n = 22$), recent fragility fracture ($n = 2$), nephrolithiasis ($n = 6$).
At the time of diagnosis, 70% had osteoporosis by BMD (measured at the lumbar spine, hip or distal one-third of the non-dominant radius), 6.6% had documented fragility fractures, and 20% had nephrolithiasis. PTH was elevated, while albumin-corrected serum calcium, serum phosphorus, alkaline phosphatase activity, and urinary calcium, were all in the mid-normal range.
Nine patients with positive localization studies (cervical ultrasonography, technetium 99 m sestamibi scanning) underwent successful parathyroidectomy, with operative findings of a single adenoma or hyperplasia. Twenty one patients who did not undergo surgery were followed for 3.1 ± 0.3 years (annual serum calcium, PTH and bone mineral density determinations). Hypercalcemia developed in 19% of these individuals. Two of the patients who developed hypercalcemia and three additional patients with persistently normal serum calcium levels underwent successful parathyroidectomy. Fourteen patients were without significant change in serum calcium or development of hypercalcemia, PTH continued to remain elevated.

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EP242

Secondary hyperparathyroidism and its implication on bone mineral density in patients with different stages of chronic kidney disease

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Secondary (SHPT) is frequent in patients with chronic kidney disease and can predispose patients to low bone mineral density (BMD). Necessity of BMD assessment in such patients is controversial.
The aim was to analyze BMD and PTH secretion in patients with different stages of chronic kidney disease. We examined 311 patients, 161 f, 150 m; age 49.2 ± 14.4 yrs; 190 patients are on continuous dialysis due to end-stage chronic kidney disease (mean dialysis duration 4.9 ± 3.9 yrs), 121 patients with CKD 1–5 not on dialysis. Serum PTH was measured and BMD was estimated by DEXA in lumbar spine and in proximal part of femur, T score < -2.5 was classified as low BMD. Median PTH level was 314.1 pg/ml (119.2; 770.7) in dialysis patients and 149.0 (65.2; 259.7) in patients with CKD 1–5 not on dialysis ($P < 0.05$). PTH was above upper limit of the reference range in all dialysis patients and in 51.6% of them was 300 pg/ml and higher. SHPT was revealed in all patients with CKD 4–5, in 38.1% of patients with CKD 3; in 25.3% of those with CKD 1–2. In dialysis patients low BMD was revealed in 24.7% of cases, significant implication of PTH level > 300 pg/ml on low BMD development was revealed. In patients with CKD 1–2 there were no cases of low BMD, with CKD 3–19.1%, with CKD 4 and CKD 5–33.3% ($P < 0.05$). Prevalence of low BMD was 10.7% in non-dialysis patients with normal PTH and 29.7% – with SHPT ($P < 0.05$).
We can assume that frequency of low BMD is 25% and higher in patients with CKD 4–5 and secondary hyperparathyroidism significantly implicates on its development. Future investigation is required to evaluate clinical implication of DEXA in patients with SHPT for fracture risk assessment.

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EP243

Impact of vitamin D on the bone quality assessed by trabecular bone score in men

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Trabecular bone score (TBS) is a recent noninvasive analytical method, based upon DXA images, related to bone microarchitecture or bone quality; together, TBS and DXA may evidence bone strength. Falls and osteoporotic fractures increase with ageing, while both BMD and vitamin D levels slowly decline. Data about the influence of vitamin D on the TBS are scarce.
Aim
To evaluate the influence of the blood vitamin D levels on the TBS in normal men.
Material and methods
The lumbar spine BMD (g/cm^2), and TBS (obtained from DXA scans) were evaluated in a group of normal men more than 40 years old. Fasting blood was collected for osteocalcin, 25(OH)D and iPTH measurements. This group was divided in normal, insufficiency and deficiency vitamin D groups (ES Guidelines) and also in normal BMD, low BMD and osteoporosis groups. Total body fat and lean masses were also assessed by DXA. Adequate statistical tests were used (statistical significance $P < 0.05$).
Results
The mean (± S.D.) BMD and TBS of the vitamin D groups are shown in Table 1. Men of the deficiency vitamin D group were the heaviest and had the lowest TBS. Significant relations were detected between the blood 25(OH)D *vs*. TBS, *vs*. weight and *vs*. total fat mass but not *vs*. BMD.
Conclusions
Blood 25(OH)D levels may play an important role on the bone microarchitecture (by TBS) in vitamin D deficient men, as they have worse bone quality. These data suggest that further studies are needed on larger cohort of men and it might be worth to investigate also elderly men with osteomalacia.

Table 1

Groups Variable	Normal (49.3%)	Insufficiency (37.7%)	Deficiency (13.0%)	*P*
TBS L_1-L_4	1.044 (±0.14)	1.087 (±0.16)	1.079(±0.15)	0.0071
L_1-L_4 BMD g/cm^2	1.294 (±0.12)	1.323 (±0.12)	1.434 (±0.07)	NSD

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EP244

Neutrophil lymphocyte ratio in 6 month teriparatide therapy of osteoporosis

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Aim
Low BMD and atherosclerosis may share similar underlying biological mechanisms including higher serum phosphate and inflammation. Neutrophil-lymphocyte ratio (NLR) as a simple marker of inflammation. There are scarce data indicating improved atherosclerosis and cardiovascular events with biphosphonate and teriparatide therapy. We aimed to evaluate NLR before and after 6 months of teriparatide therapy in patients with severe established osteoporosis.
Methods and materials
Electronic data of 53 (49 female, four male) patients with severe osteoporosis and history of fracture of femur neck and/or lumbar spine were evaluated. None of them were previously diagnosed with rheumatoid arthritis, DM, and secondary osteoporosis. Sixteen had with HT and/or other cardiovascular disease.
Results
Mean age was 74 ± 9 years, baseline 25 OH vitamin D level 25.6 ± 17.6 ng/ml, baseline NLR 2.22 ± 0.89, 25 OH vitamin D level at 6th month 27.8 ± 13.4 ng/ml, NLR at 6th month 2.10 ± 0.96.
Mean baseline and 6th month measurements of NLR, 25 OH vitamin D, parathormone, ALP, ESR, and phosphorus were similar in patients with and without cardiovascular disease. NLR did not change significantly after 6 months of teriparatide therapy.
Conclusion
NLR does not change in short term teriparatide therapy and association between osteoporosis and cardiovascular disease cannot be settled in advanced age.

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EP245

Analysis of DXA scans of males performed in clinical center of vojvodina

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The prevalence of osteoporosis among men is not well-documented. The aim of this cross-sectional study is to analyze results of DXA scans preformed in males in Clinical center of Vojvodina between years 2009 and 2016. Form the total of 2006 fist DXA scans performed in 7 years period there was 14.8% of males. DXA scan was indicated by the rheumatologists, internists and endocrinologists predominantly for suspected secondary causes of osteoporosis. We divided male subjects in groups by the age of life. In the group from 20 to 50 years of life there was 68 subjects with average BMI 26.5 ± 6.30 kg/m^2 with average T score in L1–L4 -0.8 ± 1.4 S.D., bone mineral density (BMD) was 1.152 ± 0.184 g/cm^2, and femur neck -0.71 ± 1.2 S.D., BMD 0.959 ± 0.176 g/cm^2, 9 subjects had *Z* score < 2 S.D. In the group form 50 to 70 year of life (average 60.38 ± 4.82, BMI 27.93 ± 5.31 kg/m^2) there was 174 subjects with T score L1–4: -0.82 ± 1.93 S.D., BMD 1.120 ± 0.231 g/cm^2, left femur neck: -1.41 ± 1.36 S.D., BMD 0.887 ± 0.176 g/cm^2. 56 had osteopenia and 49 had osteoporosis. Group above 70 years of life (88 maximum, average 75.6 ± 3.96, BMI 25.17 ± 4.16 kg/m^2) had 55 subjects from whom 22 had osteopenia and 23 osteoporosis and average T score L1–L4 was: -0.85 ± 2.12 S.D., BMD 1.115 ± 0.255 g/cm^2, left femur neck: -1.84 ± 1.25 S.D., BMD 0.829 ± 0.161 g/cm^2. Lower values of *T* score and BMD were measured on left femur neck in older groups. There was very high percentage of osteoporosis and osteopenia in the oldest groups of males although all males referred to DXA scan were suspected to have osteoporosis.

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EP246

Biological assessment and causes of secondary osteoporosis

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Secondary osteoporosis accounts for 10–20% of the causes of osteoporosis in menopausal women. The search for a possible etiology should not be neglected before considering the therapeutic management of any osteoporosis. There is no consensus on the first-line biological tests to be prescribed.

Goal

Determine biological abnormalities in postmenopausal women with osteoporosis.

Patients/methods

Postmenopausal women are enrolled, the mean age is 65.5 ± 8.9 years. 305 patients are classified as osteoporotic according to the WHO criteria (*T*-score ≤ 2.5). NFS, VS, CRP, serum calcium, phosphoric acid, 24-hour calcium, total alkaline phosphatase, parathyroid hormone (PTH), serum protein electrophoresis, serum creatinine, liver function test, fasting blood glucose.

Results

6.2% (19/305) patients had an abnormality.

Distribution of anomalies

Monoclonal gammopathy five cases: two myeloma, two MGUS, one unlabeled case

- HPT I: seven cases (two parathyroid adenomas confirmed by the anapath)
- 1 cases rheumatoid arthritis
- diabetes type two unknown: six cases, one case of intolerance to carbohydrates

Discussion/conclusion

In the presence of a low BMD, it is recommended that a diagnostic survey should be carried out, including physical examination, clinical examination and routine biological examinations, in order to eliminate malignant or metabolic osteopathy and to investigate the causes of secondary osteoporosis. In our study targeting a population of postmenopausal osteoporotic women followed in consultation, the discovery by biological examination of a new condition that can lead to bone demineralization is quite common.

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Calcium & Vitamin D Metabolism

EP247

Management with Cinacalcet of non-surgical primary hyperparathyroidism in the elderly.

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Primary hyperparathyroidism (PHPT) is a common condition. The prevalence since the introduction of multichannel analysers is approximately 1:1000, with the older female being the typical patient. PHPT is predominantly a sporadic disorder. Surgery remains the only curative approach to most primary hyperparathyroidism (PHPT), medical treatment with cinacalcet has been proven to be an alternative for patients with hyperparathyroidism.

Objective

Analyze treatment with cinacalcet, in older patient with primary hyperparathyroidism not tributary of surgery.

Material and patients

Between 2011 and 2015, 13 patients with PHPT who were not suitable for surgery were identified. Data collected: age, gender, comorbidities, levels of calcium and PTH and follow-up.

Results

We present 13 patients 8 women and 5 man with a mean of age 80.5 ± 6.59 year-old (range 71–92). Comorbidities, diabetes mellitus 50%, frailty 58%, heart disease 40%, depression 33%, cognitive impairment 17%. Calcium levels previous treatment was 11.85 ± 0.28 mgr/dl and PTH 123 ± 34 pg/ml. T cinacalcet 30 mg. daily was initiated, in 12 patients and 60 mgr. in one. Patients were followed for 1–4 years (2.75 ± 1.21) calcium were adequately controlled (9.98 ± 0.78 mgr/dl), but PTH 112.4 ± 42 pg/ml remains high, renal function was uncharged in all patients. Two patients died during the follow-up, not related with hyperparathyroidism. Adverse events were observed in 1 patient (vomiting) that disappeared to diminishing doses.

Discussion

Geriatricians will readily recognize the clinical conundrum of an incidental finding of PHPT in the older that was unexpected. Retrospective questioning may identify some pertinent symptoms, but none strong enough on their own to have made the diagnosis obvious prior to testing serum calcium. This group of patients is hard to define and hence there is little published guidance on how to manage the increasingly common clinical scenario of the frail, relatively asymptomatic, older patient with PHPT.

Conclusions

Cinacalcet, the first available calcimimetic, increases the sensitivity of the calcium-sensing receptor (CaR) to circulating serum calcium, thereby safely reducing serum calcium and PTH concentrations in patients with mild-to-moderate PHPT, intractable disease, and also parathyroid carcinoma. Cinacalcet in a reasonable and safe alternative to treatment of PHPT not tributary of surgery.

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EP248

Glucocorticoids regulate expression of lung calbindin-D9k in mouse

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Introduction

Calbindin-D9k (CaBP-9k), which is a calcium ion buffering and transporter gene, is known to be regulated by the vitamin D and steroid hormones, and is mainly expressed in mammalian intestine, kidney and uterus. However, CaBP-9k expression in lung has not been studied. Maintaining lung structure using pulmonary surfactant is important for pulmonary gas exchange. Steroids are known to accelerate maturation of the fetal lung and secretion of surfactant. Otherwise the relationship between pulmonary function especially in surfactant secretion and CaBP-9k expression has not been researched. In this study, we investigate the CaBP-9k expression by sex steroid hormones and glucocorticoids in mouse lung.

Materials and methods

To confirm the effect of sex steroid hormones, the immature mice age from 14 days to 16 days were respectively injected of estrogen (E_2) and progesterone (P_4) for 3 days. To confirm the effect of glucocorticoids, the mature mice age from

11 weeks were respectively injected of dexamethasone (Dex). ER antagonist (ICI187,780) and PR, GR antagonist (RU486) were injected 30 min prior to steroid hormones. We compared the changes in the CaBP-9k expression of each group using polymerase chain reaction.
Results
In the estrogen and progesterone treated immature mice lung, the CaBP-9k gene expression had no significant change in mRNA and protein level but significantly increased in Dex treated mice lung. It is suggested that glucocorticoids may play a role in regulation of CaBP-9k expression in lung.
Conclusion
Our results has significance to the regulation of CaBP-9k by Dex. By studying the effects on lung surfactant through the control of CaBP-9k, it may be presented as a basis data of pulmonary surfactant associated disease or research.

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EP249

Vitamin D intoxication caused hypercalcemia: Case report

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Introduction
Vitamin D is a fat soluble prohormone and can be produced in the body with adequate sunlight exposure or taken up by consumed foods or supplements. Recently vitamin D deficiency has been seen in pandemic. A rare disease, vitamin D intoxication is usually iatrogenic. High levels of 25(OH) vitamin D increases the intestinal calcium absorption and causes severe and refractory hypercalcemia. In this case report we presented a patient with pancreatitis and hypercalcemia secondary to vitamin D intoxication.
Case
79-years-old female patient presented to emergency department with generalized pain, lack of appetite, dry mouth, nausea, vomiting and abdominal pain. Serum calcium level was 13.8 mg/dl. In her medical history she used 12 ampules of vitamin D-3 in the last month. In her physical examination there was abdominal tenderness. Laboratory findings were as follows; 25-OH vitamin D-3: 455 µg/l (20–150), WBC: 19 570 10e3/µl (3.8–8.6), Urea: 60 mg/dl (10–50), Creatinine: 2 mg/dl (0.6–1.2), Ca: 13.8 mg/dl (8.5–10.8), phosphorus: 2.9 mg/dl (2.6–4.5), albumin: 3.7 mg/dl (3.5–5.5), amylase: 132 U/l (28–100), Lipase: 115 U/l (7–60), Parathormone: 28 pg/ml (19.8–74.9). Abdominal CT scan showed interstitial oedematous pancreatitis. In the follow up, patient was hydrated with isotonic saline infusion. To lower the calcium levels, intravenous furosemide infusion was used. Calculated QTc level when serum calcium is 9.1 mg/dl, was 443 msec. According to literature we could see osborn wave in the ECG but we did not.
Discussion
Vitamin D toxicity develops when serum levels of 25 OH vitamin D-3 levels reach 150 ng/ml or above and daily intake should exceed 10.000 IU. In the treatment, cessation of vitamin D intake and controlling of hypercalcemia is mandatory. Limiting daily calcium intake, hydration, loop diuretics, corticosteroids, calcitonin and bisphosphonates can also be used. Dialysis can be performed to those who are refractory to these treatment modalities.
Conclusion
Uncontrolled and over the counter use of vitamin supplements is a common issue worldwide. Patients who need vitamin D supplements should be followed with laboratory and clinically.

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EP250

Abstract withdrawn.

EP251

Gitelman syndrome and primary hyperparathyroidism – a rare association

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Gitelman's Syndrome (GS) is a rare autosomal recessive salt-losing tubulopathy of young adults, characterized by secondary hyperaldosteronism, hypokalemia, hypomagnesemia, hypocalciuria and metabolic alkalosis. It is caused by mutations in *SLC12A3* gene. Hypercalcemia due to hypocalciuria in these patients is extremely rare and requires further evaluation.
A 25-year-old normotensive female was referred to Endocrinology clinic for evaluation of persistent hypokalemia. She presented history of malaise, fatigue, myalgias, cramps and paresthesia. She denied diarrhea, recent treatment with diuretics or laxatives. Her physical exam was normal. Laboratory workout revealed: aldosterone 47.1 ng/mL (r.v. 4–31), active renin 374.7 µUI/ml (r.v. 4.4–46.1), K + 2.7 mEq/l (r.v. 3.5–5.1), 24 h urinary K + 84.7 mEq/24 h (r.v. 25–125), Mg2 + 0.71 mg/dl (r.v. 1.6–2.6), 24 h urinary Mg2 + 143.1 mg/24 h (r.v. 73–122), Ca2 + 12 mg/dl (r.v. 8.4–10.2) and 24 h urinary Ca2 + 133 mg/24 h (r.v. 100–300). GS was diagnosed and she was treated with spironolactone, oral K^+ and Mg^{2+} supplementation. Further investigation confirmed hypercalcemia due to primary hyperparathyroidism (parathyroid hormone (PTH) 107.3 pg/ml (r.v. 14.8–83.1)) caused by a large single parathyroid adenoma. Following parathyroidectomy calcium profile normalized. The sequencing of *SLC12A3* gene detected the variant c.602–16G > A and the mutation c.2221G > A (p.Gly741Arg), both in heterozygosity. In this context genetic study of the progenitors was required. The father presents the variant c.602–16G > A and the mother the mutation c.2221G > A (p.Gly741Arg), in *SLC12A3* gene.
The assotiation of hypokalemia, hypomagnesemia and hypercalcemia is uncommon but potentially lethal. Current knowledge favors that hypomagnesemia in GS's patients protects them from hypercalcemia. In this context of multiple electrolyte imbalances, correction of hypomagnesemia is a challenge and should be done carefully. Like in our patient hypercalcemia's etiology should be prompt diagnosed and reversed.

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EP252

The volume of parathyroid adenoma is related to presurgical PTH and 25OH-D3, but not calcium levels at patients with primary hyperparathyroidism

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Aims
We wanted to evaluate the correlations between the volume of the surgically removed parathyroid adenoma and the presurgical metabolic profile of patients diagnosed with primary hyperparathyroidism.
Materials and methods
Prospective multicentric study, enrolling 52 patients with primary hyperparathyroidism from two medical units, proposed for surgery. Serum calcium and PTH were evaluated in all patients before surgery, and 25OH-D3 was measured only in the 33 patients recruited from one of the two surgery departments. Parathyroid volume was measured immediately after excision, using the formula of a rotating ellypsoid. Data were statistically evaluated by using Pearson correlation analysis. Correlations were considered significant at P values lower than 0.05.
Results
We observed a significant correlation between the volume of parathyroid adenomas and presurgical PTH ($P < 0.001$) but not presurgical calcium levels at patients from the two medical units and in the whole group. Twenty-nine out of the 33 patients diagnosed with primary hyperparathyroidism recruited from the first medical unit had 25OH-D3 levels in the range of vitamin D deficiency or insufficiency. 25OH-D3 was not significantly correlated with PTH or calcium levels, but a significant negative correlation was found between the volume of the parathyroid adenoma and serum 25OH-D3 levels ($P < 0.05$).

Conclusion
The volume of parathyroid adenoma seems to be related to presurgical PTH and 25OH-D3, but not calcium level. D hypovitaminosis is frequently found at patients with primary hyperparathyroidism and may contribute to particular disease profiles. Higher PTH and lower 25OH-D3 levels, as well as larger adenomas may be accompanied by increased disease severity, or by a different spectrum of disease complications.

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EP253

Pseudohypoparathyroidism type Ib: a case of chronic severe hypocalcaemia and seizures diagnosed in adulthood

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Pseudohypoparathyroidism (PHP) is a rare group of genetic disorders characterised by end-organ resistance to parathyroid hormone (PTH). We describe the case of a 34-year-old Caucasian female with severe hypocalcaemia presenting with a first generalised seizure. Her medical history was significant for bilateral cataract. She had three healthy children, and no family history of note. On examination, she had positive Chvostek's sign. Biochemical analysis showed serum calcium 4.5 mg/dl (n.r. 8.4–10.2 mg/dl), phosphorus 5.8 mg/dl (n.r. 2.3–4.7;mg/dl), PTH 94.7 pg/ml (n.r. 14.76–73.1 pg/ml) and vitamin D 19.6 ng/ml (n.r. 30–100 ng/ml), with normal serum albumin and normal alkaline phosphatase. Electrocardiogram demonstrated prolonged corrected QT interval. Brain imaging revealed basal ganglia and cerebellar calcifications, and electroencephalography did not show paroxysmal activity. We excluded a number of causes of secondary hyperparathyroidism based on her medical history and investigations, and concluded that PTH resistance would be the most likely diagnosis. Since she lacked the typical clinical features of Albright hereditary osteodystrophy and did not present with other hormones' resistance, a genetic test was requested and identified abnormal methylation of the 20q13.32 region, confirming the diagnosis of PHP type Ib. The patient is currently medicated with calcium carbonate and calcitriol, maintaining a satisfactory calcium-phosphate homeostasis. This case highlights the importance of PHP as a rare but significant cause of severe hypocalcaemia. The delayed diagnosis, as seen in this case, may result in serious consequences.

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EP254

A practice review of the use of cinacalcet in primary hyperparathyroidism

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Background
The treatment of choice for primary hyperparathyroidism (PHPT) is surgical parathyroidectomy. Cinacalcet is the first calcimimetic approved by European Medicines Agency (EMA) in 2008 for use in patients with PHPT who are not fit for surgery or refuse surgery. British National Formulary (BNF) recommends it for hypercalcaemia in PHPT where parathyroidectomy is inappropriate. The main aim of treatment with cinacalcet is to keep calcium levels at safe levels.

Objectives
To evaluate the efficacy and safety of cinacalcet in patients with PHPT who were unfit for surgery, refused surgery or remain hypercalcaemic post-parathyroidectomy and not amenable to further intervention (complex PHPT).
Methods
We assessed the demographic and clinical characteristics and biochemistry in 12 patients seen in endocrinology and biochemistry clinics with complex PHPT at the commencement of cinacalcet and after approximately 1, 3, 6 and 12 months. We also checked doses, tolerability and side effects of cinacalcet.
Results
Most patients (66.67%) needed small maintenance dose of cinacalcet once a day. Mean baseline adjusted calcium level was 3.36 mmol/l (13.44 mg/dl) with a range of 2.91–5.36 mmol/l (11.64–21.44 mg/dl). There was a significant reduction in adjusted calcium levels at approximately 1 month (10.08%), 3 months (11.93%), 6 months (13.57%) and 12 months (20.17%). Calcium normalised in most patients (83.33%), and one patient developed hypocalcaemia necessitating cinacalcet dose reduction. All patients adhered to the treatment with two people experiencing self-limiting nausea and vomiting.
Conclusion
Our patient cohort indicates that cinacalcet is an effective and safe alternative to surgery in patients with complex PHPT. Cost-effectiveness analyses are needed to allow more widespread use in such patients. Further studies with long-term follow-up are required to assess efficacy in preventing osteoporosis and renal complications related to PHPT.

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EP255

Is there a threshold of Vitamin D sufficiency that can prevent secondary hyperparathyroidism?

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While nonskeletal benefits of vitamin D remain a matter o debate, its importance in bone health is known for decades. Secondary hyperparathyroidism is considered to play a significant role in the pathogenesis of age-related bone loss. In the present study we investigate the association between serum PTH, 25-hydroxyvitamin (25(OH)D) and other clinically related variables in a cross sectional sample of patients followed in an Endocrine consultation during the year 2016. Patients with diseases or medications known to affect calcium metabolism were excluded. 509 participants, 365 female and 145 male, were selected for analysis. Mean age $\pm$S.D. was 52 $\pm$ 16 yrs (2–86); 47% were diabetics; 31% suffered of thyroid disorders and 7% were obese. The mean $\pm$S.D. serum level of 25(OH) D was 20.4 $\pm$ 10.2 ng/ml; 17.8 $\pm$ 8.7 ng/ml in measurements during winter months and 23.4 $\pm$ 10.04 during summer. In 61 patients (12% of the sample) with more than one determination, there was a 51.9% increase in 25(OH) D from a mean level of 16.81 $\pm$ 9.3 ng/ml during winter to 24.94 $\pm$ 11.2 ng/ml during summer months ($P<0.02$). Patients treated with statins presented significantly lower levels of 25(OH)D than non-treated patients, 15.9 $\pm$ 6.7 ng/ml and 26 $\pm$ 10.1 ng/ml, respectively ($P<0.01$).This difference remained statistically significant after adjusting for age, sex and disease.
We found an inverse relationship between 25(OH)D and PTH. The best fitted line was obtained as a logarithmic expression of 25(OH)D ($r=0.65$; $P<0.001$). There was no further significant decrease in PTH for serum levels of 25(OH)D of more than 25 ng/ml. In conclusion, more than half of our patients were Vit D deficient (<20 ng/ml) particularly elderly people treated with statins, but serum levels of 25(OH)D above 25 ng/ml are needed in order to prevent secondary hyperparathyroidism. This value can be considered as the lower limit of Vitamin D sufficiency in the sample studied.

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EP256

Spontaneous remission of parathyroid adenoma due to parathyroid apoplexy: a case report

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Introduction
Primary hyperparathyroidism (PHPT) is a disease that is characterized by elevated calcium and parathyroid hormone levels. The most common cause of PHPT is the paratiroid adenoma and the first line treatment option is surgical removal of the adenoma. Rarely, the haemorrhage in the lesion may cause the spontaneous remission of the disease.
Case report
A 54-year-old woman patient with fatigue was referred to our department due to calcium level of 11.4 mg/dl (normal range: 8.4–10.2) and PTH level of 76.1 pg/ml (normal range: 15–65). Neck ultrasound examination revealed a 10×5 mm mass lesion in the posterior-inferior region of the left lobe of the thyroid. Sestamibi scan showed activity in the same region with neck ultrasound. Surgical resection of the parathyroid adenoma was planned but the patient refused surgical excision because of personal reasons. One year after the diagnosis of PHPT, her calcium concentration returned into the normal range (9.4 mg/dl), at the same time neck MRI showed a mass with a size of 19×13 mm, which was attached inferiorly to the left lobe of the thyroid. The mass was diagnosed as hemorrhagic parathyroid adenoma because the mass was imaged as a high intensity area by T_2-weighted MRI. At that time the sestamibi scan was negative. Six months after the haemorrhage of the lesion, it was seen that the calcium level rose to 11.1 mg/dl and the PTH level was 89 pg/ml so the PHPT has been recurred.
Conclusion
Parathyroid apoplexy can lead to spontaneous remission of the PHPT but the remission is usually temporary and finally recurrence of the disease could be seen.

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EP257

Normocalcemic versus Hypercalcemic Primary Hyperparathyroidism: a comparative study

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Introduction
Normocalcemic primary hyperparathyroidism (NPHPT) is defined as a condition in which persistently normal serum calcium levels are observed in the presence of high levels of parathyroid hormone (PTH). NPHPT is a new entity which possibly represents a clinically symptomatic disease and which has generated a considerable scientific interest.
Aim
To compare the clinical and laboratory data between the normocalcemic and hypercalcemic forms of PHPT.
Materials and methods
A comparative study of 357 patients with PHPT wich were separated into normocalcemic ($n=56$) and hypercalcemic ($n=301$) subgroups on the basis of their fasting serum total calcium value. Bone mineral density (BMD) and T-scores were evaluated by densitometry of the lumbar spine, femoral neck and total of the radius. Nephrolithiasis and bone fractures were documented by a review of the medical records.
Results
Patients with NPHPT had, on average, a lower serum PTH concentration 150 pg/ml ± 115 (*N* 15–65, Me 114) and a lower serum calcium level 2.44 mmol/l ± 0.08 (*N* 2.15–2.55) vs hypercalcemic PHPT – 408 pg/ml ± 651 (Me 186) and 2.89 mmol/l ± 0.3 respectively. There was no significant difference in urine calcium excretion. The frequency of nephrolithiasis was 27% in normocalcemic patients and 16% in the hypercalcemic ones ($P<0.05$). There were no statistical differences in relation to BMD of the lumbar spine and femoral neck, but BMD significantly differed in the total radius area. BMD in the total radius was 0.423 g/cm^2 (Me 0.415), mean T-score was −2.2 s.d. of the normocalcemic patients, 51.8% had osteoporosis in at least one of the three sites evaluated. In addition, normocalcemic patients differed from hypercalcemic patients by lower values of markers of bone turnover osteocalcin and β-C-telopeptide, $P<0.05$. 20.4% of normocalcemic patients had a previous history of fractures compared to 20.3% of hypercalcemic patients ($P>0.05$).
Conclusion
NPHPT is at present one of the most common reasons for consultation in bone metabolism departments, especially in postmenopausal women. Identifying these patients is important because of the consequences of untreated hyperparathyroidism, which include nephrolithiasis, osteoporosis and atraumatic fractures.

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EP258

Parathyroid carcinoma: experience of a Portuguese centre

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Introduction
Parathyroid Carcinomas are rare malignant neoplasms, accounting for less than 1% of primary hyperparathyroidism cases. Apart from certain genetic mutations, no additional risk factors are known. Diagnosis is challenging in the absence of metastatic disease since no consensual histological criteria have so far been developed. These neoplasms typically present with severe hypercalcemia and markedly elevated serum PTH levels. Treatment is surgical and despite frequent metastatic disease at diagnosis, clinical course is usually indolent. The authors report the experience of a tertiary reference centre in Portugal regarding parathyroid carcinomas.
Methods
Observational, retrospective study. Patients with diagnosed parathyroid carcinoma from 1999 until 2016 were included. Clinical data was obtained from patient's clinical, laboratory and imaging files. Descriptive statistical methods were used and results are presented as mean and standard deviation.
Results
The sample is composed of ten patients (five females) with a median age of 53 ± 16.9 years at the time of diagnosis. Clinical presentation was heterogeneous. All patients had hyperparathyroidism (mean 1229 ± 642 pg/ml), nine hypercalcemia (13.4 ± 2.2 mmol/l) and four hypophosphatemia (2.1 ± 0.6 mol/l). Histological findings: intratumoral septa (50%), vascular, capsular, perineural invasion (70%, 80%, 10% respectively), extraglandular extension (50%). Mitotic index was evaluated in four patients. CDC73 mutations were present in four patients. Metastases were present in one patient. All patients underwent *en bloc* resection and three received external beam radiotherapy due to recurrent loco-regional disease. After a mean follow up of 9 years, 90% are in remission and no mortality has been documented.
Conclusion
The authors describe a series of ten parathyroid carcinoma patients. Despite the clinical and biochemical severity at the time of diagnosis, most patients achieved sustained remission. Genetic mutations were identified in a significant proportion of patients, having important clinical implications. This series is noteworthy for the good outcome of such an aggressive neoplasm.

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EP259

Vitamin D prescribing bias in liver transplant referrals

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Vitamin D (VD) deficiency (25 OHD < 50 nmol/l) is common is chronic liver disease at 64%–92% regardless of aetiology. The only guidelines for routine VD supplementation are for cholestatic (C) liver disease; a population considered being at high risk of low bone mineral density (BMD). BMD decreases further following orthotopic liver transplant (OLT). To assess VD intake in an at risk population, retrospective analysis of intake was performed in OLT patients with C liver disease; this was excellent at 81%. Prospective analysis comparing C with non-cholestatic (NC) patients at time of dietetics referral at OLT assessment was then undertaken ($n=94$, 27% C and 73% NC). Median 25OHD in C patients was 86.7 nmol/l compared to 24.7 nmol/l in NC (P 0.001). 36% of C patients compared to 76% of NC had 25OHD measurement of <50 nmol/l (P <0.0001). 48% of C patients compared to 16% of NC were receiving VD supplementation

before OLT assessment. We have observed a prescription bias at referral to transplant hepatology; VD is prescribed more frequently to C than NC patients with end-stage liver disease, although both populations are at risk of reduced BMD.

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EP260

How to differentiate primary hyperparathyroidism with D hypovitaminosis from secondary hyperparathyroidism due to D hypovitaminosis?

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Background
D hypovitaminosis and primary hyperparathyroidism frequently coexist. Secondary hyperparathyroidism reactive to D hypovitaminosis is difficult to be differentiated from primary hyperparthyroidism.
Aims
To differentiate patients with D hypovitaminosis and secondary hyperparathyroidism.
Materials and methods
Prospective study involving 71 patients admitted in our department for 1 year with the initial diagnosis of primary hyperparathyroidism. Serum and urinary calcium and phosphate, PTH and 25OHD3 were evaluated at admission. Patients with vitamin D levels under 30 ng/ml were repleted with 2000 IU/day of 25OHD3 for 1 month and 1000 IU/day for other 5 months. Values between groups were compared using student's t test. Correlations were evaluated by using Pearson correlation analysis.
Results
Forty-eight of the 71 patients had vitamin D deficiency (< 20 ng/ml) and 15 had vitamin D insufficiency (between 20 and 30 ng/ml), only eight having 25OHD3 of over 30 ng/ml. Both 25OHD3 and PTH levels normalized after 6 months of repletion with vitamin D in only 24 of the 63 patients with initial low 25OHD3 levels and they were therefore diagnosed with secondary hyperparathyroidism (group S), whereas in the other 39 patients PTH levels remained elevated despite normalization of 25OHD3 levels, setting the diagnosis of primary hyperparathyroidism associated with D hypovitaminosis (group P). Initial PTH was correlated with serum calcium in both groups, but with serum phosphate only in group P. Initial PTH and serum and urinary calcium were significantly higher, whereas serum phosphate and radius BMD were significantly lower in the patients from group P when compared with patients from the group S ($P < 0.05$).
Conclusions
Patients with secondary hyperparathyroidism reactive to D hypovitaminosis are frequent. Their PTH and electrolyte profile are only mildly modified, with a milder impact on bone mass than in primary hyperparathyroidism. A clear diagnosis could be, however, set only after vitamin D repletion.

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EP261

Pseudohypoparathyroidism as an etiological cause for epilepsy: a case report

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Introduction
Pseudohypoparathroidism (PHP) is a condition mimics hypoparathyroidism biochemically with a hypocalcemia and hyperphosphatemia but differentiates from it an elevated parathyroid hormone (PTH) levels. PHP characterized by targeted organ unresponsiveness to PTH and mainly subdivided two groups. PHP type 1a an autosomal dominant disease related to mutations of GNAS1. This subtype has biochemical findings and characteristic somatic phenotype known as Albright Hereditary Osteodystrophy (AHO). AHO include short stature, round face, brachydactyly, shortened metatarsals, subcutaneous ossifications and reduced intelligence. PHP type 1b has laboratory findings but do not has phenotype of AHO. This disorder caused by methylation defects of GNAS1 regulatory region. We present a patient who was detected PHP while following for epilepsy.
Case report
A 17 years old male patient referred to endocrinology clinic with paresthesias of the hands. He had under treatment due to epilepsy for 3 years. He had normal mental activity and phenotypic features. His family history had no specialty. His laboratory examination revealed hypocalcemia and hyperphosphatemia with a calcium level 7.4 mg/dl (reference range, 8.5–10.5 mg/dl), phosphorus 6.8 mg/dl (reference range, 2.5–4.5 mg/dl), albumin 4.4 g/dl (reference range, 3.5–5.2 g/dl), magnesium 2.06 mg/dl (reference range, 1.8–2.6 mg/dl), 25 hydroxyvitamin D (25 OHD) 64.3 ng/ml (reference range, 30–70 ng/ml) and PTH 115 pg/ml (reference range, 15–65 pg/ml). His rest of the laboratory findings and ophthalmic examination were normal. Brain computed tomography scan showed basal ganglia calcifications. Calcitriol and calcium supplements were started to patient whose biochemical findings support PHP diagnosis. Genetic testing of the patient did not show GNAS coding region mutation and we planned methylation study in terms of methylation abnormality in GNAS regulatory region.
Conclusion
PHP is an uncommon cause of hypocalcemia. Blood electrolytes must be called to mind in case of epilepsy or neurological evidence. Early diagnosis and treatment of PHP prevent complications.

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EP262

Long standing primary hyperparathyroidism consequences after parathyroid surgery: fast recovery not only for bone mass

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Background
Primary hyperparathyroidism is usually a long evolving disease before the diagnosis, thus patients who are not diagnosed by routine screening tests may have a lot of complications affecting the bone, kidney, bone marrow.
Aim
Pointing out the possibility of fast recovery not only for bone mass.
Material
We present a case of primary hyperparathyroidism, a female patient 66 years old, sent to emergency room, dehydrated, asthenic, with important hip pain, low back pain. Her Ca = 14.3 mg/dl, PTH > 4000 pg/dl, Hb = 8.5 g/dl, CT: osteolotic lesion, pubis and ischium fracture, two osteolithic lesions on the right acetabulum and the S1 vertebra, bone biopsy: perytrabecullar fibrosis, aspects of bone remodeling and normal medullar celularity, DXA T score: total hip -3, L1-L4 -1.8, forearm -4.4. The complication in the moment of diagnostic were: osteoporosis, spontaneous fragility fractures, medular fibrosis with normocytic normochromic anemia.
Results
Surgery was successful with the normalization of blood calcium and PTH. Questions were raised regarding the high level of PTH(neoplasia was taken into account) and also the impact of medular fibrosis the on the prognosis of the patient. After one year BMD was in age range, DXA T score: total hip -1.2, L1-L4 -0.2, forearm -2, anemia have remitted Hb = 12.5 g/dl, and maintained during 2 years follow up.
Conclusion
In spite of high level of PTH and dangerous medular fibrosis, our case show surgical recovery of bone mass but also of medular complications.

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EP263

Associations of nitric oxide with vitamin D and other serological factors in healthy adolescents

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Nitric Oxide (NO) has been considered a very important molecule in the biological system because of its interaction with other molecules for mediating various bio-pathways. Its interaction with vitamin D in particular studied well in animal models, cell lines and patients with various diseases. However, the

relationship between NO and vitamin D has never been studied in healthy adolescents. We aimed to determine the association of NO with vitamin D and other serological factors in healthy Saudi adolescents. We recruited 740 individuals (245 boys and 495 girls) from Riyadh, Saudi Arabia. Socioeconomic status, food habits, BMI and data regarding major medical complications were recoded. Blood samples were performed for estimation of vitamin D, traces of NO and other possible serological parameters. Data revealed that NO has inverse correlation with vitamin D but showed significant and positive association with serum triglycerides and systolic blood pressure. Here, it is suggested that some unknown limiting factors may restrict the relationship of NO and vitamin D in healthy individuals. Therefore, the factors which limit the NO association with vitamin D and other molecules should be investigated *in vitro* and *in vivo*.

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EP264

Primary hyperparathyroidism in pregnancy

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Introduction
Primary hyperparathyroidism is the most common cause of hypercalcemia in the general population. Hypercalcemia during pregnancy can result in significant maternal and fetal morbidity and mortality.
Case
A 30-year-old pregnant female primigravida in the 31 weeks of gestation with complaint of obstinate constipation was admitted to our emergency department. In laboratory tests, hypercalcemia was detected. She was a Syrian refugee and was unable to communicate in English and Turkish. The parathyroid hormone (PTH) and albumin-corrected serum calcium levels were high. The results were 203 (12–65) pg/ml and 15.1 (8.5–10.5) mg/dl respectively. Urinary calcium excretion rate was 440 mg/per day. Tubular phosphorus reabsorption rate was 73%, and the chlor/phosphorus ratio was 54.7. In the light of all these data, primary hyperparathyroidism was diagnosed. Ultrasound imaging revealed a parathyroid adenoma ($6\times6\times19$ mm) at the inferior of the left thyroid lobe. In our case we started 3000 cc salin infusion and furosemid treatment but her calcium levels didn't decrease to safe range. Intravenous calcitonin was added to treatment but calcium levels didn't decrease. We started to hemodialysis but still was calcium level >12.5 mg/dl. We followed up the patient in hospital until the baby's lung maturation is completed. When the gestation reached the 35th week, parathyroid adenoma excision and caesarean section were performed concurrently. Post-operative calcium levels decreased. Hypocalcemia improved with medical treatment in the newborn.
Discussion
The main treatment modality of hyperparathyroidism is surgery but if hyperparathyroidism is diagnosed in third trimester surgical approaches have high risk. Because of the high risk, we trained our patient with medical treatment at the hospital until safe birth time. In the postpartum interval to avoid a parathyroid crisis, surgery and cesarean operation were performed simultaneously during the safe period for the baby.

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EP265

Eucalcemic parathyroid hormone elevation after parathyroid surgery for sporadic primary hyperparathyroidism

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Introduction
Serum parathormone (PTH) levels may remain elevated in some patients after surgery despite achievement of normal serum Ca levels. The factors contributing to this phenomenon have not been fully elucidated yet. In this study, we retrospectively analysed the data of patients whose serum Ca levels returned to normal after parathyroid surgery in our center.
Patients and methods
Computer records of 35 patients who had undergone parathyroid surgery and achieved normal serum Ca levels were retrospectively analysed. Despite serum Ca values within the normal ranges, patients were divided into two groups according to their PTH values 6 months after surgey (elevated PTH (ePTH) group (PTH $\geq$65 pg/ml) and low PTH (lPTH) group (PTH $<$65 pg/ml)). Fifteen patients were classified as having ePTH and 20 as IPTH. The frequency of ePTH was determined as 42%. The mean pre and postoperative PTH levels in ePTH and IPTH groups were 265 ± 119, 94 ± 32 and 206 ± 136, 39 ± 17 pg/ml, respectively. The mean pre and postoperative 25(OH) vitamin D3 levels in ePTH and IPTH groups were 12 ± 7, 22 ± 11 and 22 ± 14, 32 ± 12 ng/ml, respectively.
Results
Although ePTH group had higher preoperative PTH values as well as lower pre and postoperative 25 (OH) vitamin D3 levels, there was no statistically significant difference between the groups. For the remaining parameters, two groups had similar results.
Discussion
Several hypotheses have been proposed to explain the etiopathogenesis of persistently elevated PTH values despite normal Ca levels following parathyroid surgery. Suggested causes of this phenomenon include 25 (OH) vitamin D3 deficiency, secondary hyperparathyroidism resulting from insufficient renal function, stimulation of PTH secretion induced by relative hypocalcemia postoperatively, and increased bone turnover. However, this condition may also indicate possible recurrence due to multiglandular hyperplasia rather than a single parathyroid adenoma.

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EP266

Primary hyperparathyroidism mimicking metastatic bone disease

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We would like to present a case of primary hyperparathyroidism presumably present with clinically large cystic parathyroid adenoma with multiple destructive skeletal lesions, which is of course referred to bone metastases.
Case
A 58-year-old male patient was admitted to the orthopedy polyclinic with left leg pain and on the MR imaging performed here, multiple lytic lesions compatible with metastasis to the tibia and fibula were detected. He was directed to our internal medicine clinic for further investigation. The patient had complaints of widespread bone pain, especially the left leg which lasted for 2 months and was suffering from polydipsia. Biochemical tests showed elevated serum calcium values and increased intact parathyroid hormone (iPTH), low phosphorus, high alkaline phosphatise, compatible with primary hyperparathyroidism. Erosive and brown tumour like lesions were detected in bone x-ray. On PET CT imaging, extensive, lytic and expansile lesions were observed, especially in the kranium and ribs. On the neck ultrasonography, a 50×30 mm sized, septated, irregular contour nodule was detected in the right lobe. Thyroid fine needle aspiration biopsy was performed. Histopathological evaluation was benign and there were no findings indicating parathyroid pathology. Parathyroid scintigraphy showed no lesions compatible with neck or mediastinal adenoma. Due to resistant hypercalcemia, the patient was given bilateral neck exploration. The parathyroid mass was localized and resected intraoperatively in the lower pole of the thyroid nodule extending mediastinum, and histopathological evaluation was compatible with parathyroid adenoma. Biochemical results due to hyperparathyroidism normalized after operation and complaints resolved.
Discussion
It should be considered that primary hyperparathyroidism may have bone lesions that mimic bone metastasis. Especially in cases where the thyroid nodule is visible but there is no evidence of parathyroid adenoma in parathyroid scintigraphy intrathroidal parathyroid adenomas should be considered in the differential diagnosis of cystic neck lesions.

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EP267

Acute pancreatitis as the first presentation of primary hyperparathyroidism

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Background
Hypercalcaemia due to primary hyperparathyroidism is a rare cause of acute pancreatitis, with a reported prevalence of 1.5–8%.
Clinical case
A 25-year-old male patient was referred to the Endocrinology outpatient clinic for hypercalcemia diagnosed in the context of acute pancreatitis. He had medical and surgical pathological antecedents of: clavicle fracture after car accident, cholecystectomy and appendectomy, gastroesophageal reflux disease. Current medications included proton pump inhibitor daily. Laboratory analysis reported serum calcium of 3.46 mmol/l (2.20–2.65), phosphorus of 0.70 mmol/l (0.81–1.45) and intact parathyroid hormone of 569 pg/ml (12–88). Biochemical screening for type 1 and type 2 multiple endocrine neoplasia was performed and was negative. The neck ultrasonography showed a nodular heterogeneity with hyperechogenic contours with cystic areas, and posteriorly and inferiorly to the left lobe an hypoechogenic nodular formation, with 2.4 cm of greater axis, which may correspond to the parathyroid gland with increased dimensions. Bone densitometry showed osteopenia. Sestamibi parathyroid scintigraphy revealed a focus of significant radiopharmaceutical retention on the projection of the lower left lobe pole, alteration compatible with parathyroid adenoma. A lower left parathyroidectomy and left lobectomy of thyroid was performed without complications. The histopathological result confirmed the diagnosis of parathyroid adenoma. At the last visit, he had normal PTH and calcemia values. During the follow-up he had recurrent acute pancreatites episodes.
Conclusions
The authors present this case because of its rarity: hyperparathyroidism in a young patient whose presentation was of acute pancreatitis without the classic clinic manifestations of hypercalcemia.

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EP268

Gender difference in clinical presentation of primary hyperparathyroidism

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Objective
Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders, with a female to male ratio of 3:1. Currently most patients with PHPT are asymptomatic. However, data about the gender impact on the clinical presentation of PHPT are lacking.
Methods
We evaluated the difference in symptoms and biochemical parameters between men and women with PHPT in a single center series of 417 patients.
Results
Male PHPT patients resulted significantly younger ($P=0.046$) and more frequently symptomatic than women (62.3% vs 47%, $P=0.016$). Furthermore, renal stone incidence was higher in male than in female patients (50.5% vs 33%, $P=0.003$) while no difference was found in the incidence of osteitis fibrosa cystica (21.5% vs 20.7%). Instead, osteoporosis, established as T score < 2.5 at any site, was significantly predominant in women (56.5% vs 39.3%, $P=0.015$) rather than in men. However, no differences were found in classical biochemical disease parameters (i.e. PTH, serum calcium, phosphorus, 24 h-urine for calcium) nor in creatinine and vitamin D levels. Finally, the proportion of patients with surgical indications (symptomatic patients and asymptomatic patients meeting surgical criteria recommended by current guidelines) was similar in male and in female PHPT patients (84,6% vs 84,9%).
Discussion
Gender leads to a different clinical presentation in PHPT patients, male patients being usually younger and more frequently affected by a symptomatic form of the disease. In addition, renal stones are significantly more frequent in men, while in women osteoporosis is prevalent. On the other hand, PHPT biochemical presentation seems not to be influenced by gender. Furthermore, surgical indication is reached equally in male and female PHPT patients.
Conclusions
In male patients PHPT is less frequent but more commonly symptomatic than in female patients. PHPT clinical presentation is influenced by gender, although there are no sex-related differences in its biochemical profile.

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EP269

Prevalence of hypocalcemia in adults in Minsk, Belarus

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The prevalence of hypocalcemia among patients non-operated the thyroid and parathyroid glands has increased significantly with the introduction the screening of calcemia. The main reasons for hypocalcemia are hypoproteinemia and hypoparathyroidism.
Objective
To study the prevalence of hypocalcemia in the adult in Minsk.
Materials and methods
We studed 1207 people, average age 53.9 ± 17.25 (892 women, 315 men) from 18 to 96 years. Examination: total calcium, total protein. Hypocalcaemia was detected in total calcium level < 2.2 mmol/l.
Results
Hypocalcaemia was recorded in 40 people (3.3/100 adults), the mean age was 42.9 ± 17.63 years (32 women, men – 8). In the age group up to 30 years hypocalcemia was revealed in 12 cases (8.3%, in women – 10.3%); in the group 30–44 years – five cases (1.3%, in men – 4.7%, in women – 0.3%), 45–59 years – three cases (1.1%, in men – 2.5%, in women – 0.5%); 60–74 years – ten cases (2.5%, in men – 2.6%, in women – 2.4%); >75 years – one case (0.7%, in men – 3.2%). The prevalence of hypocalcemia in the group up to 45 years – 6.6 per 100 adults. The prevalence of hypocalcemia in the group 45 years over – 1.7/100 adults. The results of the study indicate a significant occurrence of hypocalcemia in the age group up to 45 years ($\chi^2=20.34$, $p=0.00001$).
Conclusion
The prevalence of hypocalcemia in the adult population of Minsk-city was 3.3/100 adults (33:1000). The prevalence of hypocalcemia in the age group up to 45 years was 6.6/100 adults, in the age group 45 years over was 1.7 per 100 adults. The results of the study indicate a significant occurrence of hypocalcemia in the age group up to 45 years.

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EP270

Assessment of changing in the therapeutic attitude in patients with primary hyperparathyrodism in conservative management after the realization of radial densitometry

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Introduction and objectives
In the 4th Workshop on Primary Hyperparathyroidism, it is recommended to perform BMD by DXA of third radius as well as lumbar spine and hip DXA in the initial assessment and follow up of patients with primary hyperparathyroidism. This test is not available in many centers, which means that only *T* Score values of the lumbar spine and hip are used to certify the absence of osteoporosis in asymptomatic patients wich conservative management is performed. Our objective is to evaluate if the recent addition of radius DXA has modified the management of this patients.
Materials and methods
Retrospective study including patients in follow-up by primary asymptomatic hyperparathyroidism in conservative management according to the Fourth Workshop criteria when radial densitometry for the first time in its evolution. Changes after the DXA results were evaluated.
Results
20 patients (65.4 years ± 11.14, 90% women) with a follow-up of 3.95 years ± 1.97 were included. Blood calcium levels 11.05 ± 0.45 mg/dl, mean PTH of 105.46 pg/ml ± 60.9. None presented lumbar and/or femoral *T*-Score scores values lower tan -2.5 DS (lumbar T -0.15 DS ± 2.17, femoral -0.77 DS ± 0.98). The radial *T* Score was -2.67 DS ± 2.45. The radial densitometry results changed the clinical attitude in 70% of the patients, from the recommed conservative management to surgical treatment in those with a *T*-Score lower -2.5 DS in the distal radius and *T*-Score higher than -2.5 DS in the lumbar and/or femoral.
Conclusions
Our study reinforces the importance of performing distal radius densitometry in patients in which conservative management is giving to be performed, as is

recommended as recommended by international criteria. Lack of implementation may lead to conservative management in patients with osteoporosis.

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EP271

A rare case: intrathymic parathyroid adenoma

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Primary hyperparathyroidism in the most common cause of hypercalcemia. 87% of the cases present with single adenoma, 9% of them have hyperplasia, while multiple adenomas and parathyroid malignancy are detected in 3 and 1% of the cases, respectively. Although it is rare, parathyroid adenomas may be ectopic. The most common locations for ectopic parathyroid adenomas are thymus, tracheaesophageal cleft, carotis sheet, intrathyroidal and paraesophageal area. In this study, we aimed to present an intrathymic parathyroid adenoma as a rare case.

A 46-year old female patient who received hemodialysis for chronic renal failure secondary to chronic glomerulonephritis for 7 years and then underwent cadaveric renal transplantation in 2010 was presented for routine follow-up visit. Laboratory examination revealed urea:19 mg/dl(*n*:15–43),creatinin:0.8 mg/dl(*n*:0.57–1.11)), calcium:11.5 mg/dl (*n*:8.6–10.2 mg/dl), phosphorus:2.7 mg/dl (*n*:2.4–5.1 mg/dl), albumin:4.2 g/l (*n*:3.2–4.8 g/l), iPTH:340 pg/ml (*n*:15–68), creatinin clerarance in 24-h urine: 82 ml/min, calcium in 24-h urine: 410 mg/day. Neck ultrasonography was performed, which demonstrated 12× 9 mm sized well-circumscribed nodular lesion with heterogeneous echo at inferior part of lower pole of left thyroid gland (thyroid nodule? Parathyroid adenoma?). Femoral neck and L1–L4 vertebra were osteopenic on bone densitometry. Parathyroid scintigraphic examination detected no scintigraphic signs characteristic for parathyroid adenoma in the neck and mediastinum. The patient underwent parathyroidectomy following surgical exploration. Histopathologic examination of parathyroidectomy material revealed intrathymic parathyroid adenoma. The patient was scheduled for outpatientclinic follow-up with post-operative laboratory findings of iPTH: 38 pg/ml, Ca:9.9 mg/dl, P:2.5 mg/dl, Alb:4.3 g/l, kreatinin:0.7 mg/dl.

Annual incidence of primary hyperparathyroidism is 0.27%. Since Primerhiperparatiroidizmin yıllık görülme oranı % 0.27dir. Since both thymus and parathyroid gland embrologically derive from 3rd pharyngeal cleft, ectopic parathyroid adenomas may locate within thymus. It is very important to preoperatively determine the localisation of ectopic parathyroid adenomas to prevent surgical errors.

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EP272

Audit of emergency hypercalcaemia management in the acute medical unit

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Introduction

We conducted a retrospective audit of emergency management of hypercalcaemia presenting to the acute medical team and compared our practice against the Society for Endocrinology guidelines September 2016.

Method

53 adult patients with 59 corresponding medical admissions were identified from tracking all biochemistry samples with corrected calcium (cCa) $\geq$3.0 mmol/l processed between August 2015 and July 2016 trustwide. We conducted a retrospective review of their admissions' case records.

Results

Characteristics: age 40–98 years old (median 79), 60.4% female, median length of stay 7 days, presenting cCa range: 3.04–5.36 mmol/l (median 3.31 mmol/l). 30.5% had severe hypercalcaemia (cCa $\geq$3.50 mmol/l). *Aetiology*: 47.2% malignancy related hypercalcaemia, 15.1% primary hyperparathyroidism, 5.6% secondary or tertiary hyperparathyroidism, 9.4% drug-related, 15.1% unknown. Frailty was documented reason to withdraw further investigations in 62.5% of the latter. Coexistent active prostate cancer and hyperparathyroidism was found in two cases. *Investigations*: PTH was checked in 67.8% cases, Phosphate in 64.4%, ALKP 100%. Of the cases with suppressed PTH, only 72.2% had serum paraproteins checked, 55.5% urinary Bence-Jones proteins and 83.3% imaging for malignancy. Vitamin D was only checked in 22.6%. *Management:* Patients received an average of 3L intravenous fluids in the first 24 h. 62.7% received intravenous bisphosphonates. 13.5% had less than 2L intravenous fluids prior to bisphosphonate. Second line treatment with Cinacalcet, steroids, Furosemide or Calcitonin was used in 20.7% cases. There were no cases of rebound hypocalcaemia.

Conclusions

Compliance with guidelines recommendations was suboptimal in certain areas, not entirely explained by the adoption of a palliative approach with focus on symptom control in cases. Training opportunities will be devised locally to improve practice. Bisphosphonate use in the Emergency department should be controlled for the appropriate circumstances. Vigilance is recommended assigning causality in active malignancy, given that 11.1% of pre-existing malignancy cases were found to have concurrent PTH driven hypercalcaemia, despite only 38.9% of them being investigated with a PTH level.

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EP273

Higher circulating parathyroid hormone concentration fascilitates preoperative diagnostic imagings for localization in primary hyperparathyroidism

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Introduction

For minimally invasive surgery of primary hyperparathyroidism (PHPT), the identification of the accurate localization is required. As preoperative diagnostic imagings, we perform ultrasound, technetium 99m-sestamibi scintigraphy and either or both of megnetic resonance imaging or computed tomography in all cases. The aim of the present study is to evaluate the clinical biochemical factors that fascilitate preoperative diagnostic imagings for localization.

Methods

We retrospectively searched the medical records of patients with PHPT who were admitted in our hospital from 2014 to 2016. Fifty-five patients were identified. Four patients with parathyroid carcinoma, multiple endocrine neoplasia type 1, familial hypocalciuric hypercalcemia, and detectable parathyroid hormone-related protein were excluded. Fifty-one patients were included in the study. We defined 36 patients as the 'localized' group, including 30 patients who underwent curative operation and 6 non-operative patients whose suspicious adenoma was consistently identified by two or more of diagnostic imagings. And other 15 patients were defined as the 'non-localized' group. We compared biochemical data including intact parathyroid hormone (iPTH), serum calcium, urine calcium, and tartrate-resistant acid phosphatase 5b.

Results

iPTH was statistically higher in the 'localized' group (146 [103–195] vs. 98 [82–136] pg/ml: $p=0.010$). Multivariate logistic regression analysis demonstrated that the usefulness of preoperative diagnostic imaging was ensured only in higher iPTH ($p=0.014$). When we set the cut-off value of iPTH to 150 pg/ml, sensitivity was 48.6% and specificity was 87.5% (AUC: 0.73 [95% CI 0.59–0.87]). When we used whole parathyroid hormone (wPTH) in place of iPTH, we obtained similar results: the cut-off value 85 pg/ml with sensitivity 57.1% and with specificity 87.5% (AUC: 0.84 [95% CI 0.72–0.96]).

Conclusion

Both iPTH and wPTH as circulating parathyroid hormone concentration are useful to predict whether preoperative diagnostic imagings can identify the acurate localization of the parathyroid adenoma.

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EP274

Calcifediol is more effective than cholecalciferol in the treatment of severe vitamin D deficiency in a patient submitted to malabsorbitive bariatric surgery: a case report

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Context
Vitamin D deficiency following malabsorptive bariatric surgery can lead to osteomalacia. We report a patient with severe vitamin D deficiency following malabsorptive bariatric surgery successfully treated with calcifediol but not cholecalciferol.
Case description
A 40-year-old woman, submitted to biliopancreatic diversion 20 years before and chronically treated with 50 000 IU cholecalciferol weekly, was admitted to our Endocrine Unit because of severe low-back pain, muscle weakness, generalized muscular hypotrophy, associated with hypocalcemia and elevated PTH levels. Initial evaluation revealed low albumin-corrected serum calcium (7.4 mg/dl), high serum PTH (240 pg/ml), bone-specific alkaline phosphatase (125 µg/l) and 1,25-dihydroxyvitamin D (112 pg/ml) concentrations, and undetectable serum 25-hydroxyvitamin D (<7 ng/ml). Bone mineral density (BMD) was markedly low. Normocalcemia was initially restored with i.v. albumin and calcium gluconate. Treatment with calcitriol (0.5 µg three times daily) and oral calcium carbonate (1000 mg daily) was simultaneously started and cholecalciferol was replaced with calcifediol (125 µg (5000 UI) daily)). During follow-up the calcifediol dose was progressively tapered to 25 µg (1000 UI) daily and the calcitriol dose progressively reduced and finally withdrawn. Serum biochemistry normalized, BMD significantly increased and the patient's clinical conditions progressively improved, with a substantial recovery of autonomy.
Conclusions
Our data suggest that calcifediol migth be more efficacious than cholecalciferol for prevention and treatment of vitamin D deficiency in patients treated by malabsorptive bariatric surgery.

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EP275

The effect of $1,25(OH)_2D_3$ on interferon i secretion by human mononuclear cells *in vitro*

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Vitamin D is a secosteroid hormone known for its skeletal effects. Recently, the extraskeletal effects of vitamin D are under investigation. Vitamin D is thought to exert an immunomodulatory effect, having multiple effects on the immune system. It is known to induce immune tolerance and also to enhance the immune response to bacteria.
The aim was to study the effect of $1,25(OH)_2D_3$ on interferon I secretion by human mononuclear cells *in vitro*.
Human mononuclear cells were separated from whole human blood from healthy female human subjects using the Lymphoprep protocol. Subsequently they were placed in wells 10^6 cells/well and were cultivated for a period of 6 h at a temperature of 37 °C in a humidified environment of 5% CO_2 in the presence or absence of interferon alpha 400 U, $1,25(OH)_2D_3$ 250 pmol, interferon alpha 400 U and $1,25(OH)_2D_3$ 250 pmol. Subsequently the content of the wells was centrifuged and the precipitate was treated with Trizol for RNA extraction of genes known to be stimulated by interferon alpha. Real time PCR was performed for MX1, IFIT1, IFI44 and GAPDH as a control.
Interferon alpha was shown to stimulate genes related to interferon I secretion, i.e. it was found to have a positive feedback on its own secretion. $1,25(OH)_2D_3$ was found to modulate interferon I gene augmentation induced by interferon alpha treatment.
Vitamin D is being investigated for its immunomodulatory properties. In the present study vitamin D was found to modulate the response of human mononuclear cells to interferon alpha treatment.

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EP276

The changing face of primary hyperparathyroidism

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Primary hyperparathyroidism is a disease which nowadays is being diagnosed with increasing frequency. The diagnosis of primary hyperparathyroidism is based on routine calcium measurement, which if detected abnormally elevated leads to the screening of the patient for primary hyperparathyroidism. Therefore, primary hyperparathyroidism is frequently detected early in the course of the disease. Consequently, severe musculoskeletal manifestations may be lacking in the modern world setting in patients with primary hyperparathyroidism.
The aim was to describe musculoskeletal manifestations in patients with primary hyperparathyroidism being followed up in a center of excellence in Athens.
A cohort of 38 patients, 33 female and five male, with primary hyperparathyroidism aged 62.31 ± 1.87 years, being followed up within a center of excellence in Athens was studied. Musculoskeletal manifestations were recorded in the cohort of the patients studied.
Within the cohort of 38 patients with primary hyperparathyroidism being followed up within a center of excellence in Athens, 12 patients (31.58%) had osteoporosis, 2 (5.26%) had osteopenia, 7 (18.42%) had diffuse bone pain, 2 (5.26%) had diffuse myalgia and 1 (2.63%) had suffered a wrist fracture. Within the cohort studied 18 (47.37%) patients did not have any musculoskeletal manifestations.
It appears that primary hyperparathyroidism does not have severe musculoskeletal manifestations, such as osteitis fibrosa cystica, in the real world setting in patients followed up for the disease within a center of excellence in Athens. However, patients with primary hyperparathyroidism appear to have diffuse bone pain as well as osteoporosis, which may be complicated by a fracture in some of the cases. Early detection and diagnosis of the disease seems to have altered the face of primary hyperparathyroidism in the real modern world setting.

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EP277

Single center experience of intact parathyroid hormone determination in washout samples of suspicious parathyroid adenomas

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Introduction
Minimally invasive surgery is an alternative surgical approach for primary hyperparathyroidism with less surgical trauma and anesthesia complications. Neck ultrasonography and scintigraphy are still the first step tools for localisating parathyroid lesions. Intact parathyroid hormone (PH) determination in washout samples is really very useful when parathyroid lesions can not be easily distinguished from thyroid lesions or sometimes lymph nodes.
Method
In our clinic, we performed ultrasonography guided parathyroid fine needle aspiration procedure for 119 patients diagnosed with primary hyperparathyroidism between January 2005 and January 2016. Intact parathyroid hormone determination was performed in washout samples. 80 of the study group also had a parathyroid scintigraphy. All of the patients underwent parathyroid surgery.
Results
In 106 of the study group had positive parathyroid hormone washout (phw) results according to blood PH levels. Significant difference was achieved in localisation of the lesion (p:0.006), serum calcium levels (p:0.01) and PHW levels ($p<0.001$) between washout negative and positive group. No difference was observed in gender, age, presence of stone, levels of serum phosphorus, creatinin, alkaline phosphatase, parathyroid hormone, vitamin D and 24 h urinary calcium levels. 28 patients in the scintigraphy group had negative scan whereas 47 of them had both scintigraphy and PHW positive. 24 of the patients had positive PHW results but negative scintiscans.
Conclusion
The present study represents that ultrasonography combined with PHW evaluation seems to be more diagnostic according to parathyroid scintigraphy.

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EP278

Primary hyperparathyroidism due to atypical adenoma: clinical, biochemical and histological features of an Italian cohort

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Primary hyperparathyroidism (PHPT) is mostly due to a benign parathyroid tumor (99%). Some have parathyroid 'atypical adenomas', rare tumors with histological features of parathyroid cancer (PC) (fibrous trabeculae, thick fibrous bands, mitotic figures in parenchymal cells), without local invasion or metastasis. We evaluated 20 patients with histological diagnosis of atypical adenomas. Patients were 13 women and seven males (mean age: 55 ± 13 yrs). Nineteen patients had a sporadic PHPT and one a Familial Isolated PHPT (FIHP). At least one of the following symptoms was present in 8 (40%) patients: nephrolithiasis ($n=8$), clinical fragility fractures ($n=1$), neuropsychiatric symptoms ($n=6$). In the remining patients ($n=12$) PHPT was asymptomatic. Osteoporosis was detected in 8 (40%). Preoperative imaging was positive in 16 (80%) patients. The association with other tumors was recorded: papillary thyroid carcinoma ($n=4$), adrenal bilateral hyperplasia ($n=1$), breast cancer ($n=1$), Morton's neuroma ($n=1$). Biochemical tests at baseline were: albumin adjusted serum calcium 12.4 ± 0.8 mg/dl, PTH 204 (160–277) pg/ml and 25OHD 13.4 ± 7 ng/ml. All patients underwent PTx. The histological diagnosis was of atypical adenoma (mean diameter 24 ± 10.6 mm) with the following features: fibrous trabeculae in two, thick fibrous bands in 13, capsular invasion infiltration in seven and mitotic figures in two. All but one patients were cured after PTx and remained normocalcemic (mean follow-up 5 years). One patient, with apparently sporadic PHPT, had persistent hypercalcemia and he is in follow-up. This study suggests that PHPT due to atypical adenoma is generally asymptomatic at diagnosis, it has a moderate-severe biochemical profile resembling that of PC, it is a sporadic disease and shows a benign prognosis in the majority of cases. We found an association with other tumors, that will be evaluated in further studies.

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EP279

Medullary vertebral compression in primary hyperparathyroidism

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We report the case of an ectopic parathyroid adenoma, revealed by a medullary vertebral compression by a brown spinal tumor in a 44-year-old women. Physical examination revealed a lower limb weakness, paresthesia and radicular lower extremity pain. Magnetic resonance imaging (MRI) showed osteolytic vertebral lesions suggesting metastatic localizations. A thoracic CT scan identified a mediastinal mass measuring 6.2 cm in the major axis. Biological evaluation revealed a hypercalcemia (135 mg/l) with very high PTH (1896 pg /ml), parathyroid scintigraphy confirmed the mediastinal ectopic parathyroid. The patient underwent surgical resection of the mediastinal mass that proved to be a parathyroid ectopic adenoma. She showed a remarkable improvement in her clinical condition observed 6 months after parathyroidectomy. Medullary vertebral compression by a brown spinal tumor in primary hyperparathyroidism is rare, surgery of parathyroid adenoma improved clinical condition without resection of the brown tumor, However surgical decompression may be necessary in some cases.

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EP280

Management of primary hyperparathyroidism: Experience of a large UK teaching hospital

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Background
Primary hyperparathyroidism (PHPT) is a common cause of hypercalcaemia seen in outpatient endocrinology clinic. Diagnosis is based on biochemistry and exclusion of other conditions, such as familial hypocalciuric hypercalcaemia. Symptomatic patients should usually be referred for parathyroidectomy. For asymptomatic patients there are clear guidelines for surgical referral, based on the Fourth International Workshop (2014) recommendations. This study evaluates current practice for diagnosing and managing primary hyperparathyroidism compared to international guidelines, at a large UK teaching hospital.
Methods
We evaluated all new cases of PHPT seen in outpatient endocrinology clinics between January 2014 and July 2016. Data were collected using a standardised proforma. Data fields included demographics, biochemistry and imaging. Follow-up data on surgical referrals, histology and outcomes were also collected.
Results
Of the 121 patients, at diagnosis, 50.4% were symptomatic. Complete investigation data were available for 117. 59.8% had all relevant investigations performed as recommended per guidelines. Urinary calcium was conducted in 67.5% of patients, of those, 44.3% had inappropriate vitamin D levels at the time of collection. At diagnosis, 30.0% patients had renal complications and 36.3% had osteoporosis. 84% of the 121 met criteria for surgery, although 58.8% were actually referred. The most common reasons for non-referral were patient choice (33.3%) and fitness for surgery (45.5%). On imaging, 74% had a single adenoma, 11.7% had no obvious adenoma. 75% had positive correlation between imaging and surgical findings. 3 months post-operatively, 91% of patients had normal calcium and 68% had normal PTH.
Conclusions
This study shows that the majority of patients with PHPT are diagnosed and investigated as per guidelines. Almost all patients had a normal calcium 3 months post operatively, suggesting surgery was curative. However, urinary calcium estimation was performed without the correction of vitamin D levels in a significant percentage of patients, thereby affecting accuracy of interpretation.

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EP281

Fahr Syndrome and idiopathic primary hipoparathyroidism – clinical case

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Introduction
Fahr syndrome (FS) is a neuropsiquiatric condition due to progressive basal ganglia calcification. Although physiopathology is not completely understood, it may be secondary to infectious, metabolic and genetic diseases.
Case report
A 65-year-old male Caucasian was referred to the outpatient endocrine department because of hypocalcaemia. No perioral paresthesia or tingling of the fingers and toes were noticed. He complained of longstanding hand tremor and since one year ago apathy and gait instability were evident. Past medical history revealed High Blood Pressure under treatment. He also referred previous use of anti-convulsivant medication since he was 15 because of diagnosed epilepsy. Drugs were suspended at 20th with no further seizures. No previous cervical surgery or irradiation were done. Her death mother was also diagnosed of epilepsy. Besides slow and rigid movement, physical examination was otherwise normal, with negative Chvosteck and Trouseau. Deafness, visual field defects or dismorphisms were absent. Analytic evaluation confirmed albumin-corrected hypocalcemia, hyperphosphatemia, normal serum magnesium, hypoparathyroidism with sufficient 25OH-vitamin D levels. Slight ferropenia and chronic renal disease grade 2 were diagnosed. Besides Hashimoto thyroiditis, no other endocrinopathy was evident. Ecocardiogram evidenced left auricular dilatation and reduced global systolic function. Cystic renal disease and slight cystic calcifications were documented on kidneys ultrasound and cervical ultrasound evidenced multinodular goiter. Bone densitometry of femur and lumbar spine was normal. craneoencephalic TC identified bilateral simetric parenquimatous calcifications, both supra and infratentorial, with extensive involvement of basal ganglia. I^{123}-SestaMIBI scintigaphy did not fixate in cervical imaging. Anti-NALP5 antibody was negative, as well as CASR activating mutation.
Discussion and conclusion
Parathyroid hormone and calcium abnormalities are the most common metabolic disorders associated to FS. We describe a patient diagnosed of idiopathic hypoparathyroidism. Basal ganglia calcifications support a long-standing

hypocalcemia, and chronic ion disturbance may have contributed to the absence of usual muscular complaints.

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EP282

Clinical presentations of four patients with familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumor syndrome

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Introduction
Primary hyperparathyroidism is commonly treated with targeted parathyroidectomy guided by preoperative imaging and intraoperative parathormone monitoring. Despite advanced imaging techniques, failure of parathyroid localization still occurs. Hyperparathyroidism-jaw tumor syndrome and familial isolated hyperparathyroidism are a rare autosomal dominant tumor syndrome characterized by hyperparathyroidism. In this report, we present four patients with familial isolated hyperparathyroidism and hyperparathyroidism-jaw tumor syndrome, below.
Case 1
A 26-year-old man with left maxillary tumoral lesion is referred. He had the elevated serum calcium and parathormon levels, osteoporosis, rena anomalia, nephrolitiasis, Acording to the diagnosis of hyperparathyroidism jaw-tumor syndrome, imaging modalities included neck sonography, scintigraphy, computerized tomography indicaed that a ectopic parathyroidal adenoma, then it was removed by videoscopic assisted medastinoscopy with temporarily hypoparathyroidism.
Case 2
A 43-year-old-man who is a relative of Case 1 is presented with persistent myalgia-arthralgia and nausea due to hypercalcemia caused by increased parathormon levels. Sonographic and scintigraphical evaluations of the neck showed that multiple irregular nodules of thyroid and suspected parathyroid adenomas. Fine neddle aspiration cytology of the nodules and pathological lymphadenopathy revealed a suspect of the low differentiated thyroidal carcinoma with lymphatic invasion. In wash-out sampling from suspected parathyroid adenoma, parathormon levels were increased. Total thyroidectomy with central and lateral neck dissection in addition adenomectomy with hungry bone syndrome.
Case 3
A 600-year-old-man who is in relations with Case 1 and Case 2 is complained with nausea-vomiting and lower back pain with osteoporotic fractures of left femur and left humerus. His serum levels of calcium and parathormon are highly increased. Imaging modalities showed a suspected lesion in the inferior region of the left thyroidal localization. After minimal invasive intervention and selective parathyroid sampling, the second operation included exploration and thyroidectomy with 3.5 paratyhroidectomy and implantation to sternocleidomastoid muscles were performed. Postoperatively, he had hypothyroidism with elevated serum calcium and parathormon levels. Thereafter hybrid nuclear modalities showed a suspected paratrakeal lesion, the case referred to reoperation with radioguided parathyroid surgery.
Case 4
The patient was a 51-year-old man (who is a brother of Case 3) presenting without any symptoms. He had hypercalcemia (12.2 mg/dl) and hyperparathyroidism (247 pg/ml). Parathyroid lesion detected with sonography and scintigraphical evaluations, and it is referred to minimal invasive parathyroid adenomectomy.
Conclusion
Primary hyperparathyroidism is a common clinical problem for which the only definitive management is surgery. Diagnosis of the familial primary hyperparathyroidism caused by CDC73 (formerly known as HRPT2) is based on the biochemical findings of primary hyperparathyroidism, identification of ossifying fibroma(s) of the maxilla and/or mandible on imaging studies, family history, and detection of a heterozygous germline CDC73pathogenic variant on molecular genetic testing. The spectrum of CDC73-related disorders includes hyperparathyroidism-jaw tumor syndrome, familial isolated hyperparathyroidism and parathyroid carcinoma, In familial primary hyperparathyroidism, reoperative parathyroidectomy are challenging entities that require special consideration and expertise.

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EP283

When is it worthwhile to perform parathyroid SPECT/CT scintigraphy in primary hyperparathyroidism?

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Introduction
Observed increasing frequencies of asymptomatic or oligosymptomatic PHP cases may increase the rate of false negative imaging results.
Aim
To determine the level of PTH and calcium at which an enlarged parathyroid gland can be detected by parathyroid SPECT/CT.
Material and methods
A retrospective analysis of 117 patients diagnosed with PHP (100 females and 17 males, aged 16–88 years) was performed. In each patient parathyroid SPECT/CT after administration of 500 MBq of 99mTc-MIBI was conducted (Siemens Symbia T16). Serum calcium and parathormone (PTH) were measured in each patient, serum phosphate was estimated in 109 subjects. Statistical analysis was performed with Statistica 12 Software.
Results
Median serum calcium level was 2.77 mmol/l (LQ and UQ – 2.66 and 2.87 mmol/l, respectively); median serum PTH level was 122.8 pg/ml (97.2 and 191.9 pg/ml); median plasma phosphate was 0.84 pmol/l (0.74 and 0.98 mmol/l). In 70 (59.8%) patients an enlarged parathyroid gland was detected with SPECT/CT. There was a statistically significant difference in PTH levels (median 138.15 and 114.80 pg/ml, respectively; $P=0.02$) and serum calcium levels (median2.74 and 2.67 mmol/l, $P<0.01$) between patients with positive and negative parathyroid SPECT/CT. Serum phosphate levels did not differ significantly ($P=0.19$). Receiver–operator curves (ROCs) were drawn to establish PTH and serum calcium cut-off levels for positive parathyroid SPECT/CT imaging. Sensitivity and specificity of parathyroid scintigraphy were 38 and 89.6%, respectively, for PTH cut-off level of 191.9 pg/ml, and 52 and 79%, respectively, for serum calcium cut-off level of 2.74 mmol/l.
Conclusions
Limiting parathyroid SPECT/CT to patients with significantly increased PTH and/or serum calcium levels, particularly if surgical treatment is not considered, may decrease false negative imaging rates and allow to avoid unnecessary radiation exposure. More precise determination of PTH and calcium cut-off levels requires analysis of larger patients group data.

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EP284

Parathormone (PTH) as a marker of vitamin D (VitD) deficiency

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Introduction
VitD deficiency, the pandemics of which we currently observe, may result in secondary hyperparathyroidism even if not accompanied by hypocalcaemia.
Aim
To assess VitD levels as a cause of secondary hyperparathyroidism.
Material and methods
257 healthy volunteers with normal kidney function (GFR $<$ 60 ml/min) (28.4% males), median age 57 years, were included. In each participant, serum calcium,

phosphates, creatinine, PTH and total VitD levels, as well as urinary calcium in urine morning sample, were measured. Daily calcium intake was estimated with a dietary questionnaire. Statistical analysis was performed with Statistica 12 Software.
Results
Median VitD level in the investigated group was 21.22 ng/ml; PTH – 41.17 pg/ml, serum calcium – 2.39 mmol/l, serum phosphates – 1.12 mmol/l, serum creatinine – 68 μmol/l, and urinary calcium – 2.69 mmol/l. Median daily calcium intake was 689 mg. There was statistically significant negative correlation between VitD and PTH levels ($r=-0.19$, $P=0.0018$), independent of serum creatinine. This relationship was particularly significant for measurements performed during autumn/winter ($r=-0.34$, $P<0.0001$), while losing its significance in study subjects subgroup investigated during spring/summer ($r=-0.06$, $P=0.5153$). Kruskal-Wallis ANOVA analysis showed a statistically significant difference in PTH levels in relation to VitD deficiency severity (predefined ranges: <10; 10–19.9; 20–29.9 and ≥ 30 ng/ml) ($P=0.0078$). A significantly higher PTH level was observed in subjects with severe VitD deficiency (<10 ng/ml) when compared to subgroups with VitD levels of 20–29.9 ng/ml ($P=0.0147$) and ≥ 30 ng/ml ($P=0.0401$). A significant negative correlation was found also between serum PTH and serum calcium ($r=-0.13$, $P=0.0447$).
Conclusions
Lack of significant negative correlation between serum PTH and VitD, seen during spring and summer confirms that appropriate sunlight exposure is sufficient to correct VitD deficiency. Significant increase in PTH levels is seen mostly in subjects with particularly low VitD levels, which may be an argument for redefining the recommended normal range of VitD.

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EP285

Pathological basal ganglia calcification in isolated idiopathic hypoparathyroidism: a case report

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Introduction
The isolated hyperparathyroidism (IHP) is a metabolism disorder characterized by an absent or low parathormon (PTH) and hypocalcemia. It can be acquired, autoimmune, a result of some syndrome and as a part of a family (FIHP). FIHP is an extremely rear disease which is inherited auto somatic dominant or auto somatic recessive as a result of a mutation of one or several different genes. Pathological calcifications in the cerebrum are a secondary form of calcification in patients with IHP.
Material and methods
We present two patients, a brother and a sister, age 44 and 42. The disease started in both cases, with a series of epileptic attacks, the brother at the adolescent period and the sister at age of 30. The diagnose was established based on a characteristic symptoms: Fatigue, muscle weakness, paresthesis, convulsions, speech and attitude disorder as well as cognitive deficit. The brother has cataract and the sister has hirzutism and acne. Hormone and laboratory diagnostic tests. Radio diagnostic on the kidneys, densitometry and psychological tests.
Results
The brother: PTH = 4.22 pg/ml (15–65), TCa = 1.08 (1.21–2.6), Posf = 2.01 (0.8–1.4 mmol/e), Ca++ = 1.46 (1.3–10) mmol/l, Vit. D 14.35, Mg 0.69 (0.6–1.1 mmol/l). Undergone cataract surgery. The sister: PTH = 1.2 pg/ml, TCa = 1.92, Posf = 1.7. No signs for litiasa and nefrosclerosis. KT scan of the brain: calcification in the cerebellum, basal ganglia, par ventricular and sub cortical – M. Fahr. No signs of nefrocalcinosis. Radiology finding shows osteosclerosis of the cranium, spine, long bones. Both of them have neuropsychological disorder with limited intellectual capacity and light mental retardation.
Conclusion
IPH from an unknown etiology points to a family HypoPTH which needs to be confirmed by a genetic test. The tests were not performed due to financial limitations. Timely diagnose of IPH can prevent calcification in basal ganglia.

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EP286

Diseases associated with hypercalcemia

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Introduction
According to modern studies, hypercalcemia is associated with an increased risk of urolithiasis, cholelithiasis, gastritis and peptic ulcer.
Objective
To study the prevalence of urolithiasis, cholelithiasis, gastritis and peptic ulcer in patients with hypercalcemia in Minsk-city.
Materials and methods
we studied 1207 people, average age 53.9 ± 17.25 (892 women, 315 men) from 18 to 96 years. Examination: total calcium, total protein, creatinine, ultrasonography, fibrogastroduodenoscopy, an analysis of morbidity.
Results
Hypercalcemia has been found in 31 people, mean age was 58.39 ± 11.6 years. Urolithiasis was detected in 141 cases (in patients with hypercalcemia – in nine cases) cholelithiasis was detected in 107 cases (in patients with hypercalcemia – in ten cases) gastritis was detected in 397 cases (in patients with hypercalcemia – in 21 cases) peptic ulcer was detected in 102 cases (in patients with hypercalcemia – in nine cases).
Significant differences was detected in the prevalence of urolithiasis ($\chi^2=8.54$, $P=0.0035$), cholelithiasis ($\chi^2=19.33$, $P=0.00001$) gastritis ($\chi^2=16.41$, $P=0.0001$) peptic ulcer ($\chi^2=15.69$, $P=0.0001$) in patients with hypercalcemia compared all studied patients.
Conclusion
The results of the study show an increasing risk of urolithiasis, cholelithiasis, gastritis and peptic ulcer in patients with hypercalcemia. The results may indicate an important role of hypercalcemia in the pathogenesis of these diseases.

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PTH levels in vitamin D deficiency

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Introduction
High level of Parathormone (PTH) impair bone health by increasing the risk of fracture. The aim is to determine the threshold value of PTH elevation to accompany deficiency or failure of Vit D. This may be an important parameter in assessing bone metabolism in clinical practice.
Material and method
931 patients who were referred to the endocrinology clinic were retrospectively studied and 880 patients diagnosed with Vit D deficiency included to the study. Patients were divided into three groups according to their vitamin D levels: <10 ng/dL, 10–19.99 ng/dl, 20–29.99 ng/dl. The mean Ca, P, PTH, Vit D, ALP levels were calculated.
RESULTS
880 patients included in the study, 710 were female and 170 were male.
The mean PTH levels were 68.99, 56.10, 50.92 pg/ml when Vit D levels were <10 ng/dl, 10–20 ng/dl, 20–30 ng/dl and respectively and a statistically significant difference was found between PTH levels ($P<0.0001$).
When ROC analysis was performed, while Vit D level <5 ng/dl; PTH level was >71.25 pg/ml (sensitivity 45%, specificity 78%), while the Vit D level was <10 ng/dl; PTH level was >66.75 pg/ml (sensitivity 50%, specificity 77,4%), while Vit D level <20 ng/dl; PTH level was >61.1 pg/ml (sensitivity 40.3%, specificity 80.9%)
Conclusion
As the Vit D level decreases, the calcium level decreases statistically significantly while the parathormone level increases. Patients with Vit D deficiency have elevated PTH levels but PTH levels are still in the normal reference range. Prospective studies are needed to evaluate the effect of increased but still in a normal range PTH levels on bone with measurement of bone mineral density.

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EP288

Renal complications in patients with chronic postoperative hypoparathyroidism treated with oral calcium and active vitamin D metabolites

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Patients with chronic hypoparathyroidism (HypoPT) treated with oral calcium and active vitamin D metabolites are at risk of renal complications, because of the lack of action of PTH at the renal tubule. In the present study we evaluated 90 patients (68 females and 22 males; age: 51.8 ± 14.1 yrs) with chronic postoperative Hypo (PO-HypoPT) diagnosed since at least 3 years. All patients were treated with calcitriol and 35 (39%) with oral calcium two patients were also treated with thiazide diuretics. One-hundred forty-two healthy Hospital employers, matched for age and sex, undergoing routine medical evaluation, were used as control. Mean levels of Alb-Ca and ionized calcium were in the normal range and but 39 (43.3%) patients had values that did not meet the range recommended by the recent guidelines of the European Society of Endocrinology (ESE). Serial measurements of serum calcium prior to the present evaluation were available in 78 patients: only 9 (11.5%) patients had all values within the recommended ESE range, and a large proportion of patients (32, 41.0%) had values greater than the upper recommended value. The mean serum phosphorus and creatinine levels were in the normal range, but 7 (7.7%) patients had elevated values of phosphorus and 22 (24.4%) of creatinine. The serum calcium-phosphate product was normal in all patients. Forty-four (54%) patients showed increased 24-h urinary calcium excretion and 27 (30%) microlithiasis, mostly asymptomatic. Compared to the controls, patients had statistically significant lower mean serum Alb-Ca ($P < 0.0001$) and higher serum creatinine ($P = 0.0008$) and greater prevalence of kidney stones (27/90 vs 7/142, $P < 0.0001$, OR: 8.2 (3.4–19.9)). In conclusion, conventional treatment of chronic PO-HypoPT is suboptimal and associated with an increased risk of renal complications. Careful monitoring of patients, as recommended by the ESE guidelines, should be therefore performed.

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EP289

The results of parathormone assay in parathyroid aspirates in preoperative localization of parathyroid adenomas for focused parathyroidectomy in patients with negative or suspicious sestamibi scans

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Objective
In primary hiperparathyroidism (PHPT), increasing the number of patients treated by focused parathyroidectomy should be the main objective of pre-surgical imaging modalities. Suspicious or negative imaging results do not always mean multiglandular disease, most of the patients may single adenoma and therefore these patients may still benefit from focused parathyroidectomy.
Methods
Retrospectively, we analyzed the data of 65 patients with PHPT with suspicious or negative sestamibi scans who admitted at a tertiary reference center between January 2013 and December 2016. We excluded patients who had history of chronic renal failure, renal transplant and multiple endocrine neoplasia. All patients underwent an endocrinologist operated ultrasonographic examination and parathyroid fine needle aspiration wash-out procedure.
Results
Of the 65 patients, 23 patients had nodular guatr disease. Fifty-four patients had positive parathormone (PTH) wash-out results. A total of 43 patients underwent surgery. Of the 43 patients, four patients had redo-surgery. Of the operated patients, 40 had positive parathormone wash-out results and had successful focused surgery. All of the patients with redo-surgery had positive parathormone wash-out results and successfully re-operated. Three patients with negative PTH wash-out results, two of them had successful bilateral neck exploration, but a patient's operation was not successful although bilateral neck exploration.
Conclusion
Endocrinologist operated US and PTH wash-out increases the number and success of focused surgery. Especially, patients with redo-surgery may benefit from this procedure.

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EP290

Weight has a weak influence on calcium-phosphorus metabolism in HIV-patients with vitamin d deficiency

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Introduction
In contrast to general population, clinical consequences related to low levels of 25-hydroxyvitamin D in HIV-infected patients with overweight are not established. The aim of our study was to investigate the influence of weight on clinical parameters and on calcium-phosphorus homeostasis in HIV-patients with vitamin D deficiency.
Methods/design
Prospective study of HIV outpatients treated in our hospital. Vitamin D deficiency (D-DEF) was defined as serum 25-hydroxyvitamin D below 20 ng/ml. Patients were classified as "overweight/obesity" if body mass index (BMI) ≥ 25 Kg/m^2. Their clinical, metabolic and immunological data were compared to HIV-individuals classified as "normal weight" (BMI: 18.5–24.9 Kg/m^2).
Results
One hundred and six HIV-infected individuals (86.8% male, mean age: 46.4 ± 6.5 years) were included. 51.9% were classified as "overweight/obese". Levels of vitamin D were lower in "overweight/obese", but no significant difference was observed between both groups (14.8 ± 4 vs 15.3 ± 1.8 ng/mL; $P = 0.772$). In overweight HIV-patients, although into the normal range, the serum phosphorus levels were higher as compared as those without D-DEF (3.3 ± 0.8 vs 2.9 ± 0.5 mg/dl; $P = 0.04$). Levels of i-PTH were also higher in overweight D-DEF patients (66.1 ± 35.1 vs 48.9 ± 19.8 pg/ml; $P = 0.04$). No others differences were observed between these groups. Analyzing individuals with D-DEF only, there was no difference in calcium, phosphorus or i-PTH levels between patients with or without overweight.
Conclusions
In HIV-infected patients with low levels of 25-hydroxyvitamin D, BMI ≥ 25 Kg/m^2 determines subtle changes on calcium-phosphorus homeostasis which clinical significance remains to be determined. Further follow-up studies to establish potential clinical implications of these findings are needed.

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EP291

Chronic hypoparathyroidism disease profile from 492 patients in the PARADIGHM™ natural history global registry

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PARADIGHM™ is a global registry (NCT01922440) of patients diagnosed with hypoparathyroidism (HPT) ≥6 months regardless of aetiology and management. Routine medical care data were entered using electronic case report forms; the 36-item Short Form Health Survey was completed by patients. Baseline-recorded data are reported for 492 patients enrolled as of 1 December 2016 from 41 centres. At baseline, 78% were women, mean (s.d.) age was 49 (17) years, and mean (s.d.) BMI was 29.8 (8.6) kg/m^2. Medical histories included mood disorder (29%), arthritis (16%), kidney stones (11%), fractures (8%), chronic renal disease (6%), and hypercalciuria (3%). 93% of patients had baseline symptom data (for the

previous 6 months), all reported ≥1 symptom; the most common were fatigue (40%), paraesthesia (30%), muscle twitching (24%), anxiety (20%), brain fog (17%), muscle weakness (17%), back pain (16%), and headache (16%). HPT management included oral calcium in 91% (calcium carbonate, 59%) and active vitamin D in 84% (calcitriol, 94%) of patients; 7% received recombinant PTH (1–84) in a clinical trial. 62% were taking ≥1 concomitant medication (45% thyroid hormone, 4% hydrochlorothiazide, 1% psycholeptics, <1% magnesium supplements). Key laboratory mean (S.D.) values were PTH 1.5 (1.5) pmol/l, albumin-corrected total serum calcium 2.1 (0.3) mmol/l, phosphate 1.4 (0.3) mmol/l, magnesium 0.8 (0.1) mmol/l, and 24-hour urinary calcium 7.2 (4.6) mmol/day. Among 330 patients who had imaging, calcifications were reported in 40 patients (12%): kidney ($n=12$), brain ($n=9$), cardiovascular ($n=7$), and other sites ($n=12$). In the previous 12 months, 47% of patients had 2−3 doctor visits and 49% had ≥1 emergency room visit owing to HPT. Mean (S.D., range) SF-36v2 summary scores for physical and mental components were 45.6 (10.7; 11.2−64.2) and 48.4 (11.0; 11.9−70.3). These real-world data for 492 patients enrolled in the PARADIGHM™ registry provide valuable insight into disease variability, symptom burden, and HPT treatment approach.

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EP292

Prevalence of cardiometabolic risk factors among Saudi Women with vitamin D deficiency

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Vitamin D deficiency is highly prevalent among Saudi women. The aim of this study was to determine the prevalence of cardiometabolic risk factors in apparently healthy Saudi women with vitamin D deficiency. A Retrospective chart review was conducted in the "Center of Excellence for Osteoporosis Research" (CEOR), King Abdulaziz University, Jeddah, Saudi Arabia. Only healthy women 20–40 years old, with no history of previous illnesses and not on any medications were included. Data on anthropometric measurements as well as blood pressure (BP) were obtained. Body mass index (BMI) was calculated. Laboratory results including fasting blood glucose (FBG), fasting lipid profile, 25-hydroxyvitamin D_3 ($25(OH)D_3$) and parathyroid hormone (PTH) were also obtained. Vitamin D deficiency was defined as $25(OH)D_3$ concentration <50 nmol/l. Modified NCEP:ATPIII criteria were used to define cardiovascular risk factor cutoff points. A total of 305 women were included in the current analysis. Mean (± S.D.) age of the study group was 28.4±6.1 years and median (IQR) $25(OH)D_3$ was 17.8 (11.9–28.2) nmol/l. Almost 97% of the study participants were vitamin D deficient and 70% had values below 25 nmol/l. 25-hydroxyvitamin D was significantly inversely associated with waist circumference, systolic and diastolic BP and PTH ($P=0.011$, <0.0001, <0.0001, <0.0001, respectively). Prevalence of cardiovascular risk factors were higher among subjects who fell in the lowest tertile of $25(OH)D_3$ except total cholesterol and low density lipoprotein cholesterol, however only higher PTH was statistically significant ($P=0.022$). The results of the present study confirm the high prevalence of vitamin D deficiency among otherwise healthy Saudi women. The results also suggest that the prevalence of selected cardiometabolic risk factors is higher among those with low vitamin D status. Prospective studies are needed to determine whether such deficiency will be of clinical significance with advancing age in this population, and whether vitamin D supplementation has beneficial effects.

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EP293

18F-choline PET/MRI in patients with primary hyperparathyroidism and negative sestamibi SPECT/CT – report of two cases

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Primary hyperparathyroidism is a common disorder which is curable by surgery. Exact localisation of parathyroid adenoma is essential for minimal invasive approach. The gold standard is sestamibi SPECT/CT nowadays - but fails in approximately 10% cases. In last 3 years some case report with 18F-choline PET/CT were published. We describe two cases with SPECT/CT invisible parathyroid adenoma.

First case was 36y/o woman, with osteopenia diagnosed after pregnancy (was attributed to LMWH treatment in pregnancy) and no relevant health problems. Mild hypercalcemia (2.7 mmol/l) was found in 2014 in context with vitamine D deficiency and patient was referred to our department. Primary hyperparathyroidism was clearly stated (serum calcium 2.9 mmol/l; PTH 130 ng/l; 25-OH-D vitamine 69 nmol/l), bone turnover was also slightly elevated. According to age, osteopenia and planned pregnancy we decided for surgery, but ultrasonography and sestamibi SPECT/CT was without any parathyroid adenoma. Patient did not agreed with surgical revision of all four glands and we choosed conservative approach. In 2015, hypercalciuria was appeared, therefore next SPECT/CT and ultrasonography was performed, with still negative results. In 2016 we used PET/MRI with 18F-choline for the first time in our hospital – upper left parathyroid adenoma was found (9×6 mm, SUVmax 5.8). Patient was referred to surgery and histologic examination reveals parathyroid adenoma and patient went normocalcemic, normocalciuric and with normal PTH level, with continuing D vitamine treatment due to osteopenia. No hungry bone syndrome was presented. Second case was 59 y/o man, with primary hyperparathyroidism treated for 3 years by cinacalcet, with twice negative sestamibi SPECT/CT, repeatedly negative ultrasonography. During the treatment was slightly hypercalcemic (2.6 mmol/l), normocalciuric, with non-progressing osteopenia. PET/MRI revealed 8mm left bottom parathyroid adenoma and patient was referred for surgical resection, planned for March 2017.

Despite our limited experiences, 18F-choline PET seems to be a promising diagnostic option. Using MRI instead of CT has some advantages – radiation load, no risk of iodine contrast allergy and slightly better resolution in neck region.

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EP294

Severe hypocalcemia induced by Denosumab in a patient with Osteroporosis after malabsorptive bariatric surgery

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Introduction

Denosumab is a monoclonal antibody indicated in the treatment of postmenopausal osteoporosis. Hypocalcemia is a rare adverse effect.

Case report

We present the case of a 58-year-old woman with a clinical history of bariatric surgery in 2001 and osteoporosis with multiple vertebral and hip fractures. Under treatment with Zinc sulphate, Vitamin A, 25-OH-vitamin D, calcium and iron. She came to the A&E for general malaise, generalized weakness, paraesthesia, dysarthria and weight loss of some weeks of evolution. She was admitted due to a severe hypocalcemia: calcium 5 mg/dl (8.4–10.2), ionic calcium 2.5 mg/dl (4.64–5.28), phosphate 1.2 mg/dl (2.3–4.7), magnesium 2.35 mg/dl (1.6–2.6), albumin 38.8 g/l (35–50), PTH 284 pg/ml (15–65), 25-OH-vitamin D 22 ng/ml (30–100), alkaline phosphatase 360 U/l (40–150) and normal kidney function. The ECG showed a prolonged QT. The signs for hypocalcaemia were negative. The patient had received treatment with subcutaneous Denosumab 60 mg 22 days before, with prior calcium values of 8.4 mg/dl, phosphorous 3.1 mg/dl, 25-OH-vitamin D 25 ng/ml, PTH 76 pg/ml and Ca-urine 27 mg/24 h. Treatment was started with intravenous calcium for 8 weeks, together with oral calcium, phosphorous and 25-OH-vitamin D. The patient improved symptomatically, with a normalization of the QT and analysis with ionic calcium 4.6 mg/dl, phosphate 3.5 mg/dl, magnesium 2.8 mg/dl, PTH 139 pg/ml, Ca-urine 2.3 mg/dl and 25-OH-vitamin D 39 ng/ml. The treatment to discharge was oral calcium 2.5 g/day and 25-OH-vitamin D 16.000 UI daily.

Conclusions

Hypocalcemia after Denosumab is a rare adverse effect but it can be serious. The patients who have undergone malabsortive bariatric surgery have a greater risk. It is important to monitor the 25-OH-vitamin D and calcium in patients who start treatment with Denosumab and at 15 days in patients who are at the greatest risk, as is the case of this patient.

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EP295

Performance characteristics of a new Waters MassTrak™ Vitamin D assay

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The Waters MassTrak Vitamin D Kit is designed for the quantitative determination of serum or plasma 25-hydroxyvitamin D3 (25OHD3) and 25-hydroxyvitamin D2 (25OHD2), which in combination provide the total 25-hydroxyvitamin D concentration as an aid in the assessment of vitamin D sufficiency.
The MassTrak Vitamin D Kit is validated for use with the Waters® ACQUITY UPLC® I-Class/Xevo® TQD IVD System and the sample preparation has been validated using the Tecan® Freedom 100/4 EVO® Offline Automated Liquid Handling system. Screening for vitamin D deficiency is recommended by the Endocrine Society Clinical Guidelines- Evaluation, Treatment and Prevention of Vitamin D Deficiency by the Task Force for all individuals at risk for deficiency.
Vitamin D status (Total 25OHD, which is the sum of 25OHD2 and 25OHD3) has been a challenge to measure accurately because the antibodies used in many immunoassays do not have 100% co-specificity for both 25OHD2 and 25OHD3.
Precision, sensitivity, linearity, potential interferents and carryover were all assessed during the development of the MassTrak™ Vitamin D kit and found to meet the performance criteria specified for the kit.
To further assess the accuracy and performance of the MassTrak™ Vitamin D kit assay, Waters enrolled in the CDC Vitamin D Standardisation Certification Program (VDSCP) for 25(OH)D in serum, which assesses bias and precision of assays relative to reference measurement procedures.
The MassTrak™ Vitamin D kit calibrator materials are traceable to NIST SRM2972a via a documented unbroken chain of calibrations. The accuracy of this traceability to NIST SRM2972 has been verified through participation of the Vitamin D Standardisation Certification Program (VDSCP).

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EP296

Vitamin D intoxication complicated with parathormon treatment in elderly: a case report

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Parathormon treatment for osteoporosis is rarely complicated with hypercalcemia. Vitamin D treatment with high doses frequently can cause asymptomatic intoxication.We present a case with life-threatening hypercalcemia complicated both parathormon and high-dose vitamin D.
A 85-year old woman hospitalized for sudden-onset confusion. In history she had coronary-artery by-pass operation and a serebrovascular accedant. She was treated with teriparatide 20 µr subcuraneously and cholecalciferol 0.25 µ per oral for one year. She had a pulmonary infection one month before admission. Since vitamin D is popular in media for public health, her daughter gave three doses of 300 000 IU vitamin D for infection. She has hallucinations and hypoxia. Her laboratory was; Ca 15.6 mg/dl, P 3.3 mg/dl, PTH 6.88 pg/ml, 25-(OH] vitamin D> 70 ng/dl, $1.25(OH]_2$ vitamin D 86.4 ng/l. She had also increased serum creatinine level. She was followed in intensive care unit fo 2 days. For hypercalcemia she had hydration, forced düresis, calcitonin and glucocorticoid therapy. Thorax CT showed bilaterally lineer atelectatic areas at basal zones. She continued to have nebulisation and oxygen after transmission from intensive care unit. Ejection fraction was 40% on echocardiography. She was discharged after 1 week when serum calcium was 10.2 mg/dl and PTH was 16.37 pg/ml. Vitamin D replacement, in elderly, could be life-threatening in megadoses. In this case, parathormon treatment with vitamin D replacement complicated presentation.

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EP297

Tc-99m sestamibi uptake by brown tumours in a patient with primary hyperparathyroidism

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Tc-99m sestamibi (MIBI) imaging is able to localize parathyroid adenomas/carcinomas in patients with primary hyperparathyroidism. Brown tumours are one of the skeletal manifestations of long standing hyperparathyroidism and its incidence has been reported to be 3%. Radiological features of these tumors may mimic bone metastasis. There are only a few reports showing brown tumours uptake in the whole-body Tc-sestamibi scan.
We report a 72-year-old female with a previous history of right nephrectomy for renal lithiasis at age 49 and a left clavicle mass fracture. A neck and thoracic computed tomography (CT) scan revealed multiple lytic lesions of the skeleton (including in the left clavicle) and a pathological mandibular fracture, suggesting metastatic lesions.
^{18}F-FDG PET scan showed multiple skeletal hypermetabolic lesions and a hypermetabolic nodule close to left lower pole of the thyroid gland. The biopsy of the lesion in the left clavicle revealed histiocytic proliferation with multinucleated osteoclast-type giant cells compatible with a brown tumor. Laboratory data showed an elevated serum calcium of 12.8 mg/dl (8.4–10.2), alkaline phosphatase of 264 UI/l (9–36), and parathyroid hormone of 1056 pg/ml (12–65).
Tc-99m sestamibi scintigraphy showed an uptake in the inferior left pole of the thyroid and in multiple bone lesions. The patient underwent a left inferior parathyroidectomy. Histology revealed a 20 mm parathyroid adenoma.
In this patient with a long standing hyperparathyroidism the intense uptake of brown tumors in both ^{18}F-FDG PET scan and MIBI can mimic a parathyroid carcinoma with bone metastases.

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EP298

Thyroid supression in patients with primary hyperparathyroidism may improve pre-surgical scintigraphy localisation

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Introduction
The cause of primary hyperparathyroidism (PHPT) is a single adenoma in 85% of cases. Scintigraphy with technetium-sestamibi (MIBI) is the test of choice for localising adenomas in patients with PHPT, allowing minimally invasive surgery in most patients. Some articles recommend thyroid function supression to improve scintigraphy results.
Methods
A prospective study was conducted in which 8 patients were included with diagnosis of PHPT and negative scintigraphy for adenoma localisation. These patients did not have a contraindication for thyroid hormone intake. We started treatment with a dose of 1 mcg/Kg per day with dose titulation until achievement of TSH <0.3 µU/ml. Once the objective was reached, MIBI was repeated with the same technique and interpreted by the same specialist in Nuclear Medicine.
Results
75% of patients were women, mean age 51.9 ± 20.55 years.
De los eight pacientes incluidos en el estudio, 6 eran mujeres (75%), con una edad media de 51.9 ± 20.55 años. Mean preoperative calcium level was 11.49 ± 0.61 mg/dl. Mean preoperative PTH level was 146.26 ± 97.58 ng/l. Mean TSH level before repeating scintygraphy was 0.17 ± 0.08 µU/ml. Thyroxine suppression scan was positive in four of the eight patients (50%). Only two of these four patients underwent surgery for the moment. Minimally invasive surgery was performed in these cases, confirming the existence of a parathyroid adenoma where the MIBI suggested. The level of calcium in these patients normalized after surgery.
Conclusiones
In our study suppression of thyroid function by thyroxine administration improved MIBI sensitivity for parathyroid adenoma localization in our patients with previous negative studies, however, a larger number of patients would be required to confirm these results.

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EP299

Serum vitamin D in overweight patients with normal and impaired GFR

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Introduction
Obesity is a strong risk factor for incident chronic kidney disease (CKD). Furthermore, high body mass index (BMI) is consistently associated with low serum vitamin D in the general population. The aims of the present study were to i) compare vitamin D metabolite levels in overweight/obese versus normal weight individuals with normal to severely impaired renal function and ii) to assess the impact of 25(OH)D on the development of secondary hyperparathyroidism (SHPT).
Methods
Serum 25(OH)D, 1,25$(OH)_2$D, PTH, calcium and phosphate were measured in 104 CKD outpatients with BMI >25 kg/m^2. Participants were categorized according to the eGFR (ml/min/1.73 m^2): G1: ≥ 60 ($n=53$), G2: 30–59 ($n=35$) and G3: 15–29 ($n=16$). Fifty normal-weight subjects with comparable eGFR levels composed the control group (G1-nw – G3-nw).
Results
25(OH)D was lower in overweight/obese G1 patients compared to G1-nw (21.7$\pm$6.5 vs 26.5$\pm$7.0 ng/ml, $P=0.02$) and in G2 versus G2-nw (19.0$\pm$6.0 vs 25.0$\pm$5.2 ng/ml, $P=0.005$), whereas the level did not differ among G3 groups (15.8$\pm$4.7 ng/ml vs 20.3$\pm$4.5 ng/ml, $P=0.49$ in G3 vs G3-nw respectively). Mean 1,25$(OH)_2$D and PTH levels were similar in obese/overweight versus normal-weight individuals in each eGFR category. Multivariate regression analysis in the entire cohort revealed that factors independently associated with low 25(OH)D levels were BMI >25 kg/m^2, eGFR <30 ml/min/1.73 m^2 and female gender whereas low 1,25$(OH)_2$D levels were associated with eGFR <30 ml/min/1.73 m^2, older age and increased serum phosphate. Even though serum 25(OH)D levels were suboptimal (<30 ng/ml) in both overweight and controls and in all eGFR groups, significant SHPT was only observed in the groups with eGFR <30 ml/min/1.73 m^2.
Conclusions
Lower serum 25(OH)D but similar 1,25(OH)2D and PTH levels were observed in overweight/obese compared to normal weight individuals and preserved or moderately impaired renal function. Even though vitamin D insufficiency was a common feature across all eGFR categories, SHPT was only observed in those with severely impaired renal function.

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EP300

The importance of ultrasound in the preoperative evaluation of patients with primary hyperthyroidism: a case report

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Introduction
Primary hyperparathyroidism is the most common cause of hypercalcemia in the outpatient setting, and a single parathyroid adenoma is usually the culprit. Clinical presentation is commonly dictated by hypercalcemia. Symptoms can range from mild non-specific malaise and gastrointestinal disturbances, through bone disease, kidney stones, cardiovascular and neuromuscular dysfunction to, ultimately, coma and death. However, the vast majority of patients are asymptomatic.
Case report
A 46-year-old female with a half-year endocrinology monitoring for type 2 diabetes and obesity, resorted to our hospital after 3 weeks' evolution of persistent nausea and vomiting. Laboratory workup showed increased PTH levels (596 pg/ml), severe hypercalcemia (17.4 mg/dl), mild hypophosphatemia (2.4 mg/dl), acute kidney injury (creatinine clearance 34 ml/min) and hyperuricemia (14.8 mg/dl). A 25-hydroxyvitamin D deficiency was also present (6.5 ng/ml). The first neck ultrasound did not show abnormalities; 99mTc-sestaMIBI scan was negative. Repetition of neck ultrasound revealed a left-postero-inferior nodule likely to correspond to an enlarged parathyroid. The cytological evaluation supported this hypothesis. Pamidronate, antiemetics and volume expansion with isotonic saline reverted the clinico-laboratory condition and served as a bridge to parathyroidectomy. Surgery went uneventful and a 3 cm inferior-left parathyroid was sent to anatomopathological examination. The final diagnosis was parathyroid adenoma. In subsequent postoperative follow-up the patient was asymptomatic and had normal serum calcium levels (9.3 mg/dl) and slightly upper-limit PTH (77.3 pg/ml).
Conclusion
Despite the considerable size of the resected parathyroid, initial ultrasound failed to locate it. Seeking for a topographical diagnosis, a second ultrasound was performed by a different operator in our hospital. This case highlights the importance of carefully selecting experienced centers to address parathyroid preoperative studies. Furthermore, despite the adenoma size, its inferior location, and the associated severe hypercalcemia, the 99mTc-sestaMIBI scan was negative, reminding of potential false-negative results of this method.

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EP301

Abstract withdrawn.

EP302

Ectopic production of calcitriol by non-hodgkin lymphoma as a cause of hypercalcemia: case report

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Introduction
Hypercalcemia of malignancy usually appears in patients with osteolytic metastasis and in those patients with humoral hypercalcemia due to secretion of PTHrp by the tumor. Hypercalcemia due to calcitriol production by the tumor is uncommon ($<1\%$ of cases of hypercalcemia of malignancy). It is the cause of virtually all cases of hypercalcemia in patients with Hodgkin's lymphoma and approximately one third of cases in non-Hodgkin's lymphoma. It has also been described in some cases of ovarian dysgerminoma.
Methods
We describe the case of a patient with MALT Non-Hodgkin lymphoma admitted to our hospital with severe hypercalcemia.
Results
Our patient was admitted to the hospital with calcium levels above 15 mg/dl. After hydration, loop diuretics and zoledronic acid he reached calcium level of 10.5–11 mg/dl but after withdrawal of intravenous hydration he presented recurrence of hypercalcemia up to the initial values. Analytics showed very low levels of PTHi and 25-OH-Vitamin D (5.76 pg/ml, 3 ng/ml respectively). Imaging tests (body CT) did not show osteolytic lesions suggestive of metastases. Given the suspicion of humoral hypercalcemia we initiated treatment with Cinacalcet 60 mg daily and steroids (Prednisone 1 mg/kg per day) without a satisfactory response in reducing calcium levels. Analytical result showed undetectable levels of PTH-related protein (<1.1 pmol/l) and very high calcitriol levels (148 pg/ml, N: 16–56 pg/ml). Our suspicion of calcitriol tumoral production associated with lymphoma is therefore confirmed. In view of the poor response to medical treatment and the need for intense hydration to maintain acceptable calcium levels a splenectomy with cytoreductive objective (19 cm splenomegaly) was performed. After this, calcium levels reached the normal level (9.5–10.2 mg/dl) and remained stable.
Conclusion
Although tumor production of calcitriol is an uncommon cause of hypercalcemia, it is usually related to lymphomas. We must think in this disorder in patiens with lymphoma and hypercalcemia.

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EP303

Primary hyperparathyroidism: elective parathyroidectomy versus conservative management; results of a retrospective cohort study

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Background
The optimum management strategy for primary hyperparathyroidism remains debatable especially in patients with mild or asymptomatic disease. We aimed to compare the baseline characteristics and long-term outcomes of patients with primary hyperparathyroidism who were either managed conservatively or underwent elective parathyroidectomy.
Methodology
We carried out a retrospective cohort analysis of patients with primary hyperparathyroidism under follow-up at the Royal Glamorgan Hospital, Wales from 1995 to 2016. The baseline characteristics were recorded from case records while the clinical portal was used to collate biochemical and radiological data. The patients were categorised into two main groups based on management approach (conservative treatment vs elective parathyroidectomy group).
Results
Out of a total of 336 patients with confirmed primary hyperparathyroidism, 72 (21.4%) underwent elective parathyroidectomy. Mean duration of follow up was shorter for the surgically treated patients as compared to the ones treated conservatively (3.7 vs 5.2 years). There was no significant difference between mean calcium levels at diagnosis although the mean parathyroid hormone (PTH) level at diagnosis was significantly higher in the surgical group (15.0 vs 11.4, $P=0.038$). Despite age adjustment using binary logistic regression, prevalence of hypertension and ischaemic heart disease was significantly lower in patients undergoing elective parathyroidectomy as compared to the group managed conservatively.
Conclusion
There was a significant difference in prevalence of hypertension and ischaemic heart disease in patients managed conservatively as compared to the group who underwent elective parathyroidectomy despite adjustment for age. The duration of follow up for this group was relatively shorter which can potentially off-set costs associated with surgery. The higher PTH levels at baseline for the elective parathyroidectomy group may also signify a correlation of PTH levels with increased risk of complications. Prospective large randomised controlled trials need to be designed to assess cardiovascular outcomes comparing surgical versus conservative management approach.

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EP304

Calcium metabolism and autoimmune thyroiditis

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Objectives
The objective of our – investigation is to find out the role of D3 vitamin deficiency – and calcium in patients with autoimmune thyroiditis and calcified nodules.
Methods
The research has been carried out at "Muratsan" University Hospital and "Armenia" Medical Center, in 2013–2016.
80 patients (ages ±4–0, of which 68 women and 12 men) with autoimmune thyroiditis and calcified nodules have taken part in the clinical research.
They have been tested on TSH, FT4, anti-TPO, vitamin D3, Ca^{2+}, PTH, as well as undergone a thyroid ultrasound, elastography.
Results
TSH – 58%↑, 42% N
FT4 – 60% ↓, 40%N
Anti-TPO – 100%↑
Vitamin D3 – 84%↓, 16%N
Ca^{2+} – 94%N, 6%↓
PTH – 89% ↑, 11%N
Thyroid ultrasound – Calcificates proved to be present in 76% of nodules, which have been formed on the background of autoimmune thyroidits.
Thyroid elastography after 6 month taking vitamin D3 13% 3b elastography is go to 3a. The increased level of PTH hormone and lower vitamin D3 should be taken into consideration, since this can result from secondary hyperparathyroidism and cause formation of calcificates.
Conclusions
Vitamin D3 shout be tested in the first place during the treatment of any kind of calcified nodular goiter, since calcificates can be caused not only by oncologic processes, but also secondary hyperparathyroidism.

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EP305

Pseudohypoparathyroidism (PHP) and *GNAS* gene mutations – clinical spectrum from PHP type 1a to pseudopseudohypoparathyroidism

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Introduction
Pseudohypoparathyroidism (PHP) refers to a heterogeneous group of disorders that have in common end-organ unresponsiveness to parathyroid hormone (PTH). The most frequent form, PHP type 1, results from different genetic/epigenetic changes in the *GNAS* gene.
Case 1
Woman, 25 years-old, sent to Endocrinology from Genetics consultation after her daughter had been diagnosed with PHP type 1a (heterozygous pathogenic variant at exon 13 of *GNAS* gene c.1174G>A (p.e392K)). Our patient and her father present some clinical manifestations as observed in the child, suggestive of Albright Hereditary Osteodystrophy (AHO), and both present the same mutation as encountered in index case. We tested phosphocalcic metabolism of our patient and she presented normal serum calcium/phosphorus levels as well PTH levels. Other pituitary hormones were evaluated, with normal results except elevated TSH (18.72 μUI/ml) in context of primary autoimmune hypothyroidism. Patient started treatment with levothyroxine.
Case 2
Male, 31 years-old (case 1 brother). He was sent to Endocrinology in December 2015 for lymphocytic thyroiditis evaluation. During the physical examination, it was recognized a phenotype suggestive of AHO, as was found in his relatives (round facies, brachydactyly and subcutaneous calcifications). Patient's lab tests showed normal serum calcium/phosphorus levels and high PTH in the context of vitamin D deficiency. Other pituitary hormones levels were in normal range. Patient performed genetic test - results ongoing.
Conclusion
Different pathological entities may result from mutations in the *GNAS* gene. PHP type 1a is characterized by the presence of AHO and PTH resistance. However, AHO manifestations may occur in patients without PTH resistance (pseudopseudohypoparathyroidism), as in the two cases presented. This occurs when the mutation is paternally transmitted. These cases somehow demonstrate de complexity of *GNAS* gene mutations, which merited recently a new classification. It is also highlighted that although pseudopseudohypoparathyroidism needs no treatment, genetic counselling should also be recommended.

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EP306

Hyperparathyroidism and cardiovascular risk

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Background
Primary and secondary hyperparathyroidism (HP) are associated with increased risk for cardiovascular complications and high mortality. Risk factors correlated with hypertension in HP are hyperlipidemia, glucose intolerance, insulin resistance, vitamin D deficiency, etc. The aim of the study was to assess the incidence of cardiovascular complications in HP.
Material and methods

The study included 45 patients (15 men, 30 women), with a mean age of 45 years (range 21–65 years). Thirty-two patients were diagnosed with primary HP and 13 with secondary HP due to chronic kidney disease (stages 3 and 4). The patients were evaluated by biochemical, hormonal parameters, imagistic tests, and cardiac sonography.

Results

Vitamin D deficiency was documented in all patients with secondary HP and in 24 patients with primary HP (75%). Other metabolic disturbances and risk factors for cardiovascular diseases were as follows: diabetes mellitus (24.4%), smoking (28.8%), obesity (22.2%), and dyslipidemia (46.6%). The incidence of mitral and/or aortic valvular stenosis (caused by calcifications) was similar in the two groups, affecting 31.1% of the patients. Hypertension prevailed in the group of secondary HP (12 cases), as compared to primary HP (10 cases, $P=0.0002$, Fisher's exact test). Peripheral atherosclerotic manifestations were noted in 11 cases (24.4%). Seven patients (15.5%) experienced an acute coronary event and three patients underwent PTCA procedures with stent implantation. Ten patients showed ventricular hypertrophy (22.2%); the incidence was similar in the two groups (eight patients with primary HP, respectively two with secondary HP).

Conclusion

Our study shows that hyperparathyroidism is associated with higher incidence of severe cardiovascular complications, occurring at younger ages as compared to general populations.

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EP307

Risk factors associated with osteoporosis in beta-thalassaemia major patients

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Beta-thalssaemia major (BTM) is a rare disease that encompasses a vast range of endocrinological complications, despite of the improvement of treatment protocols. The aim of this study was to identify the clinical and hematological parameters associated with osteoporosis, a frequent complication found in beta-thalassaemia patients.

Patients with BTM were evaluated in the Endocrinology Department of Elias Hospital between February 2004 and March 2016. Only patients who provided written informed consent were included in the study. A complete physical and hormonal evaluation was performed on all patients, and data regarding treatment of hematological disease were collected. The bone density was evaluated using dual energy X-ray absortiometry (DXA).

Forty-nine patients were included in the study (median age 28.37 years; range 12–47). We found that 35 patients (71.4%) had osteoporosis documented using DXA, 16 of them (45.7%) had fragility fractures caused by decreased BMD.

Patients with osteoporosis were older (median age 31.51 vs 20.5 years, $P=0.05$) and started the iron chelation therapy at an older age compared with subjects without this condition (105.72 months vs 63.58 months, $P<0.05$). Although the levels of serum ferritin were higher in patients with osteoporosis (1062 vs 777 ng/ml), the difference did not reached statistical significance. Hypogonadism was significantly more frequently found in patients with osteoporosis (30 pts, 85.7% vs 5 pts, 14.3%) in comparison to patients without osteoporosis ($P=0.014$). The risk of developing osteoporosis was six times greater in hypogonadal study subjects.

Our data show that osteoporosis is a highly prevalent complication among Romanian β-thalasaemia patients, its presence being associated with older age, delayed initiation of iron chelation therapy and the presence of hypogonadism.

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EP308

Giants walk amongst us

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We present the case of a 51-year-old gentleman who had a giant parathyroid adenoma. He has a past medical history of deep vein thrombosis and hypertension. He is taking amlodipine 10 mg od. He is a non-smoker and drinks alcohol in moderation. He was admitted with right leg swelling found to be a new thrombosis. Incidental finding of extreme hypercalcaemia found on bloods with raised PTH (CorrCa 4.23 mmol/l, PTH 83.1 pmol/l.) Patient was completely asymptomatic. CT imaging of chest, abdomen and pelvis demonstrated extensive above knee thrombosis, renal calculi and a large thyroid nodule. However, an ultrasound and Sestamibi confirmed spectacularly this was an enlarged parathyroid. He was anticoagulated with heparin and then oral anticoagulant. He was given aggressive i.v. fluids and bisphosphonate with limited effect so cinacalcet was initiated. We were still unable to control calcium levels and so in patient parathyroidectomy was performed. At operation the gland appeared grossly enlarged and vascular. However, there was no tethering to adjacent tissues and easily removed weighing 43 g. Our patient made a good recovery with normalisation of calcium. Histology showed features in keeping with parathyroid adenoma rather than carcinoma. On review in clinic two months later he remains normocalcemic. A DEXA has shown osteoporosis which we expect to improve in time.

Our case is interesting as there are features of this case in keeping with parathyroid malignancy rather than adenoma and we shall discuss this.

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EP309

Hungry bone syndrome after treatment of severe primary hyperparathyroidism

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Introduction

Persistent hypocalcemia after surgery for severe hyperparathyroidism are not uncommon and may be secondary to transient or permanent hypoparathyroidism but may also be due to bone pathology.

Observation

Patient of 44 years old was hospitalized for fractures of the pelvis, and shaft of left femur, spontaneous without trauma turned out. Laboratory tests shows severe hypercalcaemia to 156 mg/l, serum phosphorus at 22 mg/l, elevation of PTH to 1150 pg/ml and proper renal function with a serum creatinine to 8 mg/ml. PAL is increased to 709 U/l.

A spot of médiastinal fixation compatible with ectopic parathyroid adenoma was seen on the MIBI scintigraphy with several brown tumors. Ectopic mediastinal parathyroidectomy was made after medical preoperative treatment with bisphosphonates, vitamin D and active metabolite of vitamin D.

In postoperative period a severe hypocalcemia reaching 65 mg/l at the fifth day was observed, the PTH was (9.9 pg/ml) and PAL are increased to 560 U/l with a lowered serum phosphorus.

The difficulty of standardization of serum calcium despite supplementation of calcium element and 1 alpha and vitamin D, high PAL and the presence of diffuse bone lesions guide to The diagnosis of HBS.

Conclusion

HBS is a heightened greed bones for calcium. It occurs in situations of demineralization and intense bone remodeling.

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EP310

Clinical review of nine cases of pseudohypoparathyroidism

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Objective

To analyze the clinicopathological features of pseudohypoparathyroidism (PHP), that would help clinicians to consider this rare condition in children.

Methods

A retrospective review of nine patients with PHP (including seven males and three females) admitted to our hospital between 1990 and 2014 was conducted. Clinical and biochemical parameters along with epidemiological data were extracted and analyzed.

Results
The mean age at diagnosis was 61.8 ± 26.1 months, ranging from 4 to 114 months. The most frequent clinical features were: round lunar face and obesity (77.7%), followed by brachydactyly and learning/behavior disabilities (66.7%). Subcutaneous calcifications, although a landmark of PHP, were only present in four patients (44.4%). Afebrile seizures occurred in two cases, despite the majority showed multiple intracranial calcifications on cranial CT scan. Laboratory tests at diagnosis revealed most frequently hypocalcemia (mean 7.4 ± 1.9 mg/dl; 8.6–10.2), hyperphosphatemia (mean 7.9 ± 1.7 mg/dl; 2.7–4.5) and high PTH levels (mean 366.3 ± 218.4 pg/ml; 14–72). Subclinical hypothyroidism was present in eight out of nine patients (88.8%) with a mean TSH of 9.45 ± 4.2 uU/ml (0.35–5.5) and a mean free T4 of 0.95 ± 0.1 ng/dl (0.8–1.9). Vitamin D3, and calcium when needed, were prescribed to all patients to prevent symptomatic hypocalcemia and presumably to stop disease progression by lowering the PTH levels, although it is not clear whether this normalization is beneficial. Genetic testing was performed in six children.
Conclusion
PHP is a rare and heterogeneous genetic disease with a high rate of misdiagnosis and no specific treatment. It should be considered in children presenting with a round face, obesity, brachydactyly, learning/behavior disabilities, subcutaneous calcifications and subclinical hypothyroidism. Laboratory evaluation of blood calcium, phosphorus, PTH and thyroid hormones should be ordered as soon as possible, as well as neuroimaging and a genetic profile for further confirmation.

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EP311

Severe hypercalcemia revealing an atypical parathyroid adenoma

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Introduction
Primary hyperparathyroidism is a common cause for hypercalcemia, however severe hypercalcemia remain a rare complication. The atypical parathyroid adenoma is an uncommon cause to severe hypercalcemia. We report a case of a 40-year-old male with very high serum calcium due to a possible atypical parathyroid diagnosed after a spontaneous fracture.
Case report
A 40-year-old male was admitted to the traumatology department for the management of spontaneous fracture of the humerus. The clinical history revealed clinical symptoms of hypercalcemia (abdominal pain, neurologic irritation, asthenia, etc.). The initial blood work up found a severe hypercalcemia (203 mg/l) hypophosphoremia (23 mg/l) and high ALP. Parathyroid hormone level were of 749 pg/ml. The patient underwent a surgical en bloc resection after the localization of a right inferior parathyroid adenoma. Pathology showed a mixed picture consistent with possible atypical adenoma versus parathyroid carcinoma. However, due to the absence of local structures involvement, atypical parathyroid adenoma was more likely. The immunohistochimie: paratyhroidien adenoma atypical. The evolution was marked by the improvement of the clinical signs and calcium normalization.
Conclusion
It can be very difficult to distinguish between atypical parathyroid adenomas and parathyroid carcinomas as in our case and no clear-cut guidelines yet exist to differentiate the two based on histology. Close follow-up is mandatory to detect any local recurrence.

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Cardiovascular Endocrinology and Lipid Metabolism

EP312

Hypercalcemia and cardiovascular disease

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Introduction
According to modern studies, patients with hypercalcemia have an increased cardiovascular risk.
Objective
To study the prevalence of cardiovascular disease in patients with hypercalcemia.
Materials and methods
We studied 1207 people, average age 53.9 ± 17.25 (892 women, 315 men) from 18 to 96 years. Examination: total calcium, total protein, creatinine, cholesterol and triglycerides, HbA1C, ambulatory blood pressure monitoring, ECG, an analysis of morbidity (hypertension, coronary heart disease, cardiovascular events).
Results
Hypercalcemia has been found in 31 people, mean age was 58.39 ± 11.6 years. Arterial hypertension was detected in 677 cases (in patients with hypercalcemia – in 23 patients), coronary heart disease was detected in 599 cases (in patients with hypercalcemia – 21), acute myocardial infarction – in 52 cases (in patients with hypercalcemia – 1), acute cerebrovascular accident – in 39 cases (in patients with hypercalcemia – 1).
Significant differences in the prevalence of arterial hypertension ($\chi^2=4.03$, $P=0.0447$); in the prevalence of coronary heart disease ($\chi^2=3.87$, $P=0.046$) in patients with hypercalcemia were detected. In the same time the differences in the prevalence of acute myocardial infarction ($\chi^2=0.09$, $P=0.8$) and acute cerebrovascular accident ($\chi^2=0$, $P=1$) in patients with hypercalcemia were not revealed.
Conclusion
The results of the study show an increasing risk of arterial hypertension and coronary heart disease in patients with hypercalcaemia. In the same time the risk of acute cardiovascular events is not increased. The results may suggest the influence of hypercalcemia on the development of cardiovascular disease.

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EP313

Vitamin D levels in obese adults and cardiovascular risk

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Introduction
The prevalence of vitamin D deficiency is high, and yet still little recognized and treated. Cardiovascular diseases are the leading causes of morbidity and mortality worldwide and the emergence of evidence with the link suggesting an association between vitamin D deficiency and cardiovascular risk (CVR), it is pertinent to better understand this association.
Objective
This study aimed to relate the levels of 25 (OH) D in obese patients with the cardiovascular risk.
Methodology
Cross-sectional observational study with a sample of 31 individuals between 40 and 64 years, of both sexes diagnosed with obesity. They evaluated sociodemographic data, solar exposure and use of sunscreen, skin color phototype of skin color, sources of vitamin D, physical activity, anthropometric data, clinical and biochemical and CVR.
Results
The average value of 25(OH) D was 15.6 ng/ml, 71.0 and 22.6% had deficiency and insufficiency, respectively. We observed lower levels of 25(OH) D in smokers, those with less solar exposure time, with a higher waist-to-height ratio and in those with lower levels of DBP. We did not find a statistically significant association between vitamin D and CVR.
Conclusions
We found a high prevalence of vitamin D deficiency in our sample of patients with obesity and a significant association with the waist-to-height ratio. Despite the evidence that suggests that vitamin D deficiency is associated with an increased CVR, we found this association but without statistical significance. The measurement of total 25(OH) D routinely in people with central obesity can help identify those who are at most CVR.
Keywords: vitamin D cardiovascular risk; obesity; SCORE; metabolic syndrome.

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Clinical Case Reports – Pituitary/Adrenal

EP314

Partial gigantism: case report

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The aim
To study case of partial gigantism.
Methods
To evaluate the patient's condition we conducted hormonal and biochemical investigations, as well as total blood and clinical urine analysis; Doppler sonography and multislice computed tomography were performed.
Results
STH – 25.8 mIU/l (normal range: 2.0–20 mIU/l); IGF – 2.9 mg/l (normal range for the age: 13–100 mg/l); ALPase – 160 U/l (normal range: up to 644 U/l); total calcium – 2.08 mmol/l (normal range: 2.5–3.0 mmol/l); phosphorous – 1.42 mmol/l (normal range: 1.3–2.26 mmol/l). Doppler sonographyof left extremity demonstratedpresence of hyperechoic(circular) layer in the projections of the first and second left toes.
Multislice computed tomography (MSCT) of left extremitydemonstrated enlargement of the first and second left toes with the metatarsal involvement. The soft tissues of the area contain multiple poorly demarcated thin-wall cyst-like formations with cystic content density of -120 + 34 HU. Cortical layers of adjacent toe or metatarsal bones demonstrated no disruptions of continuity. Spacing intervals between the first and second toes and metatarsal bones are enlarged. Middle phalanx of the second toe is laterally displaced. Boundaries of bones are well defined; no disruptions of cortical layer or periosteal reaction can be seen. The soft tissues of right extremity have no changes. Total blood and clinical urine analysis, ECG and brain MRI demonstrated no deviations.
Conclusions
Due to few similar cases and limited experience for their managing, it is necessary to:
– choose the wait and see approach. The excessive growth making a patient's movements hard progresses, correcting surgical procedures and appropriate footwear are necessary,
– let the closure of growth zones be accomplished for correcting surgical reconstruction to be performed; the body part disproportionally enlarged should be surgically removed after that, generate a databank to generalize the results, and to develop drug and radiotherapy regimens.

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Clinical Case Reports – Thyroid/Others

EP315

An unique case of celiac disease with hypocoagulation and secondary hyperparathyreodism in elderly patient – a case report

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Introduction
Celiac disease (CD) an autoimmune disorder of the small intestine, was considered as a disease of childhood. The symptoms can be obvious. That is the main reason why CD is underdiagnosed in elderly patients.
Aims & Methods
The purpose of our study was to demonstrate a clinical case of CD which was diagnosed in a 41-year-old female patient. The patient attended our clinic with complains of weakness, tenderness, abdominal distension, weight loss. Laboratory tests find severe iron deficiency anemia (HB -9 g/dl, Ery- 3.1×10^{12}/l, serum iron 4 mmol/l) and severe hypocoagolopathy (prothrombine index-48%, INR-2.98, but mild thrombocytopenia 130×10/l). She had suffered with these symptoms for 2 years.
Results
Number of investigations was performed. We also checked parathormone which revealed secondary hyperparathyroidism (parathhormon 187 pg/ml, Ca-1.01 mmol/l). The hemolytic anemia was excluded (haptoglobin was in normal range). Stool examination revealed no pathogens.
It was believed that she has these symptoms due to her anemia. After 2 weeks occurred the oedema of abdomen and diarrhea of 3–4 watery stools daily and night tremor and seizure due to hypoglycaemia (2.3 mmol/l). Ultrasound investigation of abdomen showed very rush peristalsis of small and large intestines, but no ascites, significant meteorism.
CD was suspected. Serologic test for anti-gliadin antibodies was positive. Another examination of the biopsy after the first endoscopy revealed extensive collagen depositions in the lamina propria of the small bowel, giving the diagnosis of CD. Also antibodies against Transglutaminase were positive. After gluten-free diet the above mentioned symptoms disappeared and patient's anemia and blood clot markers as well as parathormone and Ca level were well controlled.
Conclusion
The presence of other immune-related diseases in our case suggests that immunological mechanism plays a crucial role in CD. We recommend active specific screening in older patients belonging to at risk-group like other autoimmune disorders. Disappeared and patient's anemia and blood clot markers as well as parathormone level were well controlled.

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EP316

Optic neuritis as presenting complaint in primary hypoparathyroidism

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Background
Papilledema and raised intracranial pressure has been reported frequently in patients with hypoparathyroidism but very rarely optic neuritis (1).
Clinical case
We report a case of 63-year-old male who presented to ophthalmology with right-sided visual loss and a relative afferent pupillary defect. He was diagnosed with optic neuritis and underwent MRI brain which showed bilateral white matter changes with the possibility of demyelination. He was initially diagnosed with relapsing-remitting multiple sclerosis by the neurologist but was later found to have severe hypocalcaemia (adjusted calcium 1.32 mmol/l (2.20–2.60)) and idiopathic primary hypoparathyroidism (PTH < 0.3 pg/ml (1.6–7.2)). Cerebrospinal fluid examination was entirely normal with negative oligoclonal bands. The initial MRI changes were thought to be secondary to severe hypocalcaemia as per neuroradiology MDT and subsequently, the diagnosis of multiple sclerosis was reversed. Although the underlying mechanism is not very clear, we believe there is an association between optic neuritis and primary hypoparathyroidism, especially in the absence of any other underlying cause for optic neuritis.
Conclusion
Although rare, but primary hypoparathyroidism can present as optic neuritis. Therefore, serum calcium should be checked in patients with no clear cause of optic neuritis.
Reference
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EP317

The parathyroid carcinoma in a young adult male

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Introduction
Parathyroid carcinoma is a rare malignancy of the parathyroid glands. Parathyroid carcinoma may be suspected, but it usually cannot be confirmed prior to operation.
Case
A 35-year-old male was consulted to Endocrinology department with persistant kidney stones. He was operated five times in 10 years for recurrent kidney stones. His lab results are as follows; Ca:13(8.8–10.6), P:2.2 mg/dl(2.5–4.5), ALP:84U/L(30–120), parathormone:179 pg/ml(14–72), 25(OH)Dvit:8.2 ug/l(10–80). Urine Ca: 1159 mg/24 h(100–300), urine P:134 mmol/24 h(13–42).

Neck USG revealed 17×11×12 mm PTH adenoma with cystic components, but with no pathological cervical lymphodenopathies.
Radionuclide scan confirmed increased parathyroid gland activity on the right inferior of the thyroid gland.
The patient underwent right inferior parathyroidectomy. Postoperative PTH < 6, Ca:8.17,which confirmed successful remove of the pathological parathyroid gland. The histological findings reported marked pleomorphysm in the cells, divided by the typical fibrotic septae and Ki-67: 4–5%. All those findings were consistent with parathyroid carcinoma.
After 4 months his last lab results were as follows; PTH: 57.8 pg/ml, Ca:8.8 mg/dl, P:4.6 mg/dl, urine Ca: 124 mg/24 h.
Conclusion
There is a challenge in the diagnosis of parathyroid carcinoma, because it is commonly confirmed with histological evaluation. Although, parathyroid carcinoma is a rare disease, it should be kept in mind even in young adults.

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EP318

Clinical case of atypical parathyroid adenoma with severe hypercalcemia and multiple fragility fractures

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Introduction
Atypical parathyroid adenoma (APA) is rarely encountered cause of primary hyperparathyroidism (PHPT). No definite criteria are considered to distinguish preoperatively APA from parathyroid typical adenoma or carcinoma.
The aim
To describe the clinical course of a patient with an atypical parathyroid adenoma with severe hypercalcemia and multiple fragility fractures.
Case presentation
A 61-year-old woman was evaluated for multiple fractures, skeletal deformities, pain in the large joints and bones, tachycardia, oppressive chest pain. She had severe hypercalcemia (calcium level 14.7 mg/dl), hypophosphatemia (serum phosphate 2.1 mg/dl) with an elevated intact parathyroid hormone level of 1871 pg/ml. Ultrasonography revealed a large structure (4.7 cm) of the right parathyroid gland. 99mTc-sestamibi SPECT/CT showed the lesion 43×34×40 mm behind the middle and lower third of the left thyroid lobe. Renal function was impaired, GFR 46 ml/min/1.73 m^2. Whole-body Tc-99m bone scan demonstrated multiple skeletal changes accepted as parathyroid osteodystrophy. As a result of the determination of severe hypercalcemia, heart rhythm disturbances (permanent form of atrial fibrillation), a high risk of hypercalcemic crisis, intravenous hydration was started with no significant effect. Patient received denosumab 60 mg s.c. She underwent a surgical resection of parathyroid adenoma and intra-operative PTH levels fell to 20.9 pg/ml. In the postoperative period serum calcium was decreased to 8.9 mg/dl. On pathological examination, the tumor consisted mainly of chief cells. Capsule invasion, peripherical vascular and perineural invasion of the adjacent tissue, high mitotic activity or large bands of fibrosis were not observed. Ki67 immunostaining was generally positive in about 3% of the tumor. Tumor vessel invasion was detected in the central node part. These changes corroborated the diagnosis of atypical parathyroid adenoma.
Conclusion
APA are rare and have been a challenge for diagnosis. They have some features of carcinoma but lack the indisputable evidence of malignant disease like invasion or metastases. They have unpredictable clinical course, long-term follow up is prudent to assess for local recurrence and metastatic disorder to distinguish between benign and malignant parathyroid disease.

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EP319

Congenital fibrous dysplasia and Klinefelter syndrome: coincidence or not?

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Congenital fibrous dysplasia is a rare disease with a broad spectrum of manifestations, including various endocrinopathies;precocious puberty, hyperthyroidism, excess growth hormone, hypophosphatemia mediated by FGF23.
We present the case of a 33 year old male, who presented in our endocrinology service with infertility and bone pain. He was diagnosed at the age of years old with congenital fibrous dyplasia and suffered multiple surgeries for bone decompression. Blood tests showed vitamin D insufficiency (16,01 ng/ml), very high levels of alkaline phosphatise (919 U/l), normal levels of calcium, phosphorus and parathormone. Bone mineral density was low at the femoral neck: BMD 1.385 g/cm^2, Tscore = −2.4, Zscore = −2.3.
His semen analysis showed a normal aspect, volume and viscosity, but with a low A mobility of spermatozoa and a low percentage of normal form spermatozoa.
His testosterone was within the normal range (3,44 ng/ml), with a TSH of 4,10 microUI/ml. We further performed a karyotype analysis, wich showed the presence of an extra X chromosome in 10% of the studied metaphases, with the diagnosis of mosaic Klinefelter:47XXY(10%)/46 XY (90%).
This is the first description of a case with congenital fibrous dysplasia which associates mosaic karyotype 46XY/47XXY. Although the link between the two conditions is not known, further investigations are necessary to establish a possible correlation between them. It remains to establish if karyotype analysis should be a routine investigation for those diagnosed with fibrous dysplasia.

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EP320

Parathyroid nodular hyperplasia: when imaging exams fail

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Introduction
Parathyroid hyperplasia is the second cause of primary hyperparathyroidism (PH), representing 15–20% of all cases. The scintigraphy with Tc-99m-Sestamibi is a preoperative exam used to identify parathyroid adenomas or hyperplasia. It has a sensibility of 50–90%, which increases with larger parathyroid size. The neck ultrasonography (US) has also an important role detecting parathyroid enlarged glands with 70% sensibility. We report a case of parathyroid hyperplasia where the imaging exams fail to detect a 40 mm parathyroid.
Case report
75-year-old woman with osteoporosis, spontaneous bone fracture and osteoarticular pain. Laboratory evaluation showed a parathormone (PTH) of 145 pg/ml (range 14–72), a serum calcium of 12,0 mg/dl (range 8,6–10,2) and a phosphorus of 2,2 mg/dl (range 2,5–4,5). A neck US was performed revealing a 17 mm hypoechogenic vascularised nodule consistent with the inferior left parathyroid, also visible in the Tc-99m-Sestamibi. Patient was submitted to inferior left parathyroidectomy. The intraoperative exploration conducted to the additional finding of an enlarged superior right parathyroid with 40 mm also removed. The final diagnosis was nodular hyperplasia of both glands. Retrospectively, a detailed familial history was taken and considered negative for hyperparathyroidism and/or endocrine tumours. After 2 months post surgery, the patient is under Vitamin D and Calcium and mentioned improvement in symptoms.
Conclusion
Coincidental results of an anatomic exam (US) and a functional one (Tc-99m-Sestamibi), suggesting the involvement of a single gland, do not exclude pluriglandular HP. Vitamin D and Calcium were started considering the bone disease; discontinuation and tapering of therapy will be managed according to calcium and PTH levels.

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EP321

As clear as mud: an atypical case of primary hyperparathyroidism

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Objective
A young woman presented with marked hyperparathyroidism with post-operative course complicated by hungry bone syndrome and diagnostic and management challenges of ongoing hypocalcaemia with hyperparathyroidism.
Method
ML, a 32-year-old Fijian Indian female, was referred with severe hypercalcaemia, following one-year history of migratory debilitating bone pain. Initial labs showed corrected calcium (C.Ca) 3.17 [2.10–2.60 mmol/l], parathyroid hormone (PTH) 305.4 [2.0–6.0 pmol/l] and 25-hydroxyvitamin D (25-VitD) of 22 [40–80 nmol/l]. Acute management included admission for intravenous fluids and bisphosphonates, which normalised C.Ca. A parathyroid SESTAMIBI/CT-SPECT demonstrated a 31×9×33 mm soft tissue mass in anterior superior mediastinum with focal uptake at T3. Further CT neck demonstrated 10×5×5 mm mass between left common carotid and subclavian arteries.
Results
ML's surgical resection of the mediastinal mass was immediately complicated by generalised bony pain, pleural effusions and despite aggressive replacement of calcium, marked hypocalcaemia (Day 1 C.Ca 1.99); consistent with an exaggerated 'hungry bone syndrome'. ML has been followed closely for on-going optimisation of calcium and vitamin D; three-month labs showed elevated PTH (30.7 pmol/l), despite normalisation of 25-VitD (79 nmol/l) and improved C.Ca (2.04 mmol/l). Her pre-operative DEXA scan showed T-scores: lumbar spine −5.1SD and bilateral femoral necks −5.6SD. A MRI cervical spine demonstrated widespread lytic lesions including, a lesion in the C2 spinous process and posterior pedicles, considered consistent with pathological fracture. Histopathology reported a 70×65×51 mm; 41 gm mass with no invasive features. Parafibromin was positive, whilst PGP9.5 was negative; other patterns of staining were normal, making HRPT2/CDC73 mutation unlikely.
Conclusion
This case highlights: 1) the diagnostic challenge of marked hyperparathyroidism with a clinical picture suggestive of malignancy, but histological evidence not supporting invasion; 2) the management issues of moderating post-operative severe hypocalcaemia and *hungry bone* phenomenon; and 3) the on-going diagnostic and management of post-operative hyperparathyroidism with hypocalcaemia. In summary, atypical primary hyperparathyroidism presents unique diagnostic and management challenges.

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EP322

Familial hypocalciuric hypercalcemia with a new heterozygous missense mutation of CaSR gene and cinacalcet treatment

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Introduction
Familial hypocalciuric hypercalcemia (FHH) is an autosomal-dominant genetic disease caused by an inactivating mutation in the gene encoding the calcium sensing receptor (CaSR). The loss of function leads to increased circulating level of PTH and subsequent hypercalcemia.
Case report
20-year-old male patient referred to our center with hypercalcemia which was found after the syncope. His serum calcium level was 11.7 mg/dl and the phosphorus was 2.4 mg/dl (normal: 2.5–4.5). The serum PTH was 131 pg/ml (normal: 10–65), 25-hydroxyvitamin D3: 12.2 ng/ml and 24-h urine calcium excretion was below 200 mg/day. His calcium/creatinine clearance ratio was 0.005. After replacement of vitamin D, calcium/creatinine clearance ratio was still < 0.01. The family screening planned for FHH. Both his 49 year-old father and 22 year-old brother had also slightly elevated PTH in spite of moderately increased serum calcium levels. Their calcium/creatinine clearance ratios were <0.01. Patient is tested for mutations in the CaSR gene. The patient was found to have a heterozygous missense mutation (p.Ser182Pro/c.544T $>$C) in the CaSR gene, suggesting the diagnosis of FHH. This mutation has never been reported in literature or in the Human Gene Mutation Database. In the follow up of the patient 30 mg/day cinacalcet treatment was started and increased up to 60 mg/day due to the persistant symptomatic hypercalcemia. Plasma calcium levels were normalized and PTH levels decreased slightly after the treatment.
Conclusions
FHH is a rare disorder, but it is clinically important because it can be confused with asymptomatic primary hyperparathyroidism. FHH is usually asymptomatic but rarely symptoms of fatigue, weakness, and excessive thirst and concentration problems are experienced. Cinacalcet is potentially a useful treatment of patients with intractable hypercalcemia caused by mutations in the CaSR gene.

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EP323

Parathyroid carcinoma can be misdiagnosis with medullary thyroid cancer: how is that possible?

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Background
Hypercalcemia may stimulate thyroid's C-cells to produce the calcitonin, that could lead to misdiagnosis of medullary thyroid cancer.
Clinical case
A 47-year-old woman suffered from fracture of the left knee. She could not walk and used a wheelchair. CT scan in a public hospital detected multiple bone lytic changes in the ribs and vertebrae (mts?), tumor in the liver (mts?) and node in the thyroid gland 2.6*1.9 cm. Thyroid biopsy showed follicular neoplasia (cancer?). At the same time, blood analysis showed high level of serum calcitonin 190 pg/m (0–5.5). Thus, her state was determined as the medullary thyroid cancer (MTC) with mts in bone and liver and she was sent to our center for surgery of MTC.
Medical examination uncovered primary hyperparathyroidism (PH): total calcium – 3.78 mmol/l (2.10–2.55), PTH −1513 pg/ml (15–65) in combination with 3.7*2.9*2.4 cm tumor behind the thyroid gland showed by the US exam. Osteitis fibrosa cystica was suspected after radionuclide bone imaging. Renal functions were impaired, GFR 10 mL/min/1.73 m^2. Given the fast progress of the disease the parathyroid cancer (PC) was suspected, so "en bloc" removal of the tumor was performed. The diagnosis was confirmed by histological examination. PTH, total serum calcium levels as well as calcitonin were decreased down to the reference level after the surgery. The liver biopsy shows no tumor cells. PET/CT did not observe the abnormal accumulation of 18FDG in the liver and in bones. The patient's condition has significantly improved 4 month after the surgery – she can walk without a wheelchair.
Conclusions
High level of calcitonin caused by hypercalcemia in combination with nodules in the thyroid gland can lead to incorrect diagnosis. It is important to exclude hypercalcemia in case of high levels of calcitonin.

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EP324

Clinical case of pachydermoperiostosis

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The aim
To study the case of Pachydermoperiostosisis.
Material and methods
We report a case of a 24-year old male complaining of marked changes in appearance due to the disfiguring thickening and wrinkling of skin, excessive greasiness and perspiration, marked horizontal creases on the forehead, with deep furrows between them, increase in the thickness of eye lids, "senile expression" of the face, thickening of distal parts of extremities, fingers and toes. The patient is unsocial, aloof and focused on his emotions.To evaluate the patient's condition we conducted hormonal and biochemical investigations, as well as total blood and clinical urine analysis; MRI of pituitary and ultrasonography of inner organs were performed.
Results
GH – 2.2 (normal range: 0–20 mIU/l); IGF –114.6 (normal range: 219–644 mg/l); prolactin – 5.3 (normal range: 1–18 ng/ml), TSH – 0.87 (normal range:

0.17–4.05 mIU/l), free T4 – 15.5 (normal range: 11.5–23 pmol/l). The patient was diagnosed with pituitary microadenoma, mastoiditis, ethmoiditis, and sinusitis; US revealed chronic cholecystitis, pancreatitis, and reactive hepatitis. Total blood and clinical urine analysis demonstrated no deviations. The patient presented pachydermia of scalp with moderately painful, rough skin folds in the parietal-occipital region, resembling cerebral gyri, thickening and enlargement of eyelids due to hypertrophy of the cartilage tissue, dystrophic changes of the conjunctiva, atrophy of the tarsal glands with formation of cysts and granulomas in them. The patient is unsocial, aloof and focused on his emotions.
Conclusions
Although the prognosis for patients with pachydermoperiostosis is unfavorable, and there are no specific prevention techniques, they can maintain the ability to work for a long time and live to old age if the appropriate treatment is applied (the latter can be achieved by a thorough medical and genetic counseling of families of patients. Some cases, severe articular syndrome may cause permanent disability.

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EP325

Vascular dementia in a 57-year old woman with adenoma of parathyroid gland

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Dementia describes a set of symptoms such as memory loss, difficulties with thinking, problem solving or language. Vascular dementia is a second most common type of dementia, rare under 65 year old. I report a case of 57- year-old woman with diagnosed dementia vascularis in Neurology department. Beside neurological diagnostic methods(brain scan-CT, MRI, Color Doppler of carotids, she had hypercalcaemia (2.96–3.04 mmol/l; normal range 2.20–2.60) as high calciuresis/24-hour (concentration 6.98 mmol/l). Her parathyroid hormone is elevated (hyperparathyroidism) due to adenoma of right inferior parathyroid gland (PTH is 95 pg/ml). Because of progression on patient's physiological and clinical state, immobility, difficulty to communicate and feeding with nasogastric tube, an operation of adenoma of parathyroid gland was not an option. She ended with stones in her left urether and postsurgery complications.

Keywords: dementia vascular; adenoma of parathyroid gland; hypercalcemia; hyperparathyroidism; parathyroid hormone.

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EP326

Equivocal preoperative imaging including 18F-fluorocholine PET-CT in primary hyperparathyroidism and nodular thyroid disease – case report

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66-year old woman came first for an evaluation of nodular thyroid disease. Primary hyperparathyroidism (PHPT) was incidentally diagnosed during the entrance lab test with total calcium 2.62 mmol/l and PTH 93 ng/l. Serum creatinine was normal and 25 OH vitamin D was 97 nmol/l. Dual-energy X-ray absorptiometry was carried out and revealed osteoporosis at lumbar spine. Moreover, there were two low-trauma fractures in a recent patient history. Although hypercalcemia was mild, the presence of osteoporosis constituted an indication for surgical treatment of PHPT. Neck ultrasound found a hypoechogenic lesion of 0.2 ml behind the cranial third of the left thyroid lobe evocative of a left superior hyperfunctioning parathyroid gland. 99mTc-MIBI double-phase scintigraphy was, however, negative. Due to inconclusive conventional imaging 18F-fluorocholine PET-CT was recommended and localized four abnormal parathyroid foci suggestive of parathyroid hyperplasia and/or multigland parathyroid disease. Basic assessment of hereditary forms of PHPT was, therefore, carried out. Prolactin, IGF1, chromogranin A and calcitonin were normal; calcium/creatinine excretion ratio was 2,2%. No relatives affected with hypercalcemia were found. In a postmenopausal woman with normal renal functions and sufficient vitamin D level a sporadic form of PHPT with a single adenoma would be the most expected. The result of 18F-fluorocholine PET-CT was probably modified by thyroid nodules present in both thyroid lobes. The definitive diagnosis will be made by a surgeon during bilateral cervical exploration. The present case shows how a combination of both false negative and false positive preoperative imaging might influence the extent of preoperative evaluation and the choice of surgical approach in PHPT.

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EP327

Parathyroid carcinoma: a report of cases

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Background
Primary hyperparathyroidism (PHPT) is one of the most common endocrine diseases. Parathyroid carcinoma, a rare entity, comprises a small percentage of patients with hyperparathyroidism and represents 0.005% of all cancers and $<1\%$ of cases of PHPT.
Material and methods
Patients was diagnosed at the Endocrinology Department of Diskapi Yildirim Beyazit Training and Research Hospital between 2010 and 2016. Ultrasound and 99mTc-Sestamibi confirmed the suspicion of a parathyroid mass. Parathyroid gland volumes were calculated by multiplication of three diameters and the constant value 0.52. Intraoperative findings and pathology confirmed the diagnosis of parathyroid carcinoma.
Results
Of the patients eight were female and three were male. The patient's ages were between 27–76 years. Parathyroid gland volume of two patients were lower than other cases (respectively 8.92–10.17 ml). Despite small lesion size on ultrasonography, these two patients have moderate-high PTH values. The demographic characteristics and biochemical parameters of the patients.
Conclusion
Pre-operatively, parathyroid carcinoma can be expected based on factors including a larger tumor size, palpable mass, severe primary hyperparathyroidism (PTH 3–15 times the normal upper limit) and hypercalcemia (>14 mg/dl) often with renal and bone involvement by the onset of presentation. Biochemical or ultrasonographic features (lesion size, very high serum calcium and parathyroid hormone levels) may predict aggressive disease, but this is not always the case.

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EP328

A rare case of giant parathyroid adenoma: diagnostic and therapeutic aspects

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Parathyroid adenomas (85% of cases of primary hyperparathyroidism) are usually small in size (weigh 70 mg – 1 g). Giant parathyroid adenomas (GPTA) weighing more than 3.5 g are very rare, more common in males, in the 6th decade of life, generally affect one parathyroid gland, are oxyphilic and ectopic in 50% of cases. We report the case of a 53-year-old woman presented for asthenia, fatigue, tingling in the arms and legs without other symptoms of hypercalcaemia. Laboratory analysis showed: ionized calcium 6.5 mg/dl (normal: 4.2–5.4 mg/dl), total calcium 13.9 mg/dl (normal: 8.8 to 10.0 mg/dl), hypophosphoremia 2.0 mg/dl (normal: 2.3 to 4.7 mg/dl) and 809 pg/mL intact-parathyroid hormone (normal: 11.0 to 67.0 pg/ml). Calcitonin, thyroxin and thyroid-stimulating hormone levels were normal. Cervical ultrasonography revealed a solid hypoechoic nodule located postero-inferior of the right thyroid lobe with retrosternal extension. An ectopic GPTA localised in para-aortic region of superior mediastinum stretching down to the bifurcation of the trachea was

detected using technetium-99m sestamibi scintigraphy and single photon emission computed tomography/computed tomography (SPECT/CT). GPTA measuring 8.5×4×4.5 cm was removed via cervical approach. Histopathology indicated an atypical GPTA with main cells, oncocytic cells, follicular areas, Ki67 < 5% (rarely, in very small areas Ki67 was up to 10%); chromogranin and cytokeratin AE1/3 were positive; carcinoembryonic antigen, thyroid transcription factor1, and thyroglobuline were negative.
The peculiarities of this case: GPTA but poor symptomatology of hypercalcemia and moderately elevated serum calcium levels; ablation of GPTA by cervical incision although mediastinal expansion; mild hungry bone syndrome postoperatively (not correlated with GPTA volume). In conclusion, GPTA is a very rare condition but their size is not an argument in favour of malignancy. Cervical incision should be considered before sternotomy and thoracic/mediastinal approach.

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EP329

Autosomal dominant hypocalcemia in a Portuguese family: novel mutation in the calcium-sensing receptor gene

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Introduction
Autosomal dominant hypocalcemia (ADH) is a rare condition, caused by activating mutations in the calcium-sensing receptor (*CASR*) gene. Affected individuals have hypocalcemia with inappropriately low parathyroid hormone (PTH) levels.
Case report
A 50-year-old woman, asymptomatic, was referred to our Endocrinology department for investigation of hypocalcemia detected in routine blood analysis (serum corrected calcium was 7.4 mg/dl – normal: 8.6–10.2). There was also hyperphosphatemia (5.4 mg/dl – normal: 2.4–5.1) and abnormally low PTH (9.9 pg/ml – normal: 14–72).
Her past medical history was irrelevant except for depression in the past. She denied taking any prescription. There was no history of neck surgery/radiation or known family history of hypocalcemia. Thyroid function, morning serum cortisol and 24-h urinary cortisol, fasting glucose, 25-hydroxyvitamin D, renal function, serum magnesium, sodium and potassium were normal. Auto-antibodies against thyroid, parathyroid and adrenal gland were negative. Brain computed tomography identified basal ganglia calcifications. A few first-degree relatives (74-year-old mother, sisters aged 44 and 49, and 30-year-old son) were also screened for hypocalcemia. The mother and the younger sister, both asymptomatic, had hypocalcemia and inappropriately low PTH. The mother also presented basal ganglia calcifications. The son and the older sister had normal calcium levels. Genetic analysis identified a novel heterozygous *CASR* variant: c.2269G>A (p.Glu757Lys) in the proband, her mother and younger sister whereas it was not identified in the son and older sister. Affected individuals started calcium replacement aiming to a low-normal calcium level (8–8.5 mg/dl).
Conclusion
The co-segregation of the novel *CASR* variant with the hypocalcemic phenotype in the family favor its pathogenic role. Clinical investigation and diagnosis of this condition can be challenging, but treatment and long-term monitoring are essential to prevent complications, such as neurological.

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EP330

A case of intrathyroidal parathyroid adenoma presented with severe 25(OH)D3 deficiency, bone pain and high PTH

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The most frequent pathology of primary hyperparathyroidism presented with the findings of hypercalcemia is parathyroid adenoma. Some patients having the signs of primary hyperparathyroidism may have intrathyroidal parathyroid adenoma and it may be overlooked. We present a case of intrathyroidal parathyroid adenoma presented with bone pain.
47-year-old female patient referred to our clinics with bone pain and she had no pruritus, dry mouth, dyspepsia, abdominal pain, nausea, vomiting, polyuria or polydipsia. She did not have any history of hypertension, nephrolithiasis, renal failure or bone fracture; and she was taking risedronate for one week for osteoporosis. On physical examination, vital signs and systemic findings were normal. Blood count revealed mild anemia (hemoglobin:10 gr/dl, MCV:80 fL); and in biochemical analysis, creatinine was 0.65 mg/dl, Ca:12 mg/dl, P:2.2 mg/dl, Mg:2.07 mg/dl, albumin:3.1 gr/dl, ALP:738 U/l. Hormonal parameters showed biochemical primary hyperparathyroidism (PTH:1938 pg/ml, 25(OH)D3: <3 ng/ml). BMD showed severe osteoporosis in lumbar vertebra (T score −4.0). There were osteopenia in bone X-rays and "Brown tumor" in fifth metacarpal bone of right hand. No nephrolithiasis or nephrocalcinosis were found in abdominal sonography. Neck sonography revealed a large (37×24 mm), vascular, heterogenous nodule having both cystic and solid areas in right lobe of the thyroid gland. 99mTc-sestamibi scintigraphy showed MIBI uptake in the nodule, making us to define the nodule as intrathyroidal parathyroid adenoma. Then, the patient underwent to surgery, and right hemithyroidectomy was done; and postoperative pathological examination confirmed the parathyroid adenoma. Postoperative calcium and PTH levels were 7.3 mg/dl and 24.3 pg/ml.
When clinical and biochemical findings point to primary hyperparathyroidism, we should keep in mind that intrathyroidal nodules may be parathyroid adenoma.

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EP331

The rare cause of primary hyperparathyroidism: Parathyroid Carcinoma

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Introduction
Parathyroid carcinoma (PC) is a rare endocrine malignancy which accounts for 0.005% of all cancers and less than 1% of primary hyperparathyroidism cases. This uncommon tumor usually occurs during the fifth decade of life, with equal frequency in both sexes, and has an indolent but progressive course. It's frequently symptomatic and patients may have high values of serum calcium and parathyroid hormone (PTH) with a palpable cervical mass. PC generally occurs as a sporadic disease, and less frequently in the setting of genetic syndromes such as hyperparathyroidism-jaw tumor syndrome and multiple endocrine neoplasia. In this study we present five different PC cases followed in our clinic.
Cases
There were 2 female and 3 male patients with PC. The mean age of the patients was 50.4±13.7(38–65). They had presented with weakness, headache, nausea and vomiting, and widespread bone pain. One of the patients had bone fracture and one other patient had nephrocalcinosis.The mean serum calcium, phosphorus and PTH levels were 15.3±2.7 mg/dl (ranging between 11.6 and 18.9 mg/dl), 2.4±0.8 mg/dl and 869.4±991.9 pg/ml (ranging between 87 pg/ml and 2500 pg/ml), respectively. Histopathologically, mean tumor size was 29.2±11.1 (15–44) mm. Plasma calcium, phosphorus and PTH levels were in the normal range and 36 months after surgery in 2 patients. Local recurrence was observed in 2 patients and reoperation was performed. One other patient withlung and bone metastasis had still high serum Ca and PTH levels despite recurrent surgeries for six times.
Conclusion
PC is usually that of a slowgrowing neoplasm and indicates progressive end-organ damage from disturbed calcium homeostasis. While some patients present with mild increases in serum calcium and PTH levels, some might have very severe hypercalcemia and hyperparathyroidism. Similarly, prognosis varies from cure to life threatening unresectable and metastatic disease depending on the presentation and surgical success.

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EP332

A parathyroid adenoma presented with diffuse bone lesions and anemia

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Primary Hyperparathyroidism is a common endocrine disorder characterized with high parathyroid hormone (PTH) and calcium (Ca) levels. Although most of the patients are asymptomatic, some patients may be presented with renal, gastrointestinal, musculoskeletal, neurologic or cardiovascular signs associated with hypercalcemia or elevated parathyroid hormone related findings such as bone disease, nephrolithiasis, hypophosphatemia increased production of calcitriol, hypomagnesemia, hyperuricemia and anemia. Brown tumor is one of the manifestations of Primary Hyperparathyroidism and is more commonly found in trabecular bone pattern of the mandible, bones of the upper and lower extremities and ribs.

Case

A 54 year-old female with a history of recurrent nephrolithiasis was referred with fragile bones fractures. Biochemical assay revealed an increased value of serum PTH 1570 pg/ml and calcium 13.5 mg/dl. The serum phosphorus level was 3.4 mg/dl, ALP:14 IU/l, 25OH vitamin D: <8 µg/l.

Direct radiographies revealed multipl lesions of the upper and lower extremities, iliac bones, femoral heads, sacrum, sternum, ribs and vertebrae. A complete blood count (CBC) of the patient revealed a low hemoglobin and hematocrit levels (Hg:6.93 g/dl, Htc:20.00%). There was no evidence of neutropenia or leucopenia. After consulting to Hematology department, it was reported that anemia was associated with diffuse bone lesions and it was not possible to make bone marrow biopsy due to diffuse bone lesions. Follow up of anemia for recovery after parathyroidectomy was also suggested. Ultrasound of neck revealed mass of 3 cm associated with parathyroid adenoma. After erythrocytes transfusions, the patient was planned for surgery.

Multipl bone lesions are common in Primary Hyperparathyroidism and Brown tumor may also be a part of this clinical condition. These lesions are usually localized and have a tendency for recovery of the primary disease. It should be in mind that diffuse bone marrow lesions may be seen resulting progenitor cells failure in bone marrow and cytopenia.

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EP333

Common bone lesions may be a sign of parathyroid carcinoma in the primary hyperparathyroidism

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A 60-year-old male patient who presented with left hip and knee pain was found to be compatible with primary hyperparathyroidism (PTH:2233 pg/ml, calcium: 15.7 mg/dl, phosphorus: 2.9 mg/dl creatinin:1.99 mg/dl, 25-OH-D:9.7 µg/l, ALP:532 mU/ml). Bone grafts of the patient showed multiple lytic lesions in the pelvis, cranium and long-bones. Neck ultrasonography showed hypoechoic solid nodule with cystic areas, 2×2 cm with size in the left thyroid gland inferior region and delayed wash-out was detected by the parathyroid scintigraphy. Bone scintigraphy was suspicious in terms of metastasis. Left hemi thyroidectomy and left inferior parathyroidectomy was performed. In thorax lytic lesions compatible with multiple metastases in bone structures were observed. Thoracal and lumbar vertebral MR imaging also showed lesions compatible with metastasis. Histopathological examination revealed parathyroid carcinoma with invasion to the thyroid gland.

Primer hyperthyroidism has been increasing in recent years as a laboratory diagnosis the contribution of asymptomatic cases has increased. Frequent routine examinations have also led to the early recognition of the disease, and osteitis fibrosa cystica and bone lesions such as brown tumor, which are among the complications of primary hyperparathyroidism, are increasingly rare. Primer Hyperparathyroidism is often associated with solitary parathyroid adenoma, hyperplasia or multiple adenomas, mostly seen with the genetic syndromes. Parathyroid carcinoma is very rare and is recognized only by the presence of metastases or histopathologically significant invasion findings, such as those present in our case. Clinically, incompatibility in tumor size and serum PTH levels, extremely high PTH levels may be a sign of parathyroid carcinoma. Apart from this, common bony lesions which are rarely seen in primary hyperparathyroidia due to early diagnosis and noisy clinical picture can be considered as malignancy findings as it is in our patient. Therefore, in patients with widespread pain and common bony lesions, the patient should be carefully examined for parathyroid carcinoma and an appropriate approach should be sought.

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EP334

Broken bones and blindness- a rare cause of osteoporosis

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Case History

A 37 year-old gentlemen was referred to metabolic bone clinic due to recurrent recent fragility fractures. He had several fractures throughout childhood, and these had continued to occur into his adult life. He was blind in his left eye since birth. He felt that this had contributed to his fractures, due to falls. There had been no other previous major health problems. His brother had a similar eye condition. There were no other risk factors for osteoporosis. There was nothing of significance to find on examination.

Investigations & Results

DXA scan- Spine L1-L4 T-score -3.6, Left hip T-score -2.4. CTX 0.24 mcg/L (normal), P1NP 34 mcg/L (normal). Spine X-rays: T11 grade 1 fracture & T4 grade 2 fracture. No other secondary cause of low bone mass identified (normal levels of testosterone, parathyroid hormone, vitamin D, calcium, phosphate and coeliac antibodies)

Discussion

This is a case of a young man with seemingly unexplained fragility fractures and low bone mass. The clue to the aetiology for low bone mass was the gentleman's hereditary eye condition. The eye problems are caused by a condition known as Familial Exudative Vitreoretinopathy (FEVR); a rare genetic disorder affecting retinal angiogenesis that can cause progressive visual loss. FEVR may be mediated by mutation in *LRP5* coding for the LRP5 transmembrane receptor. LRP5 plays a key role, alongside Frizzled protein, in the Wnt signalling pathway, which has effects on cellular proliferation, adhesion and migration. Importantly, Wnt signalling is also known to regulate bone mass. Therefore, it is the defect in this pathway that is the common denominator for this gentleman's blindness and bone problems. We speculate that upcoming new drugs that target Wnt signalling in osteoporosis, such as Romosuzumab (a Sclerostin inhibitor), may be particularly beneficial in patients with low bone mass associated with FEVR.

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EP335

An usual cause of post operative hypocalcemia

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Introduction

The otorhinolaryngologist can be confronted to multiple surprises after a thyroid surgery

Case description

We report the case of a 48 year-old woman admitted with post operative hypocalcaemia (after thyroidectomy?). The patient has a history of hypothyroidism since 5 years. She then presented a cervical swelling. The ultra-sound confirmed the presence of a suspicious thyroid nodule measuring 4 cm. A thyroidectomy was then conducted. Post operative, the patient presented with symptoms of hypocalcaemia, confirmed by low level of blood calcium at 1.59 mmol/. The anatomopathological examination showed no sign of thyroid tissue, along with the presence of five adenomatous parathyroid nodules. Post operative scintigraphy showed a conserved thyroid tissue, with absence of parathyroid glands. Hungry Bone Syndrome was confirmed led to the prolonged and severe hypocalcaemia, associated to the adenomatous aspect of the parathyroid measuring more than 6 cm. Because of the family history of pituitary prolactinoma, primary hyperparathyroidism and multinodular goitre and the personal history of uterine fibroma and hypothyroidism, Multiple Endocrine Neoplasia 1 (MEN1) was suspected. Genetic confirmation is underway.

Conclusion

This is the case of an asymptomatic hyperparathyroidism discovered by a severe post-thyroidectomy hypocalcaemia. This hyperparathyroidism is due to multiple parathyroid adenomas misdiagnosed as thyroid nodules, and probably falls within a multiple endocrine neoplasia type 1.

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EP336

Brown tumor in a normocalcemic patient

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Background
Brown tumor of bone is a non-neoplastic lesion resulting from abnormal bone metabolism in hyperparathyroidism. Brown tumor, as the only and initial symptom of normocalcemic primary hyperparathyroidism is extremely rare.
Case presentation
A 69-year-old female patient was admitted to the hospital with a mass in the right thigh. A mass lesion of the right distal femur with bone and soft tissue infiltration was observed in the lower extremity magnetic resonance imaging (MRI). The size of the mass was measured as approximately $10\times3.7\times4.6$ cm. Apart from this lesion, nodular lesions were detected in various dimensions on the right femur, left femur and left patella. Brown tumor was detected in pathologic evaluation of the mass of the right distal femur. The patient was examined for hyperparathyroidism. Serum parathormone (PTH) level was 2698 pg/mL (reference range 15–68), calcium level was 8.8 mg/dL (8.4–10.2), phosphorus level was 2 mg/dL (2.4–4.4) and 25-OH D level was 10 μg/L. Vitamine D treatment was given to the patient. 24-hour urine calcium could not be assessed because of the patient's low compliance. The total lomber T score was −4.7 and the femur neck T score was −5.5 in the bone mineral density. Localization studies were performed and neck ultrasonography and parathyroid scintigraphy revealed a parathyroid adenoma in the inferior right lobe. Patient underwent parathyroidectomy surgery and in histopathological evaluation solitary parathyroid adenoma was observed. The follow-up of the patient whose postoperative PTH decreased to 161 pg/mL is being continued.
Discussion
Cytologically, it is difficult to separate the brown tumor from any other giant cell lesions. To prevent unnecessary surgical procedures, PTH assay is necessary in any patient with expansive lytic lesion of the bone, even if serum calcium level is normal.

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EP337

Symptomatic bisphosphonate-induced hypocalcaemia after severe idiopathic hypercalcaemia

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Introduction
Bisphosphonates, generally considered as safe drugs, are potent inhibitors of bone calcium outflow used to treat osteoporosis and hypercalcemia associated with malignancy. Bisphosphonate-induced hypocalcaemia is an increasingly reported complication, but it has not yet been a subject of comprehensive research.
Case report
A 65-year-old woman had a history of Crohn's disease and ankylosing spondylitis medicated with prednisolone and etanercept. Due to vitamin D deficiency she had been taking calcium and vitamin D supplementation. At a consultation she presented with difficulty in concentration and balance, and blurred vision. Analysis revealed severe hypercalcemia (ionized Ca^{2+}2.18 mmol/l), elevated serum creatinine and normal parathyroid hormone (PTH). She was treated with intravenous fluids and a single intravenous dose of zoledronate, resulting in calcium normalization and clinical remission. Five days later she returned for delirium, tetany, perioral paraesthesia and carpopedal spasm. Chvostek's sign was positive. Hypocalcaemia (ionized Ca^{2+}0.97 mmol/l), vitamin D deficiency, elevated PTH, hypomagnesaemia, hypophosphataemia and hypokalaemia were detected. She required intravenous calcium and long-term oral calcium and vitamin D supplementation with gradual but sustained improvement. Densitometry revealed femur and lumbar spine osteoporosis. Study was negative for neoplasms and despite extensive study, aetiology of hypercalcemia remains unclear.
Discussion
This case illustrates a serious but still poorly recognized complication of hypercalcaemia treatment. Most patients do not develop hypocalcaemia due to compensatory mechanisms that could be affected in this case: vitamin D deficiency, diminished intestinal calcium absorption (corticoids and zoledronate) and lower tubular calcium reabsorption, and decreased excretion of zoledronate due to acute renal failure. Considering the high prevalence of vitamin D deficiency and the sudden nature of hypocalcaemia, these and other risk factors should be considered when using bisphosphonates in order to prevent this potentially fatal complication. Further studies may clarify the overall risk and approach to this situation.

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EP338

Transient hyperglycemia during the course of primary hypoparathyroidism: Case study

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Introduction
Calcium ions (Ca^{2+}) play an essential role in process of correct β-cell insulin secretion. Hypocalcemia impairs insulin secretion leading to glucose metabolism disorders and insulin resistance.
Case study
62 -year old female patient with 18 years history of type 2 diabetes, treated with insulin, suspected of hypoparathyroidism, was admitted to the Department and Clinic of Endocrinology, Medical University of Lublin because of hypocalcaemia. She was experiencing latent tetany signs like muscle tremors, paresthesia and an unpleasant tingling sensation in her hands, additionally persistent dry cough. Clinical observation and laboratory findings with classic constellation of symptoms (hypocalcemia, hyperphosphatemia, undetectable concentrations of parathyroid hormone (PTH), latent tetany signs, history of nephrolithiasis and of subcortical nuclei calcifications) have confirmed the diagnosis of late onset primary hypoparathyroidism. Significant clinical improvement following introduction of calcium and active form of vitamin D supplementation were achieved. Based on normal blood glucose levels with relatively low daily insulin requirement an attempt at discontinuing insulin therapy was made. In spite of hypoglycemic therapy cessation, patient's glucose levels remained in the normal range. For the purpose of diagnosis verification oral glucose tolerance test (OGTT) was performed, and did not reveal any glucose metabolism disorders. These observations led us to conclude that recognized hyperglycemia was secondary to prolonged hypocalcemia.
Conclusions
The optimal concentrations of organism's cytosolic Ca^{2+} are required for appropriate β-cell insulin release. Hypocalcemia is regarded as a factor implicated in pathogenesis of glucose metabolism disorders thus normalizing serum calcium levels allows for restoration of adequate insulin secretion.

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EP339

Hyperparathyroidism jaw tumour syndrome (HPT-JT)

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Hyperparathyroidism jaw tumour syndrome (HPT-JT) is an autosomal dominant disease with variable penetrance. Onset is typically in late adolescence or early adulthood. Primary hyperparathyroidism is typically caused by a single

parathyroid adenoma but parathyroid carcinoma occurs in 10–15%. Ossifying fibroma of the mandible or maxilla occurs in 30–40%, and may be locally aggressive. 15% of patients have renal manifestations which include polycystic kidney disease, Wilms tumour and renal cell carcinoma. In women there is an increased risk of uterine tumours. The gene causing HPT-JT, HRPT2, is located on chromosome 1q31.2a, coding for parafibromin (tumour suppressor gene) found in 50–75%.

We recently identified a patient with HPT-JT which led to detection of a kindred with the CDC73 pathogenic variant. A 54-year-old male presented to the maxillofacial services for surgical removal of a jaw tumour. Histology confirmed an ossifying fibroma of the maxilla. During his admission he was noted to have hypercalcaemia (Ca^{++}3.2 mmol/l, PTH 110 pmol/l).

On review of previous history, he described poor dentition since the age of 20, and he reported that his sister had died at the age of 35 from metastatic parathyroid carcinoma. Diagnosis of primary hyperparathyroidism was established and he underwent parathyroid surgery with normalisation of Ca^{++} and PTH. Histology was consistent with parathyroid adenoma.

His genetic analysis detected a mutation in the CDC73 gene (Exon 7 c.664 C to T leading to protein PArg222Ter). Family members were screened, which confirmed CDC73 mutation in one daughter and one son, and 1 son was mutation negative.

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EP340

Fahr syndrome revealing a pseudohypoparathyroidism

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Introduction

Fahr syndrome is a rare entity characterized by the presence of bilateral intracranial calcifications with predilection for the basal ganglia and dentate nuclei. It is commonly associated with endocrine disorders, particularly parathyroid and Vitamin D disturbances. Herein we report a case of pseudohypoparathyroidism revealed by Fahr syndrome.

Observation

A 29-old-year male was referred to our department for symptomatic hypocalcemia. He showed a decrease in his school performances with memory and concentration impairement. Computed tomography scan of the brain revealed bilateral, symmetric basal ganglia calcifications. Ophthalmic examination showed bilateral cortical cataract.

Physical examination showed positive Chvostek and Trousseau's signs. The rest of clinical examination was normal in particular no typical findings of Albright's hereditary osteodystrophy were observed.

Laboratory investigations revealed severe hypocalcemia of 44 mg/l (normal range: 85-105), hyperphosphatemia of 48 mg/l (normal range: 25-45), elevated parathormone level of 218 pg/ml (normal range: 15–68.3), normal renal function, normal serum albumin and normal 25 OH Vitamin D level (46 µg/l, normal range: 30–80 µg/l). Thyroid function was normal. Urinary cyclic adenosine monophosphate level and Gsα subunit assay were not available Considering laboratory findings, the diagnosis of pseudohypoparathyroidism was established. Patient was put on substitutive therapy.

Conclusion

In the absence of chronic renal failure, the coexisting of hypocalcemia, hyperphosphatemia, elevated PTH and normal vitamin D level is consisting with the diagnosis of pseudohypoparathyroidism.

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EP341

Parathyroid cyst: the forgotten diagnosis of a neck mass

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Introduction

The differential diagnosis of cystic cervical masses includes thyroid cyst, thymic cyst, thyroglossal duct cyst, branchial cleft cyst, bronchogenic cyst, lymphangioma and parathyroid cyst (PC). PC is one of the less common causes of the cervical masses.

Methods

We report the case of a 37-year-old man admitted to the hospital with a neck mass of 48 mm.

Results

Our patient presented with neck pain and an hipoechogenic nodule on ultrasound (US) on the left side of the neck adjacent to the lower pole of the left thyroid lobe. An US-guided fine-needle aspiration was performed and follicular cells where described. Measurement of TSH, T4L and AbTPO had a normal result. Given the suspicion of thyroid nodule >4 cm surgical treatment was decided. While waiting for surgery an US was performed and we observed markedly reduction on the size of the nodule (28 mm) and the radiologist suggested the possibility of a parathyroid adenoma. Our patient referred prior episodes of nephrolitisis a few years ago and that he had been told to had high serum calcium levels but did not undergo further studies. We measured PTHi levels and Calcium (100,5 pg/ml; 10 mg/dl) showing a normocalcemic hyperparathyroidism. Left thyroid lobectomy was performed showing a normal left thyroid lobe, a parathyroid cyst and ectopic thymus.

After nodule resection PTHi levels went back to normal and calcium levels remain less than 10 mg/dl.

Conclusion

PCs are rare lesions and often considered as thyroid cysts. Diagnosis is best made by monitoring serum calcium levels and sending cyst fluid for PTH analysis. Therefore, PCs must be included and be remembered within the differential diagnosis of all neck masses.

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EP342

"Pseudo or not": differential diagnosis of hyperparathyroidism with severe electrolyte imbalance in transgender patient: a challenging case report

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Introduction

Differential diagnosis between secondary hyperparathyroidism (SHPTH) and possible pseudohypoparathyroidism can be challenging in case of insufficient diagnostic tools and co-existing medical conditions. We report a diagnostic road to final diagnosis.

Case report

A 48-years old white male-to-female transgender patient was admitted to our clinic for evaluation due to mental deterioration, general fatigue, slowly progressing bilateral upper arm and epigastric area cramps over last 2 years, pain in the lumbal area and right hip region leading to reduced mobility. No remarkable history, except crural DVT during estrogen therapy, received from 2004–2015 without any specialist's supervision, not any therapy used in last year. Possible previous delusion episodes since head trauma during teenage years were reported by patient's brother. The patient was severely obese.

Biochemical tests revealed low calcium (1.74 mM/l [2.2–2.55]) and potassium (3.12 mM/l [3.3–5.5]), normal phosphate, creatinine and glucose level. Preliminary suspected Cushing's and Fahr's syndromes were excluded after seeing suppressed cortisol axis and elevated PTH (624.2 pg/ml [12–68]). No substantial changes in other tests. No electrolyte loss with 24 h urine was seen. Thyroid and gonadic axis were unchanged. Head CT scan revealead no basal ganglia calcinosis. No data of paratadenoma. In spite of high normal phosphate level and not characteristic phenotype, our first suspected diagnosis was pseudohypoparathyroidism. Additional tests showed low 25(OH)-vitamin-D ($<$ 7 ng/ml [30–50]) and elevated alkaline phosphatase (320 U/l [44–147]). Pelvic MRI showed left femoral periosteal cyst formation and right hip joint synovitis. Though we were restricted in many diagnostic tools due to multiple factors, no further data strongly supported evidence of pseudohypoparathyroidism.

Based on these findings we suggest the final diagnosis of secondary hyperparathyroidism with severe osteomalacia. Treatment was continued with calcitriol, cholecalciferol, oral calcium. Some improvement of symptoms was seen over the hospitalization course.

Conclusion

We would like to stress the importance of multi-focused investigation for bone-metabolic problems.

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Developmental Endocrinology

EP343

Adolescent onset distal renal tubular acidosis presenting with significant growth retardation without rickets

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Introduction
Distal renal tubular acidosis (RTA) can have varied presentation. Onset in infancy is usually severe. However, adolescent onset has variable presentation ranging from hypokalemia to nephrocalcinosis, and rarely with rickets or growth retardation. We describe a girl with distal RTA presenting with hypokalemia and growth retardation.
Case
12 year old girl presented with recurrent episodes of weakness of all four limbs and failure to gain height and weight for last 4 years. There was no sensory or autonomic involvement. She had normal birth history and developmental milestones, no dysmorphism or bony abnormality, no sensorineural deafness and a negative family history. Nutritional status was average. Height and weight were below Indian Academy Of Paediatrics 3rd percentile.
Investigations
$K^+ = 2.9$ mmol/l; Urine K = 30 mmol/24 hr (increased). pH = 7.324, $HCO3^- = 12.4$ meq/l, $pCO_2 = 23.9$ mm-Hg; anion gap = 10 mmol/l Urine pH = 7.0. UAG: Positive (28 meq/l), urine calcium:creatinine ratio = 0.63(N < 0.2) ANA & ENA: negative. Genetic testing not done due to non-availability CBC, LFT, serum 25-OH Vitamin D & iPTH, Ca^{++}, PO_4^{3-}, alkaline phosphatase, FT4/TSH, IGF-1 were all normal. X-ray of wrist: no evidence of rickets. USG Abdomen = Medullary Nephrocalcinosis in both kidneys.
Diagnosis
Growth retardation with hypokalemic periodic paralysis in a case of distal RTA of adolescent onset based on normal anion gap acidosis with high urinary pH with positive urine anion gap.
Treatment
She was managed successfully with intravenous potassium and is on oral sodium bicarbonate 500 mg twice daily. Her clinical response is good.
Conclusion
The take home points are that every child presenting with hypokalemia should be evaluated for RTA. The presentation of distal RTA can be subtle to severe. Even in the absence of bony involvement like rickets children can suffer from significant growth retardation. Growth failure should be actively searched for even in asymptomatic patients.

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Endocrine Tumours and Neoplasia

EP344

Differential roles of carboxylated and uncarboxylated Osteocalcin in stage I breast cancer as a diagnostic biomarker

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Objective
The finding of new biomarkers is needed to have an early diagnosis of breast cancer. In this study we evaluated serum levels of carboxylated osteocalcin (OC) and uncarboxylated osteocalcin(UcOC), CRP as a diagnostic biomarker for breast cancer.
Design and methods
Blood samples of 39 women with newly diagnosed breast cancer with stage I were obtained before surgery and 39 age and BMI matched health women were selected as controls.
Results
The mean age was 52 ± 7 years ($P = 0.8$). Circulating logOC was significantly lower in breast cancer patients compared to controls (2 ± 1.1 mg/ml vs. 3 ± 1.23 mg/ml, $P < 0.05$), while logCRP levels were significantly higher in breast cancer patients than controls (0.8 vs. -0.6, $P < 0.05$). Serum levels of logUcOC were not different between groups(6.39 ± 0.4 mmol/l vs. 6.39 ± 0.9 mmol/l, $P =$ NS). OC had a positive correlation with ucOC ($r = 0.3$, $P = 0.03$). In contrast, CRP was not correlated with OC and ucOC ($P = 0.2$, $P = 0.3$, respectively).
Conclusion
We conclude that circulating OC has a potential use as a sensitive diagnostic biomarker for early detection of breast cancer.

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EP345

Gross CDC73 deletions in young patients with primary hyperparathyroidism in Russia

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Introduction
Hyperparathyroidism-jaw tumour syndrome (HPT-JT) is a rare disorder, which is frequently characterized by the development of parathyroid carcinomas and atypical parathyroid adenomas and, thus, severe course of primary hyperparathyroidism (PHPT).
Case reports
Two patients (*1 male and 1 female, 18 y.o. and 13 y.o. at the time of diagnosis of PHPT, respectively)* among a cohort of young patients (<40 y.o.) with PHPT, underwent next-generation sequencing (NGS) (Ion Torrent™ PGM™, Thermo Fisher Scientific–Life Technologies, USA) using a custom-designed Ion AmpliSeq™ gene panel. NGS did not reveal any pathogenic variants in genes associated with familial PHPT in these two patients, but the analysis of the sequence data by the ExomeDepth program [Plagnol V et al, 2012] allowed us to assume the existence of large deletions in *CDC73* gene. To confirm this observation MLPA (MRC-Holland, the Netherlands) of *CDC73* on ABI 3500xL Genetic Analyzer (Applied Biosystems, USA) was performed. In a male with severe PHPT (serum total calcium 4.49 mmol/l (2.15–2.55), ionized calcium 2.03 mmol/l (1.03–1.29), PTH 1833 pg/ml (15–65), osteitis fibrosa cystica) and histological diagnosis of atypical parathyroid adenoma, a gross deletion including the entire *CDC73* gene and four additional genes (*TROVE2, GLRX2, B3GALT2* and *LINK0103*) was detected. In a female with severe PHPT (serum total calcium 3.57 mmol/l, ionized calcium 1.58 mmol/l, PTH 1550 pg/ml, osteitis fibrosa cystica) and histological diagnosis of parathyroid carcinoma, the deletion of 1–10 exons of *CDC73* gene was detected. The patients' mother also had PHPT due to parathyroid adenoma.
Conclusion
These two cases illustrate that NGS data could be successfully applied for indirect assessment of large gene deletions which could be further confirmed by MLPA. Search for *CDC73* mutations is necessary among patients with parathyroid carcinomas and atypical parathyroid adenomas, which could occur at any age.

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EP346

Multiple endocrine neoplasia type 1 phenocopies: role of the genes associated with familial primary hyperparathyroidism

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Introduction
The genetic causes of development of multiple endocrine neoplasia type 1 (MEN-1) phenocopies remain largely unknown.
Aim of the study
To evaluate the role of genes associated with familial primary hyperparathyroidism (PHPT) in the development of MEN-1 phenocopies with the combination of PHPT and pituitary adenomas (PA).
Materials and methods
20 patients (19 females and 1 male) were included in the study. All patients had biochemically confirmed PHPT in combination with PA of different types of

secretion: 15 GH-secreting, 3 ACTH-secreting, 1 PRL-secreting, 1 non-functioning PA. Median age at the time of inclusion was 61 years [Q25-Q75;min-max:57–66.5;54–79], median age at the time of PHPT diagnosis was 57 years [Q25-Q75;min-max:54–62;51–72], median age at the time of PA diagnosis was 47 years [Q25-Q75;min-max:40.5–57.5;21–61]. Five patients had mild PHPT, 15 – manifest PHPT (though it was difficult to assess the role of PHPT in osteoporosis development due to concomitant menopause and Cushing disease in some cases). Imaging techniques revealed: in 15 patients – solitary parathyroid tumour, in 2 patients – two parathyroid tumours, in 3 patients parathyroid tumours were not visualized. In the majority ($n=16$) of patients PA was the first manifestation, only in 4 patients PHPT was diagnosed before PA. In all patients no *MEN1* mutations were identified by Sanger sequencing, confirming diagnosis of MEN-1 phenocopy. Next-generation sequencing of a custom-designed Ion AmpliSeq™ panel of genes associated with familial PHPT (*MEN1, CASR, CDC73, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2C, CDKN2D*) using semiconductor sequencer PGM™ Ion Torrent (Thermo Fisher Scientific, USA) was performed. ANNOVAR was used for variant annotation.
Results
No pathogenic or likely pathogenic variants in the abovementioned genes were identified.
Conclusion
Mutations in the genes associated with familial PHPT are unlikely to have any role in the development of MEN-1 phenocopies with combination of PHPT and PA.

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EP347

Recurrent ectopic parathyroid carcinoma

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Background
In most cases of parathyroid carcinoma (PC) only recurrence could be a credible feature of malignancy.
Clinical case
At the age of 19 years a woman was diagnosed with urolithiasis. At the age of 22 years she had a surgical resection of the neck nodule at the right site in the projection of carotid triangle. After the histological study, ectopic parathyroid tumor was misdiagnosis with paraganglioma (material is available for review). At the age of 37 years the patient noted deteriorating state of health: severe weakness, nausea, vomiting (10 times per day), rapid loss of body weight (10 kg in 6 months). She noted the appearance of nodule in the neck to the right in the projection carotid triangle again. A month later she was diagnosed with a primary hyperparathyroidism: total calcium – 3.0 mmol/l (2.19–2.55), PTH-786 pg/ml (15–65). CT-scan showed two tumors sized up to 3.3*1.7 cm; 3.2*1.3 cm between right m. sternocleidomastoideus and the common carotid artery. The next day the hypercalcemic crisis developed (total calcium – 5.33 mmol/l) and therefore, ectopic parathyroid tumors were urgently resected in our center. PC was diagnosed after a histological examination. At the age of 47 years the local recurrence was diagnosed: total calcium – 3.51 mmol/l, PTH-450 pg/ml. PET/CT showed a focus with the pathological accumulation of 18FDG in singles upper jugular lymph node on the right at the level of C3-4, 16,7*19,7 cm. After another surgery, the tumor went through the immunocytochemical analysis which showed a diffuse intensive expression of PTH, Ki-67- 15%.
Conclusions
The diagnosis of PC is challenging due to the lack of credible diagnostic criteria. The treatment of choice in PC is an *en bloc* resection of the mass with total ipsilateral thyroid loboistmectomy and central compartment lymphadenectomy and timely detection and resection of mts.

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EP348

Exome analysis of a large family with familial isolated primary hyperparathyroidism (FIHP) and multiple cancers

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Familial Isolated Hyperparathyroidism (FIHP) is a hereditary disorder characterized by primary hyperparathyroidism (PHPT) with no evidence of other endocrine disorders. Germline *MEN1, CDC73* and *CASR* mutations have been identified, but the majority of FIHP has still unrecognized causes. The aim of this study was to identify, by whole-exome sequencing, novel gene alterations in a large FIHP kindred. The family's proband, her sister, brother and niece were affected by PHPT. The proband was negative at MEN1, *CDC73* and *CASR* gene mutations by Sanger analysis. The proband, her sister and niece were also affected by papillary thyroid carcinoma, the brother had Non-Hodgkin Lymphoma and bladder cancer. The proband had also a moderate colorectal polyposis and the niece a renal angiomyolipoma. We analyzed the proband, two affected and two healthy family's members with the Illumina NextSeq550 platform. The raw data were converted using Bcl2toFastq tools. Data analysis was performed by the SeqMule pipeline. The three affected individuals, but not the healthy relatives, shared 57 rare genetic variants. A more stringent filter related to genes involved in hereditary cancer detected one missense variant in the *APC* gene (V530A) in the three affected patients, subsequently confirmed by Sanger analysis. Moreover, the other affected relative and 2/15 healthy members carried the variant. The *APC* gene is involved in familial polyposis (FAP), an inherited disease marked by thousands colorectal polyps. The *APC* variant was predicted deleterious by three statistic model. Although the affected individuals don't have classical FAP features, the proband had the excision of two colonic polyps. We might speculate that the presence of non-truncating mutation could lead to a mild colonic phenotype, as showed in the attenuated FAP, characterized by the presence of <100 polyps. FAP tumor spectra is highly various, in about 2% of cases papillary thyroid carcinoma and bladder cancer have been reported.

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EP349

Parathyroid cancer – clinical presentation, prognostic factors and long-term evolution

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Background
Parathyroid carcinoma (PC) is a rare endocrine malignancy affecting 0.5–5% of all patients with primary hyperparathyroidism. Due to the rarity of PC there is still lack of prognostic implications of the disease and clear consensus regarding management. Our purpose was to evaluate prognostic factors and treatment outcomes of patients treated at the Department of Nuclear Medicine and Endocrine Oncology.
Methods
The target group covered 44 patients with parathyroid carcinoma treated in years 1995-2016 at the department of Nuclear Medicine and Endocrine Oncology.
Results
All the patients were treated surgically, 17 of them repeatedly, however, only in 19 patients the en bloc resection was performed, 25 patients underwent only parathyroidectomy. During an average 10-year-observation among all the patients operated non-radically the recurrence of the disease appeared. Deaths occurred only in this group, despite radio- and chemotherapy. An interesting clinical observation are benefits resulting from cinacalcet treatment: taking the medicine for 2–4 years resulted in stabilization and ever remission of the disease in four patients with metastasis. To predict outcome histopathology results, biochemical and clinical features were analyzed. Due to a limited number of patients, a parametric Weibull's regression was adopted. Among the analyzed risk factors

distant metastasis and organ complications, mainly renal failure were statistically crucial in patients survival. Occurrence of distant metastasis increases the risk of early death seven times (HR $=6.82$, $P=0.02$) whereas in renal failure the risk increases nine times (HR $=8.92$, $P=0.008$).
Conclusions
In patients with parathyroid carcinoma, definition of prognostic factors and the role of the radiation, chemotherapy and cinacalcet treatment still has to be elucidated. In our analysis distant metastases and renal failure were critical factors regarding increased risk of death.

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EP350

A suspicious case of multiple endocrine neoplasia

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Introduction
Multiple endocrine neoplasia (MEN) syndromes are rare entities characterized by the occurrence of tumors involving two or more endocrine glands in a single patient. These syndromes are classified as type 1 or 2 according to specific phenotypic characteristics. MEN2 encompasses three different subtypes: MEN2A, MEN2B and familial medullary thyroid carcinoma. More recently a syndrome related to mutations in the CDKN1B gene has been described – the syndrome of multiple endocrine neoplasia 4. It is characterized by tumors of the parathyroid and pituitary glands.
The case
A 36-years-old woman was submitted to parathyroidectomy and adrenalectomy in September/2010 due to suspected parathyroid adenoma and pheochromocytoma, both confirmed posteriorly by histology. The patient did not have a positive family history of pheochromocytoma, parathyroid adenomas or thyroid medullary carcinoma and, furthermore, genetic testing for MEN1 and MEN2 was negative. Genetic investigation for MEN 4 is pending. After surgery PTH levels normalized. However, there is a slow increase in PTH levels since 2012 and sestamibi scintigraphy shows signs of right parathyroid adenoma.
Conclusion
This case is highly suggestive of a MEN 2A due to the symbiotic appearance of parathyroid adenoma and pheochromocytoma in the same patient. A negative genetic test, however, raises suspicion for a possible different diagnosis – MEN4 or even another genetic mutation.

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Endocrine Tumours and Neoplasia

EP351

Bone mineral density in obese children

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Aim
To evaluate bone mineral density (BMD) and its relationship with calcium (Ca) and phosphorus (P) metabolism in children with obesity.
Methods
We examined 105 children in the University Hospital (Minsk) from 2011 to 2015 yrs. Their anthropometric parameters (height, weight, BMI) were determined. Body composition with evaluating of mineral component were made by dual energy X-ray absorptiometry with the calculation of feet, hands, spine, ribs, hips BMD (g/cm^2), Z-test. The levels of Ca and P, alkaline phosphatase (AlP) were determined. All children were divided into two groups: group one – children with obesity ($n=75$, boys(B)/girls(G) $=47/28$, age 15.34 ± 2.12 yrs, BMI 32.7 ± 5.3 kg/m^2; group 2 – normal-weight control ($n=30$, B/G$=19/11$, 15.08 ± 2.47 yrs ($P=0.3$), 19.4 ± 2.4 kg/m^2 ($P=0.0001$)).
Results
Legs BMD were increased in boys with obesity (0.94 ± 0.11 g/cm^2 vs 1.13 ± 0.17 g/cm^2 ($P=0.03$)) compared to control group without significant differences in G (1.29 ± 0.12 g/cm^2 vs 1.23 ± 0.02 g/cm^2 ($P=0.5$). Ribs BMD were higher in group 1 children compared to group 2 (B 0.72 ± 0.08 g/cm^2 vs 0.59 ± 0.06 g/cm^2 ($P=0.02$); G 0.71 ± 0.05 g/cm^2 vs 0.65 ± 0.06 g/cm^2 ($P=0.05$)). There were no significant differences in hand BMD (G 0.87 ± 0.10 g/cm^2 vs 0.85 ± 0.13 g/cm^2 ($P=0.836$); B 0.93 ± 0.14 g/cm^2 vs 0.85 ± 0.15 g/cm^2 ($P=0.360$)); total (G 1.18 ± 0.09 g/cm^2 vs 1.11 ± 0.13 g/cm^2 ($P=0.29$); B 1.17 ± 0.13 g/cm^2 vs 1.06 ± 0.14 g/cm^2 ($P=0.21$)) in obese children compared to control. A significant increase in Ca levels were in obese B compared to control (2.48 ± 0.07 vs 2.41 ± 0.001 mmol/l ($P=0.001$)) with no differences in G (2.43 ± 0.09 vs 2.41 ± 1.2 mmol/l ($P=0.86$)). There were no differences in P (G 1.23 ± 0.22 vs 0.95 ± 0.64 mmol/l ($P=0.78$); B 1.32 ± 0.27 vs 1.30 ± 0.18 mmol/l ($P=0.85$)), and AlP (G 108.06 ± 26.66 vs 85.13 ± 65.64 IU/l ($P=0.46$); B 217.93 ± 57.24 vs 157.27 ± 26.41 IU/l ($P=0.68$) in two groups.
Conclusions
A significant increase in ribs and legs BMD, Ca levels were found in children with obesity compared to normal weight control.

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Paediatric Endocrinology

EP352

Progressive osseous heteroplasia in a child with pseudohypoparathyroidism type I

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Introduction
Progressive osseous heteroplasia (POH) is a rare genetic condition of progressive heterotopic ossification (HO), from skin and subcutaneous tissues into deep skeletal muscles. Most cases are caused by heterozygous inactivating mutations of GNAS gene. Related disorders are Albright hereditary osteodystrophy (AHO), pseudohypoparathyroidism (PHP), and primary osteoma cutis. Distinction from other GNAS-based conditions is made by the extension of HO from superficial to deep tissues in POH.
Case report
We present the case of a 10-year-old girl who came to medical attention at 3-months of age for lumbar and scapular subcutaneous ossifications. The biopsy confirmed osseous metaplasia of the connective tissue. The ossification process progressed in size, depth and area, up to painful swelling and mechanical compression in the shoulder. She underwent surgical resection of the scapular lesion at 3-years of age but the ossification recurred 2 years later. There were no congenital hallux valgus or other skeletal deformities. She had clinical features of AHO: round facies, flat nasal bridge, short neck, brachydactyly, obesity. Lab tests revealed mild elevated TSH (4.98 μU/ml) at 5-years of age and later, at 8-years of age, elevated parathyroid hormone (395.9 pg/ml) with hypocalcemia (Ca$=$ 8.1 mg/dl) and hyperphosphatemia ($P=7.18$ mg/dl). She was diagnosed as having PHP most probably type Ia/c based on the typical clinical findings of AHO phenotype and biochemical profile. She received treatment with calcitriol and levothyroxine. Follow-up examinations revealed moderate progression of the heterotopic ossifications and favourable clinical course with spontaneous puberty and no other hormone resistance identified yet at age of 12.
Conclusions
Overlapping features of POH and PHP type I can be present, as part of the spectrum of the heterogeneous GNAS related disorders. Awareness and distinction of these conditions are important for appropriate management.

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Steroid Metabolism + Action

EP353

Genetic variations in the HSD11B1 gene in patients treated with glucocorticoids show associations with bone mineral density

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Introduction

Physiological glucocorticoids play an essential role in bone formation but can cause osteoporosis if present in excess. The key enzyme converting inactive cortisone into the active cortisol and *vice versa* is 11-beta-hydroxy-steroid-dehydrogenase (11β-HSD1). We have reported that genetic variations in the HSD11B1 gene correlate with increased cortisol levels in dexamethasone suppression and with changes in bone mineral density (BMD) suggesting individual differences in 11β-HSD1 activity caused by polymorphisms. In this study we investigated the effect of HSD11B1 SNPs on BMD in patients on glucocorticoid therapy.

Methods

In 246 patients treated with different glucocorticoids the HSD11B1 SNPs rs11811440, rs1000283 und rs932335 were determined. Patients received glucocorticoids due to rheumatoid arthritis or asthma (64%), or other rheumatic, gastrointestinal or pulmonary disorders. An equivalent glucocorticoid dose was calculated for the different glucocorticoids used. BMD of the spine or femoral neck, and the number of fractures and falls were correlated to the HSD11B1 SNPs.

Results

BMD, the number of fractures and falls did not show an association with daily or cumulative equivalent dose or type of glucocorticoid. Since the three genetically linked SNPs in intron 5 of the 11β-HSD1 gene – rs11811440, rs1000283, and rs932335 HSD11B1 highly correlated, only rs11811440 was further analyzed. In patients treated with the glucocorticoids prednisolone or methylprednisolone the presence of the A-allele was associated with lower BMD levels.

Discussion

Our results suggest that in patients treated with glucocorticoids the function of 11β-HSD1 is dependent on HSD11B1 polymorphisms. Hence, inactivation of prednisolone or methylprednisolone by 11β-HSD1 would be the crucial step for BMD levels in glucocorticoid-treated individuals.

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Eposter Presentations: Diabetes, Obesity and Metabolism

Calcium & Vitamin D Metabolism

EP354

Abstract withdrawn.

Cardiovascular Endocrinology and Lipid Metabolism

EP355

Metabolic syndrome in digestive neoplasms

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Introduction
The metabolic syndrome (MS) is a real public health problem on a global scale. People with MS are at increased risk not only for cardiovascular diseases but also for neoplasia. The aim of our study is to determine the prevalence of MS in patients with digestive neoplasia and to study the impact of MS on the epidemiological, clinical profile and prognosis of digestive neoplasms.
Material and methods
This is a retrospective study including patients with digestive neoplasia who were hospitalized in our department between January 2015 and June 2016. For all patients, BMI, waistline, systolic and diastolic blood pressure, HDL cholesterol, triglycerides, and blood glucose levels were determined. A MS was defined according to the criteria of the International Diabetes Federation IDF 2005.
Results
78 patients were included (40 men and 38 women), with an average age of 61.7 years (between 28 and 89 years). The digestive neoplasias found were: colorectal cancer (CRC) ($n=21.27\%$), hepatocellular carcinoma (CHC) on cirrhosis liver ($n=18.23\%$), gastric cancer ($n=13.16.7\%$), Cholangiocarcinoma ($n=10.12.7\%$), pancreatic cancer ($n=9.11.5\%$), oesophageal cancer ($n=3.8\%$), small bowel lymphoma and a Cancer of the gall bladder in two cases each ($n=2.6\%$). The mean tumor size at diagnosis was 6.2 cm (1.5–18 cm). The tumor was metastatic in 26 cases (33.3%). MS was present in 29 cases (37.2%). The analytical study found that MS was more frequently found in female patients (50% versus 25%, $P=0.022$), older patients (68.2 years versus 58 years, $P=0.001$) and having a CRC (57% versus 29%, $P=0.027$). However, the presence of a MS did not influence the average survival of patients (10.3 months versus 8 months, $P=0.138$).
Conclusion
In our study, more than one-third of patients had MS. It was associated with an older age, the female sex and the CRC. However, diagnosis and management of MS remains difficult in these patients because of the malnutrition and weight loss caused by the disease.

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EP356

Dyslipidemia-associated skin lesions as a short key for etiology unraveling and management of life-threatening acute pancreatitis in young male

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Background
After the gall bladder stones and alcohol abuse, dyslipidemia is among most frequent causes of acute pancreatitis, especially in youngsters. Some clinical signs can be useful to alleviate either a medical condition diagnosis confirmation or unraveling of its etiology.
Aim
We present a case 30 years old male, presented with nausea, vomiting and diffuse abdominal pain. Three months before hospital admission, patient was unsuccessfully treated for painful, reddish skin lesions 5mm in diameter, dispersed on abdominal wall, arms and legs, interpreted as 'viral papillomata'. Out of mentioned skin lesions-eruptive xanthomata, hypotension, light abdominal tenderness and moderate distention, other physical examination was normal.
Results
Laboratory findings revealed lipemic serum, elevated inflammatory, pancreas and liver necrosis markers, hyperglycemia, hyponatremia and hypocalcaemia. Performed imaging procedures (ultrasound and computed tomography) showed enlarged pancreatic body and tail, and left pleural effusion. Lipemic serum and eruptive xanthomata taken together with other case findings pointed to life-threatening acute pancreatitis caused by mixed dyslipidemia, obviously serious (lipids could not be measured initially). In association with aggressive pancreatitis management, nil-by-mouth treatment with plasmapheresis successfully lowered lipids and enabled their measurement (triglycerides 19.9 mmol/l and cholesterol 10.8 mmol/l). After plasmapheresis, diet and fibrate, triglycerides and cholesterol levels were 4.04 and 3.99 mmol/l, respectively. Patient was referred to lipid clinic, gastroenterologist and surgeon (formed pancreatic cyst).
Conclusions
Adequately interpreted eruptive xanthomata can act as a shortkey for faster confirmation of acute pancreatitis. Treatment of serious pancreatitis and dyslipidaemia is done at the same time. Plasmapheresis, as well lifelong diet and pharmacotherapy later, are the mainstay for management of dyslipidaemia that caused pancreatitis (presumably mixed one).

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EP357

Metformin and changes in blood pressure and heart rate in lean patients with polycystic ovary syndrome (PCOS)- preliminary study

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Introduction
The aim of our study was to assess the value of blood pressure and heart rate using the 24-h blood pressure monitoring (ABPM) before and after treatment with metformin to patients with polycystic ovary syndrome (PCOS) and normal lean.
Material and methods
20 patients received metformin 1500 mg/day in three divided doses. ABPM was performed to each patient with PCOS twice: before and after 6 months of treatment with metformin.
Results
In patients with PCOS and normal lean after treatment with metformin we observed: statistically significant lower systolic blood pressure (120.2 ± 22.33 mmHg vs 113.22 ± 21.43 mm Hg, $P=0.0248$); lower systolic blood pressure of daily measurements (127.1 ± 32.13 mmHg vs 116.1 ± 22.08 mmHg, $P=0.0062$); reduction in average arterial pressure MAP daily measurements (95.52 ± 22.76 mmHg vs 88.36 ± 16.41 mmHg, $P=0.048$); oscillometric pressure reduction (96.27 ± 27.93 mmHg vs 87.82 ± 21.61, $P=0.0004$ mmHg); oscillometric pressure reduction of daily measurements (102.1 ± 27.93 mmHg vs 91.85 ± 21.61 mmHg, $P=0.0032$); oscillometric pressure reduction in the measurement of the night (88.81 ± 24.85 mmHg vs 82.22 ± 20.54 mmHg, $P=0.0089$). In women after treatment with metformin has also been observed higher average heart rate (65.82 ± 13.48/min vs. 70.71 ± 16.04/min; $P<0.01$). The calculations included 500 measurements.
Conclusion
Treatment with metformin in patients with PCOS and normal lean leads to lower blood pressure and increases the frequency of heart rate.

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EP358

Screening for type 2 diabetes mellitus as a method of secondary prevention of cardiovascular lesions

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In patients with type 2 diabetes mellitus (T2DM), cardiovascular lesions are 3–4 times more often than in non-diabetics. Screening for T2DM in 1564 people from all Ukraine revealed that 12% had HbA1c at 6.1–6.4% and 16% had HbA1c above 6.5%. Those with HbA1c above 6.5% were examined for BMI, glycemia, total cholesterol, HDL-C, non-HDL-C. Dyslipidemia was defined as total cholesterol over 5.20 mmol/l, HDL-C – less than 1.02 mmol/l for males and less than 1.29 mmol/l for females. Total cholesterol averaged 6.41 ± 0.03 mmol/l in screened men and 6.23 ± 0.01 in women. HDL-C was respectively 1.89 ± 0.08 and 1.88 ± 0.07 mmol/l. Whereas non-HDL-C was 4.60 ± 0.02 and 3.38 ± 0.05 mmol/l respectively. As for total cholesterol, objects were divided into the following groups (in mmol/l): 5.2; 5.3–6.5 and over 6.5. Males with these indicators were distributed: 38%, 57%, 5%; females – 28%, 64% and 8% respectively. According to correlation of total cholesterol to fasting glucose, men with glycemia under 6.1 mmol/l had cholesterol 5.70 ± 0.01 mmol/l, those with glycemia 6.2–7.8 mmol/l had cholesterol 5.90 ± 0.05 mmol/l and those with glycemia over 7.8 mmol/l had cholesterol 5.99 ± 0.04 mmol/l. While in women, cholesterol levels were (mmol/l): 4.86 ± 0.03, 6.50 ± 0.03, and 7.50 ± 0.03 in relation to the above mentioned levels of glycemia. In accordance with division of BMI into normal weight, overweight and obesity, cholesterol levels in males were (mmol/l): 5.81 ± 0.06, 6.12 ± 0.04 and 6.10 ± 0.05 respectively, while in females 5.48 ± 0.04, 5.56 ± 0.02 and 5.77 ± 0.01. Consequently, dyslipidemias were found in 70% of our group with T2DM of both sexes. They are induced by increase in non-HDL-C, correlate with degree of compensation of diabetes and with BMI. Therapeutic correction of dyslipidemias in patients with T2DM should be: normalization of glycemia and body weight. Screening for T2DM and its active treatment are most suitable method of secondary prevention of cardiovascular lesions caused by T2DM.

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EP359

Soybean phytoestrogens reduce 27-hydroxycholesterol concentration in the liver of middle-aged female rats

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Hypercholesterolemia is associated with athero-thrombotic disease, a leading cause of mortality worldwide. Advances in both dietary and pharmacological interventions contribute to prevention and treatment of modifiable risk factors.Purified soybean phytoestrogens, isoflavones genistein (GEN) and daidzein (DAI), were reported to exert moderate cholesterol-lowering effect. In this research first we studied age-related modifications in hepatic cholesterol metabolism and serum estradiol concentration of acyclic middle-aged (MA) female rats. Then we tested if purified isoflavones may prevent or reverse these changes. Serum and hepatic total cholesterol (TCH), bile acid and cholesterol precursors were determined by comparing data obtained for MA with young adult (YA) intact (IC) females. Effects of subcutaneously administered GEN or DAI (35 mg/kg per daily during four weeks) to MA rats were evaluated vs vehicle (sterile olive oil) – treated MA females. After decapitation, perfused rat livers and serum were used to determine total cholesterol (TCH), its oxidative metabolites (7α-, 27- and 24-hydroxycholesterol) and precursors (lanosterol, desmosterol, dihydro-lano sterol and lathosterol), using gas chromatography/mass spectrometry. Serum estradiol was determined by ECLIA. MA IC females were characterized by: higher ($P < 0.05$) serum TCH, lower ($P < 0.05$) hepatic TCH and its biosynthetic precursors, lower ($P < 0.05$) hepatic7α-hydroxycholesterol but elevated ($P < 0.05$) 27- and 24- hydroxycholesterol in comparison to YA IC. Both GEN and DAI decreased ($P < 0.05$) hepatic 27-hydroxycholesterol, with no effect on any other parameter of cholesterol metabolism. We obtained age-related reduction of serum estradiol, which was reversed by both soybean phytoestrogens. In conclusion, age-related dyslipidemia was associated with reduced 7α-hydroxycholesterol, main intermediate of neutral pathway, and higher 27—hydroxycholesterol, main intermediate of alternative acidic pathway of Chol degradation to bile acid. Both GEN and DAI lowered hepatic 27-hydroxycholesterol, which might be associated with elevated serum estradiol concentrations. Further research is needed to examine this possibility.

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EP360

Awareness and prevalence of metabolic syndrome among high-risk individuals attending internal medicine clinics across Jordan

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Purpose
To examine the prevalence and awareness of metabolic syndrome (MetS) in high-risk individuals attending 30 internal medicine clinics in Amman, Jordan, and also to evaluate the various factors associated with increased risk of MetS among them.
Methods
This retrospective cross-sectional study was carried out across Amman, Jordan from October to December 2014. During the study period, 900 high-risk individuals (with hypertension, diabetes, central obesity and/or dyslipidemia) were recruited from thirty internal medicine clinics in Amman, Jordan. Data collection forms were filled based on patient interview and medical case file.
Results
The prevalence of MetS among high-risk individuals was around 40% (361/900), with around 79% (284/361) of MetS patients unaware of their condition. Older age, lower income and family history of premature cardiovascular diseases were associated with a higher prevalence of MetS.
Conclusion
Although MetS was found to be highly prevalent among high-risk individuals in this study, the awareness of the condition in this group is very poor. These findings support the need for educational programs that involve both health care providers and patients. These programs should especially target those at risk of MetS, in order to improve awareness of the concept of MetS.

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EP361

Nine months of practice in California - self-referrals in endocrinology

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Objective
A great number of patients are self-referred to endocrinologist. Most of these patients had some research of their symptoms and have a specific diagnosis that they want to investigate.
Methods
A retrospective chart review of 628 new consults conducted in one outpatient endocrine office at University of California, Los Angeles was conducted.

Results
Of the 628 new patients 326 were referred by another physician and were excluded from further review. Of 302 self-referred patients 248 patients had a preexisting endocrine diagnosis and were excluded. The remaining 54 patients were seeing endocrinologist for the first time and these patients were included in further study. Most common complaints were: weight gain (78% of patients), fatigue (72%), cold intolerance (46%), heat intolerance (31%), constipation (24%). Other common complaints observed were hair loss, low libido, erectile dysfunction, anxiety, palpitations, weight loss, hirsutism, acne, muscle weakness, stretch marks, buffalo hump and polydipsia. When asked if they had a specific hormone abnormality in mind most of the patients reported that their main concern is hypothyroidism (69%), high cortisol level (13%), low testosterone (10%), low cortisol (5%), hyperthyroidism (5%), diabetes insipidus (4%), diabetes mellitus (2%). After conducting endocrine studies based on presenting symptoms none of the 54 patients were found to have confirmation of suspected diagnosis. Four patients were found to have elevated TPO antibodies but thyroid functions tests were normal. Six patients were found to have diabetes mellitus that was previously not diagnosed or suspected. Two patients were found to have elevated cholesterol.
Discussion
Common problems lead to online research that offers a number of endocrine conditions as a possible underlying problem. With access to subspecialist care oftentimes unnecessary work-up is done.
Conclusion
A longer period of investigation would add valuable data in determining the impact of self-referrals on subspecialty practices as well as health care in United States in general.

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EP362

Identifiying underdiagnosed or undertreated patients with familial hypercholesterolemia from the central laboratory registries

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Objective
Familial hypercholesterolemia (FH) is a life-threatening genetic disease associated with elevated low density lipoprotein cholesterol (LDL-C) and premature coronary heart disease that is globally underdiagnosed and undertreated. This study aimed to search for the demographical characteristics, awareness and treatment adherence of underdiagnosed or undertreated FH patients from the records of the central biochemistry laboratory.
Methods
Patients with a central laboratory measurement of LDL-C >250 mg/dl were identified. Patients with older than 18 years without secondary causes of dyslipidemia were called by medical students and interviewed about demographic characteristics, awareness of dyslipidemia and treatment adherence.
Results
A total of 147 patients (mean age 51.7 ± 16.6 years, 59.2% female) were interviewed. The mean LDL-C levels were 292.8 ± 49.9 mg/dl. According to the Dutch Lipid Clinic Network Criteria, the patients with definite, probable and possible FH were 18.4%, 66.0% and 15.6%, respectively. Although the majority of the patients (93.9%) were aware of their high LDL-C levels, only about half of them ($n=75$, 51.0%) were under treatment. Of all the patients who were interviewed, 21% ($n=31$) had never taken, and 28% ($n=41$) had stopped taking lipid-lowering drug.
Conclusion
The results of this pilot study show that, undiagnosed or undertreated FH patients can practically be detected from the high LDL-C registries of the Hospital Laboratories. Nationwide implementation of this method may help us reach and manage these high-risk patients.

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EP363

The effect of admission hyperglycemia on clinical outcome of ischaemic stroke patients

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Background and objective
Hyperglycemia exacerbates multiple deleterious derangements and this process would influence the clinical outcome in diabetic patient. The objective of this study is to know the effect of admission hyperglycemia on clinical outcome of ischamic stroke patients admitted in Sardjito General Hospital.
Method
Observational cohort study over 5 months' period from August 1-2016 to December 31-2016 was done. All patients 18 years old and above, admitted as stroke ischaemic patients in Sardjito General Hospital Yogyakarta were screened. In order to qualify, patient were subjected to initial random blood sugar determination upon admission and monitored to 48–72 h. Capillary blood glucose was monitored using blood glucose monitor device by Bayer. Hyperglicemia status is blood glucose above 200 mg/dl. Clinical outcome was evaluated and recorded using *The National Institutes of Health Stroke Scale* (NIHSS) on day 1 and discharge. Participants who are below 18 years old, previously stroke, or those with acute co-morbid disease like acute myocardial infarction, pneumonia, or critical infection, ketoacidosis diabeticum, hyperglicemia hyperosmolar state were all excluded. All patients managed according to guidelines for stroke and hyperglycemia.
Result
Sixty four eligible subjects admitted at Sardjito General Hospital, 12 (19.35%) were hyperglycemia and 50 (80.65%) normoglycemia. The mean value of blood glucose at admission are $153.45 + 69.09$ mg/dl. Patients who have worsening clinical outcome at dischare are 18 (29.03%) based on NIHSS. Six patients (44.44%) who had hyperglicaemia had worsening clinical outcome and four patients (9.09%) did not have worsening clinical outcome (*P*-value 0.003; OR 8; min 2 001–max 31 988).
Conclutions
Hyperglicaemia at admission have correlate with worsening of clinical outcome ischaemic stroke patients.
Keywords
Hyperglycemia; Ischaemic stroke patients; The National Institutes of Health Stroke Scale.

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EP364

Deleting genomic region of *Hsd17b1* in mice results into a hypomorphic *Naglu* allele, and consequently to a phenotype mimicking a lysosomal storage disease

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Abstract
Hydroxysteroid 17-beta dehydrogenase 1 (HSD17B1) is an enzyme catalyzing the reduction of estrone (E1) to estradiol (E2), as well as androstenedione (Adione) to testosterone (T). To elucidate the physiological function of HSD17B1, we generated knockout mice with disrupted *Hsd17b1* gene using targeted ES cells (clone 10231) obtained from KOMP repository (www.komp.org). In these ES cells the whole coding region of *Hsd17b1* was replaced with *LacZ/Neo* cassette, expressing the reporter gene. As previously shown by us, the homozygous *Hsd17b1-LacZ/Neo* females were found to be subfertile and have a defect in pseudopregnancy maintenance, likely caused by the imbalance in ovarian steroid synthesis. In addition, the *Hsd17b1-LacZ/Neo* males present with a metabolic phenotype, including reduced adipose mass, increased lean mass and lipid accumulation in the liver. During the characterization of the metabolic phenotype, it became evident that the expression of N-acetyl-alpha-glucosaminidase (*Naglu*) gene, located 8399-739 bp upstream of the *Hsd17b1* transcription start site, was severely reduced (13-40-fold) in all tissues analyzed in *Hsd17b1-LacZ/Neo* mice. Furthermore, similar results were obtained from *Hsd17b1-LacZ* mice after removing the *Neo* cassette or by crossing the *Hsd17b1-LacZ/Neo* mice with transgenic mice constitutively expressing human *HSD17B1*. Deficiency of the *Naglu* gene causes the accumulation of glycosaminglycans (GAGs) in several tissues, and accordingly, GAG accumulation was observed in all the above mentioned mouse models lacking the genomic region coding for *Hsd17b1*. Furthermore, biochemically and morphologically similar metabolic phenotype, mimicking lysosomal storage disease, was observed both in *Naglu* knockout mice (with the presence of active HSD17B1), and all the mouse models lacking 2.3 kb long genomic region of *Hsd17b1* gene. Thus, the data indicate the presence of a strong *Naglu* enhancer inside the *Hsd17b1* gene, and the metabolic phenotype in mice lacking the *Hsd17b1* genomic region is caused by the off target effect.

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Salivary lactate levels during anaerobic threshold (AT) training

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Anaerobic threshold (AT) is defined as the point of maximum intensity at which lactate is being produced but does not accumulate in blood during exercise. Training at this intensity is common in athletes. Lactate is currently regard as indicator of effort intensity. It is usually quantified by reflectometry of capillary blood. This procedure although not very invasive, may be annoying during repeated measurements. Saliva is proposed as an alternative sample.
The objective of the present study is to quantify the variation of salivary lactate levels during AT training, in order to prove its usability in this field.
10 male subjects (32 ± 2.96 years) performed a treadmill test recording intensity (watts/min), VO2 and heart rate (HR) to determine AT. After two days resting they performed 6 running series of 1km at AT rhythm with 2 minutes of resting between series. Saliva samples by Salivette system (SARSTEDT, Germany) and HR were taken at pretest, the end of each series, and 3, 6 & 9 min of resting after. Eating, smoking, drinking (except water) or teeth brushing was forbidden in 2 h previous to start.
Salivary lactate concentrations increased significantly from 1st to 3rd series ($P = 0.002$). Afterwards, a plateau of saliva lactate concentration was observed in all subjects up to the end of the series (4th–6th). After a small reduction, an additional increase in saliva lactate was also consistently observed after 6 min of rest. HR hardly changed during the exercise series. Since we can conclude that: The salivary lactate was increased according to the accumulated workload despite exercise was performed at constant intensity (AT). That was confirmed because the heart rate (HR) hardly changed at this constant rate. Since, saliva lactate levels in an AT training are independent of heart rate and mostly of effort intensity.

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EP366

The effect of tocilizumab – an interleukin-6 receptor antagonist – on lipid levels in rheumatoid arthritis

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Tocilizumab is an interleukin-6 receptor antagonist used in the treatment of rheumatoid arthritis (RA). It is known to induce remission and inhibit radiographic progression in RA. Tocilizumab may be administered either intravenously or subcutaneously. Its effect on lipid levels and the cardiovascular risk has not been fully investigated. The aim was to study the effect of tocilizumab i.v. on disease activity, lipid levels and cardiovascular risk in RA patients.
Tocilizumab was administered i.v. once monthly in 25 patients with RA for a period of 1 year. Inflammation indices, ESR and CRP and lipid levels were measured before and 1 year after tocilizumab administration. The DAS28 disease activity index was also calculated.
Inflammation indices ESR and CRP decreased from 34.3 ± 4.04 mm/h and 2.02 ± 0.34 mg/dl before to 8.3 ± 1.62 mm/h and 0.27 ± 0.07 mg/dl, respectively ($P < 0.001$) after tocilizumab administration. The DAS28 disease activity index decreased from 5.02 ± 0.26 to 2.42 ± 0.26 after tocilizumab ($P < 0.001$). Total cholesterol and HDL cholesterol increased from 207.4 ± 8.53 mg/dl and 57.68 ± 2.65 mg/dl before to 231.08 ± 12.30 mg/dl and 72.51 ± 4.76 mg/dl, respectively ($P < 0.001$) after tocilizumab administration, LDL cholesterol and triglyceride levels increasing from 128.6 ± 7.45 mg/dl and 108.48 ± 7.83 mg/dl before to 136.17 ± 9.39 mg/dl and 130.58 ± 15.82 mg/dl, respectively ($P < 0.001$) after tocilizumab. No acute cardiovascular events were recorded during the study.
Tocilizumab administered i.v. in patients with RA was shown to decrease inflammation indices and disease activity. Lipid levels increased significantly. However, total cholesterol increased in parallel with HDL cholesterol. Cardiovascular events were not observed during the study period. It appears that tocilizumab may be accompanied by lipid level alterations, cardiovascular risk not increasing as the adverse effects of total cholesterol may be counteracted by HDL cholesterol.

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EP367

Homocystein-significant marker of metabolic syndrome and atherosclerosis risk

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Background
Obesity is followed by insulin resistance (IR) and low grade inflammation. In patients with metabolic syndrome (MS) and clinicaly evident vascular complications homocystein values are higher. Hyperhomocysteinemia correlates with hyperinsulinemia and IR, resulting in oxidative stress, which causes endothelial lesions and dysfunction, promoting atherosclerosis and hypertension.
Objectives
To examine homocystein levels in patients with and without MS, and find correlation between factors of MS and homocystein values.
Methods
The study included 76 obese individuals (age over 30, BMI > 25 kg/m^2) classified into two groups: I- with MS (35 patients); II- without MS (41 patients). OGTT was used to evaluate the extent of glucoregulation disorder. IDF classification was

applied for diagnosing MS. Si MS risk score by Soldatovic I et all 2016 was used. IR was determined by HOMA IR. Serum CRP was measured by immunometric assay. Microalbuminuria was determined immuno-nephelometrically. Homocistein was determined by immunoassay FPIA-Abbot.
Results
Patients with MS had increased WC:(I-110.6±15.4, II±15.4 cm), BMI:(I-35.3±6.6, II-30.4±7.4 kg/m^2), blood pressure (I-136.4±13.9 /90.5±9.5, II-118.4±12.2/78.1±9.7 mmHg), glycaemia (I-5.4±1.6, II-4.8±0.8 mmol/l), HOMA IR (I-8.8±9.4, II-5.3±3.8 mmol/μU per ml), triglycerides (I-2.17±0.95, II-1.45±0.7 mmol/l), CRP (I-7.0±0.0, II-3.7±3.8 mg/l), microalbuminuria (I-87.4±81, II-56.4±56.9 mg/24 h), homocysteine (I-13.0±3.2, II-11.8±3.7 μmol/l) and decreased HDL (I-1.07±0.2, II-1.35±0.35 mmol/l). Statistical significance between groups was found for WC, BMI, systolic and diastolic pressure, triglycerides, HDL-cholesterol ($P<0.01$) and CRP, Apo B, HOMA IR ($P<0.05$). Correlations: Homocysteine with systolic and diastolic pressure, Apo B and hyperlipoproteinemia ($P<0.05$). Si MS risk score with homocysteine ($P<0.01$), $r=0.263$.
Conclusion
Abdominal obesity, hypertension, hypertriglyceridemia, inflammation factors, IR, homocystein and microalbuminuria as markers of endothelial dysfunction were increased in patients with MS. Correlation of homocystein values with si MS risk score indicates that it is significant co-founding factor of MS. Correlation of homocystein with hypertension and hyperlipoproteinemia indicates importance of homocystein as significant marker for atherosclerosis.

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EP368

Graft vs host disease and insulin resistance after bone marrow transplantation

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Graft vs host disease is a disorder in which the graft, i.e. bone marrow, attacks the host after bone marrow transplantation. It has various manifestations, one being skin and muscle involvement with cutaneous sclerosis and diffuse muscle pain. The aim was to describe the case of a patient with graft vs host disease complicated by insulin resistance and metabolic syndrome, after bone marrow transplantation for the treatment of acute lymphoblastic leukemia.
A patient, male, aged 2.5 years old, developed acute lymphoblastic leukemia. He was treated and the disease went into remission. At the age of 7 years, the patient had a recurrence. He was found to be compatible with his elder brother and bone marrow transplantation was performed. During the following months the patient developed a skin eruption, diffuse cutaneous sclerotic lesions, muscle edema and pain.
He was treated with thalidomide and cyclosporine and clinical manifestations of graft vs host disease improved. Diffuse skin and muscle involvement improved. The patient developed hypertriglyceridemia and insulin resistance. Metformin and fenofibrate were administered. The patient developed also hypothyroidism. Thyroxine was administered. At the age of 29 the patient developed psoriasis like lesions in the maxilla and the external genital organs.
In conclusion, the case of a patient is described with graft vs host disease after bone marrow transplantation for the management of acute lymphoblastic leukemia. Graft vs host disease may have various clinical manifestations. In the case described skin and muscle involvement, along with insulin resistance and metabolic syndrome were the predominant manifestations.

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EP369

Coronary artery calcium score in prediabetes – preliminary results

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Introduction
Coronary artery calcium (CAC) is examined through multislice CT. Calcifications indicate late-stage subclinical coronary atherosclerosis. An association exists between CAC with coronary vascular disease (CVD), Agatston score being an independent predictor of CVD. Including CAC may improve CV risk prediction in addition to conventional risk factors. The AIM of our study was to assess CAC in subjects with prediabetes (preDM) at the beginning of the long term follow-up for occurrence of cardiovascular disease.
Methods
After diagnosing preDM with oral glucose tolerance test and HbA1c, ECG was performed and subjects were evaluated for CVD risk. Score charts were used to calculate the CVD risk. Thereafter, all subjects were appointed for multislice CT to obtain the CAC.
Results
70 subjects with preDM were screened for CVD. CAC score of 0 was present in 32 subjects. Minimal calcifications with a CAC score of 1–10 AU were present in 12 subjects with pre DM. Moderate calcification of11–100 AU were present in 15 subjects. Nine subjects had significant calcifications with 101–400 AU. Two subjects had a CAC score of 100 AU which meant significant calcifications. Score risk below 2% was present in only 19 subjects, while a score risk of 15% and more was present in 23 subjects. No significant correlation was found between Score charts and CAC. However, a trend of finding more calcifications in those with a 10% and above Score risk was noted.
Conclusion
An approach to risk assessment that combines the traditional risk factor-based paradigm with a more personalized atherosclerosis-imaging model may be appropriate for high risk individuals, such as subjects with pre diabetes.

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EP370

Cardiometabolic risk and female sexuality: focus on clitoral vascular resistance

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The relation between sexual and cardiovascular health in women is not well defined. Clitoral colour Doppler ultrasound (CDU) with assessment of the pulsatility index (PI), reflecting resistance to blood flow, has been proposed as an objective measurement of sexual functioning. We aimed to investigate the associations between clitoral PI and cardiometabolic risk factors. Seventy-one adult heterosexual women attending our clinic for sexual dysfunction were consecutively recruited. Clitoral PI was positively correlated with BMI ($P<0.0001$), waist circumference (WC; $P<0.0001$), glycaemia ($P=0.029$), insulin ($P=0.002$), homeostatic model assessment index ($P=0.005$), triglycerides ($P=0.011$), total cholesterol ($P=0.010$), and LDL-cholesterol ($P=0.016$). All relations, with the exception of glycaemia, retained statistical significance after adjusting for age, smoking habit, and years since menopause ($P<0.0001$ for BMI, WC and triglycerides; $P<0.05$ for all other associations). Analysis of covariance, after adjusting for confounders, showed that women with obesity or metabolic syndrome (MetS) showed significantly higher PI values (obesity: $P=0.001$; MetS: $P=0.019$). In particular, a stepwise increase of PI was found as a function of increasing MetS components ($P=0.007$). Clitoral PI was negatively associated with Female Sexual Function Index arousal ($P=0.014$) and satisfaction ($\beta=-0.289$, $P=0.026$) scores and positively associated with Middlesex Hospital Questionnaire somatized anxiety symptoms, even after adjusting for confounders ($P=0.011$). A positive association also was observed between PI and the Body Uneasiness Test (BUT) positive symptom distress index ($P=0.039$) and BUT for dislike of the womb, genitals, and breast ($P<0.0001$; $P<0.0001$; $P<0.0001$, respectively). After introducing WC as another covariate, the associations between clitoral PI and the BUT positive symptom distress index and BUT dislike of the womb, genitals, and breast retained statistical significance ($P=0.038$ for positive symptom distress index; $P<0.0001$ for dislike of womb, genitals, and breast). Clitoral vascular resistance is positively associated with MetS (in particular insulin resistance), decreased sexual arousal, body image concerns, and increased somatized anxiety symptoms. Further studies are needed to establish whether treatment of metabolic abnormalities might improve clitoral CDU indices and sexual outcomes.

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EP371

Metformin and changes in serum lipid profile in lean patients with polycystic ovary syndrome (PCOS)

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Introduction
The aim of our study was to assess the values of total cholesterol, HDL-C, LDL-C and triglycerides before and after treatment with metformin in patients with polycystic ovary syndrome (PCOS) and normal lean.
Material and methods
32 patients received metformin 1500 mg/day in three divided doses. Lipids measurements were performed to each patient with PCOS twice: before and after 6 months of treatment with metformin.
Results
In patients with PCOS and normal lean after treatment with metformin we observed: statistically significant lower LDL-C levels (4.16 ± 0.79 mmol/l vs 3.4 ± 0.86 mmol/l, $P < 0.05$) and triglycerides levels (1.8 ± 0.53 mmol/l vs 1.12 ± 0.64 mmol/l, $P < 0.05$). We observed an increase in HDL values and a decrease in total cholesterol values, but these changes were not statistically significant (1.5 ± 0.71 mmol/l vs 1.71 ± 0.69 mmol/l, $P = 0.09$; 5.87 ± 0.92 mmol/l vs 5.69 ± 0.97 mmol/l, $P = 0.11$).
Conclusion
Our study showed that treatment of 1500 mg metformin for about 6 months among PCOS women result in improvement in serum lipids. We observed a significant decrease in LDL-C and triglycerides values after metformin treatment.

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EP372

Prevalence of major cardiovascular risk factors among people living with HIV in a low risk country for cardiovascular disease

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Introduction
It is well known that the prevalence of major cardiovascular risk factors has increased in HIV-infected people since improvement of antiretroviral therapy. Currently, Spain is defined as a 'low risk country' for cardiovascular diseases (CVD) by 2016 European Guidelines on cardiovascular disease prevention. The objective of this study is to assess the prevalence and characteristics of CVD risk factors and risk for CVD in a cohort of HIV-infected adults living in the South of Spain according to current guidelines.
Methods/design
Cross-sectional study. Measurements included anthropometry, blood pressure, fasting lipids and glucose assessment. Demographic, clinical, immunological, and antiretroviral therapy data were obtained from electronic medical records. 10-year risk of heart disease or stroke was calculated using the SCORE- European low risk chart.
Results
218 patients were evaluated. Hypertriglyceridemia was the most prevalent disturbance (44.3%) found, followed by low HDLc levels (41.7%). 8.7% of the cohort had hypertension and 6.9% had type 2 diabetes. 68.5% were current smokers. High risk (10-year risk of fatal CVD $> 10\%$) was found in 13.3% of the cohort. People at higher risk were mostly men (100% vs 81%; $P = 0.005$), had higher BMI (25 ± 2.3 vs 23 ± 2.7 kg/m^2; $P = 0.04$) and had a lower CD4 count (405.5 ± 156.2/mm^3 vs 551.5 ± 211.7/mm^3; $P = 0.035$) and were more likely to receive protease inhibitors (48% vs 30%; $P = 0.04$).
Conclusions
According to our results, the prevalence of major risk factors for CVD is high in HIV-infected patients of our area, especially among those with worse immunity and higher BMI. Physicians should screen their patients for metabolic and cardiovascular risk at the regular visits to reduce CVD risk among people with HIV. Changes in antiretroviral therapy to more metabolic neutral antiretroviral drugs may also be considered.

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EP373

The role of leptin signalling in the development of cardiovascular diseases in obesity

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Cardiovascular diseases are the greatest cause of death globally. Obesity significantly increases the risk for the development of cardiovascular diseases. However research does not under stand the physiological and molecular connections of these diseases. We have identified that the hormone leptin in obesity plays a key role in elevating blood pressure in obesity. However recent findings in humans treated with leptin in the disease state of lipodystrophy, did not result in the elevation of blood pressure. In the research present here we suggest that one reason as to why leptin fails to increase blood pressure in lipodystrophy patients is that plasma leptin concentration in not increasing high enough. For the development of cardiovascular complications in obesity plasma leptin concentration needs to increase significantly to concentrations similar to that of obese animals (ten times the concentration measured in lean animals). In rodents we dose dependently demonstrate the differing effects of concentrations of leptin on changes in body weight, food intake, brown adipose tissue temperature, blood pressure and heart rate. We can demonstrated in obese hypertensive mice that changes to the signaling components of specific neurons within the Dorsomedial Hypothalamic leptin receptor expressing neurons in the brain can substantially change leptin's influence on cardiovascular control. Hence we can control in rodents the development of hypertension in obesity, via manipulating the responsiveness of leptin receptor responsive neurons. We are mapping the connections of this specific subset of neurons and are gaining a true understanding on how the adipose derived hormone leptin plays a key role in the development of cardiovascular diseases.

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EP374

Influence factors on lipid profile among patients with rheumatoid arthritis

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Introduction
Patients with rheumatoid arthritis (RA) face an increased risk of developing premature cardiovascular disease and limited ability to modify risk factors such exercise or dietetic habits. Influence of exercise, dietetic habits or treatment on lipid profile has been little studied in patients with RA. Here we aim to determine differences in lipid profile between two cohorts of patients with RA with different habits and patterns of treatment.
Methods/design
Cross-sectional study. Lipid profiles of 50 RA out-patients from South Spain were compared with 50 age and sex matched controls from Central Mexico. Traditional risk factors were analyzed such as overweight or obesity, smoking status and hypertension. Glucose and lipid profiles as well as dietetic habits and physical activity were recorded.
Results
RA patients from Spain were more likely to practice physical activity (66.7% vs 33.3%; $P = 0.001$), had lower BMI (24.9 ± 4.6 kg/m^2 vs 26.7 ± 3.6 kg/m^2; $P = 0.004$). No significant differences in smoking status, prevalence of diabetes (steroid induced diabetes or type 2 diabetes), alcohol consumption or mean dose of steroid treatment were found. Regarding to lipid profile, Mexican patients had lower levels of LDLc (86 ± 31.5 vs 128.7 ± 24.9 mg/dl; $P < 0.001$) In contrast, the European population had lower levels of triglycerides (124.9 ± 14.6 vs 145.3 ± 3.6 mg/dl; $P < 0.001$) and higher HDLc (60.5 ± 12.8 vs 52.1 ± 21.4; $P < 0.005$).
Conclusions
In patients with RA, exercise can modulate lipid profile favourably irrespective of corticoid dose or steroid induced diabetes. More accurate studies focusing on specific nutrients would be useful to confirm our results.

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EP375

Abstract withdrawn.

EP376

Oxidative stress and metabolic profiles assessment after melatonin and irbesartan co-administration in a novel pharmaceutical formulation

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The concurrence of glucose intolerance, hypertension, dyslipidemia and obesity has been termed metabolic syndrome. Each component of the metabolic syndrome is an independent risk factor for cardiovascular disease and diabetes type 2, the combination of these risk factors elevating the rates and severity of cardiac pathology.
The therapeutic use of irbesartan, a selective blocker of the AT1 receptors, administered in arterial hypertension, coronary heart disease and diabetic nephropathy, is extremely important due to the presence of these receptors both centrally and in the periphery.
Melatonin is an endogenous indoleamine hormone synthesized by the pineal gland. Melatonin release into the circulation is augmented in darkness and decreased during exposure to light, and facilitates the synchronization of the body's physiologic systems to circadian patterns. Melatonin shows properties of a powerful antioxidant, at sufficiently high concentrations as a direct radical scavenger, but, at lower, near-physiological levels, as a regulator of redox-relevant enzymes, suppressor of prooxidant excitatory and inflammatory processes and as a mitochondrial modulator. Increased oxidative stress has emerged as playing a central role in metabolic syndrome and its component pathologies and may be a unifying factor in the progression of this disease.
In the present study, we evaluated in a hamster experimental model, the influence of irbesartan and melatonin, co-administered in a novel pharmaceutical multiparticulate formulation, on metabolic markers and oxidative profile. Our results depicted blood glucose, serum cholesterol and triglycerides lowering effects, being maximum for the new formulation irbesartan and melatonin, revealing a potentiating effect of the two drugs. On the oxidative status, the new formulation presented a tremendous decreasing effect, due to the simultaneous release in the bloodstream the two medicines, depicting a synergic unique effect, reasoning the use of the two molecules in a single pharmaceutical formulation.

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EP377

The dual FXR/TGR5 agonist INT-767 counteracts nonalcoholic steatohepatitis and visceral adipose tissue dysfunction in a rabbit model of high fat diet-induced metabolic syndrome

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The nuclear Farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor 1 (TGR5) are bile acids receptors that play a key role in energy metabolism. In an animal model of non-genomic metabolic syndrome (MetS), obtained with a high fat diet (HFD), treatment with the dual FXR/TGR5 agonist INT767 reduced visceral adipose tissue (VAT) accumulation, insulin resistance, hypercholesterolemia and nonalcoholic steatohepatitis (NASH). In liver, INT767 reduced the high macrophage M1 (pro-inflammatory)/M2 (anti-inflammatory) ratio observed in MetS. Furthermore, INT767 increased the expression of: IL10 and FOXP3, markers of M2 macrophage and Treg cell, respectively; PPARα, marker of hepatic fatty acid metabolism; VAMP4 and Syntaxin5, markers of lipid droplet formation; IRS1 and STAMP2, markers of insulin signaling while decreased lipogenesis markers. Moreover histomorphological sign of NASH were significantly improved by INT767.
MetS induced insulin resistance, which shows VAT derangements like adipocytes hypertrophy and reducted GLUT4 translocation to membrane. Treatment with INT767 counteract these VAT alterations and induced the expression of brown adipocytes markers. The analysis of preadipocytes (rPADs) obteined from INT767-treated rabbit and HFD rabbit revealed that INT767 improved insulin sensitivity and mitochondrial ultrastructure and dynamic whereas reduced superoxide production. In rPADs, when compared to HFD, INT767 increased the expression of CIDEA and TMEM (brown fat markers); TFAM and NRF1 (mitochondriogenesis markers); SDHB (membrane respisatory chain marker) and MFN2 and FIS1, (mitochondria fusion/fission markers).
To conclude, INT767 significanlty improves NASH and VAT alterations induced by HFD, restoring insulin sensitivity and inducing the differentiation of rPADs to a metabolically healthy phenotype.

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EP378

Prevalence of metabolic syndrome and its relation to physical activity and nutrition in Azerbaijan

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Aim
Metabolic syndrome is a major public health challenge associated with an increased risk for cardiovascular disease and type 2 diabetes. The prevalence of metabolic syndrome in Azerbaijan is unknown. The purpose of this study was to examine the prevalence of metabolic syndrome and its relation to physical activity and nutrition in a representative sample of adult population in Azerbaijan.
Methods
The study population consisted of 288 adults, 20 years of age and over, from Guba, Azerbaijan recruited between January and April of 2016 by random sampling in line with the gender and age distribution.
Revised NCEP/ATP III criteria were used to define metabolic syndrome and prevalence estimates of each individual component were determined. Physical activity and food consumption were assessed with validated questionnaires and their relations with components of metabolic syndrome were evaluated.
Results
The participants were 159 women and 129 men (mean $\pm$s.d. age of 43.1 $\pm$ 15.2 y (range 20–83 y)). Overall prevalence of metabolic syndrome was 28.4%. Abdominal obesity was the most common individual component (49% and 85.4% in whole population and in those with metabolic syndrome respectively). Interestingly, it was also the only component that was more common in women than men ($P<0.05$ for both whole population and patients with metabolic syndrome) whereas the other components did not show a gender difference. The odds ratio for having metabolic syndrome was 0.56 (95% CI, 0.34–0.95) in moderate-high physical activity group compared to low physical activity group suggesting a reduced risk of metabolic syndrome with increased physical activity. Total calorie intake, protein, fat and carbohydrate consumption did not show a significant difference in participants with and without metabolic syndrome.

Conclusions
Metabolic syndrome in Azerbaijan is common and associated with low physical activity. Preventive measures should be taken to address this public health problem and related risk factors in the country.

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EP379

Isolated low HDL-Cholesterol in patients with type 2 diabetes about 168 cases

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Introduction
Lipid abnormalities in diabetics both quantitative and qualitative contribute to the increased cardiovascular risk.
Aim
The aim of this study is to determine the prevalence of isolated hyoHDLémie in type 2 diabetics and assess cardiovascular risk in two populations of type 2 diabetes with and without Low HDL-Cholesterol isolated.
Patients and methods
Prospective study started in diabetic patients seen in diabétologic consultation at the University Hospital of Marrakech.
Preliminars Results
One hundred and sixty eight patients were identified, 72% female, The average age of patients was 55 years, average duration of diabetes was 7 years, hyoHDLémie was found in 40.4% of cases (68 patients), the prevalence of isolated hyoHDLémie is estimated at 26.19% (44 cases), with overall cardiovascular risk estimated at more than 20% in the group of patients with isolated Low HDL-Cholesterol.
Discussion
Lipid disturbances are widely studied in diabetic patients, but few studies have examined the Low HDL-Cholesterol isolated. In diabetic patients, current treatment guidelines target low-density lipoprotein cholesterol (LDL-C) with statins. In patients with elevated TGs, non-HDL-C is considered a secondary target of therapy. Despite the use of statin therapy in diabetes, a significant number of fatal and nonfatal coronary heart events still occur, indicating the need to target other modifiable risk factors for coronary heart disease, including Low HDL-Cholesterol. This study shows a high prevalence of isolated diabetics correlated with cardiovascular risk also important that the interests of the target Low HDL-Cholesterol by lipid-lowering therapy to reduce cardiovascular morbidity and mortality in diabetics.

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EP380

Can hypoglycemic episodes in type 1 diabetics trigger cardiac arrhythmias?

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Type 1 diabetes mellitus (DM1) accounts for 5 to 10% of DM cases, and can occur both in childhood and adults. Studies show an association between severe hypoglycemia and increased vulnerability to cardiac arrhythmias due to conduction disorders, interval ST-segment changes, and even sudden death. The aim of this study is to evaluate the occurrence of cardiac arrhythmias during episodes of hypoglycemia. A prospective study with DM1 patients under insulin therapy for at least 5 years, aged 18–60 years, of both sexes. Before study initiation, all patients underwent a two-dimensional echocardiogram and laboratory tests, and those who did not present structural heart disease or any hormonal alterations that could cause arrhythmias, were included. The study was approved by the Research Ethics Committee of the Institution and after signed the Informed Consent Forms, the intermittent interstitial glucose reading device (IPro2 - Medtronic/USA) was implanted and simultaneous electrocardiographic recording was performed by the Holter system (Cardios Systems/Brazil). The patients were monitored for hypoglycemia (defined as interstitial glucose value <70 mg/dl according to the International Diabetes Federation without any induction for this occurrence and arrhythmia detection for 24 hours. Twenty-two patients were studied. From these eight patients (36.3%) did not have hypoglycemia: two patients (25%) also had no arrhythmia, while six patients (75%) had arrhythmias interpreted as non-significant. Hypoglycemic events were detected in the other 14 patients (63.7%), corresponding in this scenario from 4% (55 minutes) to 68% (16 hours) of total monitoring time. In this group, seven patients (50%) presented no arrhythmia, while the other seven patients (50%) had some non-significant arrhythmia that is common in non-diabetic subjects, being more prevalent as ventricular and supraventricular extrasystoles, isolated/paired with low frequency and sinus tachycardia. In the evaluated group, we find no relation between episodes of hypoglycemia and clinically relevant cardiac arrhythmia.

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EP381

Family hypercholesterolemia: about 4 cases

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Familial hypercholesterolemia (HF) is a rare hereditary dyslipidemia characterized by a major elevation of LDLc, cutaneo-tendinous xanthomas and atheromatous manifestations. This anomaly exposes a high vascular risk, more than 50% for men and 30% for women, occurring early.
Observations
We report four cases of HF from the same family, three girls and one boy and whose parents are affected by hypercholesterolemia. The average age of patients is 11 years. Only the eldest siblings present tendon xanthomas. The mean total cholesterol is 3.45 g/l, the average LDLc is 2.80 g/l, the mean HDLc level is 0.37 g/l, the average triglyceride level is 1.30 g/l. The search for vascular and cardiac repercussions was negative outside aortic narrowing in the elder. For lack of means the genetic diagnosis could not be made.
Discussion
Xanthomas were the main manifestation in this family. The presence of these clinical signs led to the prescription of a biological check-up in search of a lipid perturbation and of early vascular pathologies. Familial hypercholesterolemia results from a lack of binding and internalization of LDL through the LDL receptor. Identification of the mutation should be systematically performed. Genetic diagnosis provides diagnostic certainty and facilitates family screening.

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EP382

Description of an educational intervention lifestyle program in reducing cardiovascular risk factors

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Goals
The purpose of this article is to describe an educational program of lifestyle intervention rather successful, taught for 25 groups of customers of a private hospital in Amazon, for a total of 2,215 individuals between 2008 and 2014, 1448 being female and male 767 and briefly assess its results in relation to some of the main risk factors.
Methods
The PVS - Programa Vida Saudável, promotes evaluations and individual and group counselling, consisting of two phases, the first being, with eight meetings of the group with the multidisciplinary team in 12 weeks, followed by the second phase, with monthly meetings during 52 weeks for a total of 15 months. Clinical evaluations occur with individual counselling and laboratory dosages at the beginning and end of each phase, as well as an assessment of reaction to the end of each of the sessions. The goals of the intervention were presented progressively and easy to perform encouraging the adoption of habits and health principles, widely established.

Results
We analyse those who obtained 75% or more of the meetings frequency ($n=1723$) in 15 months and as controls, those who did the assessments and exams, however, did not participate in the educational program ($n=132$). Preliminary results showed a significant evolution in the percentage of each risk factor in patients with blood glucose reduction, improvement in cholesterol, with reduction in LDL-c reduction in triglycerides, reduction in blood pressure and weight reduction.
Conclusion
Based on studies of the data, this program of health education (PVS) presented a good adhesion of the customers and proved to be effective to reduce the risk levels in its active participants.

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EP383

Role of lactate dehydrogenase-A (LDH-A) in atherosclerosis

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Pathological proliferation and migration of vascular smooth muscle cells (VSMCs) has been implicated in the pathogenesis of accelerated atherosclerosis in patients with diabetes mellitus. Increased aerobic glycolysis is a key feature of cellular phenotypes including cancer and immune cells. However, it remains largely unknown about the role of aerobic glycolysis in atherogenic phenotype of VSMCs. Here, we investigated the role of lactate dehydrogenase-A (LDH-A), which is a key enzyme for glycolysis, on proliferation and migration of VSMCs. Activation of VSMCs with platelet-derived growth factor (PDGF) or fetal bovine serum (FBS) resulted in cellular proliferation and migration and increased glycolytic activity accompanied by the increased expressions of glucose transporter 1 (GLUT1), hexokinase (HK) 2 and LDH-A in primary rat VSMCs. Through wound healing assay, actin stress fiber staining and transwell migration assay, we observed that both pharmacological inhibition (oxamate) and siRNA-mediated knockdown of LDH-A (siLDH-A) effectively inhibited cellular migration. Oxamate reduced PDGF stimulated glucose uptake, lactate production, ATP production and NAD/ nicotinamide adenine dinucleotide (NADH) ratio. Nicotinamide mononucleotide (NMN), nucleotide precursor of NAD+, partially but significantly recovered oxamate treatment or siLDH-A induced inhibition of VSMC proliferation and migration, suggesting NAD+ involvement in LDH-A mediated VSMC proliferation and migration. Taken together, this study shows that enhanced aerobic glycolysis in PDGF- and FBS-stimulated VSMCs plays an important role in their proliferation and migration and suggests that LDHA can be a potential therapeutic target for the prevention of vessel lumen constriction in the course of atherosclerosis or restenosis.

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Clinical Case Reports - Pituitary/Adrenal

EP384

Prediction of type 1 diabetes in autoimmune polyglandular syndrome type 2

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Introduction
Autoimmune Polyglandular Syndrome (APS) is a very rare endocrinopaty, characterized by the coexistence of at least two glandular autoimmune mediated diseases. In this case a patient presented with hyperpigmentation of the whole body, significant weight loss for last 6 months.
Case
A-49 year old male were refered to our deparment with loss of appetite, fatigue, nausea, weight loss and with marked buccal pigmentation. Blood pressure was 80/50 mmHg. Biochemistry revealed fasting glucose:95 mg/dl, Na:127 mmol/l, K:5.35 mmol/l, Hb:16.6. CT abdomen showed normal adrenal gland morphology with no local masses or infectious pathology. Pituitary MRI demonstrated enlarged heterogeneous gland with 9 mm height, probably due to high ACTH levels. All findings were consistent with Addison disease, which was confirmed with morning cortisole of 2.44 mg/dl (normal range 6–22), ACTH: 1250 pg/ml (0–46).
Once Addison's disease had been confirmed, other autoimmune diseases regarding APS were undertaken. Subclinic hypothyroidism with automimmune thyroiditis; TSH:8 (0.4–5.3), fT_4: 0.9 ng/dl (0.6–1.25), anti-TPO:1016 IU/ml (0–9) was detected. Despite his normoglycemia; C-peptit:1.69 ng/ml, fasting insulin:22.3 uIU/ml, A1c:5.6%, he had high anti-GAD and anti-islet cell antibodies, widely used as a diagnostic and predictive tool for type 1 diabetes mellitus, indicating that he may develop type 1 diabetes mellitus in future.
After a week of steroid replacement his physical discomforts were alleviated with improved electrolytes.
Discussion and Conclusion
Herein, we reported an uncommon case, who had complete two-glandular deficiency with third component; predicted type 1 diabetes. This patient is being monitored closely on glycaemic state. Therefore, once an autoimmune disease is identified, the early screening for antibodies against associated disease such as anti-TPO, GADA, ICA, and antibodies to 21-hydroxylase is crucial, which facilitate the diagnosis of further disorder at an early stage.

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Clinical Case Reports - Thyroid/Others

EP385

Insulin autoimmune syndrome (Hirata Disease) triggered by a tyrosine kinase inhibitor drug in a Latin American patient

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Hirata syndrome is a rare cause of spontaneous hypoglycaemia, more prevalent in Japanese population, very infrequent in Caucasian patients. It has been described that it can be triggered by medication with sulfhydryl compounds or α-lipoic acid. A 73-year-old male patient was sent to the Endocrinology Division in December 2015 because he had been presenting with episodes of sweating, palpitations and feeling hungry for 6 months; these symptoms improved when he ate carbohydrates. In the last 15 days before his visit, the episodes worsened, every 3 hours. The patient had a history of a synchronous bilateral clear cell renal carcinoma, the right kidney was removed in 2007, and the left renal carcinoma was not surgically removed because he presented worsening of a large thoracoabdominal aortic aneurysm and the patient refused to be operated due to the high risk involved in this surgery. He was treated with sunitinib, but this drug was switched to sorafenib because of adverse effects in 2008. In 2013, he presented cancer progression and he began treatment with pazopanib but there was no response and the oncologist decided to switch to axitinib 10 mg/day in 2014. A year later the patient began with endocrine symptoms. Pancreatic CT and MRI were normal. Lab tests: glycaemia 41 mg%, insulin $>$ 1000 uU/ml (N: 0–12) C-peptide: 5.4 ng/ml (N: $<$ 2.6). Insulin antibodies were performed: $>$50 U/ml (N: $<$1) which confirmed the diagnosis of Hirata disease. Axitinib was stopped immediately and fractional eating was indicated. The hypoglycaemic episodes became progressively less frequent and some days there were no episodes. HLA analysis revealed the HLA-DRB1*04:15 allele. As the patient improved, insulin antibodies were repeated but they remained elevated. The patient had renal cancer progression and died a year after.
Conclusions
Episodes of hypoglycaemia with very high levels of insulin in a non-diabetic patient suggest a probable autoimmune origin. This is the first report of Hirata disease triggered by Axitinib, a drug not previously involved in this syndrome. Another novel finding is that HLA phenotype results in HLA-DRB1*04:15 allele, which has not been described before neither in Asian nor in European patients and this may be due to the fact that this patient is Latin American.

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EP386

Fulminant diabetic ketoacidosis complicating nivolumab immunotherapy

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A 56-year-old woman, recently commenced on immunotherapy as second-line treatment for advanced non-small cell lung cancer, presented at the hospital critically unwell with severe diabetic ketoacidosis (DKA) (glucose 47 mmol/l, blood ketones 7.5 mmol/l, pH 6.95, bicarbonate 6.6 mmol/l). One week prior to presentation, she was clinically well with random glucose of 6.1 mmol/l. Following admission to Intensive Care Unit, she responded well to standard treatment for DKA and discharged on basal bolus insulin regime. Her anti-GAD antibodies were 12 kU/l (0–5 kU/l), while islet cell antibodies and serum C-peptide were undetectable. Nivolumab has been recommenced without the development of other immune-mediated phenomena to date.

Besides metastatic lung adenocarcinoma diagnosed 3 years ago, she had no personal/family history of diabetes mellitus (DM), while venous glucose had been normal at numerous measurements. She was initially treated with Pemetrexed and Cisplatin followed by Pemetrexed as maintenance chemotherapy which was discontinued due to side-effects two months prior to her emergency presentation. At that stage, Nivolumab every 2 weeks was initiated. She has maintained good radiological and clinical response to treatment.

Nivolumab is an anti-PD-1 monoclonal antibody and as a checkpoint inhibitor acts as an immunomodulatory antibody that augments the anticancer immune response through downregulation of T-cell inhibition. Immunotherapy has a beneficial effect in an increasing number of tumour sites, but is associated with immune-mediated endocrinopathies. Development of new-onset type 1 DM after receiving anti-PD-1 antibodies, especially as single agent, is extremely rare.

This patient developed fulminant type 1 DM leading to severe DKA and remains insulin dependent. Both endocrinologists and oncologists need to recognise this potentially life-threatening complication and to monitor patients for hyperglycaemia prior to and periodically during immunotherapy. Further studies examining the pathophysiology and natural history of immunotherapy-associated diabetes are warranted in order to guide optimal patient monitoring and management.

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EP387

Dyslipidemia and antiretroviral therapy: a case report

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Introduction

The use of highly active antiretroviral therapy in 1996 helped greatly reduce the morbidity and mortality in patients infected by HIV. Very quickly, secondary metabolic complications to this same treatment have been described. Dyslipidemia occupy a large part of these complications and give the patients an atherogenic profile favouring the occurrence of acute coronary events. We report a case that illustrates the lipid abnormalities associated with anti retroviral treatment.

Case report

The subject was 54 years old woman, diabetic for 8 years, without history of hypertension or smoking, BMI was 29 Kg/m^2, diagnosed as HIV infected for 1 year, treated by antiretroviral therapy. Her initial lipid profile reveals a moderate hypertriglyceridemia of 2.5 g/l, total cholesterol was 1.7 g/l and HDL cholesterol was 0.3 g/l. High plasma viral loads persisted after 6 months of antiretroviral therapy, thus the patient was considered to have a treatment failure. The control of her lipid profil, after 2 months of a second-line combination therapy, reveals an aggravation of her previous dyslipidemia with a severe hypertriglyceridemia of 6.36 g/l, an hypercholesterolemia of 2.72 g/l and HDL cholesterol was 0.4 g/l.

Discussion

While the retroviral infection itself, especially at the AIDS stage, is responsible for an increase in triglycerides and a decrease in total cholesterol, antiretroviral therapy exacerbates abnormal lipid metabolism. This is mainly dyslipidemia with predominant hypertriglyceridemia, associated with an increase in total cholesterol and LDL-cholesterol; HDL-cholesterol is either lowered or slightly modified, these abnormalities are partly due to increased hepatic synthesis of large VLDL and decreased purification of remnants rich in triglycerids. The Knowledge of lipid abnormalities induced by antiretroviral treatment is critical for better patient management between infectiologist, biologist and endocrinologist.

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EP388

Diabetic patient with suppurative thyroiditis caused by *Salmonella enterica* complicated with acute kidney injury

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Incidence of acute thyroiditis is about 0.1% of thyroid gland conditions requiring surgical treatment. Main pathogen causing acute thyroiditis is *Staphylococcus aureus* while *Salmonella enterica* is extremely rare.

Herewith we report a 61-year-old obese woman with sore throat and fever. She had chronic atrial fibrillation, hypertension, and well-controlled type 2 diabetes mellitus (HbA1C 5.5%) for 3 years (on metformin and gliclazide). Her medical history was negative for thyroid and renal disorders. Ultrasound examination (US) of the neck demonstrated mixed solid/cystic lesion. Moreover, empirical therapy with clindamycin was introduced (1.2 g/day) and the patient was referred to the endocrinonogy department. On admission she was weakened and dehydrated. Physical examination revealed restricted, swollen, tender and painful lesion in the lower part of the neck. Laboratory tests indicated inflammation, acute kidney injury and hyperthyroidism. Fine-needle aspiration biopsy (FNAB) of the lesion was performed. Cytological diagnosis was consistent with acute thyroiditis, while microbiologically *Salmonella enterica* was identified as pathogenic factor. Blood and stool cultures were negative for *Salmonella*. Neck CT revealed thyroid lesion 6.8 cm in size. Patient received adequate therapy for acute kidney injury (most probably clindamycin-induced). I.v. treatment with ceftazidime according to antibiogram and thiamazole was administered. The patient was qualified for incision and percutaneous drainage. She was discharged after 11 days of hospitalization presenting significant clinical improvement. A year later on US six mixed solid/cystic lesions of size below 1 cm were visualized, benign on FNAB. She remains clinically and biochemically euthyroid. Typical infections with Salmonella concern gastrointestinal tract, while conditions associated with atypical infections are: HIV infection, transplant recipients, diabetes mellitus, thyroid gland disorders (e.g. multinodular goiter, after FNAB), anatomical abnormalities (piriform sinus fistula), corticosteroid therapy, advanced age, neoplastic disease and contact with breeding animals. The only risk factor for acute thyroiditis in our patient was diabetes mellitus, although it was well-controlled.

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EP389

Improved xanthomas after leptin replacement short therapy in congenital lipodystrophy patient

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Berardinelli-Seip syndrome is an autosomal recessive disorder characterized by generalized lipoatrophy, extreme insulin resistance with dyslipidaemia in childhood and development of diabetes and hepatic steatosis in adolescence. The metabolic derangements can be severe and lead to substantial comorbidities, including acute pancreatitis, hepatic cirrhosis, and premature cardiovascular disease. Other manifestations can include polycystic ovarian syndrome, acanthosis nigricans, and eruptive xanthomas. Lipodystrophy syndromes have caught interest because adipose tissue has been found to secrete a variety of cytokines/hormones such as leptin, adiponectin, resistin, and many others. Here we describe a dramatic response to treatment with leptin. A 15-year-old girl was given the diagnosis of Berardinelli-Seip congenital lipodistrophy syndrome (BSCL). She presented generalized lipoatrophy, muscle hypertrophy, xanthomas in elbows legs and soles, umbilical hernia, hirsutism, hyperphagia, acanthosis nigricans and hepatomegaly. Her BMI was 20.67 kg/m^2, body fat was 5.72%, and BMR was 1 440.3 Kcal. Computer tomography revealed hepatic steatosis, one cyst on the right kidney, and absence of subcutaneous and adipose tissues. Patient had difficult to manage metabolic parameters, requiring 300U of insulin and combined therapy. She started a leptin-replacement therapy (1 ml/day). After ten days, her xanthomas became vanished, cholesterol levels decreased from 550 to

196 mg/dl, and triglycerides 5.000 to 840 mg/dl. She observed progressive reduced fasting blood glucose and insulin dose simultaneously with improvement in clinical signs, symptoms and quality of life. In a ten days course, leptin replacement showed to be able to manage metabolic state of the patient and xanthomas.

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EP390

Resistant hypertension in an obese type 2 diabetic male with obstructive sleep apnea: resolution with CPAP, weight loss and Dulaglutide

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A 49-year-old male was referred to our Hypertension Clinic with uncontrolled hypertension, treatment Valsartan/Amlodipine/Hydrochlorothiazide 80/10/25 mg + Doxazosine 4 mg. Mean home BP was 156/103 mmHg. Personal history: dyslipidaemia, central obesity and type 2 diabetes, with mild diabetic retinopathy, persistent microalbuminuria and preserved renal function. Treatment: Metformin/Sitagliptin 1000/50 mg BID; Pravastatin/Fenofibrate 40/160 mg. Height 172 cm, weight 112 kg, BMI 37.8 kg/m^2, waist 126 cm, clinic BP 165/99, HR 77; unremarkable physical exam except abdominal adiposity. Glycemia 132 mg/dl, HbA_{1C} 7.2%, Cr 0.92 mg/dl, GFR (CKD-EPI) 97 ml/min per 1.73 m^2, Cholesterol 166 mg/dL (HDL 38, LDL 96), Triglycerides 161 mg/dl, Albuminuria 126 mg/g Cr; TSH, Metanephrines, Aldosterone, PRA and ratio were normal. Heart US: normal function, mild LVH (PW and IVW 14 and 13 mm). 24 h. ABPM: Awake BP 157/96, Sleeping 146/89, non-dipper.
The treatment changed to Perindopril/Indapamide 8/2.5 mg, Eplerenone 50 mg and Doxazosine 4 mg. Four months later, the patient had lost 2.5 kg with diet/exercise, but BP and HbA_{1C} had not improved. Dulaglutide 1.5 mg/week was substituted for Sitagliptin. The patient's wife reported heavy snoring with apparent pauses, and the patient was referred to polysomnography. A severe OSA was diagnosed, and CPAP was initiated.
Six months later, weight was 98.5 kg (IMC 33.1 kg/m^2); waist 114 cm, and home and office BP were normal. New ABPM: Awake 132/76, sleeping 116/69, dipper. Glycemia was 114 mg/dl, HbA_{1C} 6,7%, Cr 0.91 mg/dl, GFR 98 ml/min per 1.73 m^2, Chol. 153 mg/dl (HDL 43, LDL 79), Trigl. 156 mg/dl, Albuminuria 23 mg/g Cr. New heart US: PW and IVW 11 and 10 mm.
The diagnosis was resistant hypertension with target-organ damage (albuminuria, LVH) associated to OSA, plus type 2 diabetes, central obesity, and dyslipidemia. With CPAP, weight loss and Dulaglutide, BP and glycemic control were achieved and target-organ damage was reversed.

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EP391

Morgagni-Stewart-Morel Syndrome in a 61-years patient: case report

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Introduction
Morgagni-Stewart-Morel syndrome is a disorder defined by the presence of internal frontal hyperostosis, variably associated with metabolic disorders, endocrine and neuropsychiatric disorders. Hyperostosis frontalis interna (HFI) is a morphological change of the frontal bone like a single or multiple bilateral nodules on the inner lamina, characteristically sparing the diploë and the midline calvaria.
Case presentation
We present a 61-years old women with hypertension and diabetes mellitus (with oral antidiabetic therapy), obesity, osteoporosis; also the patient was operated in 2005 for a multinodular goiter (total thyroidectomy), treated with L-thyroxin 100 μg per day. She was referred to our department for severe frontal headache which she had suffered for several years, with gradually worsened, failing to respond to nonsteroidal anti-inflammatory drugs in last six months and a history of psychotic disorders. MRI demonstrated the internal hyperostosis frontalis with compression of the cerebral cortex and a small image in the pituitary gland, which is now under observation.
Conclusions
The clinical features of this syndrome was according to those described in the literature. Metabolic and endocrine disorders should not be interpreted as isolated pathology, but as possible pathogenetic factors. We underline the essential role of MRI in detecting the disease correlated with intense headache. The neurological symptoms and psychiatric symptoms were correlated with the severity of internal frontal hyperostosis and cortical atrophy.

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EP392

Continuous glucose monitoring in glycogen storage disease type Ia – a major improvement for patients

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Introduction
Glycogen storage disease (GSD) type Ia (von Gierke's disease) is an inherited metabolic disorder of glycogen metabolism, caused by defects in the glucose-6-phosphatase complex, with associated risk of severe hypoglycemia within 3–4 h after a meal.
The aim of the present study was to evaluate the efficacy of continuous glucose monitoring (CGM) system in determining the magnitude of hypoglycemia in patients with GSD type Ia.
Methods
We retrospectively analyzed data from three patients with GSD type Ia, who underwent CGM with iProTM2 CGM device (Medtronic, Northridge, CA), over a 7.0 days period, under real life conditions.
Results
A total of 5.520 glucose data points were analysed. Concerning to low glycemic excursions (<70 mg/dl), we identified 15 episodes (three of them below 55 mg/dl and reaching 40 mg/dl in one case). Most of the episodes of hypoglycaemia were asymptomatic and occurred 3 or more hours after meals or during the nocturnal period. The individual CGM analysis revealed a mean area under the curve of blood glucose below 70 mg/dl (AUC<70) respectively of 0.1, 0.5 and 0.8. One patient presented with important glycemic variability: MAGE 3.11 (reference range 0.0–2.8).
Conclusions
The analysis of continuous glucose monitoring data revealed significant periods of asymptomatic hypoglycemia and provided better perception into glycemic variations therefore, it may serve as a safe and useful tool for the long-term management of patients with GSD type Ia. We suggest that CGM can be used as an instrument to detect hypoglycemia, especially in the nocturnal period, helping patients with GSD to modify their nutritional regimens if necessary.

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EP393

Diabetes mellitus: one train may hide another

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A 26-year-old Chinese male with autism spectrum disorder and mental retardation, was referred to start insulin therapy for uncontrolled diabetes mellitus (DM) (HbA1c: 9%; C-peptide: 1.75 ng/ml; anti-GAD AB: negative) treated with oral antidiabetic drugs since 2012.
Clinical examination revealed a tall man with overweight and truncal obesity in light of his ethnicity. We withheld facial dysmorphism with hypertelorism, scarce facial hair, and clinodactyly. He had a true gynaecomastia and acanthosis nigricans. Tanner genital stage was IV, however testicular volume was <4 ml. Blood results showed hypergonadotropic hypogonadism (LH:14.1 U/L, FSH:25.3 U/L, testosterone: 195 ng/dl, free testosterone: 5.71 ng/dl). Additional genetic testing showed 48 XXYY karyotype.

Based on medical questionnaires, DM is described in 18% of 48 XXYY males. Following pathophysiological mechanism is proposed: low tota l and free testosterone levels are associated with truncal obesity leading to metabolic syndrome, insulin resistance and DM. Abdominal obesity and high C-peptide levels in our patient are arguments in favor of insulin resistance as possible etiological factor. Based on the pathophysiology, metformin and testosterone could be considered as therapy. Our patient was initially treated with basal-bolus insulin therapy in combination with metformin to enhance insulin sensitivity. Although in-hospital blood glucose curves were perfect, global metabolic control remained poor (HbA1c: 8.5%) due to compliance problems partially by the complexity of treatment. Therefore therapy was simplified to a combination of basal insulin and metformin. Metabolic control remained however poor. Some data suggest that testosterone treatment might improve metabolic control by increasing skeletal muscle mass and decreasing abdominal obesity. In our patient, there was however no amelioration of metabolic control after start of testosterone. Adequate DM therapy is complicated by mental retardation seen in 48 XXYY making it difficult to use complex insulin schemes. It seems reasonable to use metformin in treatment as insulin resistance seems to play a role in the pathophysiology.

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EP394

Endocrine manifestations of Woodhouse-Sakati Syndrome – a Portuguese case

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Introduction
Woodhouse-Sakati Syndrome (WSS) is a very rare autossomic recessive disorder caused by mutations in *DCAF17* gene that primarily affects the endocrine and the nervous systems. It is associated with hypogonadism, diabetes *mellitus*, hypothyroidism, sensorineural hearing loss, alopecia and extrapyramidal findings. Treatment is symptomatic and managed by multidisciplinary teams. Less than 80 cases are reported to date.
Case report
We describe a 29-year-old woman with dysmorphic facial features, alopecia, mild intellectual disability and sensorineural hearing loss, referred to the Endocrinology department for primary hypothyroidism with negative thyroid autoantibodies, hypergonadotrophic hypogonadism with ovaries not visualized on pelvic ultrasound and diabetes mellitus diagnosed at 19 years of age. She was under treatment with levothyroxine, drospirenone + ethynyl estradiol and oral glucose lowering agents. Worsening of metabolic control led to start of insulin therapy. Week positivity for Islet-cell cytoplasmic autoantibodies and positive glutamic acid decarboxylase autoantibodies were detected. IGF1, GH, prolactin, cortisol and ACTH were normal. Progressive neurologic deficits included dysarthria, dysphagia, lower limb dystonia and spastic tetraparesis. Brain MRI showed generalized leukodystrophy. She was the only child of a consanguineous couple. Common genetic, metabolic and mitochondrial disorders were excluded. WSS was suspected. Sequencing of *DCAF17* gene detected the homozygous variant c.1091 + 2T > C, not previously described in literature. However, since it affects the splice donor site of intron 10 and probably causes exon 10 skipping, it is likely to be pathogenic.
Discussion
When in presence of several endocrine disorders associated with multisystem involvement, it is fundamental to look for genetic disorders. Accurate clinical evaluation allows genetic diagnosis and counseling. A new homozygous variant of the DCAF17 gene was found in this case. The pathogenic mechanisms of the disease are still unclear; diabetes-related autoimmunity is not found in previously described cases. Also unlike other described cases, IGF1 was within normal limits. Endocrine consequences of WSS need frequent follow-up.

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EP395

Hypoglycaemia due to hydroxychloroquine in a patient who underwent Roux-en-Y gastric bypass surgery

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A 45-year-old female presented with recurrent episodes of neuroglycopaenic symptoms 6 years after Roux-en-Y gastric bypass surgery. Her symptoms occurred during both the fasting and postprandial state. She had a history of Rheumatoid Arthritis. Her symptoms did not response to a complex carbohydrate diet or Acarbose use.
Whipple's triad was demonstrated during a 72 h fast; symptomatic hypoglycaemia (1.8 mmol/l) occurred which resolved with glucose administration. Simultaneous C-peptide, IGF1, IGF2 and insulin samples were requested during the hypoglycaemic episode.
The Insulin level was 10 pmol/l, IGF1 level was 11.6 nmol/l, the IGF2 level was 36.3 nmol/l, IGF2/I ratio was 3.1 (< 10), C-peptide level was < 94 pmol/l, GH was 7.5 μg/l and Sulphonlylurea screen was negative.
Ketones was 'Zero' confirming an insulin independent mechanism for hypoglycaemia. Hydroxcholoroquine for Rheumatoid Arthritis was discontinued which led to complete resolution of her symptoms.
This is the first case of severe hypoglycaemia in a patient who did not have diabetes, who underwent bariatric surgery and developed hypoglycaemia due to hydroxycholoroquine therapy with complete resolution of symptoms on discontinuing hydroxychloroquine.
This case demonstrates the need for a structured approach to the evaluation of hypoglycaemia. Roux-en-Y gastric bypass surgery is associated with subsequent development of hypoglycaemia which can respond to a complex carbohydrate diet or acarbose therapy. The lack of response however should prompt a thorough evaluation. The demonstration of an insulin independent mechanism for hypoglycaemia excluded post gastric bypass hypoglycaemia as a cause and prompted a review of the medication list. Hydroxcholoroquine is associated with the development of hypoglycaemia and cessation resulted in complete resolution of symptoms which were occurring at a frequency of 3–4 times per week resulting in termination of employment and driving.

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EP396

A case report of insulin autoimmune syndrome in a Caucasian

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The Insulin Autoimmune Syndrome (IAS) also called Hirata's disease consists of hypoglycemia, high insulin concentration and presence of anti-insulin antibodies. IAS is the third leading cause of spontaneous hypoglycemia among Japanese population. The syndrome is exceptionally rare among Caucasians, with < 50 cases described in literature.
In this report we showcase a 67 year-old female patient. She presented with paroxysmal sweating, daily fatigue and weakness with no triggering factors for these symptoms. Her blood glucose levels during those episodes were below 50 mg% measured by using a standard home glucometer device. Prolonged 72 h fast test showed extremely high insulin-glucose-ratio with moderate elevation of C-peptide levels. CT scans did not reveal any significant masses in the abdomen. The subsequent laboratory analysis showed high levels of anti-insulin antibodies with low insulin recovery by using polyethylene glycol precipitation method. After treatment with low glycemic index diet and prednisone the average glycemia has increased with the remission of the symptoms. There have been no incidents of hypoglycemia since the establishment of the treatment.
Our report indicates that at IAS should be considered in the differential diagnosis of spontaneous hypoglycemia in Caucasians. The treatment might lead to the remission of the symptoms.

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EP397

Acquired generalized lipodystrophy associated with latent autoimmune diabetes mellitus in adults: a new metabolic phenotype

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Introduction
Acquired generalized lipodystrophies (AGL) are rare syndromes characterized by complete loss of subcutaneous adipose tissue and very low serum leptin levels.

AGL are complicated by severe insulin resistance, diabetes mellitus, dyslipidemia and fatty liver. In most patients evidence exists of an autoimmune etiology.
Case report
We herein describe the case of a Caucasian woman who was diagnosed with lipodistrophy at 5 years of age, when she began to develop a gradual loss of subcutaneous adipose tissue. At the age of 20 years insulin-resistance, hypertriglyceridemia and fatty liver were evident; diabetes mellitus was diagnosed when she was 28-years old, and 3 years after insulin therapy became necessary in order to improve metabolic control of the disease. Genetic testing were negative for PPARG and LMNA/C mutations, ruling out the principal forms of congenital lipodystrophies. She came to our attention at the age of 35 years. At clinical examination a generalized loss of subcutaneous fat that included the face and the extremities was observed. Laboratory tests showed a poor glicemic control. $HbA1_c$ was 85 mmol/mol on high doses of insulin (150UI/die). Nuclear, PMScl, Gastric Parietal Cell, and high titer Glutamic Acid Decarboxylase autoantibodies were detected.
Discussion
AGL are frequently associated with other autoimmune disorders. The coexistance with type 1 diabetes is very rare, but the association with a latent autoimmune diabetes mellitus in adults (LADA) has never been reported before. This association generates an unusual metabolic pattern characterized by severe insulin-resistance due to ectopic-lipid accumulation and severe diabetes due to an absolute insulinopenia. For these reasons the management of the metabolic syndrome in this case is extremely difficult and the association of insulin with human recombinant leptin therapy seems to be more efficient than conventional drugs. This case shows the need to screen all patients presenting with an AGL for associated autoimmune disorders including type 1/LADA diabetes.

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EP398

Humalog Mix50® massive overdose for suicidal purpose: a case report

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Intentional insulin overdose in diabetic patients is a rare critical situation. The severity is due to numerous neurological complications, electrolyte disturbances, liver and lung damage or death.
A 76-years old female, with significant cardiac pathology, diagnosed with type 2 diabetes and treated with Humalog Mix50® 0-0-24 U/day, is admitted to our center via ER (emergency room) after an episode of severe hypoglycemia after administration of 1500U Humalog Mix50. She arrived in the ER one hour after the overdose with a glycemic value of 111 mg/dl after 50 ml of glucose 33% and 500 ml 10% glucose. At admission: altered general status, profuse sweating, multiple injection sites across her abdomen and thighs. Labs exams revealed: hypocalcaemia, hypokalemia, slightly elevated creatinine and BUN, mild normochromic, normocytic anemia, A1c = 6.29%. An infusion of 10% glucose was begun at 1 L/h. The glucose infusion rhythm and concentration was adjusted according to the glycemic profile with a total duration of infusion of 46 h. Besides, multiple boluses of glucose 33% were needed to avoid the hypoglycemic events. Hypocalcaemia and hypokalemia were corrected by intravenous (i.v.) administration of calcium gluconate and potassium chloride. Psychological evaluation diagnosed depression and recommended a psychiatric consult. On day 3 since admission, the patient's general condition worsened significantly with severe hypotension (requiring continuous positive inotropic infusion), liver and renal failure and she was transferred to the ICU. Despite intensive care maneuvers, the patient died of cardiac arrest through electromechanical dissociation.
Insulin overdose requires intensive and prolonged glycemic monitoring to prevent recurrent hypoglycemia. The dose is correlated with a prolonged hypoglycemic risk higher than that deduced from the pharmacokinetics of insulin administered. To our knowledge this case represents the largest overdose with Humalog Mix50® ever reported.

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EP399

Extensive venous thrombosis of the upper extremity in a newly diagnosed type 2 diabetic female

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Upper extremity deep vein thrombosis (UEDVT) is not infrequent and accounts for approximately 14% of deep vein thrombosis. The risk of pulmonary embolism is lower than in lower extremity DVT and prompt diagnosis is essential to select those patients who deserve anticoagulant treatment. Previous studies indicated that type 2 diabetes (DM) patients carried greater risk of DVT development or recurrence than the general population.
A 49-years old female, with no previous medical history, was admitted to our center via Emergency Room (ER) for optimizing glycemic control. At admission: altered general status, bradylalia, bradypsychia, generalized edema, marked fatigability, BP = 140/90 mmHg, pulse = 96 b/min, holosystolic murmur in the mitral area. Lab findings revealed: BG = 401 mg/dl, glycosuria (1 g/dl), proteinuria (300 mg/dl), low serum iron, mild normochromic and normocytic anemia, high INR and NT proBNP levels, hypocalcaemia, low HDL cholesterol, slightly elevated CRP, cholestasis syndrome and A1c = 14.01% was consistent with a sever glycemic imbalance in the last 3 months. Intravenous insulin infusion and few boluses were needed to correct the hyperglycemic values followed by initiation of a basal regimen with glargine insulin and metformin. On 3rd day since admission, edematous swelling and cyanosis of the right arm with collateral circulation at the shoulder girdle was observed. The echo-Doppler showed a massive thrombosis from brachial to the brachiocephalic and internal jugular vein and the CT pulmonary angiogram thrombi at the level of segmental arteries bilaterally. Treatment with LMWHs was initiated and the patient was transferred to the Cardiology department with a favorable outcome. The screening for thrombophilia emphasized hyperhomocysteinemia and a slightly elevated S protein activity.
Our case illustrates an extensive UEDVT and pulmonary embolism in a newly diagnosed type 2 diabetic patient. The modifications in the thrombophilia screening together with the hypercoagulable state induced by hyperglycemia might have led to the development of this extensive UEDVT.

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EP400

Early association of three autoimmune disorders in a young male with polyglandular autoimmune syndrome type IIIA

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Polyglandular autoimmune syndromes (PAS) are a heterogeneous group of rare diseases characterized by autoimmune activity against more than one endocrine organ, although non-endocrine organs can be affected. In PAS III, *autoimmune thyroiditis* occurs with another organ-specific autoimmune disease, but the syndrome cannot be classified as PAS I or II.
A 29-years old man was refer to our center for diagnostic confirmation with the following complaints: xerostomia, polyuria, polydipsia, nocturnal enuresis, 10 kg weight loss in the last 2 months, blurred vision and marked fatigability. One week before admission the lab exams revealed: blood glucose (BG) of 527 mg/dl, severe dyslipidemia, glycosuria, ketonuria and a basal bolus regimen with insulin glargine and lispro was started. Labs findings displayed: BG = 276 mg/dl, moderate hypertriglyceridemia, glycosuria, low sodium and chloride and the A1c = 17.73% was consistent with a sever glycemic imbalance in the last 3 months. The specific antibodies for type 1 diabetes (GAD, ICA, IA_2, anti-insulin) were negative and the C peptide was low. The screening for other autoimmune diseases was positive for thyroiditis (high TPO antibodies) and celiac diseases (high IgA anti-transglutaminase antibodies) and were confirmed by thyroid

ultrasound, gastroscopy (paving stone duodenum) and histopathological examination. In order to improve the glycemic control, the insulin doses were adjusted according to the glycemic values and carbs ingestion. Nutritional education was conducted emphasizing the importance of gluten-free diet and correct estimation of the carbs intake. The lipid profile normalized after normoglycemia was achieved.
Despite the lack of specific antibodies, the patient profile, lab exams and association with other autoimmune diseases support the diagnosis of type 1 diabetes. The zinc transporter-8 (ZnT8) antibodies are not yet available in our country. The evolution in these cases may be unpredictable and requires the concomitant treatment of all the conditions involved in order to achieve the therapeutic success.

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Developmental Endocrinology

EP401

Nutritional status in ambulatory patients by Medicine Laboratory

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Nutritional status has an important effect on the progression of any disease, not only in hospitalized patients, even more in ambulatory patient of primary care. Although there are many systems of evaluating nutritional status, they are costly and subject to variability amongst individuals. The Medicine Laboratory can correctly perform a nutritional evaluation in a quick an efficient manner.
Objective
Analyze the nutritional status by CONUT nutritional evaluation method performed by the Medicine Laboratory in ambulatory patients of primary care our Health Management Area in 2016.
Materials and methods
The CONUT method for nutritional evaluation was used. This method is based on determining undernutrition according to levels of total lymphocyte count total cholesterol and serum albumin. During the study, the results of rutinary blood tests were used, not additional bllod tests were performed. The focus was a sample size of all patient admitted in primary care centers, $n = 1454$ patients. Statistics data: accepted error 3.5%, C.I. 99%. The frequency of nutritional risk was calculated analysed alongside data on patients' sex, age.
Results
1454 patients were studied, 68.5%were not undernourished, 27,4% were mild undernourished and 4,1% were moderate or severe undernourished. The mean age of patients was 57.9 years, 60.9% were women and 39.1% were men. 6.7% of men were moderate or severely undernourished, only 2.3% of women studied were moderate or severely undernourished. The statistics differences by gender were significatives.
Conclusion
The nutritional evaluation performed by the Medicine Laboratory is an effective tool to evaluate nutritional status and take corrective measures. Although there are many experiences in CONUT nutritional evaluation in hospitalized patients, we think that this method is useful in primary care too.

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EP402

Satiety, hunger and gastrointestinal hormones after a test meal in patients after gastric bypass surgery: an association with amino acids

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Background
Nutrition is essential in achieving maximal treatment success after bariatric surgery, and is simultaneously beneficial for avoiding long-term complications. Dietary protein could have an important role, because of its positive effects on preservation of muscle mass and induction of satiety in non-bariatric subjects. Therefore, we investigated the effects of dietary protein, assessed by amino acid composition, on satiety, hunger and gastrointestinal hormones after gastric bypass surgery.
Methods
Participants who previously had undergone primary gastric bypass surgery were studied during an oral Mixed Meal Tolerance Test (MMTT). Satiety and hunger were assessed every 30 min by means of a visual analogue scale. Blood samples were collected at baseline, every 10 min during the first half hour and every 30 min till 210 min after the start. The plasma samples were assessed for 24 amino acids including derivatives and four gastrointestinal hormones.
Results
30 female and 12 male subjects aged 48 ± 11 years, 31–76 months after surgery with total weight loss of $30 \pm 9\%$ completed the MMTT. After ingestion increases in satiety, the hormones PYY, active GLP1, inactive GLP1 and most amino acids were observed, while hunger, ghrelin and citrulline declined. Satiety scores above the median were associated with increased plasma levels of PYY, active and inactive GLP1. Hunger scores below the median (indicating less hunger) were associated with increased levels of PYY and a reduced attenuation in ghrelin. Higher concentrations of several plasma levels of amino acids especially histidine, serine, arginine, glutamine and glycine were observed in subjects experiencing more satiety, higher levels of PYY, active or inactive GLP1. Additional analyses are underway.
Conclusions
Our exploratory analysis shows positive associations between various plasma amino acids in groups with differences in satiety and gastrointestinal hormones. This provides new insights to optimize the outcomes of bariatric surgery.

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Diabetes (to include Epidemiology, Pathophysiology)

EP403

The fatty acid profile in diabetic children

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Several studies have shown a link between pro-inflammatory activity and the presence or relative deficit of some fatty acids. A low amount of omega 3 fatty acids, appears to promote an inflammatory profile. The omega 6 fatty acids have also the same effect. It is well known that a chronic low-grade inflammation is associated to several diseases, namely, diabetes. The follow-up of children and young people with Type 1 diabetes involves the periodic evaluation of their lipidic profile, however it is not done regularly the evaluation of the profile on the concentration of different types of fatty acids.
Objective
To characterize, and compare, fatty acids profile in children with Type 1 diabetes and healthy children.
The authors observed that the ratio of omega 6/omega 3 fatty acids was higher in the control population. Omega 6 levels were higher in the diabetic children compared to the control group. Several other differences in free fatty acid composition were observed.
Conclusion
Our findings showed higher levels of alpha-linolenic acid, EPA and DHA, as well as mono and polyunsaturated fatty acids in diabetic children. This fact is attributed to pharmacological therapy and nutritional management of these children. These findings reinforce the importance of a precocious nutritional attention and intervention in the diabetic child treatment.

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EP404

Sitagliptin use may reduce oral cancer risk in patients with type 2 diabetes

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Background
Whether sitagliptin may affect oral cancer risk has not been investigated.
Methods
The reimbursement database of the National Health Insurance in Taiwan was used. Diabetic patients newly treated with sitagliptin ($n=50033$) or other antidiabetic drugs ($n=277038$) within 1999–2008 were followed for oral cancer until December 31, 2011. The treatment effect was estimated by Cox regression adjusted for propensity score (PS) or using PS weighting by inverse probability of treatment weighting approach.
Results
The overall hazard ratios suggested a 20% lower risk without statistical significance. In tertile analyses, the PS-adjusted hazard ratios for the first (<6.53 months), second (6.53–14.00 months) and third (>14 months) tertile of cumulative duration were 1.382 (0.899, 2.125), 0.908 (0.566, 1.456) and 0.464 (0.272, 0.789), respectively; and were 1.324 (0.864, 2.030), 0.871 (0.545, 1.394) and 0.447 (0.263, 0.760), respectively, for PS-weighted.
Conclusions
Sitagliptin may reduce oral cancer risk when the cumulative duration is >14 months.

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EP405

Does a first-degree family history of diabetes impact placental vascular circulation and placental inflammatory response?

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Background
Experimental and clinical studies have demonstrated that heritability of diabetes is associated with marked hyperinsulinemia, impaired endothelial function, and inflammatory up-regulation. However, no studies have examined whether a family history of diabetes effects placental maternal and fetal vascular circulation, or placental inflammatory response. The present study was designed to investigate the impact of first-degree family history of diabetes (FHD) on placental vascular circulation and inflammatory lesions.
Methods
402 pregnant women were divided into two groups according to presence of of first-degree FHD: Group 1 included 255 subjects without FHD, Group 2 included 145 subjects with FHD. Placental histology was performed for vascular circulation and inflammation lesions of maternal and fetal origin.
Results
Maternal vascular supply (MVS) abnormalities of the placental bed was significantly higher in subjects with FHD, compared to group 2 (33% vs 52%, $P<0.005$). Fetal vascular supply (FVS) abnormalities as well as maternal and fetal inflammatory lesions (MIR and FIR) did not differed significantly between groups. In the logistic regression analysis, FDH is an independent and significant predictor predictor of maternal vascular supply abnormalities ($P=0.001$) and more than doubles risk of this outcome (OR 2.084, 95% CI 1.337–3.247, $P=0.001$). Gestational diabetes incidence was significantly higher in subjects with FHD.
Conclusion
We demonstrated that first-degree family history of diabetes is associated with an increased rate of maternal vascular malperfusion abnormalities.

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EP406

Episodes of poorly controlled diabetes in 1486 patients admitted in Orthopedic Surgery and Traumatology

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Introduction
Episodes of poorly controlled diabetes (DM) are one of the most frequent medical complications during hospitalization in the elderly population.
Objectives
To analyze the prevalence of episodes of diabetic decompensation in patients admitted in Orthopedic Surgery and Traumatology (OST) area.
Material and methods
Descriptive analysis of patients admitted to OST Service who presented abnormally high or decreased blood glucose levels according to the criterion of the Orthopedic Surgeon who performed the consultation.
Results
From June 2008 to December 2014, 1486 consultations were sent to Internal Medicine, Cardiology or Endocrinology, regarding patients admitted to the OST area who had suffered some type of medical decompensation during admission. Of these patients, 437 (29.4%) had a documented history of DM. The reason for consultation was poorly controlled DM in 124 patients (8.3%), with 111 patients (89.5%) presenting hyperglycemia and 13 (10.5%) presenting hypoglycaemia. However, since the consultations were made by the Orthopedic Surgeon who requested it, after the initial evaluation of all these patients, the diagnosis of poorly controlled DM was only considered in 108 patients (7.4% of the total decompensated patients), since the rest, despite presenting glycemia above 125 on fasting, were considered controlled taking into account their particular clinical situation. This implies an actual decompensation of 24.7% of patients with known DM.
Conclusions
DM is a cause of medical decompensation in 8.3% of patients admitted to OST. One in four known diabetics had abnormal blood glucose levels.
Together with previous studies in which we concluded that approximately one in six known hypertensive patients is decompensated during admission to surgical areas, we suggest that an early evaluation of blood glucose and blood pressure performed by Cardiology, Endocrinology or Internal Medicine could be beneficial in terms of morbidity.

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EP407

Episodes of poorly controlled diabetes in 173 patients admitted in Vascular Surgery

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Introduction
Episodes of poorly controlled diabetes (DM) are one of the most frequent medical complications during hospitalization in the elderly population.
Objetives
To analyze the prevalence of episodes of diabetic decompensation in patients admitted to the area of Vascular Surgery and Angiology (VS).
Material and methods
Descriptive analysis of patients admitted to the VS Service who presented abnormally high or decreased blood glucose levels according to the criteria of the Vascular Surgeon who performed the consultation.
Results
From February 2011 to December 2014, 173 consultations were sent to Internal Medicine, Endocrinology or Cardiology regarding patients admitted to the VS area who had suffered some type of medical decompensation during admission. Of these patients, 94 (49.1%) had a documented history of DM. The reason for the consultation was 'poorly controlled DM' in 8 patients (4.6%) of whom had hyperglycemia 4 (50%) and hypoglycemia, 4 (50%) as well as 'control of vascular risk factors' in 18 (10.4%). However, after analysis of all patients, only 22 (12.7%) were diagnosed as decompensated DM in the discharge report. This implies a real decompensation of 23.4% of patients with known DM.
Conclusions
DM is a single cause of medical decompensation in 4.6% of patients admitted to VS. However, associated with decompensation of other vascular risk factors, one out of four known diabetics had abnormal blood glucose levels.
Together with the previous studies in which we conclude that approximately one in six known hypertensive patients is decompensated during admission to surgical areas, we suggest that an early evaluation of blood glucose and blood pressure performed by Cardiology, Endocrinology or Internal Medicine could be beneficial in terms of morbidity and hospital stay, since previous studies associate the diabetic uncontrol in patients admitted to Vascular Surgery to an average stay 9 days superior compared to non-diabetics.

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EP408

Postprandial triglyceride responses and insulin resistance among night shift health care workers

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Background
A higher cardiometabolic risk has been reported in night shift workers. Post prandial hypertriglyceridemia (PPHTg) is recognized as an independent cardiovascular risk marker. Few studies have shown that acute disruption of circadian rhythm is followed by significantly altered insulin secretion and lipid tolerance.
Aim and objectives
In this study we compared the postprandial triglyceride (PPTG) responses to standard oral fat meal between health care night shift workers and non- night shift workers to ascertain if it contributes to cardiometabolic risk in them.
Methods
20 health care night shift workers ($\geq$4 night duties/month for last one year), aged 20–40 years with normal glucose tolerance (NGT) following a 75 g glucose OGTT and 20 age and sex matched non-night shift workers who had not done night duty in the last one year or ever were recruited. Anthropometric, OGTT, HbA1c (%), insulin, HOMA-IR, HOMA-β (%), fasting lipids parameters and inflammatory markers (IL-6 & Hs CRP) were measured. PPTG responses were obtained after a standard fat meal given at 8 am, and sampling done every two hours for next 8 hours, that is at 0, 2, 4, 6 and 8 h and compared between the two groups.
Results
Night shift and non-night shift workers were matched for age (29.70$\pm$3.92 years vs 29.70$\pm$2.23 years) and sex (M:F 12:8 vs 12:8). The duration of night shift exposure was relatively short (4.2$\pm$3.3 years) among cases. There was no significant difference between the two study groups with respect to anthropometric, glycaemic, fasting lipids parameters or inflammatory markers. However, 2 h postprandial glucose in health care night shift workers was comparatively higher than non-shift workers (103.8$\pm$18.53 mg/dl vs 91.5$\pm$19.96) though it just fell short of statistical significance (P=0.50). PPTG measures – PPTG area under the curve (TG AUC) and TG peak values were comparable in both the groups. PPTG response showed significant positive correlation with fasting insulin and HOMA-IR indicating insulin resistance, and HOMA-β (%) indicating insulin secretion in night shift health care workers but not in others. There was no significant correlation of PPTG parameters with any other clinical, biochemical and inflammatory measures.
Conclusions
Postprandial triglyceride burden is significantly associated with insulin resistance in night shift workers even with a relatively short duration of night shift,

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EP409

Improving safety in diabetes management and reducing insulin errors in hospital – practically achievable or a utopian fantasy?

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42 insulin related incidents were reported within our Trust in 2014. Subsequent Root Cause Analysis revealed numerous insulin errors, hyperglycemia mismanagement and highlighted significant deficits in diabetes knowledge amongst nursing staff. To address the above issues, new safety interventions were introduced and five key outcomes are:

1. A **new stand-alone insulin prescription chart** introduced May'15 has seen insulin incidents decrease from 60 (Apr'14 – May'15) to 37 (June'15 – Apr'16).
2. A **new, abbreviated DKA protocol** and **DKA App** launched Aug'15 has shown significant clinical benefits and crucially, helped earlier discharge by 3.2 days (audit of 40 patients (13 between May – July'15 and 27 between Aug'15 – Mar'16).
3. A mandatory new "**6 steps to insulin safety online module"** introduced for all junior doctors & nurses (Dec'15) - 91 staff have already completed the module. Our CCG has recently introduced this successful module for care home staff.
4. **Daily Hypoglycemia email alerts** and Precision (Abbott) web database introduced to specifically target & educate problem wards. A number of changes have been already made as a result.
5. **Ulysses SAFEGUARD IT** now reports all insulin incidents monthly which are discussed as part of Quality Improvement. A monthly junior doctor **insulin/ prescription error** alert (Aug'15) now mandates all error discussions with Educational Supervisors helping them reflect/learn from mistakes (11 insulin incidents in Jan/Feb'16 vs 19 in Nov/Dec'15).

Thus, over a relatively short period of 1 year, we have shown that our simple, yet helpful, safety innovations can be very effectively applied to reduce diabetes errors, improve staff knowledge & satisfaction. Our approach can be easily replicated by any NHS Trust to improve overall safety in insulin and diabetes management.

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EP410

Heterozygote c.313delC (p.H105TfsX11) mutation of Glucokinase gene in patient with Waardenburg syndrome type 1

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Background
Waardenburg syndrome is known as an inherited disorder associated with sensorineural deafness and pigmentary abnormalities affecting the skin, hair, and eye. There are rare case reports of Waardenburg syndrome with diabetes mellitus in the literature.
Case
A 9-years-old boy from consanguineous family was admitted to pediatric endocrine department because of fasting and postprandial hyperglycemia. In the medical history, it was learned that his aunt and uncle had brilliant blue iris, fasting and postprandial hyperglycemia. On physical examination; Height: 131.5 cm (10–25p), Height SDS: $-$0.76, Weight: 28.9 kg (25–50p), Weight SDS: $-$0.29, Body mass index: 16.72, Body mass index SDS:0.16. On physical examination, the patient with a brilliant blue iris had dystopia canthorum, skin hypopigmentation, synophrys, broad nasal root, hypoplasia alae nasi and mild sensorineural hearing loss. When our patient was evaluated for Waardenburg syndrome clinical criteria, Waardenburg syndrome was diagnosed with Waardenburg Consortium. Blood glucose was 148 mg/dl (75–100), insulin was 19.1 IU/ml (2–18) and serum C-peptide level was 3.72 ng/ml (1.1–4.4). HbA1c value was 6.2%, anti insulin antibody was 0.01 U/ml (0–0.5U), anti-GAD was $<$1 U/ml ($<$ 1 U/ml) and islet cell antibody was negative. When our patient was evaluated for maturity onset diabetes of the young, MODY type 2 was diagnosed with heterozygote c.313delC (p.H105TfsX11) mutation in glucokinase gene. Repaglinide was started for controlling blood glucose levels and blood glucose regulation was achieved.
Conclusion
We reported the case of a patient with Waardenburg syndrome accompanied by glucokinase gene mutation, To the best of our knowledge, we believed the first reported Waardenburg syndrome patient with these concomitant disorder.
Keywords: Waardenburg syndrome type 1; glucokinase gene; MODY; hyperglycemia.

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***GLIS3* rs7020673 and rs10758593 polymorphisms interact in the susceptibility for type 1 diabetes mellitus**

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Background and Aims
The transcription factor Gli-similar 3 (GLIS3) plays a key role in the development and maintenance of pancreatic beta-cells as well as in the regulation of *Insulin* gene expression in adults. Accordingly, genome-wide association studies identified *GLIS3* as a susceptibility locus for type 1 diabetes mellitus (T1DM) and glucose metabolism traits. Therefore, the aim of this study was to investigate the association of the rs7020673 (G/C) and rs10758593 (G/A) single nucleotide polymorphisms (SNPs) in the *GLIS3* gene with T1DM in a Brazilian population.

Methods
Frequencies of the rs7020673 and rs10758593 SNPs were analyzed in 503 T1DM patients (cases) and in 442 non-diabetic subjects (controls). Genotyping was performed using Real-Time PCR and TaqMan MGB probes (Thermo Scientific). Haplotypes constructed from the combination of these SNPs were inferred using a Bayesian statistical method.
Results
GLIS3 rs7020673C allele frequency was 47.3% in T1DM patients and 45.1% in the non-diabetic group ($P=0.365$), while the rs10758593A allele was present in 43.3% of cases and 41.1% of controls ($P=0.341$). Genotype distributions of these SNPs were in agreement with those predicted by Hardy-Weinberg Equilibrium in controls (all $P\geq0.05$), and did not differ significantly between groups ($P=0.468$ and $P=0.279$, respectively). In addition, frequencies of rs7020673 and rs10758593 SNPs did not differ between groups under dominant, recessive or additive inheritance models (all $P\geq0.05$). However, frequency of three or more minor alleles of the analyzed SNPs in haplotypes was higher in T1DM patients compared to non-diabetic subjects (6.2 vs 1.6%; $P=0.001$). Presence of ≥3 minor alleles remained independently associated with risk for T1DM after adjustment for T1DM high-risk *HLA DR/DQ* haplotypes, age and ethnicity (OR = 3.68 95% CI 1.22 – 11.12). Moreover, levels of glycated hemoglobin were higher in T1DM patients carrying the rs10758593A allele than patients with the G/G genotype (8.9 ± 2.1 vs 8.2 ± 2.0; $P=0.038$). In conclusion, our results indicate that the rs7020673 and rs10758593 SNPs interact in the predisposition for T1DM.

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Vitamin D level in naïve Type2 Diabetes Mellitus in Fayoum University Hospital

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Vitamin D deficiency has become a worldwide problem, although vitamin D deficiency had associated with increased insulin resistance, obesity and HbA1c in patients with T2D.
It is uncertain whether vitamin D deficiency causes diabetes or its due to confounding. The active metabolite 1α,25-dihydroxyvitamin D3 may affect the receptors of pancreatic β-cells and hence affect insulin secretion, also it may have impact on insulin sensitivity.
Several trials revealed that vitamin D improved glycaemic control in T2DM patients. However, the outcome of these trials often was not clinically relevant.
The aim of this study is to reveal to the relation between vitamin D and naïve type 2 DM. This is a case control study that was conducted on 90 Egyptian diabetic subject of both gender their ages was between 25 to 70 years, Exclusion criteria are, post-menopausal females, pregnant & lactating females, presence of mal-absorption disorders like Crohn's disease, celiac disease and cystic fibrosis, presence of any endocrinal disorder, presence of renal and hepatic disorders.
First group included 47 naïve type 2 diabetic patients (HbA1C above 7) including 51.1% male diabetic and 48.9% female diabetic patient and 46 healthy control including 47.8% male subject and 52.2%female subjects.
The 47-diabetic group their mean age was 40 ± 0.5 years and their mean BMI was 28 ± 3.6 while the 26 control subjects their mean ages is 42 ± 7.8 years and their mean BMI was 28 ± 3.8.
Vitamin D level was 22.47 ± 10.5 and 23.57 ± 9.7 ng/ml in diabetic group and in control group respectively, there were no statistically difference when comparing vitamin D level between the two groups. In this study, we found a negative correlation between vitamin D level and hyperglycemia.
Also, we found a positive correlation between vitamin D level and age, while vitamin D level was negative correlated with Body mass index.

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Association of wolfram syndrome with chronic renal failure in a boy

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Wolfram syndrome, rare neurodegenerative disorder, is known to be DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy and deafness). There are rare case reports of Wolfram syndrome with chronic renal failure in the literature.
A 19-year-old male patient was admitted to our pediatric emergency department because of headache, chest pain and diurnal and nocturnal enuresis. He had been diagnosed with diabetes mellitus at 13 years of age (Plasma glucose was 386 mg/dl, urinary ketone negative, normal blood gases, serum C-peptide level 0.1 pmol/ml (0.15–1.10) and HbA1c value of as 9.6%) and had received four doses of regular insulin (0.9 U/kg per day) treatment. Anti-insulin antibody was 3 U (0–8 U), anti-GAD 0.4 U/ml (<1 U/ml), and islet cell antibody negative at the diagnosis. In addition, fundus oculi examination had demonstrated bilateral optic atrophy and no sign of diabetic retinopathy at 13 years of age. He was the sixth child of apparently healthy consanguineous parents, born at full-term by normal vaginal delivery. Family history disclosed that his uncle, aunt and sister had diabetes mellitus. Physical examination: weight: 31 kg (<3 percentile), height: 136.5 cm (<3 percentile), blood pressure: 160/80 mmHg and pulse rate 96/dk. He had bilateral blindness. High renal function tests (BUN:78 mg/dl, creatinine: 4.7 mg/dl), serum electrolytes (Na: 133.7 mmol/l, K: 4.2 mmol/l, Cl: 103.7 mmol/l, serum calcium: 8.4 mg/dl serum phosphorus: 8 mg/dl) and high parathyroid hormone (PTH: 321.63 pg/ml range, 15 to 65) suggested chronic renal failure. Urinary ultrasound imaging disclosed small kidney size. Glomerular filtration rate was calculated as 13 ml/min/1.73 m^2. Audiometric examination for Wolfram syndrome revealed bilateral sensorineural hearing loss. A known homozygous mutation (Y508fsX541, c.1523_1524delAT) in exon 8 of WFS1 was found in the proband.
We reported a case with Wolfram syndrome accompanied by chronic renal failure. Early diagnosis and appropriate management for Wolfram syndrome would prevent development of complications.

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Hypoglycaemia in hospital is associated with longer hospital stay and decline of renal function

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Background and aims
Hypoglycemia is a common complication of diabetes treatment and it's associated with poor outcomes. A link between severe hypoglycemia and renal dysfunction was suggested. No studies evaluated the impact of hypoglycemia of inpatients in microvascular or macrovascular complications. The aim of our work was to study the evolution of renal function between admission and final visit, and the impact of nephropathy in the presence of hypoglycemia in inpatients.
Materials and methods
Retrospective, observational study of consecutive patients with type 1 ($n=13$) and 2 Diabetes ($n=85$), admitted to the medical specialties ward between 2011 and 2015 ($n=106$ admissions), who had their capillary glycemia written in the medical record ($n=14410$). We evaluated the renal function (glomerular filtration rate determined by CKD-EPI formula; glicemic variability (STD) and albuminuria) at admission and at the final visit as outpatients. We used descriptive statistics (Median ± std), t-test and non-parametric tests for continuous variables and Chi-squared distribution for categorical variables.
Results
We report 56 admissions with hypoglycemias, which were compared to 50 admissions without hypoglicemias in the same period. There were no differences in the distribution of gender (64% were females), age (60.9 ± 1.6 years), diabetes type (12.2% were type 1) or diabetes duration (5.0 ± 1.0 years). In patiens with hypoglicemia we found significant differences in glicemic variability (84 vs 56 mg/dl, $P<0.01$), in GFRe at admission (94 vs 83 ml/min/1.73 m^2, $P=0.03$), GFRe decline (25 vs 7 ml/min/1.73 m^2, $P=0.03$), and longer hospital stay (13 vs 6 days, $P=0.006$).
Conclusion
Despite having the known limitations of a retrospective study, and some heterogenecity of the population mainly in diabetes duration, we found significant associations between occurrence of hypoglicemia during hospitalization and longer hospital stay and decline of renal function. Other study design would be required to investigate if it is only a marker of fragility or if hypoglycemia may have a role in progression of microvascular complications, as suggested by some investigators.

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EP415

Could we prevent insulin induced lipohypertrophy in diabetic patients?

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Introduction
Lipohypertrophy (LH) is a chronic complication of diabetes mellitus that caused by frequent subcutaneous injections of insulin. Nowadays, on the basis of results of ultrasonography of subcutaneous fat prevalence of LH in diabetic patients is still high.
Design
The aim has been to develop prevention of insulin induced LH in diabetic patients. This study was done on 140 diabetic patients who had been under the treatment with insulin a mean 8 years. On first stage all patients were divided into two groups. First – 117 patients with LH, second – 23 diabetics without LH. Further, all known LH risk factors were statistically processed using Spearman's, Gamma rank correlation coefficients. Results were statistically significant when $P<0.05$. On second stage 65 patients from first group were divided into two subgroups. First – 50 patients with LH and corrected risk factors, second (control) – 15 diabetics with LH and uncorrected risk factors. Ultrasonography of subcutaneous fat were used in assessing new LH in these subgroups after 3 and 6 month.
Results
As a result, 10 factors from 23 were remained after statistic analysis on first stage. Statistically insignificant parameters were eliminated ($P>0.05$). On next stage, in first subgroup only two patients (4%) had new LH, while in second – 9 diabetics (60%) had new pathologic areas of subcutaneous fat after 3 month. And in first subgroup only 6 patients (12%) had new pathologic areas of subcutaneous fat, while in second – 12 diabetics (80%) had new LH after 6 month.
Conclusions
Nowadays, primary prevention of LH is necessary for diabetic patients under the treatment with insulin. There were stated that only 10 risk factors strongly influence on LH progress. Correction of these risk factors doesn't lead to development of new subcutaneous fat pathological changes and could be used to prevent LH in diabetic patients in clinical daily practice.

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Relation between serum leptin concentration and insulin resistance syndrome in patients with type 2 diabetes mellitus

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Type 2 diabetes mellitus is known for its morbidity and mortality all over the globe. It has been demonstrated in recent studies that abnormal levels of adipocytokines may contribute to insulin resistance and type 2 diabetes.
Objectives
The aim of the present study was to assess the relation between serum leptin levels and insulin resistance syndrome in type 2 diabetic patients.
Methods
Eighty persons were enrolled in this study and were divided into two groups. Twenty healthy persons as a control group and 60 patients with type 2 diabetes mellitus as a disease group. The disease group were further divided into those who have evidence of metabolic syndrome (30 patients), and those who do not (30 patients). Parameters like age, sex, anthropometric measurements and biochemical indicators such as fasting and post prandial blood sugar, HbA1c, lipid profile, leptin and fasting insulin were determined.
Results
Higher Leptin and insulin levels were observed in patients with metabolic syndrome ($P<0.001$).
Conclusion
High serum leptin is a good indicator and could provide a minimally-invasive marker for early detection of the insulin resistance syndrome.
Keywords
leptin concentration; insulin resistance syndrome; type 2 diabetes mellitus.
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Epidemiological and clinical study of diabetes in immigrants from Bangladesh in Athens versus Greek patients

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Objectives
Diabetes risk for Asians is related to a greater tendency to adiposity, which increases insulin resistance. Various studies have highlighted the fact that people from South Asia have a younger age of onset of diabetes, greater upper-body adiposity and lower body mass index (BMI) and higher risk compared to those from other nations. Greece has experienced a large wave of immigration from Asian countries, especially Bangladesh. The purpose of this study was to explore the ethnic differences and special needs that must be taken into account when treating patients with different cultural background.
Methods
A total of 166 randomly selected immigrants with diabetes from Bangladesh were compared with 123 randomly selected Greek Caucasian patients with diabetes.
Results
Patients from Bangladesh had a mean duration of living in Greece of 10.34 ± 6.2 years. The Bangladeshi group was younger compared with the Greek group (44.05 ± 8.1 vs 48.75 ± 9.2 years old, $P=0.009$) and had an earlier age at onset of diabetes (39.3 ± 7.3 vs 41.7 ± 10.1 years old, $P=0.025$). The reported duration of diabetes was lower in the Bangladeshi group (4.86 ± 4.5 vs 7.34 ± 6.21 years, $P<0.05$). The Bangladeshi group had a significantly lower BMI (24.19 ± 3.3 vs 29.04 ± 8.7 kg/m^2, $P=0.01$), and waist circumference (92.2 ± 8.9 vs 103.1 ± 15.7 cm, $P<0.001$). Bangladeshi group had a slightly worse, but not statistical significant, glycemic control as compared with the Greek group (A1C$=7.74\pm1.6\%$ vs $7.55\pm1.7\%$, $P=0.3$). A significant number of Bangladeshis stated that they rarely checked their self-monitoring blood glucose as compared with the Greek group (1.26 ± 2.6 vs 8.87 ± 9.9 times per week, $P<0.01$). There were also no significant differences between the two groups for most laboratory findings, although Bangladeshis had higher mean levels of glucose (190.3 ± 72 vs 160.8 ± 81 mg/dl, $P=0.4$), cholesterol (199.8 ± 44.4 vs 178.86 ± 44.9 mg/dl, $P=0.9$), LDL (129.3 ± 33.2 vs 110.62 ± 33.9 mg/dl, $P=0.8$) and triglycerides (231.4 ± 213 vs 181.95 ± 166 mg/dl, $P=0.07$). In the Bangladeshi group, the mean HDL level was significantly lower as compared with the Greek group (33.99 ± 9.4 vs 44.05 ± 10.43 mg/dl, $P=0.037$).
Conclusions
Bangladeshi immigrants are less likely to engage self-care behaviors and have worse glycemic control and less access to medication, laboratory test and healthcare units.

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Vitamin D levels in newly diagnosed type I diabetes mellitus and relationship with organ specific autoimmune disorders

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Based on the effects of Vitamin D on immune system it has been suggested that vitamin D may play a role in the pathogenesis of type I diabetes mellitus (T1D) and other organ specific autoimmune disorders. In our study, we aimed to show the effect of Vitamin D deficiency in the development of newly diagnosed T1D and other autoimmune disease that may associated with T1D such as autoimmune thyroid disease (ATD), celiac disease, Addison's disease, vitiligo and atrophic gastritis. In addition to 50 newly diagnosed T1D patients and 60 healthy controls, we evaluated the data of the formerly diagnosed 50 T1D patients. The frequency of vitamin D deficiency in newly diagnosed T1D patients was found 88%. 30% of these patients were anti parietal cell antibody (APA) positive which is marker for pernicious anemia, 24% of had ATD, 10% of was positive for anti-tissue transglutaminase IgA which is marker for celiac disease and 2% of had vitiligo. Levels of 25(OH)D were statistically significant lower in newly diagnosed T1D patients with positive APA than patients with negative APA. Frequency of

vitamin D deficiency was 66.7% in healthy controls and 84% in formerly diagnosed T1D patients. When we considered all T1D patients, we found the frequency of ATD was 25%, frequency of positive APA was 28%, frequency of positive anti-tissue transglutaminase IgA was 10% and frequency of vitiligo was 2%. We found that ATD and predisposition of celiac disease were much frequent in T1D patients than healthy controls. Vitamin D levels were found lower; in patients with T1D than healthy controls; when we evaluate all subjects we found that patients with ATD had lower vitamin D levels than patients without ATD and also patients with ATD and positive APA had lower vitamin D levels than patients without ATD and negative APA.

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Is secreted frizzled-releated protein 4 (SFRP-4) a possible biomarker for β cell dysfunction?

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Introduction
SFRP-4 is a recently described inflammatory cytokine influencing insulin secretion from human β cells as an extracellular modulator of Wingless (Wnt) pathway. The aim of this study is to compare serum SFRP-4 levels in patients with normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and type 2 diabetes (T2DM), and to investigate its relation with other parameters.
Methods
The study included 152 patients who applied to the endocrinology outpatient clinic of our hospital. Eighty-two patients who had history of T2DM constituted the T2DM group. Patients who underwent OGTT within the last three months were categorized in either IGT ($n=34$) or NGT ($n=36$) groups according to their test results. All patients provided blood samples between 08 am and 09 am following overnight fasting. Fasting insulin, fasting glucose, HbA1c and SFRP-4 levels were measured.
Results
T2DM group had significantly higher serum SFRP-4 levels compared to BGT and NGT groups (0.282 ng/ml vs 0.183 ng/ml, $P=0.001$; and 0.282 ng/ml vs 0.170 ng/ml, $P=0.004$, respectively). In comparison of BGT and NGT groups, although serum SFRP-4 levels were higher in BGT group, the difference was not statistically significant (0.183 ng/ml vs 0.170 ng/ml, $P=0.630$). SFRP-4 level showed significant positive correlation with fasting glucose ($r=0.274$, $P=0.001$) and HbA1c ($r=0.291$, $P=0.002$) levels.
Conclusion
Progressive β cell dysfunction is observed during the normal course of T2DM, and inflammatory cytokines are held responsible. Recent studies have demonstrated the association between increased SFRP-4 expression on β cells and reduced insulin release. Additionally, studies have found an association between serum SFRP-4 levels and high fasting glucose level and impaired insulin sensitivity in non-diabetic individuals. We found increased serum levels of SFRP-4 in patients with T2DM in our study, and SFRP-4 level was positively correlated with fasting glucose and HbA1c levels in the whole study group. We think our results support the idea that increased plasma SFRP-4 levels may be a good indicator of β cell dysfunction and insulin resistance.

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The clinical efficacy of the nucleo CMP forte usage in the combined treatment of diabetic peripheral neuropathy

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Introduction
The protocols of medical care of diabetic peripheral neuropathy (DPNP) are developed but positive effect cannot be achieved in all patients. New medications in DPNP have to be studied.
The aim
To evaluate the efficacy of Nucleo CMP Forte (Cytidine – 5'- disodium monophosphate and Uridine – 5'- trisodium triphosphate) in the combined treatment of patients with DPNP.
Methods
It was examined 59 (41–79 years old) patients with type 2 DM and DPNP. They were compared into two groups: A – 30 patients received standard treatment, B – 29 diabetics additionally were taken Nucleo CMP Forte (1 capsule three times a day). Patients filled questionnaire of life quality EQ-5D-3L (Ukraine 2004, EuroQol) on the first and tenth day of treatment. We used non-parametric test χ^2 to evaluate efficacy of therapy. Significance was set at $P<0.05$.
Results
All patients revealed positive changes after 10 days of treatment. Thus, the problems with walking decreased in 16.6% of the group A patients ($\chi^2=1.164$. $P>0.05$) and 33.3% ($\chi^2=6.171$, $P<0.05$) of the group B, the relief in performing of daily activity was marked by 25% ($\chi^2=2.286$, $P>0.05$) and 50% ($\chi^2=2.859$, $P>0.05$) of ones respectively, pain/discomfort bothered less than 25% ($\chi^2=4.267$, $P<0.05$) patients of the group A and 33.3% ($\chi^2=6.171$, $P<0.05$) of the group B, anxiety/depression decreased in 58.3% ($\chi^2=6.063$, $P<0.05$) and 66.7% ($\chi^2=6.954$, $P<0.05$), respectively.
Conclusion
Patients of both groups noted the positive effect of treatment. Usage of Nucleo CMP Forte in the combined treatment of patients has more expressed positive influence on problems with walking.

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Effect of glucose ingestion on serum fractalkine levels in healthy subjects and diabetic patients

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Introduction
Current studies suggest that fractalkine (FKN) could be a pathogenic factor associated with adipocyte dysfunction and type 2 diabetes (T2DM) and have shown that FKN serum levels are increased in T2DM patients. The aim of this study was determined as evaluating the change of FKN levels that will occur with oral glucose tolerance test (OGTT).
Methods
The study included 67 patients to whom OGTT was applied. The patients with the history of diabetes mellitus, malignity or inflammatory disease were excluded. All subjects were given 75 g of glucose orally after an overnight fasting and blood samples were taken for glucose and FKN levels at 0 and 120 min. According to OGTT results, the patients were divided into the groups of NGT ($n=33$) and newly diagnosed T2DM ($n=34$).
Results
The basal level of FKN (OGTT at 0 min) was found to be significantly higher in T2DM group than NGT group (0.374 ng/ml vs 0.259 ng/ml, $P=0.012$). The FKN level at 120 min of OGTT was significantly higher also in T2DM group compared to NGT group (0.367 ng/ml vs 0.229 ng/ml, $P=0.001$). No significant changes in FKN levels during OGTT were observed in both T2DM and NGT groups (0 and 120 min change) (0.374 ng/ml vs 0.367 ng/ml, $P=0.433$ and 0.259 ng/ml vs 0.229 ng/ml $P=0.06$, respectively). A significant positive correlation was noted between the levels of FKN and glucose at 120 min of OGTT ($r=0.331$, $P=0.006$).
Conclusion
Acute hyperglycemia or food intake is known to lead to an increase in circulating levels of many inflammatory cytokines such as IL-1, IL-6, TNF-α. Fractalkine (FKN) is a recently defined inflammatory cytokine. The results of our study, there was no change of serum FKN levels during OGTT in T2DM and NGT patients but there was a significant correlation between the levels of FKN and glucose at 120 min of OGTT. We believe that long-term studies with broad participation and serial measurements are needed to determine the role of FKN in the pathogenesis of T2DM.

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Epidemiological features of type 1 diabetes in children and adolescents in the Republic of Armenia

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Background
Diabetes is the most prevalent chronic metabolic disorder in children and adolescents, and incidence rates for both type-1 and type-2 diabetes are increasing worldwide. In recent years, the number of patients with type 1 diabetes is increasing mainly due to children under 5-years-old.
Objective
To study the epidemiological indicators of T1DM among children of the Republic of Armenia (RA) from 2007 to 2016. Methods: Retrospective analysis of the Republican Children's Endocrinology Center database using conventional statistical methods.
Results
During the period 2007–2010 in Armenia there was a relatively stable incidence of diabetes in children 0–18 years: 7.1 in 2007, 6.45 in 2008, 6.3 in 2009 and 6.8 in 2010 (per 100 000 child population), while during 2010–2016 period increased incidence is seen (6.7 in 2011, 9.4 in 2012, 8.7 in 2013, 9.99 in 2014, 10.69 in 2015). The study of age-specific morbidity in children with T1DM in RA showed that the maximum incidence in different years was at the age of 5–9 or 10–14 years. According to the Republican Children's Endocrinology Center data rejuvenation of type 1 diabetes can be traced. Mean age of patients in 2007 was 11 years. In 2014 mean age was 8.9 and 9.8 in 2016. The incidence rate in children of younger age group (0–4 years) increased from 2.24 in 2007 to 5.05 in 2010, 7.14 in 2014 and 5.8 in 2016 (per 100 000 child population).
Conclusions
In RA an increased incidence of type 1 diabetes among children and adolescents is seen. The highest incidence occurs in the age groups 5–9 and 10–14 years. Further studies are needed to look into the cause of these changes.

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High incidence of glucose metabolism disorders in patients undergoing coronary angiography without history of diabetes

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Introduction
The aim of this study was to investigate the incidence of glycemic disorders in patients undergoing coronary angiography with no prediagnosed type 2 diabetes (T2D), as well as the association of the glycemic status with the extent of the coronary artery disease (CAD).
Patients and methods
We studied 170 consecutive patients (134M/36W), 63.9 $\pm$ 13.1 (23–95) years old, with not known T2D, who underwent coronary angiography. HbA1c was measured and patients were classified into 3 groups accordingly: i) normal HbA1c $<$ 5.7%, ii) prediabetes HbA1c 5.7–6.4%, and iii) T2D HbA1c $\geq$ 6.5%. The presence of other risk factors for CAD was recorded, while the extent of CAD was examined. Vessel disease (VD) was defined when stenosis was $>$ 70%.
Results
From the total of 170 patients, 19.4% (33/170) presented normal HbA1c, 17.6% (30/170) prediabetes and 63% (107/170) were diagnosed with T2D. Patients with normal HbA1c were 60.5 $\pm$ 16.7 years old, with BMI 29.1 $\pm$ 5.2, 18.2% (6/33) were women, 48.5% (16/33) had hypertension, 36.4% (12/33) dyslipidemia, while 21.2% (7/33) had history of CAD. Of these, 33.3% (11/33) showed no VD, 33.3% (11/33) one VD 21.2% (7/33) two VD, 6% (2/33) three VD and 6% (2/33) left main along with another one VD. Patients with prediabetes were 65.9 $\pm$ 11 years old, with BMI 29.6 $\pm$ 5.1, 6.7% (2/30) were women, 63.3% (19/30) had hypertension, 43.3% (13/30) dyslipidemia and 20% (6/30) had history of CAD. Of these, 30% (9/33) showed no VD, 30% (9/30) one VD, 6% (5/30) two VD and 23.3% (7/33) three VD. Patients with T2D were 64.4 $\pm$ 12 years old, with BMI 23.8 $\pm$ 2.6, 26.2% (28/107) were women, 69.2% (74/107) had hypertension, 52.3% (56/107) dyslipidemia, while 24.3% (26/107) had history of CAD. Of them, 42.1% (54/107) showed no VD, 27.1% (29/107) one VD, 17.8% (19/107) two VD, 11.2% (12/107) three VD and 1.9% (2/107) left main along with another one VD.
Conclusion
Prediabetes and T2D were detected in the majority of patients undergoing coronary angiography without previously known glycemic disorders. Therefore, HbA1c should be determined in all patients hospitalized for possible CAD, regardless of the history for diabetes.

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EP424

The relation between type II diabetes and chronic depression in primary care practice in Jordan

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Diabetes is a major health problem that affects 8.5% of adults worldwide, and 13.2% of adults in Jordan. Studies suggest a bidirectional relationship between diabetes and chronic depression. Diabetic patients are twice as likely to suffer from depression that is symptomatically worse when compared to nondiabetic individuals. Depressed diabetics suffer from poor glycemic control and increased risk of diabetes complications. Because little is known about the bidirectional relationship between diabetes and chronic depression in Jordan, we screened for depressive disorders among diabetic patients using the Patient Health Questionnaire-9 (PHQ-9) and screened for diabetes among depressed individuals by measuring their HbA1c, in a cross-sectional study design. A total of 146 diabetic patients (74 males, 72 females) participated in the study, with a mean age of 56 $\pm$ 8.5 years. Almost 60% of participants were uncontrolled for diabetes (HbA1c $\geq$ 7%) with a mean HbA1c of 8.9% $\pm$ 1.7 and a mean PHQ-9 score of 6.2 $\pm$ 5.5. The remaining 40.4% were controlled for diabetes (HbA1c $\leq$ 7%) with a mean HbA1c of 6.1 $\pm$ 0.6 and a mean PHQ-9 score of 6.7 $\pm$ 4.5. The prevalence of chronic depression (PHQ-9 score $\geq$ 10) among diabetic patients was 27.4%. No correlation was found between PHQ-9 scores and HbA1c levels (Spearmen's $r = -0.03$, $P = 0.75$). Additionally, 20 depressed patients were recruited from the psychiatry clinic with a mean age of 41.7 $\pm$ 8.3 years, and were then screened for diabetes by measuring HbA1C levels. None of these was found to be diabetic, with a mean HbA1C of 5.4% $\pm$ 0.4. In conclusion, our results thus far deny a correlation between depression and diabetes. However, our future plan of examining the effect of treating depression on glycemic control and diabetes complications, and the effect of improving glycemic control on the severity of depression, might improve our understanding of this relationship.

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EP425

Anti-islet cell antibodies in a sample of Egyptian females with gestational diabetes and its relation to development of type 1 diabetes mellitus

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Background
Gestational diabetes mellitus is any degree of glucose intolerance with first diagnosis during pregnancy; it affects 3–10% of pregnancies. The presence of diabetes-related autoantibodies has shown to be able to predict the development of type 1 diabetes before hyperglycemia arises.
Aim of work
To recognize the prevalence of islet cell antibodies among a sample of Egyptian females with gestational diabetes and its possible relation of development of Type 1 diabetes within 1 year.
Design and methodology
Our cross sectional study was conducted on 150 Egyptian pregnant females with gestational diabetes aged 19–39 years diagnosed by 75-g 2-h oral glucose tolerance test. All females were subjected to full history, thorough clinical examination and laboratory measurement of anti-islet cell antibodies, those

females with positive antibodies were followed up 6 months and 1 year after delivery for their fasting insulin, fasting blood glucose and 2 h post prandial levels.
Results
The prevalence of pregnant females with gestational diabetes having positive anti islet cell antibodies was (44%), the prevalence of females diagnosed to have diabetes mellitus was (37.88%) 6 months and (51.52%) 1 year postpartum.
Conclusion
Gestational diabetes can be of type 1 diabetes due to islet cell antibodies and not only type 2 diabetes due to increased insulin resistance
Keywords
Pregnancy; Gestational diabetes; anti-islet cell antibodies; Type 1 diabetes; Type 2 diabetes; Insulin resistance
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EP426

A retrospective analysis of the impact of new diagnostic criteria for gestational diabetes mellitus on the endocrinology service at a tertiary hospital

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Background
The prevalence of gestational diabetes mellitus (GDM) may increase with the implementation of revised diagnostic criteria (as recommended by the International Association of the Diabetes and Pregnancy Study Groups) aimed at identifying pregnancies at increased risk of adverse perinatal outcomes. There are clear implications for health-care services in terms of resources and the associated cost-benefit relationship. Our study analysed the impact on clinic visits, the initiation of insulin treatment and fetal and maternal outcomes.
Methods
A retrospective cohort study was conducted. The medical records of patients with GDM referred to Diabetes in Pregnancy Clinic were reviewed, comparing two 12-months periods: March 2012 to February 2013 (period 1) and March 2015 to February 2016 (period 2), before and after implementation of the new criteria. Maternal and fetal outcomes were analysed for six months of each period.
Results
165 GDM patients attended the clinic in period 1 vs 323 patients in period 2. Insulin treatment increased significantly in period 2, from 34.2 to 53.1% ($P=0.002$). The mean number of Endocrinologist consultations (government billed) increased from 3.6 to 4.2 ($P=0.006$) and with a Diabetic Educator from 1.6 to 1.8 ($P=0.006$). The rate of caesarean sections (CS) in patients with GDM increased from 31.1% in period 1–47.0% in period 2 ($P=0.038$). The number of neonates grouped as "Small for Gestational Age" (SGA) increased in insulin-treated patients in period 2 vs period 1 (17 vs 0, $P<0.001$) but the number of "Large for Gestational Age" neonates was similar (6 vs 5, $P=1$).
Conclusion
The new GDM diagnostic criteria have impacted on existing health-care resources with a corresponding increase in costs with minimal evidence of clinical benefits. Hospital systems will need to plan for the increased demands on pregnancy-related diabetes services.
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EP427

Insulin autoimmune syndrome-a case report

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Introduction
Hypoglycemia is a medical emergency that can have many different causes in etiology. Autoimmune hypoglycemia in patients with very high insulin levels should also be considered in the differential diagnosis.
Case
A 50-year-old man was admitted to our clinic for investigation and treatment of hypoglycemic episodes. He did not have any evidence for the use of oral antidiabetic medications, insulin, herbal substances. However, in our history, we learned that pregabalin and alfalipoic acid were given to the patient considering neuropathic pain and proton pump inhibitors for dyspeptic complains. Physical exam revealed a healthy-appearing middle-aged male with BMI of 21.4. Initial tests showed low venous blood glucose (44 mg/dl), high insulin levels >1000 μIU/ml, C-peptide 15.6 ng/ml. To rule out pancreatic or extrapancreatic insulinoma; abdominal ultrasound, abdominal computer tomography scan, abdominal MRI and Ga-68 DOTATATE PET/CT was performed. The results did not show an evidence of insulinoma. Intra-arterial calcium stimulation test was also performed to rule out insulinoma but the results were inconclusive. Anti-insulin antibody test was performed for the differential diagnosis and it was positive. The symptoms associated with low glucose levels and high serum insulin levels along with positive anti-insulin antibody lead us to the diagnosis of insulin autoimmune syndrome. According to the current literature suggesting the relationship between insulin autoimmune syndrome and alpha lipoic acid and proton pump inhibitors we discontinued that drugs and started alpha glucosidase treatment and nutritional management. During the follow up the patient did not report a hypoglisemic episode.
Conclusion
Insulin autoimmune hypoglycemia is a rare cause of endogenous hyperinsulinemic hypoglycemia. It is a condition that should be kept in mind in patients who have very high levels of insulin and who can not detect a specific focus through imaging modalities.
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EP428

Incidence estimate of type 1 Diabetes in Youth in Dhaka

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Introduction
Analysis of epidemiologic patterns in diabetes helps with understanding of etiology, natural history and current and future needs. Bangladesh is a low-middle-income, densely populated country where there is limited information regarding incidence of childhood diabetes.
Aim
To assess the type of diabetes in children and young adults in Dhaka, Bangladesh, from July 2011 until June 2016, and estimate minimum incidence of type 1 diabetes (T1D).
Methods
Retrospective study using clinical records from Diabetic Association of Bangladesh (BADAS) clinics in Dhaka and affiliated satellite centers in other districts. Subjects under 25 years (y) diagnosed in the study period were identified. Diabetes type was classified according to clinical evaluation. Demographic information was obtained from the 2011 population census and extrapolated using the estimated growth rate. Incidence was calculated for the area surrounding the main clinics (Dhaka District) to minimize any ascertainment bias.
Results
Were identified 2347 subjects. Type of diabetes was more fully characterized for those <18 years (1634 cases), and showed 1437 (87.9%) T1D, 151 (9.2%) type 2, 23 fibrocalculous pancreatic diabetes (1.4%), 5 (0.3%) neonatal, 18 (1.1%) other types. For T1D incidence estimation a total of 526 subjects were ascertained. The mean Dhaka district incidence rate for subjects <25 y was 1.24/100 000 per y (males 0.92, females 1.71) and 0.96/100 000 for <15y (males 0.63, females 1.55) . By age group, incidence/100 000 was 0.27 (0–4y), 0.60 (5–9y), 2.46 (10–14y), 1.86 (15–19y), 1.44 (20–24y). No secondary ascertainment could be done, but ascertainment in Dhaka Division was estimated to be at least 95%.
Discussion
The support to BADAS by the Changing Diabetes in Children and IDF Life for a Child Programs have centralized care and permitted tracking of diabetes cases in young people in Bangladesh. T1D is commonest, but other forms occur which could benefit from different management: further typology studies are warranted. T1D had a female preponderance. Peak T1D onset is at 10–14 y, as in developed nations.
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EP429

Is thiol/disulfide homeostasis related to parity and gravidity in gestational diabetes?

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Purpose
The purpose of this study was to evaluate the relation gestational diabetes mellitus (GDM) and the thiol/disulfide balance, used as a marker of oxidative stress, by measuring that exchange using a novel technique.
Material/Methods
Thirty one subjects diagnosed with GDM and 30 healthy pregnant women were included in the study. Thiol/disulfide homeostasis concentrations were measured by a newly developed method in this study. After native thiol, total thiol and disulfide levels were determined; measures such as disulfide/ native thiol, disulfide/total thiol, and native thiol/total thiol were calculated.
Results
Fasting blood glucose (FBG) levels ($P<0.001$), 50-g glucose load values (OGTT 50) ($P<0.001$), parity (0.002) and gravidity ($P=0.005$) were significantly higher and native thiol ($P<0.001$) and total thiol levels ($P<0.001$) were significantly lower in patients with GDM compared to control subjects. We found negative correlations between native and total thiols and FBG and OGTT 50. Parity and gravidity had a significantly negative correlation between the disulfide, the disulfide/native thiol ratio, the disulfide/total thiol ratio, had a positive correlation between the native thiol/total thiol ratio. Low native thiol and total thiol levels in patients with GDM were found to be independent of age, gestational weeks and bmi in multivariate regression analyse.
Conclusion
It can be concluded that oxidative stress is increased in patients with GDM, can play a pathophysiological role in the development of GDM and this increase is not associated age, gestational weeks and bmi. However, studies with larger sample sizes are needed in this area.

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EP430

Endocrine factors associated with postprandial hypoglycaemia in patients with cystic fibrosis: a pilot study

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Postprandial hypoglycaemia in patients with cystic fibrosis (PWCF) is frequently reported but poorly understood. The aim of this pilot study was to investigate the aetiology of postprandial hypoglycaemia in PWCF. Serum cortisol, insulin and C-Peptide were measured at the 2 hour timepoint of the annual glucose tolerance test in 32 PWCF not known to have CF-related diabetes. Hypoglycaemia was defined as glucose $<$ 3.3 mmol/l. Patients were classified as Normal glucose tolerance (NGT; $n=17$), Post prandial hypoglycaemia (PPH; 6) and Abnormal glucose tolerance (AGT; 9–3 CF related diabetes, 4 impaired fasting glucose and 2 impaired glucose tolerance). There was a difference in insulin level at 2 hours between groups ($P=0.007$, Wilcoxon); subanalysis showed a difference between AGT (mean 48.9 mu/l) and PPH groups (16.6 mu/l)(P 0.003) and between AGT and NGT groups (28.4 mu/l) (P 0.015). Of the PPH cases none had symptomatic hypoglycaemia. Three PPH cases with cortisol $<$ 500 nmol/l underwent short synacthen test (SST); 2 had a cortisol post-SST $>$ 550 nmol/l. One patient showed suboptimal response with a cortisol level at 416 nmol/l and is undergoing further investigation. There were no differences between groups in body mass index (median 22.1 kg/m^2) or lung function. PPH occurred in 19% of the cohort and was associated with detectable insulin at the 2 hour OGTT timepoint, suggesting the possibility of dysregulated insulin release. AGT patients had higher insulin levels than NGT cases, suggesting relative rather than absolute insulin deficiency in this cohort of PWCF.

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EP431

Vascular dementia and type 2 diabetes: incidence and outcomes in elderly patients in a ten year study

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Background
To describe trends in the incidence and outcomes for vascular dementia in elderly patients with and without type 2 diabetes (T2DM) in Spain between 2004 and 2013.
Methods
We used National Hospital Discharge Data to select all patients aged 70 years or over discharged from hospital with a vascular dementia primary diagnosis. Discharges were grouped by diabetes status (T2DM or non-diabetic). Incidence was calculated overall and stratified by diabetes status and age groups. We analyzed diagnostic and therapeutic procedures, patient comorbidities, infectious complications, length of hospital stay and in-hospital mortality (IHM).
Results
We identified a total of 170.607 admissions for vascular dementia (34.3% with T2DM). The adjusted incidence was higher among people with T2DM over the study period. We found a higher incidence in men than women in all years studied. T2DM was positively associated with vascular dementia hospitalization (IRR 2.14, 95% CI). Mean age at admission was higher than 80 years for all groups and more than 70% has a Charlson Comorbidity Index (CCI) $\geq$2. Pneumonia was significantly associated with a higher mortality (OR: 2.59; 95% CI 2.52–2.67). We found that percutaneous endoscopic gastrostomy (PEG) was associated to lower IHM (OR: 0.37, 95% CI 0.31–0.45) while parenteral nutrition had the opposite effect (OR: 1.29, 95% CI 1.18–1.41). Diabetes was not associated with a higher IHM (OR: 0.99, 95% CI 0.93–1.06). For the entire sample, time trend analyses showed a significant decrease in mortality in patients admitted for vascular dementia (OR: 0.98, 95% CI 0.97–0.99).
Conclusions
Incidence rates were higher in T2DM patients. Men have significant higher incidence rates than women. Pneumonia and parenteral nutrition were associated with mortality while PEG was associated to survival. The presence of diabetes is not associated with a higher IHM during admission with vascular dementia.

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EP432

Study of the glycemic control in the hospitalized patient

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Objective
To evaluate the degree of compliance of the glycemic objectives in non-critic-hospitalized patient and determinate the factors associated to the lack of compliance of the aforesaid objectives.
Material and method
Retrospective observational study in hospitalized patients during 2014. Adult patient age 18 or older, who had at least two points of care de glucose measurements (capillary blood glucose) during their hospitalization, were included. By the revising of the computerise-clinic-history, sociodemographic, clinic and administrative datum were obtained. The results of the glycaemia were obtained from electronic devices.
Results
2610 patients were included, 54.6% were men. The average age was 71.9 $\pm$ 14.2 years old (73.7% older than 65 years old). The 73.5% of the patients were hospitalized in medical service. The main diagnoses when they were hospitalized were related with breathing system (20.1%), circulatory system (18.8%) and the central nervous system (11.1%) diseases. The main chronic diseases were diabetes (60.9%), Chronic kidney disease (18.9%), chronic obstructive

pulmonary disorder (COPD) (18.4%) and the congestive heart failure (CHF) (17.6%). 49846 glycaemia were analysed (95.8% pre-prandial, 2.9% postprandial and 1.3% night-time) with average values of 176.7±73.9 mg/dl, 250.2±108.2 mg/dl and 203.2±95.3 mg/dl respectively ($P<0.001$). The 66.7% fulfil at least one of both stablished criterion. 43.0% of patients had a pre-pandial mean glycemic <140 mg/dl, 66.4% of patients had a random blood glucose <180 mg/dl. No differences in hospital stay among patients with good and poor glycemic control (11.1±11.2 versus 10.34±9.4 days) ($P=0.081$) were found. The factors associated to the lack of compliance of the objectives were diabetes (OR:5,0[IC95%: 4.1–6.1]), the CHF (OR: 1.5[IC95%:1.2–1.8]), the COPD (OR:1.3[IC95%: 1.0–1.6]) and the urgent hospitalization (OR:2.1 [IC95%: 1.6–2.8]).

Conclusions

The glycemic control in hospitalized patients is far from adequate although we did not find differences in hospital stay between patients with / without good glycemic control. We need to update the existent insulinization protocol because with the current, the 33.3% of patients do not meet the goals.

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EP433

Hypoglycaemia: Prevalence and factors associated in the old-hospitalized patient

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Objective

To determine the hypoglycaemia prevalence in an old-patient hospitalized and to stablish the factors associated with its appearance and to study the association between the hypoglycaemia with the stay in hospital and the mortality during the hospitalization.

Material and method

A retrospective study in which all patients, older than 65 years old that were hospitalized during 2014 and at least two glycemic control have been realised, were included. By the revising of the computerise-clinic-history, sociodemographic, clinic and administrative data were obtained. The degree of comorbidity (Charlson index) was calculated which classified it in three levels: absence, moderate and high. The results of the glycaemic were obtained from electronic devices.

Results

1924 patients were included, 51,0% were men. The average age was 78,8±7,9 years old. The 86,8% of the patients were urgent hospitalized and the 74,1% of the patients were hospitalized in medical services. The main diagnoses when they were hospitalized were related with breathing system (23,0%), circulatory system (19,4%) and the central nervous system (11,2%) diseases. The Charlson index was 5,6±3,6, showing up the 98,4% a high comorbidity. The 8,7% of the patients presented at least one hypoglycaemia episode during the hospitalization, of which the 26,3% presented more than two hypoglycaemia episodes during their hospitalization.The factors associated to the appearance of any hypoglycaemia episode were the hemiplegia (OR:1,7[IC95%:1,0–2,9]), and the chronic kidney disease (OR:1,2[IC95%:1,0–1,4]. The patients hospitalised in medical services had also more hypoglycaemia risk than the ones hospitalized in surgery services. (OR:1,5[IC95%:1,1–1,4]. The median stay was 11,1 days (range: 3–107), without finding differences between patients with and without hypoglycaemia (12,1±10,9 versus 11,0±10,4 days; $P=0,181$).As for overall mortality was 7.3%, and no differences between the group of patients with / without hypoglycemia were found (4.2% vs 7.6%; $P=0.108$).

Conclusions

The hypoglycaemia episodes in elderly patients were low comparing it to the other studies and they were associated with chronic diseases such as the renal disease and the hemiplegia.Contrary to what you would expect, hypoglycemic episodes were not related to mortality or hospital stay.

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EP434

The importance of islet antigen-2 and glutamic acid decarboxylase antibodies in proper diagnosis of diabetes mellitus at the age ≥30 and <70 years

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Objective

Misclassification of type 1 (T1DM) and type 2 diabetes mellitus (T2DM) is quite common and crucial to choice of appropriate therapy. The aim of the study was to evaluate the correspondence of islet antigen-2 (Anti IA2) and glutamic acid decarboxylase (Anti GAD65) antibodies with clinical diagnosis.

Methods

The Anti IA2 and Anti GAD65 were measured in 583 patients (337 males and 246 females) diagnosed with T1DM or T2DM with not typical manifestation at the age ≥30 and <70 years. The data for analysis was collected from medical files.

Results

245 (42.02%) cases had primary diagnosis of T1DM, and 338 (57.98%) – T2DM. One or both positive antibodies were found in 271 patients (group I), and all negative in 312 (group II). The mean age at onset of diabetes mellitus was 42.55±9.29 yrs in group I vs. 41.83±8.53 yrs in group II; $P=0.33$. One or both antibodies were found in 141 patients with primary diagnosis of T1DM (odds ratio (OR) 1.84 (95% CI 1.69–2.01, sensitivity 57.55%), 77 males (OR 0.92 (95% CI 0.83–1.04, sensitivity 49.01%) and 27 females (OR 6.16 (95% CI 5.34–7.11, sensitivity 71.28%). 208 patients with T2DM had negative antibodies (OR 2.56 (95% CI 2.38–2.77, sensitivity 61.54%), 63 males (OR 3.81 (95% CI 3.45–4.22, sensitivity 66.13%), and 67 females (OR 1.61 (95% CI 1.44−1.81, sensitivity 71.28%).

Conclusion

The presence of antibodies corresponded to primary diagnosis in 49.01% to 71.28% at the age ≥30 and <70 years.

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EP435

The increase in unsaturated fatty acids is related with an anti-inflammatory profile in the hypothalamus of non-diabetic IRS2-deficient mice

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Background

IRS2-deficient ($IRS2^{-/-}$) mice are considered a good model to analyze the development of diabetes as some of them present an increase in glycemia comparable to that observed in diabetes onset in humans, whereas a high proportion of these mice do not develop diabetes. Energy homeostasis regulation by the hypothalamus can be disturbed by an inflammatory environment, which predisposes an individual to the onset of diabetes. Saturated fatty acids induce hypothalamic dysfunction, whereas unsaturated fatty acids mediate several anti-inflammatory actions.

Objectives

Our aim was to determine the pattern of fatty acids in the hypothalamus of non-diabetic $IRS2^{-/-}$ (ND) and diabetic $IRS2^{-/-}$ (D) mice and its possible association with hypothalamic inflammation.

Methods

We studied 18 male mice including controls, ND and D mice. We analyzed enzymes involved in the generation of NADPH, fatty acid synthesis and regulation of energy homeostasis by western blotting and pro- and anti-inflammatory chemokines/cytokines by multiplexed bead immunoassay. Metabolomic studies were performed by proton nuclear magnetic resonance (H-NMR) after extraction of hypothalamic metabolites in organic solvents.

Results
Malic enzyme was increased in ND mice and fatty acid synthase in D and ND, with a greater increase in ND. Acetyl-CoA carboxylase was inhibited and AMPK activated in D mice, with no changes in ND mice. Among the studied chemokines/cytokines, monocyte chemoattractant protein-1, fractalkine and interleukin (IL)-2 were increased in D and IL-4 en ND mice. Metabolomic studies revealed an increase in the levels of ω3-fatty acids, phosphatydil-ethanolamine, linolenic acid and MUFA plus PUFA in the hypothalamus of ND mice with respect to controls. A negative correlation of the analyzed metabolites with fractalkine and a positive correlation with IL-4 was observed.
Conclusion
The favorable hypothalamic lipid profile suggests a beneficial role against hypothalamic inflammation in non-diabetic $IRS2^{-/-}$ mice.

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EP436

Epidemiological indicators and prevalence of risk factors of diabetes type 2 among the inhabitants of Almaty city and Almaty region of Kazakhstan

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Relevance
The main risk factors for developing diabetes type 2, such as obesity, overeating and a sedentary lifestyle are common to a variety of chronic non-infectious diseases.
Purpose of the study
Investigate the source of epidemiological indicators, risk factors for type 2 diabetes based on cross-sectional study of the population of Almaty city and Almaty region of Kazakhstan.
Methodology
The material for the research were population at the age of 18–69 years living in Almaty city and Almaty region. The study was conducted in three stages: interviews with respondents, physical measurements and laboratory tests.
Results of the study
Analysis of the survey results on a national basis has revealed a significant prevalence of diabetes among Russians (15.35%) compared with the Kazakhs (4.9% r·0.01), with other Asian ethnic groups (10.7%, r·0.05). But compare the results of Russians with other European nationality (8.3%) and Ukrainians (7.1%) have not showed significant differences ($P>$ 0.05). The age has been proved as a significant risk factor in the development of type 2 diabetes, and the ratio is 1: 9 (OR $=$9.266), ie in the age group over 45 years the risk of developing type 2 diabetes increases by 9 times. Genetic inclination of diabetes refers to a group of the absolute risk of diabetes; the analysis showed that the 271 respondents pointed to first-degree relatives with diabetes history, where diabetes occurred in 14.8%. The remaining 1304 people had no family history of diabetes, and diabetes among them was 5.8%. The ratio is almost 1: 3 (OR $=$2.920). Risk factors, obesity, blood pressure, concomitant cardiovascular disease, glucose and cholesterol in the blood plasma. Comparison of these factors in the groups of respondents with diabetes and without diabetes showed significant differences in body mass index (BMI), blood pressure, both systolic (SBP) and diastolic (DBP). The values of all parameters in patients with diabetes were significantly higher than in those without diabetes ($P<0.05$). The survey revealed that people with diabetes compared with those without diabetes suffer the hypertension 2 times harder, ischemic heart disease - more than 3 times, myocardial infarction occurs 6 times, stroke – 4 times more often.
Conclusion
Analysis of risk factors for type 2 diabetes of the population has confirmed the impact of such factors as race, age and genetic inclination on the prevalence of diabetes.

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EP437

Association of FGF21 soluble levels with metabolic profile in Gestational Diabetes patients

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Introduction
Gestational Diabetes Mellitus (GDM) has been associated with complications both in the neonate and in the mother; including increased risk of Type 2 Diabetes Mellitus (DM2), obesity, and cardiovascular disease. Fibroblast growth factor 21 (FGF21) is a key regulator of glucose and lipid metabolism. Recently, the relationship between FGF21 and metabolic component diseases such as diabetes mellitus and obesity has been demonstrated. In addition, FGF21 mRNA and protein levels, as well as soluble levels of this molecule, have been reported to be increased in patients with GDM compared to normoglycemic pregnant women.
Objective
To associate FGF21 serum levels with metabolic profile of patients with GDM.
Material and methods
Twenty patients with GDM and fifteen clinically healthy pregnant women were included; serum FGF21 levels were determined by ELISA, and glucose, triglycerides, total cholesterol, HDL, LDL and VLDL values were measured.
Results
Our results shown that serum levels of FGF21 are significantly higher in the group of patients with GDM compared to the control group (313.72$\pm$84.58 vs 116.46$\pm$ 31.41 pg/mL, $P=0.013$). The values of triglycerides, cholesterol and VLDL showed a similar behavior between groups; while HDL levels were higher in the control group. Serum FGF21 levels positively correlated with triglyceride values (r$=$0.344, P·0.05) and postprandial glucose (r$=$0.356, P·0.05). There was no correlation between total cholesterol, HDL, LDL and VLDL levels and FGF21 levels in our study group.
Conclusion
The FGF21 molecule may play an important role in the GDM pathophysiology, since it alters the metabolic profile, both glycemic and lipid, of these patients.

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EP438

Site-specific cancer risk in people with type 2 diabetes: Nationwide population-based cohort study in Korea

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Background
Many studies indicated an increased cancer incidence and cancer mortality in subjects with diabetes mellitus. But most of studies have been surveyed in western countries and have problems in applying the results to Korean. We aimed to evaluate the site specific cancer risk of diabetic patients in Korea over 30 years, and investigate causal relationship and temporal relationship by analyzing the organ-specific cancer risk in diabetics according to duration.
Methods
Using a database provided by NHIS, we conducted a retrospective, population-based cohort study for adults over 30 years from January 1, 2005 to December 31, 2013. We calculated the hazard ratio (HR) for each cancer by using Cox regression. And we compared HR for each cancer according the duration of diabetes divided in to 6month, 6months to 3years and more than 3years to verify the possibility of detection bias or reverse causation.
Results
The incidence of total cancer per 1,000 Subjects with diabetes was higher than with non-diabetes group. Hazard ratio(HR) for cancer of pancreas, liver, kidney, bladder, colorectum, thyroid, lung, stomach and leukemia were significantly higher in diabetes group after adjusted. HR for cervix, endometrium and breast cancer in female diabetes group were higher than those of non-diabetes group. HR for laryngeal cancer in male was higher in diabetes group. The total cancer risk was higher in $<$ 6 months of diabetes duration (HR 2.03; 95% confidence interval [95% CI]. 1.99–2.07), whereas the hazard ratio decreased with increasing duration of diabetes, raging from 1.19 (95% CI, 1.18–1.21) between 6 months and 3 years to 1.12 (95% CI, 1.11 to 1.13) at over 3 years, but remained significantly higher than the non-diabetic group. HR for pancreas, liver, colorectum, prostate and endometrium were higher in diabetes group for entire duration of diabetes. When excluding diabetes duration less than 6months, HR for stomach, colorectum, liver, pancreas, kidney, bladder, thyroid, prostate, endometrium and cervix showed similar pattern including diabetes duration less than 6 months.
Conclusion
Cancer incidence risk increases in T2DM patients, and the phenomenon is more prominent in short durations, i.e. shortly after diagnosis of diabetes. As the duration increases, incidence risk of cancer varies depending on the site of cancer

and patient's gender. Thus, in diabetes patients, cancer screening should be individualized regarding duration of diabetes, sex, and the site of cancer.

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EP439

Erosio interdigitalis blastomycetica- discrete and early sign for diabetes mellitus

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Erosio interdigitalis blastomycetica is a special form candidiasis commonly seen in the third web space of digits, but can spread to all web spaces. Diagnosis is clinically suspected in the presence of maceration and ulceration, erythema, sometimes associated with pain. The main predisposing condition is chronic maceration (for example in launderers), irritant chronic agents and prolonged moisture affect skin barrier with subsequent colonization of *Candida spp*. Direct mycological examination and fungal culture certify the diagnosis and exclude similar clinical disorders, mostly irritant contact dermatitis and psoriasis. Erosio interdigitalis blastomycetica is frequently diagnosed in daily practice especially in diabetes patients. We present cases series of erosio interdigitalis blastomycetica as initial sign of undiscovered diabetes mellitus. Suspicion of diabetes should be made in any case of erosio interdigitalis blastomycetica. Screening for diabetes is mandatory in case of erosio interdigitalis blastomycetica.

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EP440

Postpartum Tip 2 DM follow-up after gestational diabetes mellitus

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Purpose
GDM is defined as any degree of carbonhydrate intolerance that is first diagnosed during pregnancy. Patients diagnosed with GDM are expected to have complications such as Type II DM, obesity, hypertension in the long term. Prevalence of GDM diagnosis during pregrancy changes between 2 and 10%. Our purpose is to revaluate the OGTT of the patients diagnosed with GDM, with regard to their postpartum Type II DM progress.
Materials and methods
450 pregnant women who were not diagnosed with diabetes in the beginning of their pregrancy were included to the study, who had consulted to our clinic between 2012 and 2014. Seventy-two of those quitted the study willingly, 20 of those quitted during follow-up, 12 of those quitted due to spontaneous abortion in the first trimester. 346 remaining patients were included to the study. After 75 g OGTT, GDM screening was made to those patients between 24th and 28th weeks of their pregrancy. With 75 g OGTT, 61 patients were diagnosed with GDM. They were reevaluated with regard to their postpartum Type II DM progress. But 36 of these 61 patients were made 75 g OGTT. Two of those became pregnant again, two of those moved out of the city, 21 of those could not be reached; thus, they could not be reevaluated. Among the patients diagnosed with GDM, 29 of them were followed with diet, four of them with basal and short-acting insulin, two of them only with basal insulin, one of them only with short-acting insulin. Three of those who were followed with diet and one of those who were followed with basal and short-acting insulin were followed with metformin during postpartum period. None of the patients used insulin during postpartum period.
Results
Patients called postpartum in the mean month period 20.82 ± 5.66. Mean age average of the patients was 32 ± 5. Postpartum BMI was 29.10 ± 5.47 kg/m^2. HbA1c average of the patients was 5.77 ± 0.39%. Four patients who were using metformin during postpartum period were accepted as type 2 DM and were not given OGTT. According to 75 g OGTT; with their basal average being (101.83 ± 10.77 mg/dl) and 2nd hour glucose average being (124.66 ± 39.53 mg/dl), 11 (34.3%) patients were not diagnosed with diabetes. Thirteen (36.11%) patients were diagnosed with impaired fasting glucose, three (8.33%) with impaired glucose tolerance, three (8.33%) with impaired fasting glucose and impaired glucose tolerance, six (16.67%) with type 2 DM.
Discussion
Our study included pregnant women who had not been diagnosed with DM in the beginning of their pregnancy who later on were diagnosed with GDM during pregnancy. We followed them during their postpartum period. With these results, it is found necessary to follow and evaluate the postpartum period of the patients diagnosed with GDM during pregrancy with regard to Type II DM progress.

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EP441

Diabetic nephropathy in type 1 diabetes mellitus

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Nephropathy is a serious complication of Type 1 diabetes mellitus (T1DM) with a grave prognosis after the onset of proteinuria. End stage of renal disease remains the major cause of excess morbidity and premature mortality in patients with T1DM. The aims of the present study were to investigate the prevalence of diabetic nephropathy and to evaluate risk factors for its development among patients developing T1 DM. Seventy six patients with T1DM history over 20 years were included in our study. We analysed the occurrence and risk factors of diabetic nephropathy. Microalbuminuria and macroalbuminuria were defined as urinary albumin excretion 31–299 mg and 300 mg, respectively, per 24 h in at least two of three consecutive samples, kidney failure was defined as a glomerular filtration rate (GFR) <30 ml/min/1.73 m. The following risk factors were considered: sexe, diabetic control (HbA1c) and duration, hypertension, smoking. A total of 76 patients were enrolled: 43 men and 33 women, the mean age and the mean diabetes duration was 39.9 years ± 9.5 (24–61 years) and 28.18 ± 5.9 years respectively. During follow-up, persistent microalbuminuria developed in four patients (5.3%); macroalbuminuria developed in seven patients (9,2%) and kidney failure in 12 patients (15.8%). the risk of diabetic nephropathy was significantly higher in men than in women ($P=0.012$). Our study suggests that several potentially modifiable risk factors predict the development of nephropathy in type 1 diabetic patients.

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EP442

Diabetes and smoking: epidemiological study in two ethnic groups

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Objectives
Smoking tobacco is a risk factor for several diseases and has been increasing in many developing countries. Smoking cessation counseling should be a routine component of diabetes care. The aim of the present study was to examine the association between smoking status in two different groups of patients with diabetes: Immigrants from Bangladesh who live in Greece and Greek-born subjects.
Methods
A total of 166 immigrants with diabetes (122 with Type 2 and 44 with Type 1 diabetes mellitus) from Bangladesh were compared with 123 Greek Caucasian patients (82 with Type 2 and 41 with type 1 diabetes mellitus). Patients from

Bangladesh had a mean ±s.d. duration of 10.34±6.2 years of living in Greece. A questionnaire was formulated and pilot-tested for the comprehensibility of questions by both ethnic groups. Interviews were conducted, a physical examination followed and blood samples for plasma glucose and HbA1c were collected. Demographic characteristics and diabetes-related information was collected.
Results
A total of 40 (24.1%) patients from Bangladesh and 58 (47.2%) patients from Greece were smokers, 18 (10.8%) patients from Bangladesh and 37 (30.1%) patients from Greece reported that they were ex-smokers at the time of examination and interview, whereas 108 (65.1%) patients from Bangladesh and 28 (22.8%) patients from Greece never smoked ($P<0.001$). Patients from Bangladesh reported less tobacco use than Greek patients (5.61±11.91 vs 24.77±24.20 pack-years, $P<0.001$).
Conclusions
Most immigrants reported less tobacco use than native Greeks. Higher education is associated with less smoking prevalence in both ethnic groups. Patients living alone were more likely to smoke than those who live with families. Employed persons had a lower smoking prevalence than unemployed persons in both ethnic groups. Smoking is associated with higher glucose and HbA1c values in both ethnic groups. From the literature tobacco smoking is related to insulin resistance, systemic inflammation, decreased β-cell function and pancreatic inflammation. Understanding some culturally relevant predictors of tobacco use among different ethnic population might assist health care providers in designing successful smoking control programs, especially for patients with diabetes.

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EP443

Prevalence of hyperglycemia in patients hospitalized in the health area of cuenca (Spain)

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Introduction and objectives
Hyperglycemia is a common problem in hospitalized patients, that increases infections, mortality, costs and the hospital stay. The objective of this study is to know the prevalence of hyperglycemia in our hospital.
Methods
We designed a cross-sectional observational study. We included patients admitted in the hospital every 3 days in 2 months. We excluded patients younger than 15 years, stays less than 3 days and those of the pediatric, gynecological, emergency and intensive care services. We collected the data from these patients the third day of admission and at discharge. We defined hyperglycemia as two or more capillary glucose values greater than 140 mg/dl.
Results
A total of 328 patients (173 females and 155 males) were included, with a median age of 73 years. The 75% were in medical services and 25% in surgical services. The main reason for admission was infection (26%), followed by organ failure (12%). 33% (109) patients had hyperglycemia. Of these patients, 71.6% (78) were known diabetics, while 28.4% (31) were not known diabetics. The median age of patients with hyperglycemia was 80 versus 68 years old in patients without hyperglycemia.
Conclusions
The prevalence of hyperglycemia in our hospital is higher than another areas, probably due to a higher mean age in our population. Almost one third of patients with hyperglycemia were not diabetic. Therefore hospitalization is an opportunity to diagnose and treat adequately these patients.

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EP444

Testosterone levels in men with diabetes mellitus. What relation?

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Background
Low serum testosterone (LST) is associated with some chronic diseases, changes in body composition and resistance to insulin. Diabetes is one condition that has high prevalence of LST.
Objetive
To determine the prevalence of LST in men with diabetes and its relationship with age, anthropometric and biochemical data.
Material and methods
A cross-sectional study of 65 men with type 1 and type 2 diabetes was conducted, with age ranging from 25 to 73 years. Clinical data was obtained from clinical records, like disease duration, diary insulin dose, retinopathy, hypertension and medication. Biochemical parameters evaluated were: total testosterone (TT), free testosterone (FT), gonadotropins, prolactin, glycated haemoglobin (A1C), urinary albumin/creatinine relation. LST was considered TT <3.0 ng/ml.
Results
Mean age was 51.9±19.9 years, 60% had type 2 and 40% type 1 diabetes and the mean disease duration was 15.6±10.2 years. 76.9% had body mass index (BMI) ≥25 kg/m^2. Twenty-seven patients (41.5%) had LST, 6 (23.1%) in type 1 group and 21 (53.8%) in type 2. In patients under 40 years-old 5 (26.3%) had LST. In multiple linear regression model TT was associated with BMI (β −0.355, $P=0.005$) and age (β −0.255; $P=0.044$) and no associations were found with FT. However, patients with FT<15 pg/ml had a significantly higher A1C, 8.40±1.71% vs 7.54±1.38% ($P=0.029$). BMI ≥25 kg/m^2 was associated an increased risk of LST (odds ratio (OR): 6.50; 95% confidence interval (CI) 1.33–31.83), such as antiplatelet medication (OR: 5.83; CI: 1.40–24.23).
Conclusion
In this sample we found a high prevalence of LST in men with diabetes, similar to data described in other studies. Age and BMI were correlated with testosterone levels such as in men without diabetes, and no association was observed with A1C levels. Only FT< 15 pg/ml was associated with higher A1C. To clarify this relation, more data is needed.

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EP445

Vitamin D and testosterone in diabetes mellitus: cross-sectional study results

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Background
In the recent years, Vitamin D role has grown in cardiovascular and inflammatory diseases, and some relations were made with low serum testosterone (LST) levels. It is equally known that in patients with diabetes, the prevalence of LST is higher.
Objetive
To determine the prevalence of low levels of vitamin D and its relation with LST in men with diabetes.
Material and methods
A cross-sectional study of 65 men with type 1 and type 2 diabetes was conducted, with age ranging from 25 to 73 years. Clinical data was obtained from clinical records, such as disease duration, diary insulin dose, retinopathy and hypertension. Biochemical parameters were: 25-hydroxi-vitamin-D (25[OH]D), total testosterone (TT), free testosterone (FT), gonadotropins, prolactin, glycated haemoglobin (A1C). Low levels of 25(OH)D were considered when <30 ng/ml (insufficiency 20–29 ng/ml and deficiency<20 ng/ml) and LST when TT <3.0 ng/ml.
Results
Mean age was 51.9±19.9 years and the mean disease duration was 15.6±10.2 years, 60% had type 2 and 40% type 1 diabetes. 76.9% had BMI ≥ 25 kg/m^2. Forty-two patients (64.6%) had low vitamin D levels (40% had 25(OH)D 20–29 ng/ml and 24.6% had 25(OH)D<20 ng/ml). In multiple linear regression model, low levels of 25(OH)D were associated with triglycerides (β −0.314; $P=0.011$) and FT (β 0.273; $P=0.03$) when adjusted for age, BMI and disease duration. Men with low levels of vitamin D had significantly lower FT (15.82±9.53 vs 22.72±10.72 pg/ml; $P=0.013$) and higher serum triglycerides (164.1±122.1 vs 104.9±45.2; $P=0.029$). Mean A1C was 8.07±1.61% vs 7.48±1.40%, respectively, but was not significantly different ($P=0.250$).
Conclusion
In this sample, the prevalence of low levels of vitamin D was similar to data described in other studies (52–77%). When adjusted for age, BMI and disease

duration, these levels of vitamin D were associated with higher serum triglycerides and lower free testosterone, which may indicate the metabolic effects of this vitamin in patients with diabetes.

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EP446

The relationship between serum uric acid and insulin resistance and sensitivity parameters in Turkish type 2 diabetes mellitus patients

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Summary
Hyperuricemia is associated with glucose metabolism disorders clinically. In this study, we evaluated the relationship between serum uric acid concentrations and some insulin resistance/sensitivity parameters in Turkish type 2 diabetes mellitus patients.
Methods
The anthropometric and laboratory data of 87 type 2 diabetes patients of both sexes (35 male, 52 female) were evaluated retrospectively. HOMA-IR (homeostatic model of insulin resistance) and QUICKI (quantitative insulin sensitivity check index) measurements were made by the formulae of [glucose (mg/dl) $\times$ insulin (μu/ml)]/405 and 1/[log ins (μu /ml)+log glu (mg/dl)] respectively.
Results
The mean age of the patients were 54.4$\pm$11.2 (minimum 20, maximum 77) years. The serum uric acid values ranged from 1.7 to 9.6 with a mean of 4.82$\pm$1.39. HOMA-IR values ranged from 0.51 to 25.99 with a median of 3.27$\pm$2.57. QUICKI values ranged from 0.25 to 0.43 with a median of 0.32$\pm$0.04. There was a positive and significant correlation between serum uric acid and insulin levels ($r=0.301$; $P=0.005$). There was a negative and significant correlation between serum uric acid and A1c and glucose levels ($r=-0.372$; $P=0.000$ and $r=-0.313$; $P=0.003$). The correlation of uric acid to age, diabetes duration and body mass index did not reach statistical significance. Although the correlation of uric acid to HOMA-IR and QUICKI values did not reach statistical significance ($r=0.128$; $P=0.236$ and $r=-0.128$; $P=0.236$), HOMA-IR values increased but QUICKI values decreased with increasing uric acid levels.
Conclusion
Although the correlations did not reach statistical significance, serum uric acid levels are positively correlated to insulin resistance parameter (HOMA-IR) and negatively correlated to insulin sensitivity parameter (QUICKI) as expected. The small sample size of our cohort might be responsible for this statistical insignificance. The negative correlation of serum uric acid to glucose and A1c might be related to increased renal excretion of uric acid together with glucose due to osmotic diuresis. These results must be confirmed with larger studies.

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EP447

Relationship with T helper 1 cytokines and type 2 diabetes

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Objectives
T helper1 (Th1) cells were determined to have important roles in the development of type 2 diabetes (T2D). We aimed to investigate relationship between Th1 cytokines (IFN γ, IL-2 and TNF-α) and T2D.
Material and methods
The study included 32 newly diagnosed type 2 diabetic patients (T2DPs) who had not begun to take antidiabetic agents except from insulin and 30 healthy subjects (CG) who did not have glucose intoerance (fasting or after glucose load). Serum IFN-γ, IL-2 and TNF-α levels were measured using ELISA method. Serum levels of those ctokines in T2DPs were compared with those in controls.
Results
TNF-α levls of T2DPs were higher ($P<0.05$) than those in controls. There were no differences between the IFN-γ and IL-2 levels of T2DPs and controls ($P>0.05$).
Conclusion
TNF-α levels increase in T2D. Decreased insulin action in T2D may be due to the increased TNF-α levels, since TNF-α has been suggested to down regulate the tyrosine kinase activity of the insulin receptor.

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EP448

Adipocytokines, incretins, insulin resistance and body composition coherence in women with previously diagnosed gestational diabetes mellitus

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Introduction
Adipose tissue is a major source of adipocytokines. It plays an important role for the development of insulin resistance (IR). Data implicate that incretins enhance insulin sensitivity. One aspect of the pathophysiology of gestational diabetes (GDM) is IR. The relationship between adipocytokines, incretins and GDM might be closely associated.
Aim
To evaluate the coherence of adipocytokines (adiponectin and leptin), incretins (GLP-1, GIP), insulin resistance and BMI in women with previously diagnosed GDM.
Methods
We examined 126 women with previously (16–43 years ago) diagnosed GDM. BMI, incretins, adipocytokines were evaluated. IR was calculated with HOMA-IR index. Data expressed as mean$\pm$S.D. for parametric data or median (min–max) for non-parametric data. ANOVA was used to compare data between groups of three or more variables. Non-parametric data correlation analysis was performed using the Spearman's correlation coefficient. The results were considered statistically significant at $P<0.05$.
Results
Women's average age was 53.52$\pm$8.34 years (39–77 years). The coherence between adipocytokines, incretins and BMI was observed: increased BMI determined decreased adiponectin ($r=-0.361$, $P<0.01$), and increased leptin ($r=0.838$, $P<0.01$) either incretins concentrations (GIP $r=0.270$, $P=0.01$ and GLP-1 $r=0.167$, $P=0.21$). HOMA-IR was higher in obese women ($r=0.641$, $P<0.01$). Data analysed in different BMI categories (normal weight/overweight/obese): adiponectin (26.8(12.2–76.8)/21.4 (10.8–54.4)/17.9 (5.2–41.6), $P<0.01$), leptin (5.9(0.2–16.1)/12.5(3.8–122.1)/24.7(11.1–74.9), $P<0.01$), GIP (0.8(0.2–2.9)/0.97(0.2–5.2)/1.29(0.2–18.2), $P=0.145$), GLP-1 (0.06(0.04–21.7)/0.06(0.04–6.1)/0.06(0.04–18.2), $P=0.517$), HOMA-IR (2.2(0.5–4.7)/2.5(0.4–6.4)/4.6(1.2–27.2), $P<0.01$). No significance between adiponectin and GIP, GLP-1 was defined ($r=-0.152$, $P=0.156/r=0.02$, $P=0.824$). Women with lower adiponectin had higher HOMA-IR ($r=-0.22$, $P=0.03$). The correlation between leptin and GIP, GLP-1, HOMA-IR ($r=0.3$, $P=0.05/r=0.231$, $P=0.03/r=0.697$, $P<0.01$) was observed. The positive correlation between GIP, GLP-1 and HOMA-IR ($r=0.388$, $P<0.01/r=0.352$, $P=0.001$) was found.
Conclusion
Adipocytokines and incretins are closely linked to the amount of fat tissue in the body: increased BMI correlates with decreased adiponectin and increased leptin/incretins levels in women with previously diagnosed GDM. HOMA-IR is closely associated with leptin and incretins.

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EP449

The coherence of carbohydrate metabolism and metabolic parameters (adipocytokines, incretins, insulin resistance) in women with previously diagnosed gestational diabetes mellitus

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Introduction
There is growing evidence that gestational diabetes mellitus (GDM) significantly increases the risk of adverse consequences, the most significant of which is a predisposition to the development of metabolic syndrome and diabetes mellitus (DM). The reasons why some women develop DM, while the others not, are still studied. The relationship between various metabolic parameters and GDM might be closely associated.
Aim
To evaluate the coherence of carbohydrate metabolism and metabolic parameters (adipocytokines, incretins, insulin resistance) in women with previously diagnosed GDM.
Methods
We examined 126 women with previously (16–43 years ago) diagnosed GDM. BMI was evaluated. Fasting plasma glucose (FPG) was examined for women with DM. OGTT was performed for carbohydrate metabolism testing for the rest. Women assigned to different groups: NG – normal glucose, IFG-IGT – impaired fasting glucose/impaired glucose tolerance and DM group. Incretins, adipocytokines were evaluated. IR was calculated with HOMA-IR index. Data expressed as mean $\pm$ SD for parametric data or median (min-max) for non-parametric data. ANOVA was used to compare data between groups of three or more variables. Non-parametric data correlation analysis was performed using the Spearman's correlation coefficient. The results were considered statistically significant at $P<0.05$.
Results
Women's average age was 53.52 $\pm$ 8.34 years (39–77 years). Age differed in separate carbohydrate metabolism groups ($P=0.001$). Carbohydrate metabolism was set for 58%: IFG-IGT for 16.7%, DM for 41.3% patients. The correlation between adipocytokines, incretins and FPG was evaluated: higher FPG was seen in women with lower adiponectin ($r=-0.186$, $P=0.037$), higher leptin levels ($r=0.340$ $P<0.01$) as well as incretins concentrations (GIP $r=0.368$, $P<0.01$ and GLP-1 $r=0.05$, $P=0.004$) and HOMA-IR ($r=0.656$,$P<0.01$). Data analysed in different carbohydrate metabolism groups (NG/IFG-IGT/DM): BMI (26.7 (18.8–52.2)/27.9 (20.1–52.9)/34.8 (20.5–52.9), $P=0.001$), adiponectin (21.6 (10.3–76.8)/18.7 (9.9–54.4)/17.7 (5.2–52.9), $P=0.07$), leptin (14.7 (0.2–74.9)/10.9 (2.2–48.6)/19.6 (1.6–66.3), $P=0.327$), GIP (0.8(0.2–12.1)/0.8 (0.2–5.2)/0.07 (0.05–21.7), $P=0.416$), GLP-1 (0.06 (0.04–16.6)/0.07 (0.04–5.4)/0.07 (0.05–21.7), $P=0.044$), HOMA-IR (2.3 (0.5–4.7)/2.4 (1.4–7.2)/4.5 (0.5–27.2), $P<0.01$).
Conclusion
Age, BMI, adipocytokines, incretins and IR are closely linked to the carbohydrate metabolism: IFG-IGT and DM was more frequently seen in elder overweight/obese women, having lower adiponectin, higher GLP-1 concentration and higher HOMA-IR.

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EP450

Instable diabetes revealing pheochromocytoma

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Introduction
Pheochromocytomas are secreting tumors, producing catecholamines (dopamine, noradrenaline and adrenaline), responsible for arterial hypertension; Pheochromocytoma in the diabetic may be responsible for an unbalanced glycemic and this considerably modifies the management. We present the case of a patient for whom the diagnosis of pheochromocytoma was posed before a glycemic imbalance.
Clinical case
A 70-year-old patient is hospitalized for unexplained unstable diabetes mellitus (Several episodes of severe hypo-hyperglycaemia per week with a 7.5% Hba1c. It is diabetes mellitus evolving for 20 years, marked by instability of glycemic figures For 3 years, during his hospitalization for management of severe hypertension was discovered associated with headache and slimming.Infectious and inflammatory balance without anomaly, no lipodystrophy, in search of endocrinopathy responsible for this hypertension and unstable diabetes Biological assays: chromogranin at 10 times normal and Metanephrine at 3.33 times normal, abdomino-pelvic ultrasound finds a supra-renal mass supplemented by pelvic CT recovering an oval tissue formation measuring 46.8 $\times$ 36.5 mm Enhancing intensely after injection of contrast medium, evoke a pheochromocytoma confirmed by a MIBG scintigraphy which finds a focus of intense hyperfixation of the tracer radio corresponding to a right adrenal neurectodermal tumor of 52 $\times$ 36 mm. In search of other pathologies coming within the framework of a multiple endocrine neoplasia the assessment of extension is without anomaly. Patient is programmed in surgery for a management
Conclusion
In patients with pheochromocytoma 35% are diabetic, the diagnosis of pheochromocytoma in the diabetic may be responsible for a glycemic imbalance and this considerably alters the management.

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EP451

Unacylated ghrelin does not seem to influence glucose homeostasis in obese women

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Background and Aim
Unacylated ghrelin (UAG) is the major form of circulating ghrelin. Initially considered as a non-functional peptide, soon after UAG has been associated to a negative action on energy balance, suppression of hepatic glucose production and decrease in circulating levels of insulin. The aim of this study was to analyze the association between the serum levels of UAG and glucose metabolism parameters in obese women, independently from the eventual interference of adiposity.
Material and Methods
One hundred lean and 254 obese Caucasian women were studied. Each woman was characterized for total body weight, body mass index (BMI), waist and hip circumferences, glucose at fasting and 2 hours after an oral glucose tolerance test (OGTT), fasting insulin, glycated hemoglobin (HbA1c), and UAG. Insulin resistance was assessed by the homeostasis model assessment (HOMA-IR). Obese women were classified in three glycemic status subgroups (normoglycemia, prediabetes and diabetes) according to HbA1c and glucose values.
Results
When compared with the lean group, significantly lower UAG levels were observed in obese women when compared with the lean group (350.2 $\pm$ 251.9 vs 219.2 $\pm$ 149.7 pg/ml; $P<0.001$). However, no significant difference was observed through obesity classes I to III. UAG levels were not significantly different among glycemic status subgroups and did not show any direct association with glucose, insulin, HOMA-IR, or HbA1c values.
Conclusions
Although the level of the unacylated form of ghrelin shows an association with anthropometrics it seems not to be involved in glucose homeostasis.

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EP452

Influence of a part of Korean red ginseng on blood glucose control and complication markers of type 2 diabetic NSY rats

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Objective
Ginsenoside or saponin, is considered as the major bioactive component mediating the therapeutic properties of Korean red ginseng (KRG). However, the exact physiological mechanism underlying anti-diabetic effects is still not fully Clarified. More than 30 different saponins together account for only about 3–4% of KRG, thereby, it is assumed that non-saponin fraction of KRG also carry potential anti-diabetic effects; however, there is no study reporting the differentiated effects of saponin and non-saponin fractions of KRG on glycemic indications and hyperglycemia-associated complication markers.

Methods
12-week-old male Nagoya-Shibata-Yasuda (NSY) mice were allocated into 4 groups: control group given standard rodent diet (SRD) or treatment groups given either Korean red ginseng extract (*KRG*), saponin fraction from KRG extract (*Spn*) or non-saponin fraction from KRG extract (*NSpn*) admixed in SRD. The targeted administration doses of *KRG*, *Spn* and *NSpn* were all 200 mg/kg/day; all mice were fed assigned regimens for 24 weeks. Parameters for glycemic control, blood lipid profile, inflammation, oxidative stress, and anti-oxidant enzymatic activities were measured.
Results
KRG had positive effects on glycemic control by attenuating the increase in FBG at 24-week and by increasing glucose clearance and insulin response during *i.p.* GTT as compared to control. *KRG* also attenuated increases in TNF-α, oxidized LDL (oxLDL), advanced glycation end-products, and accumulation of malondialdehyde in skeletal muscle. *Spn* had a positive effect on insulin response while *NSpn* attenuated oxLDL as compared to control.
Conclusion
This study showed that anti-diabetic properties of KRG are not mainly mediated by saponin, but the therapeutic potentials of KRG may be due to the orchestral effects of both saponin and non-saponin.

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EP453

The prevalence of diabetic neuropathy, painful diabetic neuropathy and the at risk diabetic foot in Qatar

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Objective
To define the prevalence of Diabetic Peripheral Neuropathy (DPN), painful diabetic neuropathy (PDN) and the at risk diabetic foot in 2 out of the 3 National Diabetes Centres in Qatar.
Methods
712 people with Type-1 & Type-2 diabetes recruited from Alwakra Hospital and Hamad General Hospital underwent assessment for DPN & PDN using the Neurothesiometer and the DN4 questionnaire, respectively.
Results
The average age, duration of diabetes, systolic BP, BMI, HbA1c were: 52.2±0.49, 10.8±0.32 years, 132.6±1.26 mmHg, 32.2±0.52 kg/m2 and 8.3±0.11%, respectively. The prevalence of DPN and PDN were 31% and 36%, respectively. However, 4 in 5 adults with DPN and 9 in 10 adults with PDN were undiagnosed. One in ten adults with diabetes were at high risk for diabetic foot ulceration (VPT >25) and had not been diagnosed. Patients with DPN were significantly older (57.1±0.73 v 49.8±0.62, $P<0.0001$), had a longer duration of diabetes (14.34±0.57 v 9.1±0.36, $P<0.0001$), higher systolic blood pressure (139.8±2.25 v 129.2±1.46, $P=0.001$) and higher creatinine (118.6±16.76 v 70.9±2, $P=0.007$), but no difference in HbA1c (8.6±0.21 v 8.2±0.13), vitamin D (23.7±1.7 v 23.3±0.9) or B12 (344.7±39.17 v 323±21.3).
Conclusion
The overall prevalence of DPN, PDN and those at risk of foot ulceration in Qatar are comparable to that reported in Europe and the US. However, an alarmingly low proportion of patients are diagnosed and treated for DPN and PDN. There is a need for a systematic screening for DPN and PDN in Qatar. Age, duration of diabetes, blood pressure and high creatinine are risk factors for DPN.

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EP454

Changes in gene expression MADCAM1, S1PR1, CXCR4 and CCR7 in offspring of rats with experimental gestational diabetes

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Introduction
Mesenteric lymph nodes (MLN) is a major transition point for recirculating lymphocytes of GALT. Homing of lymphocytes in MLN is regulated with adressin MAdCAM-1, chemokine receptors CXCR4 and CCR7. Sphingosine-1-phosphate receptors S1PR1 activate T-cell exit from MLN.
Methods
We use RT-PCR method for investigating of mRNA expression levels of genes MAdCAM-1, CXCR4, CCR7 and S1PR in MLN of the offspring of rats with experimental gestational diabetes. To determine the level of target genes was performed RT-PCR in real-time by thermocycler CFX96™ Real-Time PCR Detection Systems. The relative level of gene expression were studied with rat reference genes GAPDH by the method $_{\Delta\Delta}$Ct. Statistical analysis were conducted using available software «Bio-Rad CFX Manager 3.1» (Bio-Rad, USA).
Results
Expression analysis of homing receptors in MLN revealed an expected significant increasing of CCR7 and MAdCAM-1 mRNA in offspring of animals with EGD, indicating the activation of the immune cells in the GALT, which is accompanied by intensification of lymphocytes homing and confirms the involvement of these receptors in the pathogenesis of diabetes. We were unable to detect changes in the mRNA levels of another regulator – CXCR4 in MLN of the offspring of rats with EGD. Increased expression level of S1PR1 mRNA of MLN lymphocytes in the offspring of animals with diabetes confirms its important role in the progression of diabetes.
Conclusions
Signals of chemokine receptors affect the activation of different Th cells subsets and we may assume their pivotal role in the development of autoimmune diseases, particularly diabetes mellitus. The revealed changes evidence of abuse of formation of peripheral immunological tolerance and can trigger the development of AID in the offspring of mothers with EHD.

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EP455

Study of expression of genes mTOR, Foxp3, IL1β and IL17A in parapancreatic adipose tissue of rats with streptozotocin-induced diabetes and after metformin administrations

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Introduction
mTOR is not only a central regulator of lipid metabolism, controlling the processes of adipogenesis and lipolysis, but also a regulator of immunometabolism of immune cells infiltrating the adipose tissue. In its turn, the level of progression of diabetes is largely limited by Treg subpopulation, the complexity and heterogeneity of which is confirmed by the detection of numerous tissue-specific Tregs, including the so-called VAT Tregs (visceral adipose tissue CD4+ Foxp3+ regulatory T cells). Therefore, the purpose of the work was to find out the level of expression of mRNA genes of mTOR, Foxp3, IL1β and IL17A in parapancreatic adipose tissue of rats with experimental streptozotocin-induced diabetes after introduction of metformin.
Methods
We use RT-PCR method for investigating of mRNA expression levels of genes mTOR, Foxp3, IL1β and IL17A. To determine the level of target genes was performed RT-PCR in real-time by thermocycler CFX96™ Real-Time PCR Detection Systems. The relative level of gene expression were studied with rat reference genes GAPDH by the method $_{\Delta\Delta}$Ct. Statistical analysis were conducted using available software «Bio-Rad CFX Manager 3.1» (Bio-Rad, USA).
Results
the development of diabetes causes the transcriptional activation of the gene of the protein kinase mTOR, does not affect the expression of mRNA of Foxp3, increases the level of expression of mRNA of proinflammatory cytokines IL1β and IL17A. At the same the introduction of metformin in diabetic rats inhibits the expression of mRNA of mTOR and increases the level of transcriptional activity of the gene Foxp3 in parapancreatic adipose tissue.

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EP456

Response to stroke in diabetic versus non-diabetic patients. Should Diabetes education systematically include advise on stroke symptoms and the correct response to them?

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Introduction
Stroke is the second cause of death in the world and the first cause of disability. It is also the second cause of Diabetes-related death. The success of reperfusion therapies is time-dependent, with most delays being patient-related. We investigated the response to stroke in diabetic patients (DM), as their risk of stroke is increased by 1,8-6 times.
Material and Methods
Consecutive patients with acute stroke or transient ischemic attack were prospectively included. Sociodemographic and clinical data, time from stroke onset to decision to seek medical attention (Decision delay (DD)) and to hospital arrival (Prehospital Delay (PD)) and first medical contact (FMC) were obtained. Decision to call the 112 Emergency Services (112-ES) within the first 15 min was considered the correct decision.
Results
382 patients were included. 138 (36,1%) were diabetic. DD was $<$ 15 min in 41 (29,7%) DM vs 57 (23,4%) non-diabetic patients (non-DM) ($P=0,17$). FMC was 112-ES in 20 (14,5%) DM vs 50 (20,5%) non-DM ($P=0,14$), and a correct decision was made in 13 (9,4%) DM vs 32 (13,1%) non-DM ($P=0,28$). PD was $<$60 min in 14 DM vs 29 non-DM. No significant differences were found after adjustment for potential confounders.
Conclusions
Response to stroke symptoms in DM was not different to non-DM, while carrying a greater load of vascular risk factors and a higher risk of stroke. Even more, although not significant, the use of the 112-ES was quite lower in DM. We propose to systematically incorporate information on stroke risk, symptoms, consequences and how to respond to stroke into DM education.

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EP457

The T allele of the rs1746661G/T polymorphism in *FNDC5* (irisin) gene is associated with increased systolic blood pressure

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Background
Gestational diabetes mellitus (GDM) is a risk factor for type 2 diabetes and both conditions are characterized by insulin resistance (IR) and decreased insulin production by pancreatic beta-cells. FNDC5 gene encodes a type I membrane protein that is proteolytically processed to form a hormone secreted into the blood, termed irisin. After induction by exercise, irisin activates profound changes in the subcutaneous adipose tissue, stimulating browning and UCP1 gene expression. This causes a significant increase in total body energy expenditure and resistance to obesity-linked IR. Studies have shown that circulating irisin is decreased in women with GDM and the FNDC5 gene is also expressed in the human placenta. Thus, genetic variants in FNDC5 gene may be associated with DGM.
Objective
To evaluate if the polymorphisms rs3460A/G and rs1746661G/T in the FNDC5 gene are associated with GDM and/or its clinical features.
Methods
We analyzed 132 pregnant women without GDM (controls) and 219 pregnant women with GDM (cases). Polymorphisms were genotyped by Real-Time PCR using TaqMan MGB probes. Haplotypes constructed from the combination of rs1746661 and rs3480 polymorphisms were inferred using the Phase 2.1 program.
Results
Genotype and allele frequencies of the rs1746661 and rs3480 polymorphisms did not differ significantly between cases and controls ($P>0.05$). The haplotype frequencies also did not differ between the two groups ($P=0.913$). Interestingly, patients carrying the T allele of the rs1746661 polymorphism had higher values of systolic blood pressure (SBP) than patients with the A/A genotype (127.2 ± 18.7 vs 122.9 ± 17.3 mm/Hg; $P=0.004$), adjusting for the use of antihypertensive medications.
Conclusion
This study showed no association between the rs1746661 and rs3480 polymorphisms and GDM; however, the rs1746661T mutated allele seems to be associated with increased SBP in pregnant women independently of GDM.

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EP458

The relations of apelin with the carbohydrate metabolism in hypertensive patients with type 2 diabetes or without it

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Purpose
The aim of the study was to evaluate the relationships of apelin with the parameters of the carbohydrate metabolism in hypertensive patients with type 2 diabetes (T2D) and without T2D.
Methods
The study involved 93 patients with hypertension grades 2–3 combined with T2D or without it (45 men and 48 women) in age from 43 to 70 years old. The investigation complex included measuring levels of fasting blood glucose, fasting blood insulin with insulin resistance index calculation (HOMA), glycated hemoglobin (HbA1c). The blood level of apelin was tested using an Enzyme-linked immunosorbent assay. Two groups of patients were formed: 1. hypertensive patients with T2D ($n=63$), 2. hypertensive patients without T2D ($n=30$). The control group consisted of 14 practically healthy volunteers.
Results
The levels of apelin in both groups were significantly lower than in control group – 0,882(0,788;0,924) ng/ml in hypertensive patients with T2D and 0,886(0,846;0,937) ng/ml in hypertensive patients without T2D versus 1,097(0,944;1,171) ng/ml in healthy volunteers ($P<0,001$ and $P<0,01$ respectively). The significant difference in apelin levels between patients with T2D and without T2D has been not found ($P>0,05$). The hypertension patients with T2D had significant negative correlations of the apelin with HbA1c ($r=-0,45$, $P<0,05$), insulin ($r=-0,48$, $P<0,05$) and HOMA ($r=-0,47$, $P<0,05$). The patients without T2D had significant positive correlations of the apelin with insulin ($r=0,71$, $P<0,001$) and HOMA ($r=0,76$, $P<0,001$). The levels of apelin were significantly higher in the patients without T2D, but with the insulin resistant (HOMA $>2,77$), than in patients without T2D and normal HOMA - 0,937(0,916;1,112) ng/ml versus 0,851(0,839;0,884) ng/ml, $P<0,001$.
Conclusion
The presented data are confirmed the compensatory increasing of the antidiabetic apelin factor in the initial manifestations of carbohydrate metabolism disorders and its subsequent decline is associated with the development of the T2D.

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EP459

Maturity-onset diabetes of the young type 5 (mody 5): a case report

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Introduction
MODY 5 is a rare type of dominantly inherited diabetes mellitus. It is asociated with mutations of the hepatocyte nuclear factor-1beta (HNF-1beta) gene. They are mostly missense mutations that produce truncated proteins with a variable clinical spectrum that encompasses among others: kidney, genital and pancreatic abnormalities.
Case-report
A 35 years-old man without relevant medical history, presented with acute hypergycemia (541 mg/dl) and ketosis but wihout metabolic acidosis. He had had cardinal symptoms for a 2-week period before presentation. Further investigation revealed a diagnosis of early onset diabetes in his mother, three siblings and a niece who also had undergone nephrectomy due to polycystic kydney disease. Laboratory workout revealed acute renal injury (MDRD4 57.2 ml/min per 1.73 m^2) and elevated liver enzymes with a cholestatic pattern (Gamma-GT 74U/l; Alkaline Phosphatase 154 U/l; Bilirrubin 1.7 mg/dl), both resolved before

discharge. No other abnormalities were detected. Abdominal US was normal. During hospitalization, the patient progressively achived adecuate glucose and he was discharged with a basal-bolus insulin regimen, pending on the results of pancreatic autoimmunity, and the performance of a magnetic cholangioresonance. During follow-up the patient showed no evidence of islet-cell antibodies nor glutamic acid decarboxylase autoantibodies (Anti GAD65 0.46 IU/ml, Anti IA2 2.13 U/ml, anti insulin 0.51 U/ml), a C- peptide of 237 ng/ml and the magnetic cholangioresonance that revealed aplasia of the dorsal pancreas. The diagnosis of MODY 5 diabetes was made after a genetic study for detecting HNF-1beta gene mutations confirmed a missense mutation (M_000458.2:c.884G > A - p.Arg295His-) in the DNA-binding homeodomain. The insulin was progressively withdrawn and metformin was introduced.

Conclusion

MODY 5 encompasses a wide clinical spectrum. Analysis for mutations of HNF-1B is warranted in young patients with an AD pattern family history of diabetes particularly when pancreatic atrophy, kidney or genital abnormalities are present.

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EP460

New-onset diabetes after transplantation (NODAT): an evaluation of risk factors in renal transplantation

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Background

The identification of patients with high risk of diabetes mellitus (DM) after renal transplantation in the pre-transplantation period is crucial for the prevention of this pathology and reduction of the risk of cardiovascular morbidity and mortality. With this study we intended to identify the risk factors for NODAT in renal transplantation.

Methods

All patients submitted to renal transplantation at Centro Hospitalar do Porto between 01/01/2009 and 12/31/2013 were retrospectively evaluated. Patients with history of DM, transplantation of more than one organ, younger than 18 years at transplantation, and patients with less than 6 months of follow-up were excluded. DM was defined according to WHO criteria. To identify risk factors for DM, two groups were formed: people with diabetes (DM+) and without diabetes (DM−).

Results

Of the 556 patients undergoing renal transplantation, 247 patients were excluded and 309 patients were eligible for the analysis. A total of 68 patients (22%) with DM criteria were identified, with a mean time to onset of the disease of 8.9 ± 15.3 months posttransplant. Patients were followed for an average of 4.2 ± 1.5 years (DM+) and 4.2 ± 1.8 years (DM−). DM + patients were significantly older at the time of transplantation (54.1 ± 11.5 vs 45.7 ± 13 years, $P < 0.001$), had higher frequency of family history of DM (30.9% ($P < 0.001$), higher obesity rate (17.6% vs 4.6%, $P < 0.001$) and higher deceased-donor rate (86.8% vs 75.5%, $P = 0.048$). There was no statistically significant difference between groups in recipient sex distribution, donor age and sex, renal disease etiology, immunosuppressive therapy used or HCV/CMV infection occurrence.

Discussion and conclusion

The only modifiable pre-transplant risk factor found is obesity, whereby a healthy lifestyle and weight loss should be encouraged within the specific limitations of patients with end-stage renal disease. Since cardiovascular diseases are the main cause of morbidity and mortality in these patients, a tight control of all vascular risk factors is required.

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EP461

Malnutrition and sarcopenia in diabetic institutionalized older people: are there differences with non diabetic people?

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Backgrounds and aims

The aims of the study were, on the one hand, to analize the prevalence of type 2 diabetes mellitus in a population of institutionalized older people and, on the other hand, to evaluate if the anthropometric parameters and the prevalence of malnutrition and sarcopenia were different in diabetic patients compared with the group of non-diabetics.

Methods and material

A total of 312 institutionalized elderly people volunteers with a mean age of >65 years were selected, being 207 women and 105 men. They had preserved functional capacity and absence of cognitive impairment. Anthropometric variables were measured, test of physical performance were carried out and muscle mass was determined by bioelectrical impedance analysis (BIA). For the diagnosis of sarcopenia, the criteria recommended by the European Working Group on Sarcopenia in Older People (EWGSOP) were used, which consist of using the presence of both low muscle mass and low muscle function (strength or performance), and the method to evaluate if the patients had malnutrition was the Mini Nutritional Assessment test.

Results

The prevalence of type 2 diabetes mellitus in this population was 21.15%, being 57.6% of them women and 42.4% men (P 0.089). There were statistically significant differences in the variables age, weight, BMI, arm circumference, tricipital skinfold and abdominal circumference, between diabetic and non diabetic people, being all this variables higher in the diabetic group. According to the results of the MNA test, the prevalence of malnutrition in the diabetic group was of 52.2%, while in non diabetic people was 44% ($P < 0,05$), and with regards to the prevalence of sarcopenia, there were statistically significant differences between the non diabetic group, in which the prevalence of sarcopenia was 27.3%, and diabetic people, with a higher prevalence (36.58%).

Conclusion

The prevalence of type 2 diabetes was 21.15%, which was higher in women than in men, without statistically significant differences. Moreover, there were significant differences in the anthropometric parameters evaluated and the prevalence of malnutrition and sarcopenia was higher in the diabetic group.

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EP462

New onset diabetes after transplantation (NODAT): frequency and characterization of patients in renal transplantation

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Background

The identification of patients with NODAT in renal transplantation is essential to establish adequate treatment and to reduce cardiovascular risk and graft failure. With this study we intended to evaluate the frequency of NODAT and to characterize patients with NODAT in renal transplantation.

Methods

All patients submitted to renal transplantation at Centro Hospitalar do Porto between 01/01/2009 and 12/31/2013 were retrospectively evaluated. Patients with a history of DM, transplantation of more than one organ, younger than 18 years at transplantation, and patients with less than 6 months of follow-up were excluded. DM and intermediate hyperglycemia were defined according to WHO criteria. Patients with hyperglycemia in the postoperative period were considered diabetic only if they maintained criteria 3 months after transplantation.

Results

Of the 556 patients undergoing renal transplantation, 247 patients were excluded and 309 patients were eligible for the analysis. DM screening was performed on all patients by assaying fasting blood glucose; No patient performed PTGO; 88 patients (28.5%) had no recorded HbA1c. The mean follow-up time was 4.2 ± 1.7 years; 99 patients (32.4%) presented alterations in glucose metabolism: 68 (22%) DM criteria, 17 (5.5%) fasting glucose anomaly and 14 (4.5%) transient postoperative hyperglycemia. The mean time to onset of DM was 8.9 ± 15.3 months, with 73.5% of the diagnoses performed in the first 6 months after transplantation. The diagnosis was established through fasting glycemia in 51 patients (75%), HbA1c in 13 (19%) and typical symptoms in 4 (5.9%). Of the 60 patients currently undergoing follow-up, 15 (25%) were without anti-diabetic drugs, 22 (36.7%) with non-insulin anti-diabetics and 23 (38.3%) with insulin. The mean values of fasting blood glucose and HbA1c are 113 ± 33 mg/dl and 6.8 ± 1.4%, respectively.

Discussion and conclusion

We believe that the prevalence of DM found is underestimated considering the use of fasting glycemia as a preferential screening method, which is not very sensitive to the diagnosis of DM in patients undergoing corticosteroid therapy. PTGO would be a valuable complementary diagnostic test to increase diagnostic sensitivity, especially in patients with fasting blood glucose anomalies or classic risk factors for DM.

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EP463

Incidence of diabetic ketosis and ketoacidosis in Caucasian adults with type 2 diabetes mellitus: a population-based study

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Aims
Diabetic ketosis (DK) and diabetic ketoacidosis (DKA) are known complications of type 1 diabetes mellitus (T1DM). However, DK and DKA have been described in T2DM. Referred to as *ketosis-prone T2DM,* this subtype of *T2DM* has been described in Hispanics and Afro-Americans of sub-Saharan Africa, but the incidence and pathogenesis remains unknown. We aimed to analyze characteristics of patients with diabetic ketosis (DK) and diabetic ketoacidosis (DKA) in Caucasian adults with T2DM.
Methods
Studied population included 261 749 adults. DK criteria included plasma glucose >13.9 mmol/l, and ketonuria >2; while in DKA bicarbonate <18 mEq/l or pH <7.30 was also required. Hyperglycemic crises without these criteria were defined as non-ketotic hyperglycemia (NKH).
Results
During 5-year period, we observed 630 episodes of DK and 215 episodes of DKA. Only 8.6% of DK episodes and 34.4% of DKA were attributed to T1DM. Patients with T1DM were younger, leaner, majority had newly diagnosed disease, and hyperglycemia was the main cause of admission. Stadardized incidence ratio for DK was 48.1 (95% CI 44.5–52.1) and 17.0 (95% CI 14.9–19.4) for DKA. Incidence for both DK and DKA was increasing with age. Patients with T2DM had a risk of 0.8% for developing DKA and 2.9% for DK over 5-year period.
Conclusions
Our study showed that DK and DKA are not uncommon in Caucasian adults and the majority of episodes were contributed to T2DM. Further studies are needed to assess the impact of these clinical entities.

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EP464

HOMA-IR and HOMA-islet indices in the evaluation of different carbohydrate metabolism disorders during glucocorticoid therapy

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Introduction
Diabetogenic effect limits the use of glucocorticoids (GC).
Aim
To evaluate the role of modified HOMA-IR and HOMA-islet indices in different carbohydrate metabolism disorders (CMD) during oral (OGCT) and PULSE (GCPT) glucocorticoid therapy (GCT).
Patients and methods
A study including 165 patients with systemic lupus erythematosus ($n=53$), systemic vasculitis ($n=45$) and chronic glomerulonephritis ($n=67$) was performed. 98 patients received GCPT (course dose – 1800–3000 mg) and 67 – OGCT 15–30 mg/day.
Results
GCPT was associated with less CMD compared to OGCT. Impaired fasting glucose (IFG) was observed in 8 (8.2%) and 14 (20.9%), impaired glucose tolerance (IGT) – in 13 (13.3%) and 21 (31.3%) and diabetes mellitus (DM) – in 12 (12.2%) and 19 (28.4%) patients receiving GCPT and OGCT, respectively. There was a significant decrease of HOMA-islet during glycemic peak in DM patients from 13.96 to 6.17 after GCPT ($P<0.05$), compared to insignificant changes in other groups. After a course of GCPT HOMA-islet was significantly lower in DM patients compared to patients with no CMD (11.8 vs. 15.4). No rapid decrease of β-cell function was observed in OGCT group, instead there was a compensatory increase. Significant differences were observed in patients receiving OGCT both at baseline and after OGTT on HOMA-IR (4.53 vs. 9.81 in patients with IGT; 5.6 vs. 11.27 in patients with DM); no differences were observed in patients without CMD (2.59 vs. 2.88) and with IFG (2.88 vs. 5.85). A significant decrease of β-cell function was observed in DM patients, reflected by a decrease of HOMA-islet after OGTT compared to baseline (147 vs. 78.4).
Conclusion
The evaluation of modified HOMA-IR and HOMA-islet indices before the start of intensive GC treatment and during OGCT may improve early detection of risk groups for serious CMDs – IGT and DM.

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EP465

Carbohydrate metabolism disorders associated with different glucocorticoid therapy schemes

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Introduction
Glucocorticoid therapy (GCT) is one of the risk factors of carbohydrate metabolism disorders (CMD) in patents with systemic inflammatory diseases. CMD development is a concern not only with long-term therapy, but also during intensive short-term glucocorticoid (GC) administration, which can lead to different CMDs, including impaired glucose tolerance (IGT) and diabetes mellitus (DM).
Aim
To evaluate the prevalence of CMD after long-term and intensive GCT in patients with systemic lupus erythematosus (SLE), systemic vasculitis (SV) and chronic glomerulonephritis (CGN).
Patients and methods
The study included 165 patients, among them with SLE – 53, SV – 35 and CGN – 67 patients. Ninety-eight patients received GC pulse-therapy (GCPT) (one series of three sessions), and 67 – oral GCT (OGCT). All patients underwent standard clinical and laboratory evaluation, oral glucose tolerance test (OGTT), evaluation of C-peptide, HOMA-IR and HOMA-islet indices.
Results
CMDs developed less often in patients receiving GCPT compared to long-term OGCT ($P=0.035$). In patients receiving OGCT the most prevalent CMDs were IGT and DM – in 21 (31.1%) and 19 (28.4%) patients respectively, which was significantly higher compared to patients in GCPT group ($P=0.038$ and $P=0.049$). In both groups of patients with DM and IGT baseline C-peptide and HOMA-IR before the treatment and OGTT was higher than in patients without CMD or with IFG, which indicates the presence of insulin resistance in this patient group. In DM patients a decrease of HOMA-islet index was observed in the first group from 13.96 before OGTT to 11.8 after glucose load and in the second group from 147 at baseline to 78.4 after the test.
Conclusion
GCT leads to IGT and DM in patients with increased insulin resistance both during GCPT and long-term OGCT. Long-term OGCT is associated with more CMDs compared to GCPT.

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EP466

Type B insulin resistance syndrome in a patient with connective tissue disease

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Introduction
Type B insulin resistance syndrome is an autoimmune disorder characterized by the production of autoantibodies against the insulin receptor. It leads to glucose metabolism disorders, extreme insulin resistance, hyperandrogenism and is associated with other features of autoimmunity.
Case report
A 27-year-old man, with a 2-years history of psoriasis, was admitted to our Department because of loss of weight (20 kg in 1 year) and fatigue. He also

reported Raynaud's phenomenon. One year earlier the patient underwent careful haematological assessment because of peripheral lymphadenopathy and enlarged parotid glands, which showed changes characteristic for viral infection. Screening for cancer was negative. On admission, physical examination revealed malnutrition (BMI 16.4 kg/m^2), acanthosis nigricans, sclerodactyly, psoriatic lesions, enlarged parotid glands, palpable cervical and axillary lymph nodes, tachycardia. Laboratory analyses revealed anaemia, leucopaenia with lymphopaenia, thrombocytopaenia, blood glucose concentration – 361 mg/dl with tendency to morning hypoglycaemia, HbA1c – 12.4% and glycosuria. Fasting C-peptide concentration was normal and increased adequately in glucagon stimulation test (0′ 2.87 ng/ml, 6′ 4.56 ng/ml). Fasting insulin concentration was extremely high (>300 μIU/ml). In hyperinsulinaemic euglycaemic clamp insulin sensitivity index was decreased (M-2.1 mg/kg FFM/min). We confirmed the presence of anti-insulin-receptor antibodies, indicating type B insulin resistance syndrome. Anti-GAD, IAA, IA2 antibodies were negative. Based on the clinical features, presence of antinuclear antibodies, anti-RNP/Sm antibodies, and positive direct Coombs test diagnosis of mixed connective tissue disease/lupus erythematosus was made. Tumour of blood cells was excluded. Firstly patient was treated with insulin and metformin and then with metformin, prednisone and chloroquine phosphate, which resulted in weight gain, normalization of blood glucose levels (HbA1c – 7.3%) and improvement of blood cell counts and skin lesions. Currently the patient is under metformin and hydroxychloroquine therapy.

Conclusion

We presented a case of severe type B insulin resistance syndrome, associated with another autoimmune disease. Anti-insulin-receptor antibodies are crucial to recognize the syndrome. The treatment is challenging and requires multidisciplinary approach.

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EP467

Parvovirus B19 infection may have a role in the etiopathogennesis of type 1 DM

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Parvovirus (Erythrovirus) B19 (EVB19) infection may trigger autoimmune diseases like SLE, RA, and vasculitis. Parvovirus B19 belongs to the parvoviridae family and to the erythrovirus genus. The etiopathogenesis of autoimmune diabetes mellitus could not been explained yet. The aim of our study was to investigate whether EVB19 may have a role in the etiopathogenesis of type 1 DM. Therefore have we examined whether EVB19 is more frequent among type 1 diabetics. 32 patients with type 1 diabetes and 30 control patients were included in the study. 25 of the 32 type 1 diabetic patients had parvovirus B19 IgG positive sera. The seroprevalence of IgG parvovirus B19 among controls were in 16 of 30 persons. This was statistically significant (p level was 0,039). 25-OH vitamin D levels were lower among Parvovirus B19 IgG seropositive patients than higher patients. This may be related to the fact that the immune status is impaired in vitamin D insufficiency. In conclusion, parvovirus B19 infection may play a role in triggering type 1 diabetes and low vitamin D levels may increase susceptibility to parvovirus B 19 infection.

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EP468

Hyperinter study: evaluation of glycemic values in acute inpatients from medical and surgical units. population without diabetes

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Introduction

Although inpatients hyperglycemia is a current uneasiness among the medical community, its prevalence in Portugal in unknown. We aim to identify 'Stress hyperglycemia' and 'New onset diabetes' cases in inpatients in a district hospital.

Methods

We evaluated inpatients from Internal Medicine (IM), General Surgery (GS), Orthopedics and Traumatology (OT) and Stoke Unit (SU) departments, admitted from the emergency department, during August 2017. Excluded patients who were diabetic (phase 1). Non diabetic integrated a 3 phase study: phase 2 – Capillary glycemia evaluation 2 h after first meal; if >140 mg/dl, patient did another evalution (fasting, 2 h after meal) (phase 3); if patient still hyperglicemic, the evaluated HbA1c and hemoglobine (phase 4).

Results

Evaluated 317 patients (121 diabetic, 196 non diabetics). Non diabetic group: 89 female, 107 male, age average 68.75±18.55 years, 75 patient from IM, 75 from GS, 33 from OT and 13 from SU. 134 patients finished in phase 2, 47 in phase 3 and 15 in phase 4. From patients that finished in phase 4, A1c average was 6.12± 1.3% (four: A1c ≥6.5% and three: 5.7 <A1c < 6.5%). In the previous group, only one patient had a hemoglobine <12 g/dl and three were under corticosteroids. There was no statiscal signficance between glucose values and the section of internament or days of hospital admission.

Discussion

In the non diabetic group we calculated a 23.98% of 'Stress Hyperglycemia', 7.66% of the patients were at higher risk of developing diabetes, because they had at least two hyperglycemic values and 2.04% were positive for Diabetes Mellitus (HbA1c ≥6.5%). The study identified a relevant percentage of people with a higher risk of developing diabetes, but a small percentage of people with diabetes; this might be explained by the efficiency of the national screening programmes.

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EP469

Evaluation of oral glucose tolerance test as a screening test detecting glucose metabolism impairment in patients chronically treated with glucocorticoids without previous history of diabetes

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Introduction

One of the most common side effects of glucocorticoid treatment is glucose intolerance and diabetes. Although glucocorticoids cause mainly postprandial hyperglycaemia the International Diabetes Federation, American Diabetes Association and The European League Against Rheumatism recommend to screen patients chronically treated with glucocorticoids by regularly determining fasting plasma glucose. Such an approach can lead to false negative results. Since pre-diabetes and diabetes lead to life-threatening conditions such as chronic renal failure and myocardial infarction it is important to correctly diagnose these conditions.

Objectives

The aim of the study was to evaluate if oral glucose tolerance test (OGTT) is a better screening tool than plasma fasting glucose levels in diagnostics of diabetes in patients chronically treated with glucocorticoids without previously diagnosed pre-diabetes or diabetes. The second objective was to determine the risk factors of developing steroid-induced glucose metabolism impairment.

Material and methods

In 50 patients on GCS treatment diagnosed with connective tissue diseases OGTT was performed. All participants underwent clinical and biochemical evaluation (age, sex, time of treatment, current and cumulative dose and type of steroid, family history of diabetes, BMI, WHR, HbA1c, HOMA-IR).

Results

13 patients (28%) had impaired glucose tolerance (three of them had coincide impaired fasting glucose). One patient (2%) diagnosed with diabetes had normal levels of plasma fasting glucose. 36 patients had normal glucose metabolism. Apart from age the statistical analysis showed no significant difference between groups in the rest of analyzed parameters thus the prediction of risk factors was impossible.

Conclusions

Only by performing OGTT 22% of patients could be correctly diagnosed with pre-diabetes and diabetes. The oral glucose tolerance test is the only standardized tool that is able to effectively detect the steroid-induced impairment in glucose metabolism. It should be performed in every patients chronically treated with GCS even without other risk factors of diabetes.

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EP470

Impact of exercise training on insulin sensitivity estimated by HOMA model in elite athletes: association with body composition

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It has been shown that low values of insulin sensitivity have been related to metabolic diseases. Exercise prescription is crucial to prevent low insulin sensitivity in general population, and athletes are good physiological model. If this assumption is correct, examine insulin sensitivity in elite athletes should reflect the positive effect of exercise on insulin sensitivity. The aim of this study was to investigate the effects of regular exercise on insulin sensitivity estimated by HOMA model in elite athletes, as well as the possible relationship the insulin sensitivity with body composition. Sixteen low fat athletes (LFAG, BF $<$ 12%), 15 high fat athletes (HFAG, BF $\geq$ 12%) and 15 sedentary subjects participated in study. The subjects underwent to an assessment of body composition. All subjects were exposed to one bout exercise test on treadmill in order to examine acute changes of insulin response. Blood samples were obtained at rest, immediately after the exercise test and 30 minutes after recovery. Separated serum were used for insulin ELISA analysis and glucose levels. Insulin resistance index (HOMA-IR) was calculated. At rest, LFAG had significantly lower insulin compared to control group ($P < 0.05$). Also, there were no statistically differences in basal level of glycaemia and HOMA index between groups. In all three study groups insulin levels were higher immediately after an acute bout of exercise compared to baseline values ($P < 0.05$), and remained equal (LFAG, $P < 0.05$ compared to baseline) or even higher ($P < 0.05$, HFAG, $P < 0.05$, controls) in recovery. There is no significant correlation between the parameters of body composition and HOMA-IR in all groups. In conclusion, our findings show that insulin respond to acute exercise depends on body composition. Acute exercise elicited higher insulin response in HFAG and controls. Also, these results suggest that chronic exercise dose not altered insulin sensitivity estimated by HOMA model in elite athletes.

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EP471

Abstract withdrawn.

EP472

Dysregulation of the splicing machinery could represent an early, predictive event in the development of type 2 diabetes

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Metabolic syndrome (MetS) and type-2 diabetes (T2D) development is critically affected by the loss of phenotypic flexibility (i.e. the difficulty to cope with stressors to maintain metabolic homeostasis). Thus, it is essential to identify key modifiers of phenotypic plasticity that define individual susceptibility to develop T2D. Particularly, there is emerging evidence that alternative mRNA splicing is dysregulated under adverse metabolic-conditions, such as T2D, in several tissues. Therefore, we hypothesized that, as gene expression pattern in PBMCs commonly reflects disease-characteristic expression patterns, changes in spliceosome components of PBMCs may serve as early indicator of MetS/T2D development. To explore this, the expression of selected components of the major ($n = 13$) and minor spliceosome ($n = 4$), and associated splicing factors (SFs; $n = 28$) was evaluated in PBMCs of individuals with high risk to develop T2D due to a previously occurred cardiovascular event (CORDIOPREV study). Specifically, 87 patients that developed T2D during the first 3-year follow-up (43 during the first, 23 during the second and 21 during the third year) and 87 non-T2D matched controls were selected. PBMCs were isolated from basal and post-prandial blood at the inclusion in the study. Results revealed that the basal expression of certain splicing-machinery components was altered in PBMCs from patients who developed T2D (e.g. SRSF5, U2AF1) compared to controls, especially on those patients that developed T2D in a short-term (first year of study). The most remarkable changes were observed during the post-prandial response wherein expression of several SFs (e. g. PTB, Tra2beta) was drastically induced in T2D-developing individuals compared to controls, which might suggest that the alteration of these SFs precedes the development of T2D. Taken together, our results reveal the existence of pre-T2D development-associated spliceosome alterations, which could be related to the loss of phenotypic flexibility, and could help to predict development of T2D in high-risk patients.

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EP473

Abstract withdrawn.

EP474

Debut diabetes characteristics

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Background
The diabetes type 1 (DM1) is a chronic autoimmune disease, it tends to appear in childhood, its incidence continues to rise and the complications arising from improper care poses serious health problems for those who suffer. LADA diabetes is autoimmune diabetes which appear in adults.
Objetive
To describe the characteristics of the new diabetes debut in our environment.
Material and methods
We included all patients who attended the Diabetes Day Hospital of our hospital for unknown type 1 or MODY diabetes from October 2015 to September 2016.
Results
A total of 43 patients were enrolled. With an average age of 36 ± 13 years, 48.8% were men. The 34.9% were LADA type diabetics and the rest DM1. At diagnosis they had a mean BMI of 23 ± 4 kg/m^2, with an abdominal perimeter of 86 ± 12 cm, mean arterial tension $116 \pm 17/70 \pm 12$ mmHg. An average glucose concentration of 238 ± 106 mg/dl and an HbA1c of 11 ± 3%, initial cholesterol of 173 ± 40 mg/dl, HDL 46 ± 16 mg/dl, LDL 103 ± 34 mg/Dl was noted. The level of peptide C at the diagnosis was 0.3 ± 0.2 ng/dl (*N* up to 0.5 ng/dl). In DM-1, 72% of patients had positive anti-GAD antibodies and 78% had anti-IA2 antibodies. In the patients with diabetes type LADA 61% had positives only the Anti IA2, 24% antiGAD, the rest had positives both. Of the patients, 8% associated autoimmune thyroid disease. Without other autoimmune comorbidities.

Conclusions
The incidence of type 1 diabetes and MODY type diabetes is increasing in recent years. In our setting, 78% of patients with DM-1 have positive antibodies. There were few comorbidities al diagnosis.

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EP475

Effect of vitamin D supplementation on Glucose Tolerance, HOMA indices and on the risk of GDM in pregnant women with vitamin D deficiency - a prospective interventional study

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Background
Vitamin D deficiency and GDM are highly prevalent with long term implications. Prospective studies to analyse the effect of vitamin D supplementation on glucose tolerance in pregnant women are limited.
Objectives
Objectives of the study are: 1) To determine the relation between vitamin D deficiency and HOMA indices and glucose tolerance in the first trimester among pregnant women. 2) To study the effect of vitamin D supplementation on HOMA indices and on the occurrence of GDM in pregnant women with vitamin D deficiency.
Methods
50 pregnant women in first trimester were enrolled. FPG, 2 hrPG, FPI, Plasma 25(OH)D were done and HOMA IR and HOMA B were calculated at baseline and at 28 weeks of gestation. Vitamin D deficient women were prescribed 2000 IU of vitamin D per day as per ACOG recommendations.
Results
There was no correlation between 25(OH)vitamin D and FPI, FPG, 2hrPG, HOMA IR and HOMA B in both vitamin D deficiency and sufficiency groups in the first trimester. At 28 weeks of gestation, in the vitamin D deficiency group, significant rise in FPG, 2hrPG, FPI and HOMA IR occurred despite correction of vitamin D deficiency with supplementation. The risk of GDM was similar in both the groups.
Conclusion
There is no correlation between 25(OH)D and HOMA IR, HOMA B, FPG or 2hrPG in the first trimester of pregnancy. Vitamin D supplementation, in pregnant women with vitamin D deficiency, has no role in decreasing the risk of GDM at 28 weeks follow up.

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EP476

Rapid tests use in the evaluation of neurocognitive effects of Ramadan fasting in type 2 diabetic patients: Results of a pilot study

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Introduction
Ramadan is the 9th month of the Muslim calendar, where people fast from the sunrise to the sunset. Despite medical recommendations, 100 million Muslims in the world with diabetes and 79% of patients with type 2 diabetes fast during Ramadan.
The aim of our study is to determine the impact of fasting during Ramadan on the cognitive performances for patients with type 2 diabetes using two fast tests.
Materials and methods
Patients voluntarily accepted to participate to this study. The socio demographical and metabolical characteristics were collected. The evaluation of the neurocognitive performances was obtained using two tests: Digit Span test which explores the short-term memory and Cancellation test which explores the Visio spatial component. Patients were explored before, during and after Ramadan. The results obtained were analyzed by ANOVA one factor.
Results
The study concerned 16 type 2 diabetic patients. Females represent 66.7% and mean age was 55.8 ± 14.73. The mean duration of diabetes was 5.06 ± 4.02 years. The mean HbA1c was 7.52%. The means of Digit Span test were 5.26 before Ramadan, 5.80 during Ramadan, and 5.13 after Ramadan. The comparison by repetitive measures did not show any difference between the three means. Concerning the Cancellation task test, the comparison showed a significant difference in the time response and the scores of the tests between the measures during Ramadan ($P=0.029$) and those after Ramadan ($P=0.015$).
Discussion
These results show that fasting could impact the spatial recognition in type 2 diabetic patients. However, the evaluation of the short-term memory does not show any difference between the three periods. We suggest that the difference in the response time in our patients could be explained by the decrease in the neuronal activity, secondary to the alteration of the carbohydrates intake cycle. This suggests the importance of the regularity of the food intake in the conservation of an appropriate cognitive functioning. However, this difference in results of the two tests shows the complexity of the neurocognitive processes. Thus, they represent an interesting way to explore it.

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EP477

Lack of postpartum reclassification test in gestational diabetes – factors conditioning loss of follow-up

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Introduction
Gestational diabetes mellitus (GDM) is a risk factor for maternal-fetal complications and development of diabetes or intermediate hyperglycemia after pregnancy. The follow-up should be done by a multidisciplinary team. After delivery, all women diagnosed with GDM should undergo an oral glucose tolerance test (OGTT) for reclassification
Aim
To evaluate the non-adherence factors to reclassification OGTT after GDM.
Methods
A cohort of 5271 Portuguese women from the National Registry of GDM was studied. Demographic, anthropometric and analytical data and maternal-fetal outcomes were evaluated. The diagnosis of DGM was made according to WHO criteria.
Results
In our sample, 1666 (31.5%) women with DGM did not undergo reclassification OGTT. Of those who underwent OGTT, 92.2% had a normal test, 0.9% diabetes and 6.9% intermediate hyperglycemia. The chance of follow-up loss was 46.5% higher in women below 30 year-old (OR = 1.465, 95% CI = 1.294–1.660, $P<0.001$) and 40.9% higher in those with ≥ 3 pregnancies (OR = 1.409, 95%CI = 1.243–1.599, $P<0.001$). Women treated with insulin during pregnancy had increased adherence to the reclassification test (OR = 1.377, 95% CI = 1.222–1.552, $P<0.001$), but those with worse glycemic control with HbA1c $\geq 5.7\%$ in 3rd trimester had 60% more chance of follow-up loss (OR = 1.608, 95% CI = 1.318–1.962, $P<0.001$). The adherence to postpartum reclassification was also significantly lower when there was fetal (OR = 5.085, 95% CI = 2.402–10.763, $P<0.001$) or neonatal (OR = 4.661, 95% CI = 1.365–16.055, $P=0.013$) death. Age, number of pregnancies, HbA1c in the 3rd trimester and insulin treatment remained statistically significant in the multivariate analysis.
Conclusion
Younger women, with a higher number of pregnancies, worse glycemic control and fetal/neonatal mortality associated with pregnancy appear to be more likely to lose the follow-up. Given the risk of diabetes after pregnancy, we should emphasize the need for OGTT reclassification in the puerperium and define strategies to promote their accomplishment.

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EP478

Gonarthrosis, Diabetes Mellitus (Type 1 or 2), Leptin, Nesfatin-1

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Gonarthrosis is a severe problem of movement system. It is a restrictive health problem for modern human. And also; it is the other restrictive problem which coexistence of diabetes mellitus (DM) and gonarthrosis. Perhaps; an other parameter that is deserved to research for this coexistence is metabolic syndrome. Today, relationship between this clinical conditions are clear enough. And also two lobotuary parameters as Leptin and Nesfatin-1 are an other headstone for obesity and metabolic syndrome. Many studies established relationships between obesity and Leptin, Nesfatin-1 separately. Leptin is a hormone that is made by adipocytes and affects NeuroPeptid-Y levels. Its gene Ob is located in Chromosome-7. Leptin regulates food intake and gain weight. Nesfatin-1 is a hormone that is released by hypothalamus. It regulates hungry and fat sorage. We aimed to evaluate the levels of these two hormones in diabetic patients that have gonarthrosis. 101 patients were measured clinically and laboratory by X-rays, levels of insulin, Leptin and Nesfatin-1 on 2014-2016. 46 patients have Type 1 DM and 55 patients have Type 2 DM. All patients have gonarthrosis clinically and radiologically. 31 of all patients have overweight (25–29.9), 43 patients have obese (30–34.9), 20 patients have severely obese (35–39.9) and seven patients have morbidly obese (40 and up) accoding to BMI. In the Leptin results; there were high levels of 81 patients with insulin resistance. And these patients have increasing BMI. In the Nesfatin-1 results; there were significant lower in diabetic patients except in 11 patients. And also there were correlation between Nesfatin-1 lowerity and overweighty. It seem like Leptin levels is related with BMI directly. High insulin levels may increase Leptin levels. But; Nesfatin-1 is lower almost all patients with insulin resistance. Leptin and Nesfatin-1 has severe regulation on body energy storage. And they deserve more studies about diabetic population with gonarthrosis.

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EP479

A right time for pregnant women with type 1 diabetes mellitus

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Objective
Pregnancy in women with type I diabetes mellitus (T1DM) is associated with an increased risk of various obstetric complications. The purpose of this study was to evaluate relation of HbA1c, delivery age and various diabetes aspects on pregnancy outcome and gestation in women with T1DM.
Methods
This was a cross-sectional study. A total of 48 women hospitalized to the Hospital of Lithuanian University of Health Sciences Kauno klinikos Endocrinology Department were included. Diabetes control was assessed by HbA1C according to An Endocrine Society Clinical Practice Guidelines.
Results
In the 48 women with T1DM, the mean age was 28.7 years old ($\pm$6.1). Based on the area under Receiver operating characteristic (ROC) curve (59.6, $P<0.05$) the optimal age mean for pregnancy and successful delivery was 25 years old. It was found that only 27.1% of women in their first trimester of pregnancy with T1DM had good glycaemic control (HbA1c $\leq$6.5% (48 mmol/mmol)) and 72.9% had poor glycaemic control (HbA1c $>$6.6% ($>$49 mmol/mmol)). Moreover, it was a significantly increase of premature deliveries in women with poor glycemic control ($P=0.002$). To further explore pregnancy outcomes, we fit a logistic regression model to predict the risk of adverse birth outcomes. We found out that pregnant women with T1DM and older than 26 years old had 7.4 times higher risk for negative birth outcomes than younger women fitting the same criteria ($P=0.034$ (95% PI 1.16–47.19).
Conclusion
This short study showed that glycemic control during pregnancy is insufficient in women with T1DM. We found out that poor glycemic control causes premature delivery ($P<0.002$) and age is an important risk factor for pregnancy outcome and gestation, among pregnant women with T1DM. Older than 26 years old women has 7.4 times higher risk for negative birth outcome.

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EP480

The assessment of possible eating disorders among patients with type 2 diabetes mellitus using EAT-26 questionnaire

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Controversial data exist regarding the prevalence of eating disorders in individuals with diabetes. EAT-26 questionnaire is as a validated widely used self-reported tool recommended in general population for assessing eating disorder risk. The study aimed to determine the prevalence of abnormal eating behavior in patients with type 2 diabetes mellitus and a matched sample of nondiabetic control subjects.
Research design and methods
A total 63 participants were randomly selected: 29 patients with type 2 diabetes mellitus and 34 nondiabetic control subjects. No significant differences existed between cases and controls for age or ethnicity. Responses of diabetic patients to the EAT-26 were compared with those of a nondiabetic control group. The score of 20 or higher defined as positive cut off, the mean values of each question in both groups were taking into account.
Results
A total of 14.7% ($n=5$) of the control subjects and 34.4% ($n=10$) of the diabetic subjects scored above the predetermined screening cut off. The majority among screen positive participants were women: 100% in control group and 60% in diabetes group. However, the assessment of the mean values on each item revealed the statistically significant differences registered on 16, 17 question concerning 'eating dieting foods' and 'avoiding food with sugar' ($P<0.001$). The higher average scores were in group of patients with DM 2.03 and 1.58 accordingly vs 0.53 and 0.38 in control group. We suggest that these items could reflect the total scores and distort the data.
Conclusions
Recent research indicates the higher prevalence of possible eating disorders among patients with type 2 diabetes mellitus on the total EAT-26, as compared to the control subjects (34.4% vs 14.7%). Moreover, further work is needed to establish the diagnostic validity of EAT-26 across diabetic subgroup.

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EP481

Mediterranean diet and glycaemic control in a Mediterranean population with type 1 diabetes: a pilot study

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Background
The Mediterranean diet (MD) is the traditional diet of the people living in the Mediterranean basin and has been linked with positive health outcomes e.g. reduced incidence of cardiovascular and neoplastic disease. No study has investigated the relationship between the MD and glycaemic control in a Mediterranean population with type 1 diabetes mellitus (T1DM). Furthermore, it is unknown how well controlled are such patients and whether they follow the MD.

Methods
Patients known with T1DM were randomly conducted through the registry of the Cyprus Diabetes Association. Ethics: Received from the University of Stirling and the Cyprus National Bioethics Committee.
Results
Twenty patients were conducted; eight patients fulfilled the inclusion criteria and completed antropometrics and the questionnaires; six had biochemistry. Age was 34.6 ± 10.7 years. All patients were classified as having moderate adherence to the MD using the MedDietScore scoring system (28.9 ± 5.2; max score 55). Lowest score was seen for potatoes and non-refined cereals (1.4 ± 0.7 and 1.4 ± 0.9; max score 5) and the highest for use of vegetables and olive oil in cooking (4.1 ± 1.5 and 4.8 ± 0.7; max score 5). All six patients with biochemical testing had undetectable levels of fasting blood c-peptide. HbA1c was 63.5 ± 5.8 mmol/mol and fasting glucose levels 227.7 ± 64.8 mg/dl; none had optimal diabetes control i.e. HbA1c ≤ 53 mmol/mol. MD score was unrelated to HbA1c ($\rho = -0.65$; $P = 0.16$) or fasting glucose ($\rho = -0.66$; $P = 0.15$). Mean BMI was 27.0 ± 5.5; 67% were overweight or obese; BMI was marginally related to HbA1c ($\rho = 0.8117$; $P = 0.0499$).
Discussion
Our results show a no association between the MD and glycaemic control although a type 2 statistical error is plausible. Adherence to the MD diet was moderate in-line with our previous research that showed a moderate and reducing adherence in the general population in Cyprus. Furthermore, our results are worrying regarding glycaemic control. A larger study is underway to further investigate these relationships.

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EP482

Analysis of zinc status in type 2 diabetic patients and its correlation with glycemic control

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Introduction
Recent studies have highlighted zinc's dynamic role as a cellular second messenger in the control of insulin signaling and glucose homeostasis. The aim of our study was to assess the concentration of serum and urinary zinc levels in type 2 diabetic patients and to investigate the correlation between this variable and glycemic control.
Methods
Total 54 type 2 diabetic patients and 23 non diabetic healthy subjects (age matched) were enrolled in a cross-sectional study. Patients with malabsorption syndrome, chronic liver disease and chronic renal failure were excluded. Physical examination and laboratory tests, including serum and urinary zinc measurements were performed.
Results
The mean duration of diabetes was 4.32 ± 7.95 years and mean HbA1c was 6.6 ± 2.15%. Compared to control subjects, mean serum zinc level was significantly lower in diabetic patients (1.15 ± 0.29 and 1.07 ± 0.29 mg/l respectively, $P = 0.02$). However, urinary zinc level was significantly higher in diabetic patients than in control group (1.04 ± 1.06 mg/24 h and 0.57 ± 0.4 mg/24 h, respectively, $P = 0.02$). There were a negative correlation between serum zinc and HbA1c levels ($r = 0.85$, $P = -0.01$) and between serum zinc and fasting plasma glucose levels ($r = 0.51$, $P = -0.01$). However, a positive correlation between urinary zinc and HbA1c levels ($r = 0.23$, $P = 0.02$) was observed.
Conclusion
In our study, patients with T2D had lower serum zinc concentration than non-diabetic controls. This reduction could be associated with low zinc dietary intakes and increased urinary excretion relating to polyuria. Further studies were required to determine the role of zinc supplementation in improving glycemic control and preventing vascular complications in type 2 diabetic patients.

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EP483

Bone mineral density in male patients with type 2 diabetes mellitus, with and without hypogonadism

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Introduction
Type 2 diabetes mellitus (T2DM) affects bone metabolism, but its relation with bone mineral density (BMD) remains controversial. It is also known that T2DM is associated with hypogonadism in males. Male hypogonadism can also affect BMD. Thus the aim of this study was to evaluate BMD in male patients with T2DM with and without hypogonadism.
Methods/design
Hypogonadism was defined as serum free Testosterone (fT) value < 5 ng/dl or 5–9 ng/dl + 1 major sign suggestive of androgen deficiency and eugonadism was defined as fT value > 9 ng/dl. We studied 119 patients with T2DM and hypogonadism (Group H) (age: 61.2 ± 8.2 years) and 45 patients with T2DM without hypogonadism (Group NH) (age: 58.4 ± 10.3 years) matched for age, duration of diabetes, BMI and HbA1c. In both groups, we measured, lumbar spine (LS) BMD and total Tscore by Dual-energy X-ray absorptiometry (DEXA).
Results
Mean BMI (kg/m^2) was similar in both groups (H: 30.9 ± 5.0 vs NH: 29.6 ± 5.9, $P = 0.17$). Mean duration of diabetes was 9.4 ± 8.5 years in Group H and 8.6 ± 7.8 years in Group NH ($P = 0.54$) and mean HbA1c was 7.8 ± 1.9% in Group H and in Group NH 7.61 ± 1.5%($P = 0.47$). BMD at LS (g/cm^2) and total T-score measured by DEXA were lower in Group H compared to Group NH (0.53 ± 0.08 vs 0.81 ± 0.07, $P = 0.041$) (−0.12 ± 1.0 vs 0.78 ± 0.72, $P < 0.001$).
Conclusion
Male patients with T2DM and hypogonadism are found to have lower BMD compared to T2DM males without hypogonadism. Thus, in male patients with T2DM, hypogonadism is a risk factor for low BMD.

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EP484

Pregnancy outcome in relation to a disorder of glucose tolerance during pregnancy

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Introduction
Pregnancy as a state of insulin resistance can predict diabetes development in some women, and is associated with increased risk for adverse outcome of neonate and for mother.
Aim
The aim of this study is to analyse pregnancy outcome in relation to a disorder of glucose tolerance during pregnancy.
Matherial and methods
The study included 77 healthy pregnant women in third trimester registered in Center for endocrinology CC Kragujevac that were tested, according to conducted 3 h OGTT with 100 g glucose (ADA criteria). As parameters of adverse outcomes we included: premature labor (before 37 gw., Low Apgar score (< 8), neonatal malformations, respiratory complications, hypoglycemia, birth body weight > 4 000 g or < 2 500 g, hyperbilirubinemia
Results
The mean age of patients was 30.8 ± 4.7 years. The frequency of risk factors for diabetes were: obesity (3.9%), hypertension (5.2%), previous gestational diabetes

mellitus (23.5%), smoking (23.4%), positive family history for diabetes (27.3%). From 77 patients, 18 was with GDM (23.3%). It has been shown that the number of risk factors significantly affect the outcome of pregnancy ($P<0.005$, χ^2 test), and that the degree of disorder of glucose tolerance during pregnancy affect the outcome of pregnancy ($r=0.164$, χ^2 test). It has been shown that patients with normal glucose tolerance usually have a favorable outcome of pregnancy, and a growing number of pregnancies with an adverse outcome.
Conclusion
This study demonstrates that glucose intolerance during pregnancy predicts unfavorable adverse outcome
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EP485

Single standard labour tactic at 39–40 weeks in pregnancy with gestational diabetes – is it the best policy?
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Objective
To assess labour outcomes in pregnancies with gestational diabetes (GD) regarding different delivery tactics.
Design and methods
The retro- and prospective study evaluating labour outcomes included 443 age matched patients with GD had given birth during 2014 (1st group – $n=251$) and 2015 (2nd group – $n=192$) according to the two clinical protocols, respectively. Expectant management in 2014 was supposed to use until 39–40 weeks of gestation in the absence of any earlier delivery indications, in 2015 – until 40–41 weeks similarly. Statistical analysis was performed with SPSS 21.0 (SPSS Inc.) program. Statistical methods used: Student criteria for quantative analysis, χ^2 criteria for quality analysis; $P<0.05$.
Results
Labour induction rate was lower in the second group: 13.5% (26 of 192), than in the first: 17.1% (43 of 251), thus the rate of spontaneous labour raised (74.9% (188 of 251) and 78.2% (150 of 192)). The rate of pre-arranged and urgent caesarian section, macrosomia, diabetic embryopathy did not significantly differ between groups, the same as dysthyroidism and fetal distress after induction of labour: 7% (3 of 43) and 9.3% (4 of 43) – in the first, 7.7% (2 of 26) and 11.5% (3 of 26) – in the second group, respectively. However, uterine inertia rate after induction was twofold lower in the second group comparing to the first one: 7% (3 of 43) and 15.4% (4 of 26), respectively.
Conclusion
Expectant management until 40–41 weeks in patients with GD in the absence of earlier delivery indications has led to the labour complications rate fall and spontaneous labour rate rise. Probably, single standard tactic for labour at 38–40 weeks in all patients with GD is not one of choice. Such management is preferable for high risk antenatal fetal death pregnancies: fetal distress, macrosomia, diabetic fetopathy or severe maternal conditions, first of all, preeclampsia.
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EP486

Insulin autoimmune syndrome: the relationship between insulin, c-peptide and glucose in active and recovering disease states
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Insulin autoimmune syndrome (IAS) is a very rare cause of hypoglycaemia in western countries. One proposed mechanism is anti-insulin antibody capture of prandial insulin followed by the dissociation of insulin from anti-insulin antibody. The first objective was to study the relationship between glucose, insulin and C-peptide during a prolonged glucose load in two patients with active IAS. The second was to study the variation of these parameters between the active and the recovery disease states.
Methods
Two patients with IAS and frequent hypoglycaemic episodes at the time of the first study underwent an extended oral glucose tolerance test with 75 g of glucose (4 h). After apparent clinical and biochemical recovery, the procedure was repeated.
Results
The data observed during the active and recovery states are shown in Table 1.

Table 1

	Hyperglycaemia phase		Hypoglycaemia phase	
State	Glucose Mean peak at 1 h (mg/dl)	Ins/c-pep ratio (uU/ng)	Glucose Mean peak at 3–4 h (mg/dL)	(uU/ng)
Active disease	199 (range 187–210)	7.0	52 (range 45–59)	13.6
Recovery disease	166	11.2		4.9

Active disease state
The insulin/c-peptide ratio increased significantly from hyperglycaemia to hypoglycaemia ($P=0.023$) even after adjusting for the glucose levels (glycaemia to insulin/c-peptide ratio) ($P=0.027$).
Recovery disease state
Patient showed a decrease in hyperglycaemia peak with a corresponding increase in the insulin/c-peptide ratio and a decreased insulin/c-peptide ratio during hypoglycaemia phase.
Discussion
During active disease, a lower insulin/c-peptide ratio during hyperglycaemia and the paradoxical increase during hypoglycaemia seem to support the role of insulin antibodies in the disease. During the recovery state, there is a reversal of these ratios supporting an increase in bioavailable insulin with lower antibody titters.
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EP487

Lipoprotein particle size in women with type 1 diabetes mellitus and its relationship to carotid intima-media thickness
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Although cardiovascular disease (CVD) is greatly increased in type 1 diabetes mellitus (T1DM), patients typically have apparently healthy lipid profiles. Simple measurement of plasma lipids however does not provide information regarding lipoprotein particle size which in the nondiabetic population is independently predictive of CVD. Plasma lipids and lipoprotein subclasses (using polyacrylamide gel-tube electrophoresis) were studied in reproductive age women with T1DM and compared to a matched control group. Outcomes were correlated with carotid intima-media thickeness (CIMT), a validated marker of atherosclerosis. Compared to nondiabetic women, T1DM women were younger (29 vs 34 years) and of lower BMI (24.7 vs 31.3 kg/m^2), with all data reported as median. Total (TC) and LDL-cholesterol (LDL-C) did not differ between groups. Triglyceride (TG) levels were lower (0.76 vs 0.91 mmol/l, $P=0.0331$) and HDL-cholesterol (HDL-C) greater (1.65 vs 1.49 mmol/l, $P=0.00331$) in T1DM. T1DM women had a greater proportion (46% vs 5%, $P<0.0001$) of small LDL-C particles,

lower mean LDL particle size (269 vs 272 Å, $P<0.0001$) and a greater percentage of small-dense-LDL particles (%SDLDL; 3 vs 0%, $P<0.0001$). CIMT correlated positively in T1DM with %SDLDL (r 0.2983, $P=0.0098$) and negatively with LDL size ($r-0.3118$, $P=0.0068$), but did not correlate with TC, HDL-C, LDL-C or TG. Despite apparently healthy lipid profiles, women with T1DM have a greater proportion than nondiabetic women of atherogenic small LDL particles. The likelihood that this is clinically relevant is strengthened by the observed correlation of CIMT with particle size and lack of correlation with standard lipid profile. Further studies are needed to explore the mechanisms underlying these abnormalities.

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EP488

The upper limb infection in diabetic patients (about 32 cases)

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Introduction
The diabetic patient is vulnerable to infection compared to the general population. This is due to the deleterious effect of hyperglycemia on the basis of chemotaxis, phagocytosis and bactericide neutrophils → What weakens the defenses of the diabetic person to infections. Infections of the upper limb in diabetics are not uncommon, and are often characterized by severity and often unfavorable developments. The objective of this work: determine the prevalence, clinical and therapeutic characteristics of the infection of the upper limb in diabetics.
Matériels et méthodes
Study including 32 patients seen in the emergency. The parameters: epidemiological characteristics âge, sex, weight, size, marital status, housing environment, origin, nature of the work, the pets, Characteristics of the diabetes: type, age of the beginning, evolution, treatment, glycemic balance, the follow-up. Characteristics of the lesions: type, Seat, the mechanisms, bacteriological sample. Deadline between the consultation and the appearance of the lesions. Management emergency: medical treatement, surgical care.
Discussion
At our patients, the hurts were grave and spread, this can give some explanation by the delay of the consultation been understandable by the educational lack and by the particularly vulnerable fragile ground to the infections seen the diabetes. The diabetes was discovered on the occasion of the lesions of the upper limb in 18% of the cases, during the evolution, in spite of the institution of a local treatment and an antibiotic treatment, a locol extension regional and sometimes general of the infection drove to make an amputation in 25% of the cases for saving of the patient.

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EP489

The peculiarities of structural and functional state of the myocardium and blood vessels in patients with type 2 diabetes mellitus and arterial hypertension depending on the dynamics of adipokines

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Purpose
To study the features the structural and functional state of the myocardium and blood vessels in patients with diabetes mellitus and arterial hypertension depending on omentin level.
Methods
A total of 65 patients (32 men and 33 women, mean age 51.6 ± 5.2 years); 31-with type 2 diabetes and hypertension (group 1), 34 – with isolated arterial hypertension (group 2). Control group 20 healthy volunteers. We evaluated data transthoracic echocardiography and ultrasound thickness of the intima-media complex of the common carotid artery (IMC CCA). Omentin level in blood serum were determined by ELISA kit.
Results
Left ventricular hypertrophy (LVH) was diagnosed in 67.5% of patients in group 1 and 34.2% of patients in group 2 ($P<0.05$). IMC CCA patients of group 1 was significantly higher than in the comparison group ($P<0.001$). Omentin level in group 1 was reduced in comparison with the 2 – nd group and the control (262.24 ± 10.46, ng/ml versus 296.43 ± 12.72, ng/ml and 379.46 ± 6.22 ng/ml, respectively, $P<0.001$). There was a negative correlation relationship between the content omentin plasma and left ventricular hypertrophy ($r=-0.54$; $P<0.05$) and IMC CCA ($r=-0.46$, $P<0.05$).
Conclusions
It was found that patients with type 2 diabetes and hypertension observed the progression of LVH and remodelling of the vascular wall, which are related to an imbalance omentin serum. Thus omentin reduction level can be considered as a biomarker of cardiovascular complications in these patients.

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EP490

Casuistic from Endocrinology Medical Consultation at Clinica Girassol 2015

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Introduction
There are few studies either hospital bases or population based in Africa and in Angola we also have the same situation regarding endocrinology data. With this paper, the Angolan Society of Endocrinology Diabetes and Metabolism (SAEDM), wants to contribute to the systematic and continued study of endocrine pathology in Angola.
Objective
Study of the casuistic of endocrine pathology in ambulatory setting regarding the year 2015.
Methods
Compilation of data obtained from medical notes files from the ambulatory appointments available in digital and physical support. Files with incomplete data or without prove or clinical-laboratory correlation have been discarded. We designed the distribution of patients according to the pathology, or group of pathologies at the respective frequencies as per sex and age group. Diabetes Mellitus and Obesity have been considered as specific pathologies. Thyroid diseases have been included in the same entity considered as Thyroid Pathologies and the others in a group classified as Other Endocrine Pathologies. Diabetes Mellitus and Obesity (including overweight) were profiled according to the WHO criteria; Disturbances of Thyroid have been established obeying to the ultrasonography criteria or to functional anomalies.
Results
We worked with a pool of 1630 processes (files) related to patients that had endocrine pathology. Ninety one (5.58%) were incomplete. Therefore were excluded because had not confirmation data of endocrine disease. The validated files (1539 files) could be distributed as follows: 1159 (75.3%) corresponding to Diabetes Mellitus, 156 (10.1%) corresponding to Pathologies of Thyroid, 85 (5.5%) corresponding to Obesity and 139 (9.0%) classified as Other Pathologies. Distribution per sex: 794 (51.6%) were women and 745 (48.4%) men. The distribution of pathologies per sex: **Diabetes Mellitus**: 533(45.9%) women and 626 (54.1%) men; for **Obesity**: 56 (65.9%) women and 29 (34.1%) men and for **Pathology of Thyroid** we found 132 (84.6%) women and 24(15.4%) men.

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EP491

Depression and quality of life in patients with type 2 diabetes mellitus

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Introduction
Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease. People with DM have 2.4–4.3 times greater risk of depression than people without DM as well as patients (pts) treated with insulin. Women experience depression more often than men. Symptoms of depression can make it more difficult to successfully manage diabetes and prevent diabetes-related complications.
Materials and methods
A total of 138 subjects (74 males, 64 females; aged 18–80 years) with T2DM participated in cross-sectional study. Two questionnaires: BDI (Beck depression inventory) and SF-36 (Short-Form-36 Health Survey) were used. Using BDI the severity of depression was detected; SF-36 was used for measuring self-reported physical and mental health status.
Results
The prevalence of depression was higher in females with diabetes (45.3%) compared to males (35.1%). Women with depression (29/64 of pts) were aged 39–76 yrs, BMI 22.3–44.6 kg/m^2, HbA1c $>7\%$ was observed in 17/29 of depressive women, duration of DM2 was 2–192 months. Men with depression (26/74 of pts): age 35–79, BMI 23.2–43.2 kg/m^2, HbA1c $>7\%$ in 13/26 of depressive men, duration of DM2 was 6–360 months. According to BDI questionnaire scores, mild depression was reported in 17 male and 15 female pts, moderate depression was found in 6 males and 9 females and severe depression in 3 male and 5 female pts. Mean scores of SF-36 questionnaire were compared between diabetics with and without depression, and correlated to BDI scores. Depressive pts had statistically lower scores than non depressive (both sexes) in Physical functioning, Emotional role functioning, Mental health, Bodily pain (just males) and General health perceptions.
Conclusion
T2DM is associated with an increased risk of depression. In order to prevent negative consequences of non recognized and untreated depression, evaluation of psychological status in patients with T2DM is recommended.

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EP492

Diabetes Mellitus type 1: characterization of patients at the endocrinology ambulatory follow up during the year 2015

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Introduction
Diabetes Mellitus is a chronic disease that has serious effects on the morbi-mortality. Diabetes type 1 is less prevalent, representing 5–10% of the total cases. Data collected in Africa are scarce, and prevalence and incidence at sub - Saharan Africa are about 3-12/100,000 and 1.1–2.1/100,000 people, respectively. The Angolan reality is not known.
Objective
To show the casuistic of diabetes type 1 obtained from the ambulatory consultation of Endocrinology for the year 2015.
Methods
We performed a retrospective study of the available clinical files in digital and physical support. The diagnosis of type 1 diabetes was according to the diagnostic criteria defined by the WHO. Parameters that have been studied: sex, age, A1c, clinical onset, duration of the disease.
Results
In the year 2015, 1630 patients have been observed at the Endocrinology Ambulatory Service. Only 1539 process were considered for analysis. Among these patients, 1159 (75.3%) were diabetic, being 19 of them (1.63%) type 1 diabetics. The distribution by sex was: 9 (47.4%) men and 10 (52.6%) women. The age spread from 4 to 40 years with a mean of 23 years. Diabetic ketoacidosis (63.11%) was the clinic presentation found at the time of the diagnosis. The time of evolution of the disease varied from 6 months to 15 years of age with an average of 4.6 years. The average glycosylated hemoglobin (HA1c) was 8.86%.
Conclusion
The epidemiology of diabetes is not known, and we cannot advance conclusions from the data collected by our team. Most of the patients observed in endocrinology (75.3%) had the diagnostic of Diabetes Mellitus. The fact that type 1 diabetes is more prevalent among women is in accordance to the international data. It is important to highlight that significant number (63%) of the patients have been diagnosed in the status of diabetes ketoacidosis.

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EP493

Bronze diabetes – a rare secondary cause of diabetes

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Introduction
Secondary causes of diabetes refer to a category in which diabetes is associated with other diseases. They are thought to constitute less than 2% of the total cases of diabetes.
Case report
A 56 year-old caucasian man, with no relevant medical history, presented to the Emergency Department with fatigue, polyuria, polydipsia, polyphagia and involuntary weight loss (6 kg in two weeks). He was hemodynamically stable and exhibited a glycaemia of 445 mg/dl without acidosis. Insulin perfusion was initiated and the patient was hospitalized with the diagnosis of new-onset diabetes. Physical examination revealed a greyish skin tone, body mass index of 19 kg/m^2 and hepatomegaly. Blood analysis showed a haemoglobin A1c of 13.4%, negative anti-GAD and anti-insulin antibodies, transferrin saturation of 98% and high ferritin levels (4533 ng/ml). This clinical picture raised the suspicion of diabetes secondary to hemochromatosis. Abdominal ultrasound showed an enlarged liver (19.5 cm) with bright echostructure and the hepatic magnetic resonance imaging described signs of iron overload. Liver biopsy was then performed showing accentuated iron deposits in the hepatocytes, sinusoidal lining cells and bile ducts epithelia. Genetic study identified a HFE gene mutation (C282Y homozygote). Due to possible iron accumulation in the pituitary gland and the patient complaints of erectile dysfunction, pituitary function was evaluated revealing hypogonadotropic hypogonadism (total testosterone 0.59 ng/ml; FSH 3.40 mUI/ml; LH 2.78 mUI/ml) with no other axis affected. Patient was discharged from hospital with a basal-bolus insulin regimen and a 250 mg testosterone monthly enanthate injection. He maintains follow-up with an A1c of 7.3% and undergoing periodic phlebotomies.
Conclusions
In hemochromatosis iron accumulation in the skin and pancreas can lead to hyperpigmentation and impair insulin production causing the so called 'bronze diabetes'. This case alerts clinicians not to overlook secondary causes of diabetes that can be precociously suspected based on a careful physical examination.

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EP494

The epidemiology of type 2 diabetes mellitus and its complications in South Korea

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Background
The prevalence of diabetes in South Korea has drastically increased, and 8.6–11.0% of Korean adults aged ≥ 30 years were suffering for the disease in the early 2000s, according to the Korea National Health and Nutrition Examination Survey.
Objective
The present study was performed to estimate the incidence and prevalence of type 2 diabetes mellitus (T2DM) and its complications in South Korea using the Health Insurance Review and Assessment (HIRA) database from 2010–2015, which covers 96.3% of the claim data of the Korean population.
Methods
T2DM, coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD) were defined as underlying disease and its complications of T2DM. We used the Healthcare Common Procedure Coding System codes provided by HIRA to identify associated procedures or surgeries.

A Poisson distribution was assumed when calculating 95% confidence intervals for prevalence and incidence rates.
Results
After age standardization, the prevalence of T2DM in Korean adults aged more than 30 years, was 6.3–7.5% and the annual incidence rates of T2DM ranged from 9.0–11.0/1,000 person-year during the six year. The incidence rates of T2DM in men and women aged more than 30 years significantly decreased from 2013 to 2015 ($P \leq 0.001$). On the other hand, the incidence in women aged more than 65 years significantly increased from 2013 to 2015 ($P \leq 0.001$). The incidence rates of CAD and CVD with T2DM patients were 21.4 and 13.6/1,000 person-year.
Conclusion
This study estimated the incidences and prevalence of T2DM in most of Korean population which is the great concern for public health. We also confirmed the relatively higher risk of as the complications with the T2DM patients compared to the general population in Korea.

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EP495

Prevalence of obesity and diabetes among in a developing country (Albania)

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It is well known nowadays the positive effect that early detection of prediabetes has in preventing and postponing the diabetes onset. The aim of our study is to explore the diabetes prevalence in Albania and to identify and stratify the population at risk for developing diabetes.
Material and methods
A large scale multicentre screening was performed in Albania as part of a National Campaign. 15744 patients were consecutively recluted. The following data were obtained: age, weight, height, BMI, waist circumference, glicemia, total cholesterol, LDL, Triglycerides, HDL. The subject were suddivided according gender and age group.
Results
In 15744 subjects, 62% females, 38% males, 49% was aged between 40–49 years old, 46% between 50–59 years old and 20% between 60–65 years old. 6.3% were already diagnosed with diabetes mellitus (5.5% female and 7.4% male of the explored population). 15% of the patients who declared not having diabetes had a fasting glycaemia $>$ 100 mg/dl. Of these 15%, 24% had a glycaemic value above 126 mg/dl and 75.6% have glicemic value between 100–126 mg/dl (impaired fasting glucose (IFG) or pre-diabetes. In the population with IFG 39.8% have a BMI between 25–30 and 44.8% kg/m^2 a BMI $>$ 30 kg/m$^{2.}$ 89.5% of females have a WC (Waist circumference) $>$ 80 cm and 74% of males a WC $>$92 cm.
Conclusions
Albania is a developing country who went trough important socio-economical changes in the last decade. We find a high diabetes mellitus prevalence which could be higher because of the not yet diagnosed diabetes. An important role have the pre-diabetes population where a high prevalence of overweight and obesity is observed. Campaign to rise diabetes and pre-diabetes awareness and encourage lifestyle modification are very important to prevent and postpone the diabetes onset in the prediabetes population.

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EP496

Maturity onset diabetes of the young - clinical characteristics of a portuguese cohort

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Introduction
Maturity onset diabetes of the young (MODY) accounts for 1-2% of all forms of diabetes mellitus (DM). As classic criteria that lead to its suspicion have low sensitivity, patients are often misdiagnosed with type 1 or type 2 DM. Correct classification of this type of diabetes becomes essential for proper management of the disease. Our objective was to describe clinical features of patients with MODY diagnosed at our institution.
Methods
We collected clinical data from patients with clinical characteristics and genetic confirmation of MODY.
Results
We included 30 patients (15 females). All patients but one had diagnosis of DM (one female had gestational diabetes, but currently has no criteria for diabetes). Mean age at diagnosis of DM and MODY was 27.5 +/− 10.8 and 46.3 +/− 13.2 years, respectively. Genetic testing was positive for mutation in the Glucokinase (GCK) gene in 3 patients, the ATP-binding cassette transporter sub-family C member 8 (ABCC8) gene in 1 patient and the hepatocyte nuclear factor-1 homeobox A (HNF1A) gene in 26 patients. Currently, 9 patients are exclusively treated with oral antidiabetic agents and 3 patients have no pharmacological treatment. Last mean HbA1c was 7.5 +/− 1.3%. Peripheral neuropathy was diagnosed in 11 patients (36.7%), autonomic neuropathy in 5 patients (16.7%), diabetic retinopathy in 16 patients (53.3%), diabetic kidney disease in 11 patients (36.7%), ischemic cardiac disease in 2 patients (6.7%), vascular cerebral disease in 3 patients (10%) and peripheral arterial disease in 4 patients (13.3%).
Conclusions
There is a relevant delay in MODY diagnosis and clinicians should be alert for this type of diabetes. The most frequent mutation identified in our population was in the HNF1A gene. This study confirms the clinical heterogeneity of MODY patients.

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EP497

The relationship between Serum Vaspin and atherogenic risk factors in T2DM

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Introduction
Increased visceral adiposity is usually associated with a clustering of atherogenic risk factors, such as insulin resistance, hypertension, dyslipidemia, alterations in coagulation and inflammatory cytokine profiles. Visceral adipose tissue derived serpin (Vaspin) is an adipokine with insulin sensitizing effect which is markedly elevated in high body mass index (BMI) people.
Aim
To evaluate serum Vaspin level in relation to atherogenic risk factors such as insulin resistance, dyslipidemia, hypertension, inflammation in obese subjects with T2DM and obese subjects without T2DM.
Method
80 subjects participated, with BMI ranging from 27-39 selected from outpatient clinic of Endocrinology of Ain Shams University Hospital. They were divided into 2 groups 40 obese subjects with T2DM (group I) and 40 obese subjects without T2DM (group II). History, clinical examination, FBS, 2-PP, HBA_{1C}, Total cholesterol, Triglycerides, HDL and LDL, HOMA/IR, Serum Vaspin level (by ELISA) and CRP were done.
Results
Serum Vaspin was higher in group II than group I ($P \leq 0.01$). HOMA-IR was higher in group I than group II (esp. females) with $P \leq 0.01$. Regarding hs-CRP there was no significant difference. In Group I serum vaspin had a negative correlation with age ($P = 0.010$), diabetes duration ($P = 0.015$), a positive correlation with Waist/Hip ratio ($P = 0.047$), and LDL ($P = 0.034$). There were no correlation with BMI, systolic blood pressure, diastolic blood pressure, HA1c, fasting blood glucose, 2 HPP, total cholesterol, triglycerides, HDL, hs-CRP and HOMA-IR ($P > 0.05$). In group II, serum vaspin had no correlation with any of the variants (P-value > 0.05). Vaspin level was found to be independently correlated with male gender and younger age with ($P = 0.031$).
Conclusion
Obese subjects with T2DM have more atherogenic risk profile and lower Vaspin level than obese subjects without T2DM. It was inversely correlated with age and diabetes duration and positively correlated with Waist/Hip ratio, LDL. Male gender and age are strong independent predictors of serum vaspin level. Vaspin may be an important adepokine that may play an important protective role against metabolic disturbance and cardiovascular risk in obese subjects with T2DM.

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Diabetes Complications

EP498

Prevalence of diabetic neuropathy and nephropathy in different ethnic minorities

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Introduction
The focus on diabetic complications has increased over the years yet it is only recently that research has identified a link between ethnicity and the development of diabetic complications.
Aims
To establish the relationship between ethnic group and the prevalence of either diabetic nephropathy or neuropathy.
Method
A retrospective note review was undertaken for all diabetic patients who had a status of 'current' in the database. This returned 6608 patients, however, only 1838 patients met the inclusion criteria. The notes were reviewed, analysed and compared with the current literature on ethnicity and diabetic microvascular complications.
Results
Of the 1838 patients: 56.9% were Caucasian, 13.9% Afro-Caribbean, 23.0% South Asian and 6.3% Other. Afro-Caribbean's had a higher mean systolic blood pressure (139.03 mmHg) compared to other ethnicities with Caucasians having the lowest mean at 132.91 mmHg. Afro-Caribbean's were found to have poorer glycaemic control (69.5 mmol/mol) compared to the remaining ethnic groups. Nephropathy was found to be most common in Afro-Caribbean's (14.3%) followed by South Asians (13.1%). Caucasians and Other groups had lower rates at 7.8% and 8.6%, respectively. Neuropathy was most common in Caucasians (24.4%) and lowest in Afro-Caribbean's (14.7%); the other two ethnic groups, South Asians and Other, had similar levels at 17.4% and 16.4% respectively.
Conclusion
The link between ethnicity and complications was found to be statistically significant ($P<0.01$). Future research and epidemiological studies must focus on why these differences occur and if they are independent of socio-demographic, anthropometric and clinical characteristics.

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EP499

Correlation of homocysteine with macro and microvascular complication in patients with diabetes mellitus type 2

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In recent years, plasma homocysteine (Hcy) level, has been reported to be associated with the vascular complications of diabetes mellitus type 2 (DM2). In patients with DM2, elevated Hcy levels were associated with insulin resistance and nephropathy. The aim of this study was to investigate the association of hyperhomocysteinaemia with micro and macrovascular complications, increased levels of HbA1c and lipid parameters in patients with DM2 in a Macedonian population. 80 DM2 patients were enrolled for the study and were classified into two groups: 30 patients with no associated complications, control, and 50 patients with complications. Homocysteine levels and the other conventional parameters (HbA1c, lipid profile, and microalbuminuria) for identifying complications of DM2 were measured. The Hcy levels were significantly higher in DM2 patients (16.05 ± 6.12 vs 10.44 ± 3.33 micromol/l) compared with control. Significantly elevated homocysteine levels were found in DM2 patients with CAD ($P<0.001$), neuropathy ($P<0.000$), retinopathy ($P<0.05$), high blood pressure ($P=0.02$) and microalbuminiria ($P<0.000$) as compared to control subjects. There was a positive correlation between elevated HbA1c ($r=0.475$) levels and serum LDL-cholesterol ($r=0.871$) with Hcy concentration in DM2 patients with complication. The results of this study have shown that homocysteine levels were significantly higher in DM2 patients with developed micro-/macro-vascular complications and highly positive correlated with HbA1c and serum LDL-cholesterol, also. Results have shown that hiperhomocysteinemia is risk factor in etiology of vascular complications in DM2 patients.

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EP500

Overweight and obesity in pregnant with diabetes mellitus type 1

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Objectives
Pregnant women who are overweight or obese have an increased risk of complications during pregnancy, as do pregnant women with type 1 diabetes mellitus (DM1). The objective of this study is to describe the prevalence of overweight/obesity in pregnant women with DM1, and associated complications.
Patients and methods
Retrospective descriptive study of pregnant women with DM1 (2004–2014). Variables analyzed: age, initial body mass index (BMI), HbA1c, abortions, type of delivery and fetal malformations. Statistical analysis: comparing proportions with the chi-squared and comparing means with Student's test.
Results
156 pregnancies in women with DM1. Age 31.41 ± 4.51 years. At the beginning of pregnancy, 50.4% were normal weight, 36.2% were overweight (12.4% grade 1 and 23.8% grade 2) and obesity was 10.5% (7.6% grade 1, 1.9% grade 2, 1% grade 3). 3% women had BMI <18.5 kg/m^2. Normal weight vs overweight/-obesity: unplanned pregnancies 70.4 vs 66.7% ($P=0.85$); HbA1c (%) previous gestation 7.4 ± 1.4 vs 7.4 ± 1.2 ($P=0.98$), first trimester 7.4 ± 1.7 vs 7.1 ± 1.3 ($P=0.88$), second trimester 6.3 ± 0.8 vs 6.5 ± 0.8 ($P=0.31$), third trimester 6.5 ± 0.8 vs 6.5 ± 0.8 ($P=0.88$); newborn weight 3516.1 ± 735.22 vs 3617.07 ± 693.10 g ($P=0.42$); newborn size 50.9 ± 2.4 vs 50.8 ± 2.5 cm ($P=0.76$). Maternal and neonatal complications (%) normal weight vs overweight/obesity: maternal hypoglycemia 3.7 vs 6.7 ($P=0.7$); gestational hypertension 5.7 vs 12.2 ($P=0.3$); abortions 3.8 vs 9.5 ($P=0.33$); induced childbirth 58 vs 61 ($P=0.92$); caesarean section 38 vs 55 ($P=0.12$); macrosomia 29.4 vs 24 ($P=0.71$); congenital malformations 8 vs 7.1 ($P=0.78$); newborn hypoglycemia 6 vs 5 ($P=0.93$).
Conclusions
In our series, the prevalence of overweight/obesity in pregnant women with DM1 is high, occurring in almost half of pregnancies. There were no differences in glycemic control during gestation or in the occurrence of maternal or neonatal complications associated with overweight/obesity.

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EP501

Does empowerment from an 'ABC approach' and 'Telemedicine' improve outcomes in a nurse-led diabetes kidney clinic?

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Aims
Implementation of a protocol-driven, nurse-led clinic to see influence on cardiovascular risk and renal disease progression using a simple 'ABC' approach – target HbA1c $<7\%$, BP $<125/75$ mm Hg and Cholesterol <4 mmol.
Method
Weekly Diabetes Specialist Nurse (DSN) clinic with emphasis on ABC approach and guided FLORENCE Telehealth free texting technology for medication reminders and self-monitoring of BP (machines provided).
Results
May 2008 – Apr 2009 (12 months) – Cohort A 41 patients. May 2010 – June 2014 (24 months) – Cohort B 133 patients. Mean age 64 years, 78–90% patients Asians/Afro Caribbean. Excellent patient satisfaction scores, significant reductions in HbA1c in Cohort A and B by 0.7% (7.62 vs 8.32%) and 1.5% (9.1 vs 7.6%) respectively, SBP (12–16 mmHg) and DBP (3–6 mmHg) and Cholesterol in all cohorts were achieved. Urine ACR decreased significantly in both cohorts (by mean 17–39 mg/mmol). Number of BP medications (3) increased in all cohorts. 95 and 85% patients respectively in both cohorts were prescribed ACE, ARB or both.
Conclusions
Outcomes suggest that our nurse-led clinic is highly effective in DN patients. The 'ABC approach' and simple information sharing strategy (Telehealth

FLORENCE) were effectively used to inform strategic decision making/intensification of therapy through patient empowerment, up-skilling of knowledge and improved medication compliance – 3 key processes in any chronic disease management.

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EP502

Causes of diabetic ketoacidosis: type 1 diabetes versus type 2 diabetes

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Aim
The aim of our study was to compare the clinical profile of type 1 and type 2 diabetic patients who are hospitalized in our service for diabetic ketoacidosis.
Methodology
This was a descriptive study involving 121 diabetic patients hospitalized for diabetic ketoacidosis in the C department of diabetology of the national institute of nutrition of Tunis.
Results
Of the 121 subjects studied, 57.85% are type 2 diabetic patients and 42.15% are type1. Type 2 diabetic patients are older, have a higher glycated hemoglobin level and a higher BMI compared to the type 1 diabetic patients. For both type of diabetes, the principal causes of ketoacidosis are infectious diseases represented mainly by urinary tract infection. For type 2 diabetic patients cessation of treatement, inaugural diabetes, insulinopenia and lipodystrophy are observed respectively in 22.7, 12.3, 11.9 and 10.1% of patients presenting ketoacidosis. For type 1 diabetic patients cessation of treatment, inaugural diabetes, pregnancy and lipodistrophy are observed respectively in 18.4, 14.6, 8.9 and 7.1% of patients hospitalized for ketoacidosis.
Conclusion
The main causes of diabetic ketoacidosis are infectious diseases and cessation of treatment, in type 2 diabetic patients as well as in type 1 diabetic patients. So that, education remains the best way to prepare diabetic patients to face situations of stress and to have a good therapeutic compliance.

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EP503

Abstract withdrawn.

EP504

Is proteinuria always associated with diabetes mellitus?! Do we always make right diagnosis?!

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Introduction
Proteinuria is a condition in which urine contains an abnormal amount of protein. Proteinuria is a sign of chronic kidney disease (CKD), which can result from diabetes, high blood pressure and other diseases that cause inflammation in the kidneys. If CKD progresses, it can lead to end-stage renal disease, when the kidneys fail completely.
Case presentation
Sixty-three years old female patient attended our clinic as her glycaemia was poor controlled. She is diagnosed with diabetes mellitus (DM) type 2 during 9 years. Laboratory studies were performed: HbA1c- 9.4%, elevated plasma creatinine *176.32* (N53, 0–97.2) and proteinuria in urine with dipstick 1.01 g/l was observed. Additional investigations were performed: kidney ultrasound, which revealed shrunken kidneys, Urea- 64.21 (N 15.0–45.0), Phosphorus-1.98 (N 0.48–2.19), Parathyroid hormone-*273.76* (N 9.0–79.5),Vitamin D-7 (N 30.0–100.0); Potassium-*5.59* (N3, 5–5), pH-*7.26* (N 7.32–7.72) Hemoglobin-*10.2* (N 12–16). The patient had no diabetic specific complications. When DM was diagnosed the patient has already got dipstick proteinuria 0.3 g/l and it was considered as the result of diabetes. Therefore no further investigations were performed to find out the cause of proteinuria. We have not performed renal biopsy to diagnose the real cause of proteinuria, we just started to treat CKD.
Conclusion
Often proteinuria is revelaed when DM is diagnosed, that's why, no further investigations are performed to precise the real cause of it. Yes, hyperglycemia can cause various damages of kidney, but not in all cases. So, we always have to remember that in diabetic patients the cause of proteinuria may be due to other reasons. We always have to pay attention to other diabetic specific complications and always ask about detail clinical history, for correct diagnosis, better management and prevention of progression of renal disease.

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EP505

A Review of the literature: What are the impacts of hypoglycaemia in insulin-dependent diabetic adults?

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Background
The prevalence of diabetes has reached epidemic proportions and according to the World Health Organisation (WHO) more than 220 million people worldwide have diabetes. The main complication in insulin-dependent diabetes mellitus (IDDM) patients is hypoglycaemia, with approximately 90% of all IDDM patients having experienced a hypoglycaemic episode. Hypoglycaemia has a substantial clinical impact in terms of mortality, morbidity and quality of life.
Methods
A systematic search of MEDINE and EMBASE was performed for all relevant published articles. Reference lists of all included studies were also searched. Studies were included assessing fear of hypoglycaemia, recognition of symptoms, health-seeking behaviour and impact on overall wellbeing. One reviewer screened abstracts of all identified citations, selected potentially eligible studies and assessed their full-text versions using the STROBE (Strengthening the reporting of observational studies in epidemiology) checklist for cohort, case-control and cross-sectional studies (combined.) Findings from the studies were then narratively synthesized.
Results
Eight studies were included in this review. After hypoglycaemia, IDDM patients have significantly ($o < 0.01$) raised fears of future hypoglycaemia, more fatigue, reduced alertness and a negative impact on health-related quality of life (HRQL.)
Conclusion
Hypoglycaemia has a wide range of negative emotional, social and behavioural consequences on IDDM patients. These impacts, hence are a major barrier to IDDM patients achieving optimal glycaemic control. There remains a need for a large multi-country study that incorporates mixed-methods data collection, including a qualitative aspect to provide more in-depth views of the effects of hypoglycaemia.

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EP506

A protective effect of lobeglitazone on renal fibrosis in unilateral ureteral obstruction mice model

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Renal tubulointerstitial fibrosis is a common feature of the final stage of nearly all cause types of chronic kidney disease. Although classic peroxisome

proliferator-activated receptor-gamma (PPARγ) agonists have a protective effect on diabetic nephropathy, much less is known about their direct effects in renal fibrosis. This study aimed to investigate possible beneficial effects of lobeglitazone, a novel PPARγ agonist, on renal fibrosis in mice with unilateral ureteral obstruction (UUO). Through hematoxylin/eosin and Sirius red staining, we observed that lobeglitazone effectively attenuates UUO-induced renal atrophy and fibrosis. Immunohistochemical analysis in conjunction with quantitative RT-PCR and western blot analysis revealed that lobeglitazone treatment inhibited UUO-induced upregulation of renal Smad-3 phosphorylation, alpha-smooth muscle actin, plasminogen activator inhibitor-1, and type 1 collagen. *In vitro* experiments with rat mesangial cells and NRK-49F renal fibroblast cells suggested that the effects of lobeglitazone on UUO-induced renal fibrosis are mediated by inhibition of the TGF-β/Smad signaling pathway. In conclusion, the present study demonstrates that lobeglitazone has a protective effect on UUO-induced renal fibrosis, suggesting that its clinical applications could extend to the treatment of non-diabetic origin renal disease.

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EP507

Using the plastic closure techniques of wound defecting treatment of patients with diabetic foot syndrome

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Purpose
To improve methods of plastic closure of wound defects in patients with diabetic foot syndrome using skin flaps on vascular pedicle of the perforating vessels.
Methods
The study involved patients with diabetes type 2 complicated with diabetic foot syndrome neuroischemic form. The study included 31 patients, 15 people in the study group and 16 people - the control group. Area wounds ranged from 3.8 to 21 cm^2. Cleansing the wounds was performed by ultrasonic cavitation. On the wound bandage with sorption-based antimicrobial composition of nanosized silica. Thus, the wound was purified for 2–3 days. On the third day, the wound was applied vacuum-assisted closure with a standard negative pressure of 125 mm Hg. The device was applied for 3–6 days. The number of colony-forming units for the success of the operation should be less than 10. Formed flap, which corresponds to the size and configuration of the defect on the foot.
Results
In the study group noted engraftment graft in 14 patients. Time of full engraftment and the healing of the wound defect in patients of the main group was 14 ± 3 days in the control group healing ulcers - 51 ± 10 days.
Conclusions
Improved techniques in the treatment of wound autodermoplastic defects in patients from diabetic foot syndrome, which is preparation wounds using an ultrasonic cavitation, vacuum bandage hardware. Using a split skin flap can effectively cover the bandage wounds, supporting the ability to save limbs and improve the quality of life.

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EP508

Insulin therapy with an impact on inflammation can change the risk for cardiovascvular diseases in type 2 diabetes

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Introduction
Patients with diabetes (DM) are at increased risk for cardiovacular disease (CVD). Possible effects of insulin therapy on development of atherosclerosis and CVD were studied.
Patients and methods
Relevant metabolic parameters were determined in 348 patients assigned into groups with DM2 on oral hypoglycemic drugs (DM2-OH) and insulin (DM2-INS), and with DM1.
Results
A significant among-group difference was found in adiponectin (ApN) (DM1 vs DM2 vs DM3 = 15.23 ± 11.54 vs 7.93 ± 5.75 vs 4.47 ± 2.14; ANOVA: $F = 11.56$, $df = 2$, $P < 0.0001$), C-reactive protein (CRP) (DM1 vs DM-OH vs DM-INS = 2.14 ± 2.42 vs 4.15 ± 5.13 vs 2.16 ± 2.32; $F = 7.27$, $df = 2$, $P = 0.026$), high density lipoprotein (HDL) (DM1 vs DM-OH vs DM-INS = 1.71 ± 0.21 vs 1.37 ± 0.35 vs 1.52 ± 0.31; $F = 14.01$, $df = 2$, $P < 0.001$), uric acid (UA) (DM1 vs DM-OH vs DM-INS = 249.12 ± 71.3 vs 351.4 ± 88.1 vs 321.9 ± 137.13; $F = 14.23$, $df = 2$, $P < 0.001$) and body mass index (BMI) (DM1 vs DM-OH vs DM-INS = 24.35 ± 4.01 vs 30.45 ± 7.17 vs 28.51 ± 5.17; $F = 12.01$, $df = 2$, $P < 0.0001$), between tested groups. Tukey post hoc test showed a significant difference ($P < 0.05$) in ApN between DM1 and DM-OH, DM1 and DM-INS, and DM-OH and DM-INS, but not in BMI ($P = 0.12$), CRP ($P = 0.21$), UA ($P = 0.41$) and HDL ($P = 0.89$) between DM-OH and DM-INS. In DM-INS the best model ($R^2 = 0.942$) for ApN included HDL ($R^2 = 0.66$, $P = 0.002$) and UA ($R^2 = 0.35$, $P = 0.007$). In DM-INS ApN correlated significantly ($P < 0.05$) with HDL ($r = 0.55$), FPG ($r = 0.42$), CRP ($r = 0.49$), and fibrinogen (FIB) ($r = 0.69$). Duration of insulin therapy did not correlate with ApN in DM-INS ($P = 0.82$).
Conclusions
ApN was decreased in DM-INS compared to DM-OH, which could be explained with an effect of insulin on adipocytes and C-peptide, consequently on ApN level. Decreased ApN suggests increased risk of vascular disease in insulin treated patients. HDL was among the main predictors of ApN. In DM-INS HDL was not decreased, while CRP was not increased, which could be beneficial in CVD protection.

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EP509

Prayer marks in immigrants from Bangladesh with diabetes mellitus who live in Greece

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Introduction
Prayer marks (PMs) have been reported in the literature among Muslim prayers. PMs are found most often on the forehead, knees, ankles and dorsa of the feet. The most common changes consist of thickening, lichenification and hyperpigmentation of the skin, the causative factors being repeated pressure and friction during pray.
Objectives
Immigrant populations are disproportionately affected by diabetes and its complications. Moreover, diabetic foot ulcer is a major complication of diabetes mellitus, and probably the major component of the diabetic foot. PMs are foot lesions that can ulcerate. In our study we focused on the frequency of PMs among Bangladeshi immigrants who live in Athens, Greece and have diabetes.
Methods
A total of 166 immigrants from Bangladesh (150 men and 16 women) with diabetes mellitus and 65 (58 males and eight females) normal subjects from Bangladesh were recruited. Characteristic pictures of PMs are taken and provided.
Results
The mean duration of living in Greece was 10.34 ± 6.2 years. The mean age was 44.05 ± 8.1 years old and the reported duration of diabetes 4.86 ± 4.5 years. The mean A1C was $7.74 \pm 1.6\%$ and the mean Glucose values 190.3 ± 72 mg/dl. A total of 28 patients with diabetes (16.9%) (one patient with type 1 DM, and 27 patients with type 2 DM) and one subject in control group (1.5%) had PMs and all of them where males. Diabetic patients with PMs and diabetic patients without PMs had similar and not statistical significant BMI (23.67 ± 2.89 vs 24.30 ± 3.42 kg/m^2, $P = 0.187$), age (44.04 ± 7.3 vs 44.06 ± 8.35 years, $P = 0.488$), disease duration (3.86 ± 3.0 vs 5.07 ± 4.74, $P = 0.080$), and A1C values (7.4 ± 1.3 vs $7.8 \pm 1.6\%$, $P = 0.408$). None of the PMs had infection, ulceration or bleeding at the time of examination. The marks were not itchy or painful and they were observed on the dorsal aspect of the left foot.
Conclusions
PMs can often provide clinicians with helpful information for the patient's cultural background. PMs could ulcerate and our study emphasizes the need for clinical awareness of PMs, especially for patients with diabetes. Moreover, people

come from different ethnic groups and ethnicity can have important effects on health and on the management and treatment of diabetes.

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EP510

Therapy of hormonal disorders in women with acne

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Introduction and objectives
About 9% of world population suffer from acne, which occupies the 8th place among all human diseases, and the 3d place among dermatological disorders. Acne is diagnosed in 54% of 18 year aged women. Acne manifests mostly in 12–14 year age and regresses after 20 year age, even though more and more women have recently addressed their doctors for acne problem developing after 20 year age. Location of this dermatosis in open areas of skin leads to depression and social disadaptation, which underlines the actuality of this problem. It is well known that a leading role in the development of adult acne is played by hyperandrogenism, which is often caused by polycystic ovarien syndrome (PCOS). Well known also is that combined oral contraceptives are used for the treatment of female acne caused by hyperandrogenism syndrome. However, not all patients benefit from this kind of treatment. Therefore, the aim of our study was to better investigate endocrine system status and establish disorders stimulating the appearance and development of acne in adult women and then prescribe the proper therapy.
Material and methods
Our study involved 126 women with acne, of 18–37 year age. It included the performance of Sonography of thyroid gland and pelvic organs as well as the determination of levels of the following hormones: Prolactin, TSH, FSH, LH, 17-Hydroxyprogesterone, DHEAS, Free testosterone, Oestradiol, Progesterone, Anti-Mullerian hormone.
Results
The investigation confirmed high androgenic hormones level in 86.5% of women with acne, although clinical manifestations of hyperandrogenism syndrome were found only in 45% of these women. i) PCOS was found in 20.2% of women with acne. ii) Hyperprolactinemia – in 34.9%. iii) Atypical (late) form of congenital adrenal dysfunction – in 44.9%. So, it was established that, other than PCOS, Hyperprolactinemia and Atypical (late) form of congenital adrenal dysfunction are also main causes of hyperandrogenism in women, which can lead to acne. Depending on the endocrine pathology of patients, appropriate treatment was prescribed: i) Oral contraceptives for PCOS. ii) Dopamine agonists for Hyperprolactinemia. iii) Synthetic glucocorticoids for Atypical (late) form of congenital adrenal dysfunction. Also, regardless of the type of hormonal disorders, all women received proper topical therapy in accordance with the severity of acne.
Conclusions
As a result, we got to the following conclusions: i) On the background of the proposed differentiated combined therapy within 6 months, positive effects were achieved in 85% of women with significant reduction of the eruption and without its recurrent appearance. ii) The condition of skin and acne eruptions was clearly dependent on hormone levels in the blood. iii) In order to achieve efficient treatment of female acne, combined therapy should be based on the correction of hormonal disorders.

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EP511

N-Terminal pro-B-type natriuretic peptide level in type 2 diabetic patients

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Objective
A diabetic state is causally related to heart failure (HF) which is a leading cause of mortality. Early detection of high-risk individuals is imperative for primary prevention. The aim of this study was to investigate the role of N-terminal pro-B-type Natriuretic Peptide (NT-proBNP) in patients with diabetes type 2 (DT2).
Methods
We investigated 86 patients both sexes with DT2 aged 65.54 ± 11.37 years (from 50 to 65 years) without clinical cardiovascular disease at baseline. Plasma levels of NT-proBNP and other biochemical data were measured. Control group included 34 healthy subjects the same age.
Results
NT-proBNP level increased with age in both the diabetic and control group but patients with DT2 had higher NT-proBNP levels ($P<0.05$). NT-proBNP was significantly correlated with HbA1c ($r=0.53$, $P<0.001$), serum creatinine ($r=0.62$, $P<0.001$), serum cystatin C ($r=0.48$, $P<0.001$), and age ($r=0.31$, $P<0.001$). Multivariate linear regression analysis of the significant variables showed that age ($P=0.011$), male gender ($P=0.012$), triglyceride ($P<0.001$), systolic blood pressure ($P<0.001$), and cystatin C ($P<0.001$) were the independent predictors of fasting serum log-NT-proBNP levels in diabetic patients.
Conclusions
We showed the role of risk factors to heart failure in patients with DT2. In these patients, the presence of dyslipidemia, hypertension, and renal impairments were predictors of fasting serum log-NT-proBNP levels. Thus adjustments for the age, sex and renal function are necessary for determining cardiac risk based on NT-proBNP level.

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EP512

Metabolic risk factors in adolescent girls with type 1 diabetes

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Background
Adolescent girls with type 1 diabetes (T1DM) have a higher incidence of metabolic risk factors like hypertension, dyslipidemia, non-alcoholic hepatic steatosis (NASH), abdominal adiposity and polycystic ovarian syndrome (PCOS) when compared with their non-diabetic peers. Moreover, metabolic risk factors seem to appear even in T1DM girls without overweight or obesity. We aimed to determine the prevalence of several metabolic risk factors in adolescent T1DM females, according to their nutritional status.
Methods
Girls older than 14 with T1DM for a period longer than 2 years were included. They were divided into two groups according to their body mass index (BMI above or below the 85th percentile). The two groups were compared in what regards the presence of abdominal adiposity, hypertension, lipid profile abnormalities, NASH and PCOS.
Results
44 adolescents were included: 25 with normal weight and 16 (39%) with obesity or overweight. No difference was found between age (17 ± 1.8 for girls with normal weight vs 17 ± 1.7 for obese and overweight girls; $P=0.49$) or mean A1c among groups (8.5 ± 1.4 vs 8.5 ± 1.1; $P=0.98$). Girls with normal weight had a longer duration of T1DM (9 ± 4 vs 7 ± 4; $P=0.03$). In what regards overweight or obese girls, 23% had abdominal adiposity, 14% hypertension, 21% lipid profile abnormalities, 23% NASH, 23% PCOS and 20% metabolic syndrome. Among normal weight diabetic girls, 6% had abdominal adiposity, 19% hypertension, 5% lipid profile abnormalities, 6% NASH and 6% PCOS. No statistical significant differences were found between the two groups.
Discussion
The prevalence of metabolic risk factors, including NASH and PCOS, was similar of that reported in the published data concerning diabetic young women, although there are few studies in the pediatric population. Even though metabolic syndrome and its components were more prevalent among overweight and obese T1DM girls, they were also present among normal weight diabetic individuals.

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EP513

Transcultural prevalence of depression in type 2 diabetic patients in Egypt and Yemen

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Background and aims
Depression is a common co-morbidity among people with diabetes that reduces quality of life and is associated with morbidity, mortality, and health care costs. We aimed to assess the prevalence of depression among patients with type 2 diabetes in two Arabic nations, Egypt and Yemen and to examine its relationship with socio-demographic data and diabetes complications.
Methods
We conducted a cross-sectional analysis on 200 subjects with type 2 diabetes, divided into two groups: 100 Egyptian and 100 Yemeni subjects. All selected subjects were subjected to full medical history and clinical examination. Laboratory tests included fasting plasma glucose and HbA1C. MADRS scale was used for diagnosis of depression.
Results
Both groups were age and sex matched. The prevalence of depression was 39% in Egyptian and 34% of Yemeni patients, with no statistical significance. In Egyptian diabetics, depression was significantly associated with female gender, duration of diabetes, poor glycemic control, higher number of children, low and very low socioeconomic levels, high mean number of cigarette smoking, lower mean number of years of education and presence of diabetes complications**.** However**,** in Yemeni diabetics, depression was significantly associated with female gender, birth order, poor glycemic control, Low and very low socioeconomic levels, lower mean number of years of education, diuretic usage for medical co-morbidities. The most important predictors of depression were female sex, higher number of children, divorce, Low and very low socioeconomic levels and lower mean number of years of education.
Conclusion
High prevalence of depression among Egyptian and Yemeni type 2 diabetic patients. Depression associated with poor glycemic control.
Keywords: Diabetes mellitus; depression; Egyptian; Yamani.
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EP514

Telmisartan attenuates hyperglycemia-aggravated VCAM-1 expression and monocytes adhesion in TNFα-stimulated endothelial cells by increasing GSK3β-Ser^{9} phosphorylation

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Uncontrolled hyperglycemia accelerates endothelial damage and vascular inflammation caused by proinflammatory cytokines including tumor necrosis factor α (TNFα), which leads to arteriosclerotic cardiovascular diseases. Glycogen synthase kinase 3β (GSK3β) is reported to mediate TNFα-stimulated nuclear factor-κB (NF-κB) activation and expression of vascular adhesion molecules. Although a few clinical trials have suggested that telmisartan, an angiotensin II type 1 receptor blocker (ARB), decreases cardiovascular complications in diabetic patients, the underlying molecular mechanisms for the beneficial effects have not been fully elucidated. Here, we investigated a molecular mechanism mediating the telmisartan's beneficial effects on vascular inflammation in hyperglycemia-treated endothelial cells. Telmisartan dose-dependently attenuated the hyperglycemia-aggravated vascular cell adhesion molecule-1 (VCAM-1) expression and THP-1 monocytes adhesion, which accompanied an increased GSK3β-Ser^{9} phosphorylation and a decreased NF-κB p65-Ser^{536} phosphorylation. Among ARBs, including losartan and fimasartan, only telmisartan induced GSK3β-Ser^{9} phosphorylation and showed the inhibitory effects on expression of VCAM-1 and phosphorylation of NF-κB p65-Ser^{536}. The telmisartan's beneficial effects were not changed by pretreatment with GW9662, a specific and irreversible peroxisome proliferator-activated receptor γ (PPARγ) antagonist, although GW9662 clearly inhibited rosiglitazone-induced CD36 expression. Ectopic expression of GSK3β-S9A, a constitutively active mutant of GSK3β, significantly restored the telmisartan-attenuated VCAM-1 expression, NF-κB p65-Ser^{536} phosphorylation, and THP-1 monocytes adhesion. Finally, both increased NF-κB p65-Ser^{536} phosphorylation and decreased GSK3β-Ser^{9} phosphorylation in the aortas from high-fat fed mice were reversed by treating with telmisartan. Taken together, our findings demonstrate that telmisartan ameliorates hyperglycemia-exacerbated vascular inflammation at least in part by increasing GSK3β-Ser^{9} phosphorylation, which mediates a decreased VCAM-1 expression in a PPARγ-independent manner. Telmisartan may be useful for the treatment of DM-associated vascular inflammation and cardiovascular diseases.
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EP515

Continuous glucose monitoring system in the value of diabetes mellitus type 1 control

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Purpose
Estimation of the continuous glucose monitoring system (CGMS) in the value of diabetes mellitus type 1 (DM1) control.
Materials and methods
162 DM1 patients have been divided on 2 groups: 1st group with adequate control DM1 – glycated hemoglobin (HbA1C) $\leq$7.5% (n=38) and 2nd group with inadequate control – HbA1C$>$7.5% (n=124). All patients carried out CGMS with glycemia symmetrization scales and an estimation of probability of a dysglycemia, hypo- and hyperglycemias risks with calculation of indexes of risk (InR). High risk of a hypoglycaemia at InR more than 4.5; low – less than 2.5. The high risk of a hyperglycaemia at InR is more 9.0, low risk – less than 4.5. InR dysglycemias – a difference of InR hyper- and hypoglycemias.
Results
HbA1C level in the 1st group of patients was 6.75% (6.40; 7.25) – adequate control DM1, and in 2nd – 9.40% (8.30; 11.10) – inadequate control. InR in group 1 was less (8.25 (4.80; 14.70)), than in the 2nd group – 16.24 (10.45; 20.60) ($P<$ 0.001). In the group with inadequate control of DM1 InR of a hyperglycaemia has been raised at 85% of patients, in comparison to 48% of patients in the 1st group. Low InR of a hyperglycaemia in 2nd group was at 2% vs 1st group – 23% ($P<$ 0.001). InR hypoglycemias has made 5.60 (3.00; 10.50) in 1st group and 5.00 (1.60; 9.20) – in 2nd group. In the absence of differences between groups in InR hypoglycemias, InR of a dysglycemia significantly differed: 2.40 (3.00; 8.20) vs 9.85 (2.80; 18.55), ($P<0.001$). Hypoglycaemia InR exceeded 4.5 independently of adequacy of control DM1 (high risk of hypoglycemias) at 53% of patients of 1st group and at 62% of patients 2nd group. Low InR of a hypoglycaemia in 2nd group was at 19% that is significantly less ($P<0.001$), than in 1st group – 31%.
Conclusions
Inadequate control of HbA1C level among the patients with DM1 was observed three times more often than adequate. By results of CGMS the insulin therapy scheme has been optimizated according to a daily nutrition that allowed to reach improvements of control DM1.
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EP516

Chronic kidney disease in elderly patients with type 2 diabetes: 6 years of follow-up study

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Objective
To evaluate prevalence of chronic kidney disease (CKD) and risk factors for decline of renal function in elderly patients with type 2 diabetes (T2DM) after 6 years of follow-up.
Methods
A cohort of 208 elderly patients (65 years or older) with T2DM participated in an examination during 2005, a 6-years follow-up examination during 2011. An estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease equation. CKD was defined as eGFR $<$60 ml/min per

1.73 m^2 and worsening nephropathy was defined as eGFR <45 ml/min per 1.73 m^2.
Results
Among the 208 elderly patients with T2DM, 95 patients (45.7%) had CKD at baseline. Obesity, longer diabetes duration, and usage of ACEI or ARB were independent factors related to the presence of CKD. Mean follow-up duration was 54.9 months. On multivariate Cox analysis, elderly patients with diabetes duration ≥10 years had a 2.85-fold increased risk for worsening nephropathy compared with those with diabetes duration <5 years (95% CI 1.29–6.30; $P=0.010$). Compared with HbA_{1c} <8.0%, HbA_{1c} ≥9.0% had a 2.82-fold increased risk for worsening nephropathy (95% CI 1.40–5.69; $P=0.004$). Elderly patients with obesity showed worse renal prognosis than those without obesity (HR 1.89; 95% CI 1.01–3.53; $P=0.045$).
Conclusions
Since CKD was commonly accompanied in elderly patients with T2DM, it is important to monitor and manage renal function in those patients, especially who had diabetes duration ≥10 years or HbA_{1c} ≥9.0% or obesity.

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EP517

Association of metabolic risk factors with hyperfiltration and urine albumin creation ratio in represent Korean population (Korea National Health and Nutrition Examination Survey 2011–2014) without chronic kidney disease

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The development of glomerular hyperfiltration precede the diagnosis of diabetes, but most study had undertaken with diabetes or obesity patients. In this study, we determine the association between glomerular hyperfiltration and other metabolic risk factors which associated diabetes in represent Korean population without chronic kidney disease. We analyzed 19 244 subjects with a estimated glomerular filtration rate(eGFR) above 60 ml/min per 1.73 m^2 and urine albumin creation ratio (ACR) below 30 mg/g from the 5th (V-2,3, 2011–20012) and 6th (VI-1,2, 2013–2014) Korea National Health and Nutrition Examination Survey (KNHANES). The estimated glomerular filtration rate was calculated on the basis of the CKD-EPI equation. Hyperfiltration was defined as eGFR above the age- and sex-specific 95th percentile for healthy subjects. According to glucose tolerance, the prevalence of hyperfiltration were increased 4.7% in normal, 4.9% in prediabetes, and 5.4% in diabetes (P for trend <0.001). After adjusting age, sex, body weight, hyperfiltration associated with higher body mass index ($P<0.001$), waist circumference ($P<0.001$), systolic blood pressure ($P=0.003$), HbA1c ($P=0.039$), fasting plasma glucose ($P=0.005$), triglyceride ($P=0.001$), energy intake ($P=0.001$), protein intake ($P=0.034$), and sodium intake ($P=0.002$). Hyperfiltration was independently associated with ACR (B= 0.053, $P<0.001$) in multiple regression analysis with above mentioned factors. Higher waist circumference ($P<0.001$), systolic blood pressure ($P<0.001$), HbA1c ($P<0.001$), fasting plasma glucose ($P<0.001$), and triglyceride ($P=0.001$) were also independently associated with ACR. In Korean general population, both hyperfiltration and ACR were associated with similar metabolic risk factor and each were independently associated. Longitudinal studies are needed to explore the risk for hyperfiltration and microalbuminuria.

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EP518

Clinical correlates of TNF alpha levels in anemic patients with early diabetic nephropathy

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Anemia occurs early and predicts high risk of cardiovascular events and death in patients with diabetic nephropathy (DN). It results from various factors including erythropoietin (EPO) deficiency and inflammation. The aim of this study was to evaluate clinical correlates of TNF alpha levels in anemic patients with early diabetic nephropathy. We investigated 95 anemic patients with type 2 diabetes mellitus and chronic kidney disease (stages 1–3). Glomerular filtration rate was calculated by Cockcroft-Gault formula. Anemia was defined according to World Health Organization criteria (2008). In addition to routine clinical tests we measured serum levels of EPO and TNF alpha using immunoassay. Correlations were assessed by Spearmen's correlation coefficient (rs). We found EPO deficiency in 46.3% and decreased serum ferritin levels in 11.6% patients. Serum level of TNF alpha correlated negatively with hemoglobin level (rs = −0.311, $P=0.003$). It had no significant interrelations with age, serum creatinine, ferritin, cholesterol, glomerular filtration rate and urinary albumin excretion. In patients without EPO deficiency TNF alpha level correlated with mean cell hemoglobin content (rs = −0.700, $P=0.003$), serum EPO (rs = 0.375, $P=0.017$) and urea concentrations (rs = 0.433, $P=0.011$). In EPO-deficient patients it correlated with serum urea (rs = 0.393, $P=0.032$) but not with mean cell hemoglobin content ($P=0.950$) and EPO level ($P=0.247$). The results of the study suggest that anemia in patients with early DN is multifactorial. EPO-deficient and EPO-sufficient anemic patients with DN are characterized by different clinical correlates of serum TNF alpha level. Further larger studies are needed to elucidate clinical implications of these findings.

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EP519

Non-alcoholic steatohepatitis and diabetes mellitus: a case report

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Non-alcoholic steatohepatitis (NASH) is a clinical entity characterized by the infiltration of fat into the liver associated with hepatic inflammation. The etiology is unknown, however its most frequently observed in patients with type 2 diabetes mellitus (DM 2), obesity or insulin resistance. DM 2 is an independent risk factor for the progression of NASH. Usually there are no symptoms, so it is not possible to estimate its prevalence. The treatment focuses on the control of associated diseases such as DM 2 and obesity. A 65-year-old woman without alcohol or toxicophilic abuse, without obesity (BMI of 22.7) and with clinical history of immune thrombocytopenic purpura, DM 2 (controlled under diet), hypertension and cystic lesion of the pancreas (5 years before biopsy compatible with mucinous lesion). Due to the increasing of the pancreatic lesion, with dilatation of the wirsung canal, the patient was submitted to body-caudal pancreatic resection. During the intraoperative period, the liver presented with a cirrhotic pattern, and liver biopsy was performed. Histology showed steatohepatitis, with fibrosis grade 5/6 and focal balloonization of hepatocytes. Additional study: ANA 1/160, remaining autoimmunity (AMA, SMA, LKM and antibodies anti-liver antigens) and viral serologies (HIV, hepatitis B and C) negative. After the surgery, insulin therapy was initiated with good metabolic control. The patient did not present micro or macrovascular complications. The present case describes a diabetic patient with an incidental diagnosed cirrhotic liver caused by NASH. The association of NASH and DM2 is present in more than 75% of the diabetics and in this case other related conditions (as obesity, hyperlipidemia, insulin resistance, and drugs) were excluded. The early intervention in DM 2 is crucial, in order to reduce related pathologies and their progression especially in this case with silent steatohepatitis and cirrhotic liver.

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EP520

A novel lipid tetrad index as predictor of premature coronary artery disease in diabetic patients

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Background
The aim of this study was to explore if evaluation of lipid risk factors like Lipoprotein(a) (Lp(a)) and conventional lipid profile parameters can be a efficient predictor of the cardiovascular risk in the patients of Diabetes.
Methods
Sixty individuals with angiographically proven premature CAD and 30 healthy individuals matched for age and sex were studied a tertiary health care centre, New Delhi, India, over a period of 18 months. CAD patients were divided into

two groups based on presence ($n=30$) (group I) and absence ($n=30$) (group II) of type 2 diabetes mellitus (DM). The serum levels of Lipoprotein (a) were measured by ELISA and routine lipid profile (serum triglyceride, total cholesterol, HDL-C and LDL-C) was measured by automated analyzer. Angiographic clinical vessel scoring was also done for all the patients.
Results
Lipoprotein (a) levels for Group I was 40.26 ± 8.23 mg/dl, Group II was 40.81 ± 11.16 mg/dl respectively which was significantly (i.e. $P<0.01$) higher than the levels in healthy controls (Lp(a) $=16.39 \pm 5.71$ mg/dl). We found a significant increase in mean levels of Total cholesterol (TC), Low Density Lipoprotein-Cholesterol (LDL-C) and Triglyceride (TG) in cases than controls ($P<0.01$). In contrast High Density Lipoprotein-Cholesterol (HDL-C) values decreased. Non HDL-C was calculated using the equation = (Total Cholesterol[TC] − LDL-C). Lipid Tetrad Index (LTI) and Atherogenic Index were also calculated for all patients. The Modified Lipid Tetrad Index that we propose was calculated using the equation MLTI = (non HDL-C × triglycerides × lipoprotein(a)/HDL-C). On analyzing by cumulative probability plot the new modified Lipid Tetrad Index defined by us is able to discriminate case and control populations more precisely than the existing LTI and Atherogenic Index. The Modified Lipid Tetrad Index has a better sensitivity and specificity than the existing LTI and also has a better correlation with the angiographic vessel score in all patients.
Conclusion
The new proposed Modified Lipid Tetrad Index is a better marker and predictor of severity of premature CAD diabetic patients from India, than the existing Lipid Tetrad Index and Atherogenic Index.

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EP521

Assessing the impact of 'nephrogenic' risk factors on the development of cardiac pathology in patients with long duration diabetes type 1

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Aim
The aim of study is to investigate the effects of renal pathology on the cardiovascular system in patients with T1D, the detection of the most important cardiovascular risk factors associated with CKD.
Methods
The study includes 156 patients with a long duration of T1D (more than 20 years): 24 patients without CKD, 82 patients with 1–4 stages of CKD, 29 patients on hemodialysis, 21 patients after kidney transplantation. In addition to the routine methods of survey assessed indicators of phosphorus-calcium metabolism (calcium, phosphorus, parathyroid hormone (PTH), vitamin D, fibroblast growth factor 23 (FGF-23)), the markers of: cardiac disease - atrial natriuretic peptide (NT-proBNP), endothelial dysfunction - asymmetric dimethylarginine (ADMA), systemic inflammation (C-reactive protein, fibrinogen). All patients underwent ambulatory blood pressure monitoring, echocardiography, had a multi spiral computed tomography of heart with Agatston index definition.
Results
Decrease of glomerular filtration rate (GFR) was associated with: increased systolic blood pressure (SBP) ($r=-0.209762$; $P<0.05$), mass index myocardium of left ventricular (LVMI) ($r=-0.221375$; $P<0.05$), the level of NT-proBNP ($r=-0.465808$; $P<0.05$), ADMA ($r=-0.355866$; $P<0.05$), C-reactive protein ($r=-0.204248$; $P<0.05$), fibrinogen ($r=-0.224840$; $P<0.05$), triglycerides ($r=-0.287844$; $P<0.05$), a decrease of HDL-C ($r=0.179257$; $P<0.05$)/Albuminuria is positive correlated with hypertriglyceridemia ($r=0.335853$; $P<0.05$), SBP ($r=0.262411$; $P<0.05$), NT-proBNP level ($r=0.218696$; $P<0.05$). The mineral and bones disorders of CKD (CKD-MBD) such as secondary hyperparathyroidism (SHPT), deficiency of vitamin D, calcification of the coronary arteries was the most relevance factors among the nephrogenic risk factors of cardiac disease.
Conclusion
CKD and conditions accompanying it for, especially MBD-CKD, are powerful predictors of cardiovascular disease. The reason of such a close relation is caused not only by the negative impact of nephrogenic risk factors, but also by worsening conditions such as dyslipidemia, systemic inflammation, endothelial dysfunction, as demonstrated in our study.

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EP522

Abstract withdrawn.

EP523

The prevalence of common risk factors for depression development in diabetes mellitus of the type 1

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Objective
To evaluate the frequency of common risk factors for depression development in patients with the diabetes mellitus of the type 1 (DM1).
Materials and methods
163 patients with DM1 at the age of 18–65 years old, period of DM is 11.18 (4.28; 22.33) years. The evaluation of the anxiety and depression level was carried out with the use of the Hospital anxiety and depression scale *(HADS);* a questionnaire was carried out with the use of specially developed form to reveal common risk factors for depression development. A study group was divided into two subgroups depending on the level of depression in accordance with the HADS: group 1 included patients with DM1 and depression ($n=46$) and group 2 included patients with DM1 without depression ($n=117$).
Results and conclusion
i) There are more patients that live alone (23.9% in comparison with 9.4% consequently, $\rho=0.04$) and person with disability status (69.6% in comparison with 47.9% consequently, $\rho=0.03$), among patients with DM1 and depression, than among patients with DM1 without depression. ii) The disability status is associated with the risk for depression development in DM1 (OR = 2.41; $P=0.01$; 95% CI 1.16–4.19).

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EP524

Comorbilities and morbimortality of patients with hospital hyperglycemia in the health area of Cuenca (Spain)

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Introduction and objectives
Hyperglycemia (HG) is a common problem in hospitalized patients that increases infections, mortality, costs and the hospital stay. The objective of this study is to know the association of the HG with cardiovascular risk factors (CVRF), stress factors, hospital stay and mortality.
Methods
We designed a cross-sectional observational study. We included patients admitted in the hospital every three days in two months. We excluded patients younger than 15 years, stays less than three days and those of the pediatric, gynecological, emergency and intensive care services. We collected the data from these patients the third day of admission and at discharge. We defined HG as two or more capillary glucose values greater than 140 mg/dl. We consider stress factors as infection/sepsis, surgery and corticosteroids treatment.
Results
A total of 328 patients were included 109 of patients had HG. Regarding CVRF, the hyperglycemic patients had hypertension in 67%, dyslipidemia in 45.9% and

both disorders in 38.5%; compared to 42.9%, 24.7% and 17.8%, respectively in non-hyperglycemic patients. The HG group had two stress factors in 33.7% vs 8.4% in non-HG group; and three stress factors in 10.6% vs 3.6% respectively. Hyperglycemic patients were treated with corticosteroids in 36.7% vs 15.6% in non-hyperglycemic patients. The mean hospital stay was 9.17 days in HG group compared with 7.53 days in non-HG group ($P<0.52$). Longer stays were observed in HG group. Finally, the rate of mortality in hyperglucemic patients was of 3.7%, vs 0.5% of the non-hyperglycemic patients ($P<0.044$).

Conclusions

Patients with hospital HG are more likely to have other CVRF associated. Stress factors such as surgery, corticosteroids treatment and infection/sepsis increase the risk of HG. Finally HG is associated with a longer hospital stay and higher mortality.

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EP525

Diabetes and mental health disorders: not a good combination

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A 49 year old lady presented to the hospital unconscious with severe hypoglycaemia. She had type 1 diabetes for 24 years and coeliac disease. She was hypo-unaware and had multiple admissions with DKA and hypoglycaemia over the years. She did not engage in the self-management of diabetes, therefore, insulin was being injected by the carers in the community and by nurses in the hospital. Her erratic and unpredictable glycaemic control was attributed to non-compliance. She admitted to eating gluten diet, and recent upper GI endoscopy showed mark villous atrophy. Her meal size and pattern were variable at home. During admission, she was found to be self-injecting her own insulin without a clinical indication. She was assessed by a psychiatrist and was diagnosed to have a personality disorder. She was deemed to have full mental capacity and insight into her condition and the harm that can occur with her behaviour. She was seen by a psychologist and admitted to self-injecting insulin without a clinical indication. It transpired that this was due to an ongoing court battle with her children, and the secondary gain was to get the attention of her children. Diabetes can contribute to the pathogenesis of psychiatric disorders, and some psychiatric disorders are significant risk factors for the development of diabetes. Up to 45% of mental disorders and severe psychological distress goes undetected in people being treated for diabetes. Psychiatric disorders co-existing with diabetes include delirium, mood disorders, substance abuse, anxiety, eating disorders and psychosis. There could also be some overlap between physical features of diabetes especially hypoglycaemia and symptoms of psychiatric disorders. Physicians and endocrinologists should actively seek these issues especially in people with 'brittle' diabetes as early recognition and treatment of psychiatric and behavioural problems may lead to satisfactory diabetes control and avoid hospital admissions.

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EP526

Management of diabetic peripheral neuropathy (DPN) using low frequency pulsed electro magnetic field (LF-PEMF)

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Objective

To evaluate the effectiveness of low frequency pulsed electro magnetic field (LF-PEMF) in the management of diabetic peripheral neuropathy (DPN) symptoms.

Methods

A comparative observational study of 60 patients, male and female (1:1) aged 60–85 years. Enrolment criteria – known diabetics, HbA1c 7–9 and DPN of 1–5 years. Patients were randomized into 2 treatment groups G1 and G2. The study period was 4 weeks (w) with results assessed at baseline and bi-weekly follow-ups using diabetic neuropathy symptom (DNS) score. G1: 30 patients with an established DPN were treated with PEMF therapy – frequency of 10 Hz, thru two emitters of 20 mTesla and 6 mTesla, keeping north polarity was towards the body. A total of 15 sitting of 20 ($10+10$) min – one per day. G2: 30 patients with an established DPN were continued on oral symptomatic treatment options like – amitriptyline, duloxetine, gabapentin, pregabalin and tramadol. Patients in both the groups were on Vitamin B $12+$ Alpha Liponic Acid which were continued.

Results

In G1 application of LF-PEMF therapy significantly facilitated the regression of the main clinical symptoms of DPN. Patient scores were more differentiated on DNS score. Complete relief in the symptoms of DPN was achieved in four patients at 2 w which sustained at four patients at 4 w. DNS score of 1 was achieved in ten patients. DNS score of 2 was achieved in 18 patients at 2 w which was sustained at 4 w. Overall 32 patients had a relief of main clinical symptoms on the DNS score. In G2 there was a mild regression of the main clinical symptoms of DPN. Complete relief in the symptoms of DPN on DNS score was achieved in 0 patients at 2 w and in one patient at 4 w. DNS score of 1 was achieved in two patients at 2 w which increased to three patients at 4 w. DNS score of 2 was achieved in seven patients at 2 w which was increased to 11 patients at 4 w. Overall 14 patients had a relief of main clinical symptoms on the DNS score.

Conclusion

The present study provides convincing data regarding the effectiveness of LF-PEMF therapy, on patients with DPN symptoms. The usage of oral symptomatic drugs is limited due to the high frequency of adverse events, lack of evidence of long term efficacy and concern about dependence. Considering the benefits and safety, in comparison to oral symptomatic drugs, LF-PEMF can be used as an adjacent in the management of diabetic neuropathy cases. A bigger study is warranted to determine whether DPN can be modulated with LF-PEMF and how it can influence nerve regeneration. Limitations of this study include small sample size, short duration of treatment and non-availability of follow-up data.

Keywords: LF-PEMF – low frequency pulsed electro magnetic field, DPN – diabetic polyneuropathy, DNS – diabetic neuropathy symptom, w – weeks.

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EP527

Correlation of NGAL and thyroid function in patients with type 1 diabetes

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Neutrophil gelatinase-associated lipocalin (NGAL) was shown to be highly useful in assessing kidney injury in patients with diabetic nephropathy. Taking into account recent data that dysthyroidism may have reversible effects on GFR the purpose of the study was to investigate potential relationship between serum NGAL levels, thyroid status and ultrasound thyroid characteristics in patients with type 1 diabetes (T1D) with CKD.

Materials and methods

We recruited 118 patients (43m; 75f; age 40.78 ± 12.241 years; BMI 25.50 ± 4.956 kg/m^2; duration of T1D 22.86 ± 9.737 years) with CKD. Hypertension was observed in 76 (64.41%) patients, 56 (47.46%) took ACE inhibitors. Lipid profile changes were found in 87 (73.73%) patients, and only 30 (25.42%) of them received statins. GFR was estimated by CKD-EPI formula. All patients were divided into two groups: group 1 comprised 95 patients with GFR >45 ml/min, group 2 – 23 patients with GFR <45 ml/min. Biochemical parameters, NGAL, thyroid hormones levels were measured. USG of thyroid gland was performed. Nonparametric statistical methods were used. A P-value <0.05 was considered significant.

Results

Groups were matched by age, gender, HbA1c, TSH, fT4, ATPO levels, thyroid gland volume (VolThG). Comparative analysis of patients in the subgroups according to GFR revealed reliable differences in fT3 ($P=0.028$) and NGAL levels ($P=0.0003$). Low-fT3 was occurred significantly more often in group 2 –

34.78% vs 16.84% ($\chi^2=4.5$, $P=0.034$). Mean NGAL levels in patients with GFR < 45 ml/min (1.98 [0.91; 3.29]) were higher than those in group with GFR > 45 ml/min (0.88 [0.48; 1.30]). Presence of nodal pathology observed more frequently in group 2 – 39.13% vs 16.84% ($\chi^2=5.5$, $P=0.019$), despite the fact that there were no differences in presence of hypoechoic nodes >1 cm. Correlation of VolThG and NGAL ($r=-0.288$) and serum creatinine levels was revealed ($r=0.222$).

Conclusion

Decline of GFR leads to deviation from the normal structure of thyroid gland and developing of local nodal pathology in group of patients with T1D and is accompanied by an increase of NGAL levels and low-fT3.

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EP528

Impaired awareness of hypoglycemia in adults with type 1 diabetes is not associated with peripheral neuropathy

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Objective

The impaired awareness of hypoglycemia (IAH) affects people with type 1 diabetes and is a risk factor for severe hypoglycemia. This study aims to evaluate the association between the impaired awareness of Hypoglycemia by diabetes type 1 and the peripheral neuropathy (PNP).

Methods

276 adults with type 1 diabetes, 135 men and 141 women, were studied from Mai 2015 to January 2016 to the outpatient department of University hospital of Jena. A cross sectional study was performed, using the Gold Score for assessing hypoglycemia awareness and the peripheral neuropathy was evaluated with the Neuropathy Symptoms Score (NSS) and the Neuropathy disability Score (NDS) from Young and Boulton.

Results

The median age of the group was 51±16 years with 23±13 years diabetes duration. The BMI score was 27±5 kg/m^2 and the DDCT adjusted HbA1c was 7.27%±1.1. 85 patients had PNP and 80 had IAH. 27.6% of patients without PNP and 38.8% of patients with PNP had IAH ($P=0.067$). The HbA1c did not show any difference between the adults with and without IAH (7.1 vs 7.3%; $P=0.121$). The duration of diabetes was longer for the adults with IAH (31.34 vs 26.95 years; $P=0.001$). In the regression analysis, a significant association of the IAH to the diabetes duration (Exp(B)=1.031; $P=0.007$), but not to PNP (Exp(B)=1.387; $P=0.284$) or HbA1c (Exp(B)=0.801; $P=0.115$), is shown.

Conclusions

This study revealed in adults with diabetes type 1 association between the diabetes duration and the IAH but not with the presence of PNP.

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EP529

A rare presentation of diabetic ketoacidosis: Rhino-orbito-cerebral mucormycosis

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Aim and objective

Mucormycosis is a rare life-threatening fungal infection. Immunocompromised patients are often affected. We report a rare diabetic patient with pancreatic adenocarcinoma who was presented diabetic ketoacidosis and rhino-orbito-cerebral mucormycosis.

Case presentation

A 66 years old man with pancreatic adenocarcinoma and type 2 diabetes mellitus was presented diabetic ketoacidosis and severe infection of the facial sinuses, orbita, and soft palate in the right half of the face. It was learned that the infection developed after tooth extraction. Diabetic ketoacidosis improved after fluid and electrolyte replacement and insulin treatment. Non-septate hyphae structures were shown in biopsy sample from affected tissues. Brain MRI showed that this infection was extended to the brain. Amphotericin B therapy was started immediately due to delay rapid progression and recommended surgical debridement. Surgical debridement is the main therapy for mucormycosis but patient and his relatives did not accept surgical treatment. Amphotericin B therapy was continued but he dead within the following 2 months.

Conclusion

In diabetic patients with impaired immunity, procedures such as tooth extraction can cause rare serious infections like mucormycosis.

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EP530

Renal function preservation with Manidipine vs Amlodipine in type 2 diabetic hypertensive patients with persistent microalbuminuria

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Objectives

The AMANDHA randomized study (PROBE design) showed that the addition of Manidipine 20 mg vs Amlodipine 10 mg for 2 years in 91 hypertensive type 2 diabetic patients with persistent microalbuminuria, uncontrolled with a renin-angiotensin system inhibitor (given full-dose for at least the 6 previous months) was more effective in reducing albuminuria in spite of similar blood pressure control. Patients with significant renal impairment (PlCr >1.4 mg/dl in women and >1.5 in men) had been excluded. However, no data were published on the progression of renal dysfunction, with only PlCr values reported, which were not significantly different. We undertook to establish if there were differences in glomerular filtration rate (GFR) progression.

Methods

Post-hoc analysis of AMANDHA. GFR was estimated by the MDRD-4 equation for each individual measurement. Point-to-point GFR were compared by unpaired t-test and progression was compared by the Kruskal-Wallis test. (non-parametric ANOVA). Values are given as mean (± standard error).

Results

Baseline GFR were 67.3 (±5.2) and 70.2 (±5.0) ml/min/1.73 m^2 with Manidipine and Amlodipine, respectively; at 6 months they were 68.6 (±5.6) and 69.5 (±5.3), and at 2 years 66.9 (±4.7) and 65.5 (±5.0). During follow-up, patients treated with Manidipine lost 0.4 (±3.9) ml/min/1.73 m^2 of FGR vs 4.7 (±5.2) with Amlodipine. Point-to-point GFR were not significantly different between the groups, but GFR loss after 2 years was lower with Manidipine ($P=0.032$).

Conclusions

The previously published data of AMANDHA showed a markedly greater albuminuria reduction (about 40% more) with Manidipine vs Amlodipine, which was attributed to efferential arteriole dilatation. The present *post-hoc* analysis also shows a better preservation of renal function with Manidipine. These results strengthens the case for combined treatment with Manidipine and a renin-angiotensin system blocker in hypertensive type 2 diabetic patients with persistent microalbuminuria.

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EP531

Significance of hemorheological approach for screening diabetic nephropathy in the type II diabetes mellitus

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Objective
Hemorheologic alterations or changes in blood viscosity have been suggested to play a role in the pathogenesis of diabetic microvascular complications. We measured various hemorheologic parameters in type 2 diabetes patients and assessed their possible role as a diagnostic tool for diabetic nephropathy.
Methods
Four hundred-seventy patients with type 2 diabetes were included in this study. Hemorheologic parameters, including erythrocyte deformability, elongation index (EI), critical shear stress (CSS), and aggregation index (AI) were measured using microfluidic hemorheometer. Various metabolic parameters were assessed from fasting blood samples and urinary albumin to creatinine ratio was used to assess diabetic nephropathy.
Results
There were significant differences in Elongation index at 3 Pascal (EI at 3Pa), Fibrinogen/EI, and shear stress among patients in different stages of chronic kidney disease (all $P<0.05$), EI at 3 Pa, Fibrinogen/EI, and shear stress significantly differed among the groups. Fibrinogen/EI differed between normal or CKD 1 and CKD 2 patients. In multiple regression analysis, Fibrinogen/EI at 3Pa was an independent predictor of albumin to creatinine ratio independent of age, ESR, hematocrit, HbA1c, and body mass index ($ß=0.101$, $P<0.05$). Also, critical time, critical stress, fibrinogen/EI at 3Pa, CSS/EI et 3Pa, ad fibrinogen/CSS at 3Pa were significantly different among patients at different stages of diabetic nephropathy (all $P< 0.05$). Among the variables, Fibrinogen/EI at 3Pa showed area under the ROC curve of 0.721, suggesting 860 mg/dl% as a cut off point for diabetic nephropathy with the sensitivity of 74% and specificity of 62%.
Conclusion
Fibrinogen/EI is a sensitive parameter measured via point-of-care testing for screening diabetic nephropathy in patients with type 2 diabetes.

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EP532

New features of pathogenetic treatment of diabetic neuropathy (DN) at on early stage

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Goal of research
To evaluate the clinical efficacy of phosphocreatine in the combined metabolic therapy of diabetic neuropathy at an early stage.
Materials and methods
A pilot study was carried out with participation of 36 patients suffering from DM 2. Using the method of randomization the patients were divided into two groups. Apart from the standard therapy the main group ($n=24$) received phosphocreatine (intravenous infusion dose 2 g per 100.0 of saline solution). DN was evaluated using the Neuropathic Symptomatic Score (NSS) by means of filling in a questionnaire used for analysis of the presence and strength of neuropathic symptoms. As well as using the Neuropathic Dysfunctional Account (NDA), at that vibration, tactile, temperature, pain sensitivities of lower limbs. The main parameters of efficacy were NSS score after 6 weeks of treatment and NDA score after 6 weeks of therapy.
Results, discussion
A faster clinical effect was noted in the main group during analysis of the score, relief of neuropathic symptoms occurred even without changes in the metabolic control. Apart from the slow-down of neuropathic symptoms some patients from the main group demonstrated growth of hair on legs (12.5%) which was considered as a positive potentiating effect of phosphocreatine on the background therapy of diabetic neuropathy.
Conclusions
1. The ITT-analysis in the primary end point after the combined therapy with application of phosphocreatine showed the decrease of NSS score by 42.1%, and NDA score by 13.3%.
2. Use of phosphocreatine as a cytoprotective agent in the combined DN therapy is pathogenetically substantiated and allows to expand the opportunities of drug therapy for patients suffering from DN.
3. Results of the conducted trials demonstrate a potential for further study of administration of this medicine in a larger long-term randomized and controlled trial.

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EP533

The effect of different antihypertensive treatment protocoles on glycemic control and lipid profile in type 2 diabetic patients with microalbuminuria and stage 1 hypertension

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In hypertensive diabetic patients, renal angiotensin system blockers are first preferred due to their antihypertensive and antiproteinuric activities. Carvedilol, a third generation beta blocker, may provide additional benefits in diabetic patients. We aimed to compare the short-term efficacy of losartan treatment alone and in combination with cilazapril or carvedilol on blood pressure, glycemic control and lipid profile in microalbuminuric type 2 diabetic patients.
Methods
The study conducted in 30 consecutive patients with type 2 diabetes mellitus and stage 1 hypertension. After 2 weeks follow-up period (Period 1), all patients received losartan 50 mg/day as a single dose for 6 weeks (Period 2). Then, patients were randomized into 3 groups at the end of 6th week. Losartan dose was increased to 100 mg/day in the first group (Group 1, n:10). Carvedilol (25 mg/day) in the second group (Group 2, n:10) and cilazapril (5 mg/day) in the third group (Group 3, n:10) was added to losartan 50 mg/day treatment for another 6 weeks (Period 3).
Results
In all three groups, effective blood pressure control was provided during losartan 50 mg administration and post-randomization treatment period. Body mass index in Group 1 significantly decreased during the losartan dose-increasing period. When the losartan dose was increased in Group 1, fasting glucose values were significantly decreased, but not in other groups. There was no significant difference in measurements of post-prandial glucose, and serum fasting insulin, fructose, lipid and apolipoprotein levels between the three groups. A1c values in the losartan group significantly decreased from baseline $8\pm1.2\%$ to 7.8 ± 1.0 at 6^{th} week and $7.5\pm0.9\%$ at 12^{th} week. The reductions in A1c values of losartan plus carvedilol and losartan plus cilazapril groups were not significant ($P>0.05$).
Conclusion
As a result, the use of high-dose losartan in hypertensive microalbuminuric type 2 diabetic patients provided short-term more effective glycemic control when compared to carvedilol or cilazapril treatments with low-dose losartan. Significant decreases in the high dose losartan group in terms of body mass index, fasting blood glucose and A1c levels, it could explained by diet compliance and better weight control when compared with other groups.

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EP534

Impact of skin bundle implementation on hospital aquired pressure foot ulcers and lenght of stay in inpatients with diabetes

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Objective
To assess the impact of launching SKIN (Surface, Keep moving, Incontinence, Nutrition) bundle on development of pressure foot ulcers among in-patients with diabetes.
Methods
SKIN Bundle was launched at Dudley Group of Hospitals Foundation Trust in mid- February 2011. Data on pressure foot ulcers were collected among patients with and without diabetes admitted during February 2010– February 2011 and then from February 2011–March 2012, from pressure ulcer database.
Results
Between 14/02/2010 and 13/02/2011, number of admissions to adults' wards was 64,000. Of these, 5,452 had diabetes. Out of the latter, 72 patients were identified to have foot ulcers, of them 23 patients developed the foot ulcers during their hospital stay, giving rise a 0.42% rate of development of hospital acquired foot ulcers among in-patients with diabetes. During the thirteen and a half month period following SKIN bundle launch (14/02/2011 – 31/03/2012), there were 13 patients who developed hospital acquired foot ulcers out of 6,232 in-patients with diabetes admitted during the same period, giving rise to a lower rate (0.21%) of development of foot ulcers in the hospital among patients with diabetes. The development of hospital acquired foot ulcers among patients with diabetes, therefore, dropped significantly by 51% P value of 0.04 ($P<0.05$) after the launching SKIN bundle. The average length of hospital stay (LOS) among patients with diabetes who had foot ulcers was significantly shorter by an average of 3.55 days, P value of 0.044 ($P<0.05$), after this SKIN bundle implementation.
Conclusion
SKIN bundle resulted in more than 50% reduction in pressure foot ulcers, with significant decrease in LOS among those who developed ulcers. SKIN Bundle can therefore be considered as a tool to reduce inpatient pressure Ulcers.

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EP535

Continuous glucose monitoring system in patients with gestational diabetes mellitus: a prospective study

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Introduction
Gestational diabetes mellitus (GDM) is associated with an increase of maternal-fetal complications. Continuous glucose monitoring system (CGMS) detects postprandial hyperglycemia and hypoglycemia during 24 h.
Methods
Women with GDM in gestational weeks 26–32 were allocated a CGMS (Ipro^{TM}2) after diagnosis in an observational prospective study. It was analysed:
- CGMS: Mean glucose and standard deviation, area under the curve (AUC) with glucose >140 and <70. Percentage of glucose above or below the limit of normality before and after breakfast, lunch, dinner and night. (Target ranges: before meals 70–95, after meal 70–140 and night 70–120 (expressed: mg/dl)).
- Maternal and neonatal outcomes.
Results
$n=32$. Maternal age 33 years (>35 years $=43.8\%$), family history of diabetes 47%, personal history of diabetes 34.4%, prepregnancy BMI 25.9 kg/m^2 (>30 kg/m^2 $=21.8\%$), weigh gain 7.7 kg, HbA1c 4.9%, insulin treatment 28%. *CGMS:* Glucose before breakfast 90 ± 7.5, after breakfast 120 ± 20, before lunch 86 ± 9.9, after lunch 112 ± 19.6, before dinner 93 ± 12.3 and after dinner 110 ± 17.8. AUC $>140=0.81$ and $<70=0.59$. Percentage of glucose above or below targets: before breakfast $>95=33.6\%$ and $<70=5.4\%$, after breakfast $>140=24.6\%$ and $<70=0.6\%$, before lunch $>95=20.8\%$ and $<70=11.9\%$, after lunch $>140=14.5\%$ and $<70=2.2\%$, before dinner $>95=37.6\%$ and $<70=6.3\%$, after dinner $>140=8.1\%$ and $<70=2.9\%$, night $>120=8.4\%$ and $<70=8.9\%$. *Maternal and neonatal outcomes:* Caesarean 25%, gestational age at delivery 39 week, macrosomia 12.5%, large for gestational age 25%, small for gestational age 6.3%, neonatal hypoglycaemia 21.9%, need for supplemental oxygen in the neonatal 6.3%.
Conclusions
SMCG showed preprandial hyperglycemia, mainly before breakfast and dinner. Few hypoglycemias were detected but before lunch and night. Maternal and neonatal outcomes were similar to other studies.

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EP536

The analysis of interrelation of filtrational ability of kidneys and indicators of the androgenic state at patients with diabetes mellitus type 1

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Objective
To analyze correlation between the duration of diabetes mellitus (DM), renal function and androgenic state indicators in patients with DM type 1.
Material and methods
191 males with DM 1 type in the age of 18–55 years. The control group included 25 almost healthy males in the age 21–41 years. The compensation of DM was estimated by the level of glycosylated hemoglobin. Also, the indicators of lipid profile, glomerular filtration rate MDRD, total testosterone, luteinizing hormone/follicle-stimulating hormone (LH/FSH), prolactin, sex hormone-binding globulin.
Results
It was defined that diabetes duration significantly it is above at patients with GFR <60 ml/min/1.73 m^2. In the group with GFR <60 ml/min/1.73 m^2 in the absence of compensation (Hb A1c $>7.5\%$) more than LH, FSH, LH/FSH high levels and significantly lower levels of the general and free testosterone were noted significantly. At patients with GFR MDRD >60 ml/min/1.73 m^2 significant distinctions on the level of testosterone and gonadotrophins at various compensation of SD haven't been revealed.
Conclusion
The revealed changes are important risk factors for development and progression of vascular complications and require appropriate arrangements.

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EP537

PDE5i preserves renal function in models of Diabetic Nephropathy: from bench to bedside

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One third of diabetic patients suffer from Diabetic Nephropathy (DN) that leads to end-stage renal disease (ESRD). The molecular pathways involved remain underexplored. We showed that chronic phosphodiesterase-5 inhibition (PDE5i) improve vascular inflammation [1] and tissue remodelling, reducing proteinuria [2] in murine diabetes. Our aim was to investigate the effect of PDE5i on animal and human models of DN.
Materials and methods
16 mice were randomly assigned to four groups: control (CTRL), sildenafil (SILD), streptozotocin (STZ), STZ+SILD. Renal Doppler ultrasound (RDU) was performed at baseline and after 6 weeks. Renal resistive index-RRI, GFR (ml/min), mean Blood Pressure-MBP (mmHg) were recorded. FITC-dextran (2 mg/kg) was used to assess permeability and integrity of renal endothelium. 30 type 2 diabetic (T2DM) patients were randomly assigned to placebo (PLC) or tadalafil (TAD) 20 mg/die. RDU was performed at baseline and after 5 months.
Results
All STZ-treated animal developed diabetes. Compared to the STZ, STZ+SILD preserved renal function. Specifically, SILD treatment prevented: (a) the ESRD-related hypertension (MBP, mean change from baseline: STZ 28.72 ± 3.76, STZ+SILD -9.46 ± 4.84, $P=0.002$); (b) the fall in GFR (STZ -15.24 ± 3.67, STZ+SILD 17.79 ± 3.67; $P=0.005$); (c) the rise in RRI (STZ 0.10 ± 0.03, STZ+SILD -0.07 ± 0.03; $P=0.026$); (d) the reduction in FITC-perfuse vessels

(microvascular density mean change STZ -2.45±0.48, STZ+SILD 2.1±0.49, $P=0.005$); (e) pericytes detachment from endothelial cell coverage (STZ 10%, STZ+SILD 60%, $P<0.01$). TAD treated T2DM patients: (a) improved renal microcirculation (RRI: PLC 0.01±0.04, TAD −0.04±0.03; $P=0.014$); (b) decreased diastolic pressure (PLC 0.71±9.00, TAD −6.00±9.11; $P=0.012$).
Conclusions
PDE5i treatment reversed ESRD in a hyperglycemic mouse model targeting renal pericytes and restoring intrarenal haemodynamics. In humans, PDE5i improved renal microcirculation slowing worsening of renal function in course of DN. PDE5i could disclose novel treatment strategies for DN.
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EP538

Relationship between microvascular complications of Diabetes Mellitus and trace element levels

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Objective
To determine whether relationship between trace element levels and microvascular complications of type 2 Diabetes Mellitus (T2DM).
Methods
One hundred eighteen patients with type 2 DM (mean age: 56±6.2 years) and 40 control subjects (mean age: 40.0±8.8 years) were included in the study. Group 1 ($n=40$ patients) was composed of patients with no had microvascular complications and it divided into two subgroup, first subgroup ($n=20$) included patients with glysemic regulation, the second subgroup ($n=20$) with not glysemic regulation. Group 2 included 38 patients with diabetic retinopathy (19 patients had proliferative retinopathy, 19 patients had nonproliferative retinopathy). Group 3 included 40 patients with both diabetic retinopathy and nephropathy (20 patients had microalbuminuri, 20 patients had macroalbuminuri). Patients with type 2 DM who had liver disease, renal disease, malabsorbtive disease and who had been taken any diuretic drugs were excluded. Trace elements including Crom (Cr)(μg/l), Copper (Cu)(μg/l), Zinc (Zn)(μg/l) were measured by Inductively Coupled Plasma-Mass spectrophotometry (ICP-MS). And, Iron (Fe)(μg/dl) was measured by ELISA.
Results
Difference of age was only found between control subject and all patients with DM ($P<0.001$). Mean age were found not difference between in Group 1,2,3 ($P=0.24$, $P=0.22$, $P=0.26$). Magnesium, Fe, Zn, Cr levels were lower in all diabetic patients than control healthy subjects ($P<0.001$, $P=0.039$, $P=0.001$, $P<0.001$). Crom levels were found lower in patients with both only diabetic retinopathy and only diabetic nephropathy than patients with not any microvascular complications ($P<0.01$, for both). Also, Cr levels were found lesser in patients with only diabetic nephropathy than in only with diabetic retinopathy ($P<0.01$).
Conclusions
The study indicated that an association between low Crom levels and existence of microvascular complications of DM when trace element levels were measured by ICP-MS.

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EP539

The frequency of different risk factors for diabetic ketoacidosis in real clinical practice in Russia

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The purpose
To estimate the frequency of appearance of different risk factors for the DKA (diabetic ketoacidosis) developing in a real clinical practice in Rostov-on-Don.
Materials
Patients who had a diagnosis of DKA.
Methods
Survey about the character of nutrition, alcohol drinking and other risk factors.
Design
All patients were divided into two groups according to their age. The first group-12 patients younger then 65 y.o.-Nutritional Risk Screening survey, the second group – 3 patients (65–90 y.o)-Mini Nutritional Assessment survey. 'Alcoholic agnosia' survey for identification of alcohol addiction.
Results
Fifteen patients – 11 men and 4 women. Average age – 36±0.93 y.o. According to diabetes types: 11 patients of type 1, 4 patients of type 2. From 15 members of the nutrition 10 members (66.66%) had nutrition problems. Five patients (33.33%) were closed to the nutrition risk questions. According to 'Alcohol agnosia' survey: five patients had alcohol problems(33.33%), three of them (60%) realized this problem, two (40%) were indifferent. Ten patients did not have (66.66%) alcohol addiction. The risk factors DKA: inadequate insulin therapy – 7 patients (46.66%), 5 of them (71.42%) had alcohol problems, 2 of them (13.33%) had sober life style. Two patients took drugs (13.33%) and alcohol problems. Exacerbation of concomitant diseases – 6 patients (40%), 4 of them had problems with alcohol (66.66%).
Conclusion
The most significant risk factors for DKA developing were inadequate insulin therapy, exacerbation of concomitant diseases (40%), alcohol drinking (33.33%), taking drugs (13.33%). 66.66% had nutrition problems but this state is rather result then cause of DKA.

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EP540

Somnological parameters for patients with type 1 diabetes and nocturnal hypoglycemia

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Objective
To determine the effects of hypoglycemia while sleeping on somnological parameters for patients with type 1 DM.
Materials and methods
The study included 57 person with type 1 DM (Group 1 – patients with blood glucose levels (BGL) during sleep <3.9 mmol/l; Group 2 – Patients with BGL – from 3.9 to 10.0 mmol/l. The examination included: daily monitoring of blood glucose by 'CGMSGold' ('MedtronikMINIMED' (USA)), polysomnography «SOMNOlab2 (PSG) Polysomnography (R & K)», the definition of HbA1c.
Results
Table

Indicator	Group 1 $n=14$ Me [25;75]	Group 2 $n=43$ Me [25;75]
BGL during sleeptime (mmol/l)0	2.35[2.00;3.10]*	6.10[4.10;7.50]
Hypoglycemia «before sleep» (%)	7.00[3.00;27.00]*	5.23[0.00;5.00]
HBA1c (%)	7.00[6.00;8.10]	7.67[6.40;9.00]
Total sleep time (TST) (h)	6.24[5.40;7.10]*	5.30[4.51;6.20]
REM (%)	39.50[26.00;48.00]*	29.70[23.00;45.80]
N1(%)	14.11[10.60;23.00]*	8.80[4.70;14.30]
N2(%)	38.8[35.20;61.40]	48.20[34.00;53.30]
N3(%)	3.00[1.20;6.10]	3.44[2.30;6.30]
N4(%)	1.45[0.00;2.89]*	3.00[1.00;8.40]

*$P<0.05$.

Discussion and conclusions
For patients of Group 2 marked shortening of TST – 5.30 [4.51; 6.20] hours vs 6.24 [5.40; 7.10] hours ($P=0.0219$). Night hypoglycemia extend REM-sleep (39.50 [26.00; 48.00]% vs 29.70 [23.00; 45.80]% in the comparison group ($P=0.0479$), N1 sleep stage (14.11 [10.60; 23.00]% vs8.80 [4.70; 14.30]% ($P=0.0110$), as well as reduce the N4 stage of sleep (1.45 [0.00; 2.89]% vs 23.00 [1.00; 8.40]%). The share of hypoglycemia 'before sleep' extends N1 ($r=0.5442$); an increase

in the length of N1 leads to a reduction in the duration of the deep stages of slow-wave sleep N3 ($r=-0.6835$), N4 ($r=-0.5673$); an increase in the duration of REM reduces N3 ($r=-0.5887$).
Conclusion
Hypoglycemia during sleep lengthens REM-sleep, REM sleep so reduces glycemia, providing interactive effects relative to each other, helping to increase the N1 and reduction of deep sleep stage (N3 and N4).
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EP541

The value of blood glucose levels for the parameters of nocturnal sleep for patients with type 1 diabetes

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Objective
To establish the differences in terms of sleep for patients with type 1 diabetes, depending on the level of blood glucose levels (BGL) during the night.
Materials and methods
The study included 43 participants with type 1 diabetes (Group A – patients with BGL during sleep from 3.9 to 7.4 mmol/l, Group B – 7.5–10.0 mmol/l. Patients had daily monitoring of BGL 'CGMSGold' by 'MedtronikMINIMED' (USA), polysomnography «SOMNOlab2 (PSG) Polysomnography (R & K)», the definition of HbA1c.
Results
See Table.

Indicator	Group A $n=25$ Me [25;75]	Group B $n=18$ Me [25;75]
BGL during sleep time (mmol/l)	4.50[4.00; 5.60] &	8.20[7.50; 9.50]
BGL "after sleep" (mmol/l)	7.90[7.40; 9.20]&	9.65[8.50;11.30]
HBA1c (%)	7.00[6.00;8.50]&	8.95[7.50; 9.30]
Total sleep time (TST) (h)	5.59 [4.80; 6.53]&	4.90[4.23; 5.39]
REM (%)	29.40[22.50;43.00]&	39.90[24.70;41.40]
N1 (%)	11.05[5.00; 18.30]	7.00[4.70;14.00]
N2 (%)	48.50[38.00;53.10]	41.29[25.70;53.90]
N3 (%)	4.00[2.70; 7.80]&	2.65[0.00; 5.25]
N4 (%)	3.50[1.90;13.50]&	1.30[0.00; 7.50]

&$P<0.05$
TST is longer in the group with BGL 4.50 mmol/L. REM sleep 10.5% increase in Group B. The shares represented a deep sleep are larger in Group A. In Group A the increase of TST decreases BGL during sleep ($r=0.4098$) and N2 sleep stage ($r=0.4246$). Decrease in N2 share decreases BGL during sleep ($r=0.4997$) and reduces N4 ($r=0.5182$), and has a negative coefficient with a value of REM sleep ($r=-0.4330$). In group B, REM sleep phase is inversely correlated with BGL "after sleep" ($r=-0.5056$), N3 ($r=-0.8371$), N4 ($r=-0.7594$).

Conclusion
BGL 4.5 mmol/l during sleep increases the duration of sleep by increasing the N2, N4 and extending reduce REM sleep.

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EP542

Emotional state association with microvascular complications, disease duration and glycaemic control in type 1 diabetic patients

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The aim
Of the study was to determine the relationship between depression and anxiety symptoms and chronic diabetes complications, disease duration, glycaemic control in type 1 diabetic patients.
Methods
18–54 year old 215 patients with T1DM were enrolled in the study. Participants filled questionnaires about DM, disease duration, complications and Beck's depression (DB) and anxiety (BA) inventory. All patients were evaluated for microvascular complications. Laboratory tests: HbA1c, creatinine, albumin in 24 h urine sample were performed.
Results
124 females (57.67%) and 91 males (42.33%) participated in the study. Cohort consisted of 66 participants with DN (mean age 32.44 ± 6.5 years) and 149 without DN (mean age 31.53 ± 9.99). The group without DN consisted of 53 patients without any complications (mean age 29.49 ± 9.25) and 96 patients with DP and/or DR (mean age 31.07 ± 9.11). The emotional state of females was worse than males (BD: female 9.78 ± 9.07; male 7.51 ± 7.11; $P<0.05$; BN: female 13.86 ± 9.99; male 8.86 ± 7.79; $P<0.01$). There was no statistically significant difference between BD among patients with or without complications ($P>0.05$). There was a statistically significant difference ($P=0.04$) between BA scores among patients without any complications ($N=53$, female 31/male 22) (BA 9.42 ± 8.1) and those with DN ($N=66$, female 36/male 30) (BA 12.05 ± 8.84). The emotional state of patients with longer disease duration (>30 years) (BD 13.59 ± 11.49; BN 15.61 ± 9.79) was worse than patients with shorter one (<10 years) (BD 8.14 ± 8.55; BN 10.86 ± 9.67) ($P<0.05$). There was nofound statistically significant differencebetween the emotional state and glycaemic control in T1DM patients.
Conclusions
The emotional state of females' with type 1 diabetes mellitus is worse than males'. Patients with chronic diabetes complications have more anxiety symptoms than those without any complications. Emotional state is worse in diabetics whose disease duration is longer.

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EP543

The trigger off severe vomiting and hypertension during pregnancy in type 1 diabetic patient: case report

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Diabetic mothers have an increased risk for pregnancy (early pregnancy loss, polyhydramnios, pre-eclampsia, premature labor) and progression of diabetic complications. We present a case of the progression of diabetic-related complications including autonomic neuropathy (AN) which caused severe vomiting during pregnancy. A 27-year-old type 1 diabetic woman with pregnancy of 8 weeks gestational age (GW) was admitted to our hospital for glycemia and diabetic-related complications control. She has had diabetes for 13 years. The control of diabetes was poor (HbA1c 9.13%). She was already diagnosed with multiple diabetes-related complications (nonproliferative diabetic retinopathy and maculopathy, polyneuropathy, nephropathy). An insulin-pump therapy was started to achieve a better glycemia control during pregnancy. The minor progression of albuminuria was noticed during first hospitalization. Around 11 GW she was hospitalized for the second time because of the sudden blood pressure (BP) elevation (160/110 mmHg), nausea, vomiting, headache, glycemia variability. The progression of diabetic nephropathy was observed, antihypertensive (AH) drugs for the treatment of secondary hypertension were started. Despite the better glycemia control which was achieved (HbA1c 6.1%) in few months, the patient was hospitalized for the other nine times during the pregnancy. The main complains were severe nausea, vomiting, BP elevation and ketonemia. The progression of all diabetes-related complications was observed. The maximum doses of AH drugs were required for management of BP. Albuminuria progressed to nephrotic level, hypoalbuminemia and hypoproteinemia occured. Diabetic retinopathy developed to proliferative. Severe vomiting led to electrolytes dis-balance. Nausea and vomiting was considered to be caused by the progression of AN, when other possible causes were excluded. At 36 GW during planned C-section a healthy girl was born (Abgar 8/8). Poor control of diabetes may lead to the severe

progression of the diabetes–related complications. The progression of diabetic autonomic neuropathy remains forgotten in many cases during pregnancy.

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EP544

Predictor factors of hypertension induced in pregnancy in patients with gestacional diabetes mellitus

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Gestational diabetes mellitus (GDM) is associated with an increased risk of pregnancy-induced hypertension (PIH). Ambulatory blood pressure monitoring (ABPM) has been used to screen for PIH and preeclampsia. To date, there are no data regarding ABPM in women with GDM. Currently, little is known in GDM about the role of inflammatory biomarkers in PIH development and their impact on perinatal morbility and the risk of future complications. With this study we aim to identify, in women with GDM, at an early stage inflammatory markers and BP profiles (detected by ABPM) that could define a population at higher risk of developing PIH and preeclampsia. We prospectively studied 113 normotensive women with GDM consecutively recruited at 28–32 weeks of pregnancy. ABPM was carried out for one 24-h period on each patient, using the SPACELABS 90207 ABP monitor. Serum biomarkers (PAI-1, IL-6, IL-8, leptin, IL1-β, TNF-α, adiponectin, resistin, NGF, HGF and MCP1) were determinated in 61 patients by MILLIPLEX kit. Clinical and metabolic data, obstetric and perinatal outcomes were analysed. The mean age was 34.4 ± 4.2 years and BMI was 27.5 ± 5.3 kg/m^2. Fifty-six percent of the patients had non-dipper pattern. In this group, BMI was significantly higher ($P < 0.05$) and the levels of night-time systolic (105.3 vs 98.8 mmHg) and diastolic BP (63.1 vs 57.2 mmHg), and furthermore, higher levels of PAI-1 (296.99 ± 161.3 vs 162.07 ± 117.52 pg/ml) and resistin (175.69 ± 92.17 vs 101.74 ± 64.34 pg/ml) were observed. Seventy-eight women delivered to date, 3% had preeclampsia and 7% PIH. Higher levels of adiponectin ($125\,992.7 \pm 94\,472.4$ vs $39\,850 \pm 31\,136$ pg/ml) were observed in patients who not develop PIH. We concluded that a higher rate of non-dippers pattern and night-time systolic/diastolic BP were observed. The non-dipper group had higher BMI and levels of PAI-1 and resistin, which could be a useful predictor of PIH. Adiponectin was significantly lower in patients with PIH and then could point at a protective mechanism in PIH. Further studies will be needed to determine the relationships between BP alterations and inflammatory markers, and obstetrics and perinatal outcomes.

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EP545

Patient first admitted as diabetic ketoacidosis and diagnosed as MODY 3

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A male patient aged 63 years old was admitted to the emergency department with the complaints of polydipsia, polyurea and dizziness. He had hypertension which was on a calcium channel blocker and his hypertension was in control. His plasma glucose was measured as 564 mg/dl and hospitalized due to his new onset diabetes. His family history showed that, his mother, uncle, aunt and all six brothers were diagnosed as diabetes mellitus. His uncle, aunt and aunts children were using oral antidiabetics. His system query showed that he had pollakuria and nocturiafor the last 3 months. His physical examination was normal except diminished skin turgor tonus. His laboratory was normal except blood glucose of 564 mg/dl, HbA1c 8.2%, urea 50 mg/dl, creatinin od 1.34 mg/dl, urine ketone bodies were $+++$, urine glucose 500 mg/dl. He was treated with i.v. saline, and insulin. On the follow up basal-bolus regimen was initiated. He had hypoglycemias due to four units bolus insulin and 14 units basal insulin glargine so bolus insulin was stopped and vildagliptine-metformin and insulin glargine was added. He had hypoglycemias as well and insulin glargine was stooped and gliclazide MR 60 mg was started and discharged. After 2 weeks his HbA1c was 6.9%, fasting plasma glucose was 122 mg/dl so vildagliptine-metformin was stopped and gliclazide was tapered to 30 mg/day. After 3 months his fasting blood glucose was 98 mg/dl and HA1c was 5.1%. His peripheral blood analysis was consistent with HNF1A gene and diagnosed as MODY 3. Transcription factor defects are the most common reasons of the MODY. Insulin secretion is decreased up to 85% but is sensitive to sulfonylureas. Low dose sulfonylureas generally control glycemia very well. But diabetic ketoasidosis is a very rare complication for MODY 3.

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EP546

Screening for macrovascular complications in diabetic patients in Korça, Albania

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Background
Diabetes mellitus (DM) is a common metabolic disorder and is associated with development of chronic macrovascular complications leading to significant morbidity and mortality. The aim of the study was to evaluate the prevalence and clinical profile of macrovascular complications in diabetic patients in Korca, Albania.
Material and methods
A total of 456 cases with type 2 DM attending Department of Endocrine (outpatient/inpatient), from January 2012 to March 2016 (4 years), were recruited in this study. Ages (15+) cases were screened for macrovascular complications. Demographic, clinical and laboratory parameters were included in analyses. A thorough cardiovascular and cerebrovascular history as documented by previous medical records (including medical and hospital records) was collected for all of the patients. Standardised electrocardiogram and a careful examination of the lower extremities was made for all patients.
Results
During the 4 years study 456 patients were evaluated. The mean age of the study population was 63.78 ± 10.02 S.D., with female:male ratio 270/186; duration of diabetes 7.32 ± 7.0 S.D. Of those 82 cases (18%) were newly diagnosed with DM. Mean HbA1c was 8.5 ± 1.5 DS. Mean BMI was 28.06kg/m^2 ± 4.37 DS (range 17.6–45.9). 47% of the patients were overweight and 27.5% were obese.77.4% of the patients had hypertension. 13.4% of patients were tabacco users. The prevalence of macrovascular diseases in total was 25.7%. The prevalence of cardiovascular disease, cerebrovascular disease (stroke), diabetic foot wounds and amputacion of an extremity were 16.9, 4.16, 4.37 and 0.21% respectively. The prevalence of cardiovascular disease was three times more often in males than females. There was significant positive correlation ($P < 0.05$) between macrovascular complication and the duration of diabetes, age of the patients, BMI and hypertension respectively.
Conclusion
There was high prevalence of macrovascular disease, especially cardiovascular disease in Korça population with DM. Screening for chronic macrovascular complications of diabetes is recommended in order to prevent and treat them, reducing morbidity and mortality from diabetes.

Keywords: Type 2 Diabetes Mellitus;macrovascular diseases, cardiovascular disease, cerebrovascular disease, diabetic foot wounds, amputation.

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EP547

Osteoprotegerin as a cardiovascular risk marker in diabetic patients

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Introduction
It's known that type 2 diabetes is an independent risk factor for cardiovascular disease. Osteoprotegerin (OPG), a glycoprotein secreted mainly by osteoblasts, is also produced by heart muscle and vessels. Its role in the pathogenesis of atherosclerosis and future cardiovascular events is still discussed.
Material and methods
The study was conducted in 113 patients (48 F, 65 M) with type 2 diabetes mellitus (DM2) and coronary heart disease (CHD), aged mean 68.22 ± 9.56. The studied group was divided into subgroups: 61 subjects with acute coronary syndrome (ACS) and 52 subjects with stable angina (SA). Among patients with ACS two groups were separated: with myocardial infarction (MI) and with unstable angina (UA). The control group was composed of 46 well-balanced patients (33 F, 13 M) without DM2 and CHD. Determinations of serum OPG levels with the use of MicroVue OPG-EIA (an assay sensitivity of 0.4 pmol/l) were performed. Statistica 10.0 StatSoft was used for data analysis. OPG concentrations were shown as medians.
Results
Patients with DM2 and ACS as well as subjects with DM2 and SA had significantly higher OPG levels than patients in control group (6.5 pmol/l and 5.64 pmol/l vs 3.48 pmol/l) ($H = 62.258$; $P = 0.000$) ($P < 0.001$). The tendency of higher OPG concentrations in subjects with ACS compared to patients with SA was observed ($P > 0.05$). Higher OPG levels were noted in patients with MI (7.36 pmol/l) than in those with UA (4.72 pmol/l) ($P < 0.05$). Patients with complications in the course of ACS such as: cardiac arrhythmias, pulmonary oedema, cardiac tamponade had statistically significantly higher OPG concentrations (8.40 pmol/l) compared to subjects with uncomplicated course of ACS (5.86 pmol/l) ($P < 0.05$). Higher OPG levels were also found in patients with transmural MI – with Q-wave MI (8.37 pmol/l) than in patients with subendocardial MI – with non-Q wave MI (6.44 pmol/l) ($P < 0.05$).
Conclusions
OPG may be a marker of cardiovascular disease and ischemia's severity in diabetic patients.

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EP548

Diabetic ketoacidosis in an intensive care unit – review

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Diabetic ketoacidosis (DK) is one of the most serious complications of diabetes mellitus (DM). We performed a case review of DK patients admitted to the intensive care unit (ICU) of our Hospital between 1 June 2012 and 30 June 2016. A demographic analysis was made, time of DM evolution, the therapy and the factors that led to its decompensation. Thus, a total of 42 DK patients were admitted to the ICU in the referred period, mean age was 45 years, a clear predominance of female patients (67%) and Caucasian patients (76.7%). The majority of the patients were type 1 diabetics (57%), 40% were diabetic type 2 and 3% had a diagnosis of diabetes secondary to corticosteroids. The mean duration of the disease was 12 years, and diabetes was previously unknown in 12% of the patients, where appears as an inaugural diagnosis. The mean HbA1c value of these patients was 12.6%. Regarding the treatment, 64% of the patients were exclusively treated with insulin, 21% only with oral antidiabetics and 12% did not do any type of therapy, considering that the disease was not known. Half of the patients presented nausea and vomiting, and prostration was the second most frequent presentation (33%). Infection was the most common decompensation factor (50%), followed by therapeutic failure (40%). Add that, 21% of patients required ventilatory support, 19% needed vasopressor support and only 2.3% of the patients were dialyzed. This review shows that despite all the teachings and warnings about the disease and its severity, many patients maintain a poor understanding of it, and it continues to be necessary to develop strategies to improve adherence to therapy and to achieve a better metabolic control.

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Prognostic factors and all-cause mortality in patients with type 2 diabetes presenting with diabetic ketoacidosis: a population based, case-control study

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Introduction
Little is known about diabetic ketoacidosis (DKA) in type 2 diabetes mellitus (T2DM). Moreover, the clinical impact of diabetic ketosis (DK) in T2DM is elusive. The aim of this study was to analyze characteristics and mortality of patients with DKA and DK and to identify possible prognostic factors.
Methods
This was a population-based, cross-sectional study that included all patients with T2DM presenting to emergency department with DKA, over the 5-year period. We analyzed all first admissions of 137 patients with DKA and 137 age- and gender-matched patients with non-ketotic hyperglycemia (NKH) and DK.
Results
During a median follow-up of 35.0 months, 55 (39.9%) patients in the NKH group, 32 (23.2%) patients in the DK group and 61 (44.2%) patients in the DKA group died. Patients with DKA had significantly higher mortality rates when compared with DK (HR 2.55, 95% CI 1.65–3.92, $P < 0.001$) and NKH (HR 1.27, 95% CI 1.05–1.53, $P = 0.012$). In patients with DKA, age, serum urea and sodium, the use of calcium channel antagonists, ASA and insulin therapy correlated positively with mortality, while weight loss and increased body temperature prior to the DKA episode, smoking and alcohol consumption were associated with decreased mortality. A nomogram derived from these variables predicted mortality with a sensitivity of 69.7%, specificity of 90.0% (AUC = 0.866).
Conclusion
DK and DKA represent two distinct subgroups of patients with T2DM. A nomogram derived from independent prognostic factors may have important clinical role in selecting high risk patients with DKA.

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EP550

Can the most frequent DRB1* gene's alleles be associated with cardiovascular autonomic neuropathy among patients with type 1 diabetes mellitus? A case – control pilot study

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Background and aim
HLA alleles are associated with type 1 diabetes (T1D) and a spectrum of risk can be from increased to neutral or to protective. We aimed to evaluate the association

of cardiovascular autonomic neuropathy (CAN) with DRB1* gene's alleles among T1D.

Methods

The case – control pilot study included 70 patients with T1D at the age 18-54 years. 36 patients with CAN were assigned to the case group and 34 patients without CAN – to the control group. The groups were homogeneous according to the duration of diabetes, mean age at diabetes presentation and gender. The diagnosis of CAN was confirmed when 2 or more pathological standartized cardiovascular tests were present. HLA alleles identification was determined for all participants by using the polymerase chain reaction with sequence specific primers.

Results

70 patients with T1D were included in the study: 26 males and 44 females. Patients mean age was 30.48 ± 11.22 years, mean duration of diabetes - 17.52 ± 6.96 years, mean HbA1c 9.26 ± 1.74%. The frequency distribution of DRB1 gene's alleles among case group showed, that the most frequent alleles were: *04 allele - 18 (25.00%), *03 – 12 (16.66%), *01 – 11 (15.27%), *07 – 8 (11.11%), *08 – 6 (8.33%), and among control group - *04 allele – 22 (32.35%), *01 – 14 (20.58%), *03 – 8 (11.76%), *13 – 6 (8.82%). We confirmed the 3.20 (p = 0.018) increased relative risk for CAN in T1D with DRB1 gene's *08 allele, also *11 (OR 1.67), *07 (OR 1.66) and *03 (OR 1.63) alleles were associated with increased risk. The highest probability was to find heterozygotes of *08/*X (OR 3.20), *03/*04 (OR 3.20), *07/*X (OR 2.07), *03/*X (OR 1.79) genotypes among T1D with diagnosed CAN.

Conclusion

DRB1 gene's *08 allele and *08/*X, *03/*04, *07/*X, *03/*X genotypes are associated with increased risk for CAN among patient with T1D.

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EP551

Genome-wide DNA methylation analysis for type 2 diabetes mellitus and cardiovascular disease: from a 23-year follow-up in the Da Qing diabetes prevention study

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Background

Cardiovascular disease (CVD) is a serious complication of diabetes mellitus (DM) and is associated with considerable morbidity and high mortality. There is increasing evidence to suggest that dysregulation of the epigenome is involved in diabetes and CVD.

Objective

To assessed the alteration of DNA methylation in patients with/without diabetes but developed CVD in a cohort study of Chinese patients.

Methods

40 patients were randomizely selected from diabetics/nondiabetics with/without CVD after 23 years follow-up, including 20 DM without CVD, 20 DM with CVD. Then a genome wide methylation analysis was conducted using the recently developed Illumina Infinium® Methylation EPIC BeadChip, and focusing on individual cytosines at CpG loci throughout the promoter regions.

Results

DNA methylation data was analyzed with RnBeads software, and we observed CpG sites in promoter area of CPT1C, CREB5, ACACB, OLR1, CXCL11 showing higher methylation levels and HADHB showing lower methylation levels in DM with CVD patients after enrolling top 500 regions among combined rank (combined P value <0.05, respectively). Singular Value Decomposition (SVD) analysis indicated that significant βvalue of DNA methylation correlated with patient BMI, fasting glucose, cholesterol, triglyceride. After adjusting for confounding factors, these CpG sites were correlated with fasting glucose. These genes were then clustered in Fatty acid degradation, Glucagon signaling pathway, Adipocytokine signaling pathway and PPAR signaling pathway according to KEGG analysis, which play a role in the synthesis of key enzyme in lipid metabolism.

Table 1. Baseline Characteristics.

	NDM + NCVD	NDM + CVD
N	20	20
Age, years	62.86 ± 6.15	65.57 ± 8.40
*BMI, kg/m2	24.05 ± 1.52	26.53 ± 3.36
Sex (M/F)	3/10	3/10
Age at Diagnosis	41.5 ± 6.52	44.6 ± 8.55
Duration T2D	23	23
*Fasting glucose, mmol/l	8.65 ± 3.73	10.12 ± 2.71
HbAlc, %	8.63 ± 2.25	8.9 ± 0.98
Cholesterol, mmol/l	4.54 ± 0.57	5.29 ± 1.09
Triglyceride, mmol/l	1.17 ± 0.45	1.21 ± 0.89

Means ± SD *: $P<0.05$

Conclusion

Our results provide evidence that diabetic CVD is associated with methylation changes in metabolic pathway alterations in blood leukocyte DNA. These differences in methylation are worthy of further validation using larger cases of diabetic patients with and without cardiovascular disease.

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EP552

Prevalence of eye complications and its correlation with kidney function: clinical practice data of diabetes patients

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Background

Type 2 Diabetes Mellitus (T2D) patients are at very high risk to have eye complications. Purpose of the study was to determine the prevalence of diabetes eye complications (DEC) and its correlation with glomerular filtration rate (GFR) in diabetes population attending community clinics across India.

Methods

A total of 1547 T2D patients (935 males and 612 females) EMR records were retrospectively analyzed. For DEC correlation with GFR, patients were grouped into GFR ≤ 60 and GFR >60 mg/ml/1.73m^2. Statistical analysis was done using SPSS version 20, with significance $P \leq 0.05$.

Results

In 1547 T2D patients, 204(13.1%) had DEC, mean (SD) age 56.7(10.0) years; 122(59.8%) males and 82(40.2%) females. Of these, GFR calculated for 443 patients had mean GFR of 91.2 mg/ml/1.73 m^2; 388(87.5%) and 55(12.5%) patients had GFR >60 and ≤ 60, respectively. DEC was observed in 79(17.8%) patients, mean (SD) age 55.5(13.8) years; among them 49(62%) males and 30(38%) females. GFR was significantly lower in patients with DEC compared to patients without DEC (79.4 vs. 93.8 mg/ml/1.73m^2; $P=0.000$). Prevalence of DEC in patients with GFR ≤ 60 was higher compared to patients with GFR $>$ 60(38% vs. 15%; $P=0.000$). However, there was no specific gender preponderance.

Conclusion

Our study is one of the few studies from India that reports the prevalence of DEC from a community based clinics based on fundus photographs and correlating with GFR, thus diabetes kidney disease (DKD). The correlation of DEC with low GFR can suggest presence of DKD in a community, thus, reiterating the significance of EC screening in community diabetes practices. Implementing these findings into clinical decision pathways may improve the quality of health care delivery.

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EP553

Atherosclerotic cardiovascular risk assessment score in diabetes patients: a retrospective analysis of clinical data

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Background
The study aimed to minimize the risk causing factors and evaluate new atherosclerotic cardiovascular disease (ASCVD) risk score using Million Hearts® Longitudinal ASCVD risk assessment tool among type 2 diabetes mellitus (T2D) patients.
Methods
A non-interventional retrospective analysis of electronic medical records of Apollo Sugar Clinics, India. A total of 365 patient's data was collected, and were categorized into normotensive (<120-129/80, mmHg), prehypertensive (130-139/80-89, mmHg), and hypertensive (>140/90, mmHg) based on their blood pressure (BP). ASCVD risk score of each patient was calculated using Million Hearts® Longitudinal ASCVD Risk Assessment Tool, as per ACC/AHA 2016 guidelines. Statistical analysis was done by using SPSS version 20, with significance set at 2 tailed $P \leq 0.05$.
Results
Total 365 patients were analysed, their mean (SD) age was 52.6 (11.9) years, 63.6% were males and 36.4% were females. Of these patients 45.8%, 24.4%, and 29.9% were normotensive, prehypertensive, and hypertensive, respectively. The indicators of ASCVD risk, age, BMI, and total cholesterol (each $P<0.05$) were significantly different among three groups. Of the 365 patients only 161 patients who met the ASCVD risk assessment criteria the score was calculated. The 10-year baseline risk score was 16.8% and expected risk would reduce to 12.5% if statin therapy is initiated. A significant difference in risk score was observed among three groups at baseline (14.4%; 15.6%; 19.4%, $P=0.05$), and expected 10-year risk (10.8%; 11.6%; 14.4%, $P=0.07$) if statin therapy initiated.
Conclusion
Treatment of cholesterol level by moderate or high intensity statins should be an essential component of multifactorial intervention for primary prevention of CV disease in diabetes patients.

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EP554

The association between pancreatic steatosis and diabetic retinopathy in patients with non-obese type 2 diabetes mellitus

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Background
In the previous study, it was demonstrated that pancreatic steatosis was significantly associated with subclinical atherosclerosis in patients with non-obese T2DM. As the result, it was suggested that pancreatic steatosis might be related to macrovascular complication of T2DM. However, the association of pancreatic steatosis on microvascular complication of T2DM has been unknown.
Objective
This study aimed to investigate the relation between pancreatic steatosis and diabetic retinopathy in T2DM subjects.
Method
Attenuations of pancreas and spleen of 168 patients with T2DM were measured by using non-enhance computed tomography (CT) imaging. Then the difference of attenuation between pancreas and spleen (P-S) and attenuation ratio of pancreatic-to-spleen (P/S) values were calculated for evaluation of pancreatic steatosis. Obesity was defined when subjects had BMI >25 k/m^2 according to the Asian-specific BMI cut-offs. The presence of diabetic retinopathy was assessed by an expert ophthalmologist using dilated fundoscopy.
Results
The attenuation values of P-S and P/S were significantly related to diabetic retinopathy in patients with non-obese T2DM. In the non-obese group, compared with those without, P-S odds ratio (OR) of patients with pancreatic steatosis was 0.192 (95% CI 0.051, 0.727) and P/S OR was 0.12 (95% CI 0.028, 0.515) for diabetic retinopathy, after adjusting for age, gender, and BMI. However, there was no association between pancreatic steatosis and diabetic retinopathy observed in the obese group.
Conclusion
In this study, pancreatic steatosisis was strongly associated with diabetic retinopathy in non-obese subjects with T2DM. This result suggests that pancreatic steatosis might affect the prevalence of microvascular complication in patients with T2DM. However, we still need more studies to define the relationship between pancreatic steatosis and microvascular complication of diabetes mellitus in details.

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EP555

Dyslipidaemia and diabetes: a real world clinical evidence in Indian scenario

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Background
Dyslipidaemia, a major risk factor for cardiovascular disease (CVD) is considerably increasing in patients with diabetes. The purpose of the study was to evaluate the lipid profiles of diabetes patients attending Apollo Sugar Clinics across India.
Methods
The current study was a retrospective analysis of electronic medical records of 1487 type 2 diabetes (T2DM) patients who registered at (Dec 2014 to Oct 2016) Apollo Sugar Clinics, across India. Patients with diabetes were diagnosed as per the ADA guidelines, and the data was collected from the patients after signing informed consent. Statistical analysis was done by using SPSS version 20, and a 2-tailed $P \leq 0.05$ was set to be significant.
Results
In total (N=1487) T2DM patients, males and females were 64.9% and 35.1%, respectively and had mean (SD) age 53.0 (10.6) years. Of these patients analysed, 54.8% had high low density lipoprotein (LDL; >100 mg/dl), 86.1% had low high density lipoprotein (HDL; <50 mg/dl), 40.7% had hypercholesterolemia (>180 mg/dl) and 76.3% had hypertriglyceridemia (>100 mg/dl). In low HDL group of 86.1%, 54.3% had high LDL and 79% had high TG. Further, mean concentrations of LDL (111.1 vs 105.6; $P=0.01$), HDL (43.3 vs 38.9; $P<0.001$), and TC (177.9 vs 169.2; $P<0.001$) were significantly higher in females compared to males ($P \leq 0.01$). However, of these patients 45.2% and 59.3% are at LDL and TC targets, respectively.
Conclusions
The prevalence of dyslipidaemia was observed to be high in diabetes patients than reported in normal population. The pattern of dyslipidaemia is different in India which is termed as 'atherogenic dyslipidaemia' where, in addition to low HDL, there were elevated levels of both TG and LDL. This increases morbidity of non-communicable disease and needs multifactorial intervention for primary prevention of CVD in diabetes.

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EP556

Markers of nonalcoholic fatty liver disease in patients with diabetes

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Given the significant correlation between the indices of lipid metabolism, liver dimensions, glycated hemoglobin and indicators cytolysis of hepatocytes identified a number of predictors that have had a significant influence on the formation of NAFLD. At a BMI above 26.5 kg/m^2, the relative risk (RR) for BMI was 20.02 and was statistically significant (8.25÷48.61). When VLDL level above 0.6 mmol/l relative risk for NAFLD also was statistically significant (RR=28.50; 11.18÷72.65). With increasing levels of triglycerides above

1.43 mmol/l relative risk for NAFLD was 34.69 and was statistically significant (12.68 ÷ 94.91). In the course of the factor analysis, we analyzed the contribution of isolated predictors in the development of NAFLD patients with diabetes. So with type 2 diabetes have made the contribution to such predictors as a BMI (65.4%), and increase level of triglycerides (16.85%), while type 1 diabetes - BMI (65.4%) and the level of VLDL (81.0%). In type 2 diabetes the leading influence obesity and atherogenic focus lipogenesis. Patients with type 1 diabetes on the development of obesity affects both NAFLD and associated levels of atherogenic lipids, and the degree of compensation of carbohydrate metabolism and associated level of glycation of proteins.

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EP557

Meal composition affects risk markers for kidney disease differently in type 2 diabetes and healthy subjects

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Background/aims
Oxidative stress and inflammation play a role in development of diabetic kidney disease. Postprandial hyperglycemia and hyperlipidemia are speculated to be associated with increased oxidative stress and inflammation. The aim was to examine the effect of meal composition on post-prandial risk markers for kidney disease among those with type 2 diabetes (T2D) and healthy subjects (HS).
Material/methods
On four occasions 21 patients with T2D and 21 HS ingested an isocaloric lunch (600 kcal) with different compositions of carbohydrate (CH) (54%), CH & fibers (15 g), fat (50%) and protein (40%). Blood samples were taken and urine samples collected before and up to four hour after the meal. B-glucose, insulin, triglycerides, CRP, IL-6, IL-18, and urine IgG2, IgG4 and ACR were analyzed. Statistical method: repeated measure ANOVA and area under the curve.
Results
T2D had a mean age (±SD) of 63 (4) years while HS had a mean age of 52 (16), $P=0.004$, and T2D had higher BMI (29 vs 24 kg/m^2, $P<0.001$). There were postprandial differences between the meals for glucose, insulin and triglycerides for both groups, all $P<0.05$. High CH meals resulted in higher peaks of glucose and insulin, while high fat meal gave higher peaks of triglycerides. Both groups had an overall increase in IL-6 for all meals. IL-18 decreased after CH meal only in HS, $P=0.003$. Urine IgG2 and IgG4 responses were different between the groups after CH-meal ($P=0.02$). CRP, urine ACR, urine IgG2 & IgG4 was not affected by meal composition within the groups.
Conclusion
CH meal showed higher glucose and fat rich meal higher triglyceride levels suggesting risk for oxidative stress in T2D. However, CRP, IL-6, IL-18, urine albumin excretion, IgG2 & IgG4 were not significantly modulated by meal composition in this population.

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EP558

Audit of a nurse-led and pharmacist assisted diabetes renal out-patient clinic – does it help improve medicines management and clinical outcomes?

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Aim
To audit clinical outcomes and adherence to prescription recommendations in a diabetes renal clinic.
Method
Baseline data was compared to the final clinic visit within a 12 month period, using information from clinic letters and electronic records of patients attending our hospital diabetes renal clinic in 2016 (1st January – 31st December). Patients with at least 1 follow-up within a 12 month period were included.
Results
82 patients were seen in total. 64 patients had full medicines management review whilst the pharmacist individually reviewed 34 patients. Complete data for this audit was available in in 48/82 patients. 30/48 (62%) were males. Ethnicity distribution was - Asian 17, Afro-Caribbean 16, Caucasian 12, others 3. A mean reduction in HbA1c from 75 to 70 mmol/mol ($P=0.01$) was achieved. Systolic blood pressure reduced from 136.8 to 137.2 mmHg (NS). No significant change in diastolic blood pressure was seen either (71.5 to 71.0). Significant urinary albumin:creatinine ratio (ACR) improvement was observed: 49 down to 40 mg/mmol ($P<0.01$). 28/64 (43%) patients were not on an antiplatelet agent. 60/64 (94%) were on a lipid-lowering agent. 47/64 (73%) patients received an ACE inhibitor, ARB or both. 9/48 (19%) patients were either referred to renal physicians or discussed in the renal-diabetes MDT. 11/48 (23%) patients used Telemedicine and patient held records to improve self – management skills (FLO Telemedicine-8, Patient Knows Best PKB-3).
Conclusion
These results suggests that the nurse-led clinic is effective in reducing HbA1c and urine ACR levels in this high CV risk patients and should help improve cardiovascular and renal outcomes in future. Pharmacist presence helps improve medication knowledge and adherence - most patients received lipid-lowering agents and majority were on ACE/ARBs, whilst aspirin prescription remained low. We hope to further improve results as the clinic progresses to its full potential in future.

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EP559

Inhibin B levels and bone health in male adult patients with Type 1 Diabetes Mellitus

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Introduction
Existing data suggest that Type 1 Diabetes Mellitus (T1DM) can affect both hypothalamic-pituitary-testis axis and bone health. The mechanisms by which sex steroids influence bone remodeling remain incompletely understood. Data linking gonadal function and bone turnover in male patients with T1DM are lacking. The purpose of this study was to examine any possible association between sex steroids levels and parameters of bone assessment in male adult patients with T1DM.
Methods/design
We studied 53 male patients with T1DM (Group-D) and 42 healthy controls (Group-C) matched for age, sex and BMI. In both groups HbA1c, Inhibin B (InhB), total testosterone (TT), SHBG, LH, FSH, β-crosslaps, type 1 procollagen total N-terminal propeptide (TP1NP) and BMD at lumbar spine (LS), femoral neck (FN) and total hip (TH) by dual energy X-ray absorptiometry (DXA) were measured.
Results
Mean age (years) (D: 34.9 + 10.6 vs C: 34.1 + 9.9, $P=0.41$) and BMI (kg/m^2) (D: 23.7 + 8.1 vs C: 24.5 + 7.7, $P=0.38$) were similar in both groups. In Group-D, mean duration of DM was 14.4 + 8.5 years and mean HbA1c was 7.8 + 1.3%. Higher levels of FSH ($P=0.043$) and SHBG ($P=0.041$), and a trend towards lower InhB ($P=0.049$) and TT ($P=0.051$) concentrations, were observed in Group-D compare to controls. LH was similar in both groups ($P=0.069$). Total BMD (tBMD, g/cm^2) and z-scores were lower in Group-D at all three sites ((LS: $P=0.031$ and $P=0.036$), (FN: $P=0.042$ and $P=0.039$), (TH: $P=0.046$ and $P=0.044$)). No significant difference in β-crosslaps ($P=0.080$) and TP1NP ($P=0.086$) was found between the two groups. Regression analysis showed: a negative association between InhB and HbA1c ($P=0.038$), InhB and tBMD at LS ($P=0.041$) and a positive association between InhB and β-crosslaps ($P=0.044$) and InhB and TP1NP ($P=0.047$).
Conclusion
These data suggest that InhB might contribute to bone turnover changes observed in T1DM. Further studies are needed.

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EP560

Cardiovascular disease and risk factors in patients with type 1 diabetes mellitus

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Objective
The occurrence of cardiovascular disease (CVD) in patients suffering from type 2 diabetes is a widely discussed issue, less so in those with type 1 (T1DM). The purpose of this study was to evaluate the frequency of these complications as well as certain risk factors that they are associated with.
Material and methods
We conducted a retrospective observational study by analyzing data from the observation charts of 106 patients evaluated in our clinic between January 2015 and December 2016. All patients had a history of T1DM of more than 20 years. We assessed the occurrence of hypertension (HT), stroke, acute coronary syndrome (ACS) and peripheral artery disease (PAD), as well as certain risk factors. One patient was excluded due to insufficient information.
Results
We included 105 patients (46% women), with a mean age of 51.46 ± 12.58 years, mean disease duration of 30.16 ± 8.69 years and the mean age at diagnosis of 21.31 ± 11.82 years. The frequency of chronic diabetes complications was: 87% retinopathy, 89% neuropathy, 42% nephropathy and 12% amputations, and for CVD: 60% HT, 10% ACS, PAD 19 and 5% stroke. There was a statistically significant higher risk in patients diagnosed with CVD in regard to the mean age, mean duration of disease and mean age at diagnosis of T1DM. There was a statistically significant correlation for the presence of peripheral neuropathy and nephropathy in patients with HT (P-value 0.0205 and 0.0001 respectively). Patients suffering from PAD had a worse glycemic control (HbA1C 9.4 vs 8.80%, P-value $= 0.033$) and lower HDL-cholesterol levels (54.04 vs 63.30 mg/dl, P-value $= 0.040$) than those without. Patients who had suffered a stroke had better cholesterol and LDL-cholesterol levels (158.8 vs 189.04 mg/dl, P-value $=$ 0.000196 and 81.8 vs 106.33 mg/dl, P-value $= 0.029$ respectively).
Conclusion
More attention should be awarded in the screening for CVD in patients with a long history of T1DM.

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EP561

Platelet aggregation and physiological anticoagulants in acute insulin-induced hypoglycemia in patients with type 1 diabetes (DM1)

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Background and aims
Hypoglycemia can be a risk factor for adverse cardiovascular and cerebrovascular events. However, changes in platelets and coagulation hemostasis during hypoglycemia have not been extensively studied. The aim of this study was to assess the impact of insulin-induced hypoglycemia on the platelet activity, endothelial dysfunction and the physiological anticoagulant level in patients with DM1.
Research design and methods
We studied seven patients with DM1 (four male and three female, age 26.5 ± 5.8, A1C $8.4 \pm 1.8\%$) without microvascular complications during hyperinsulinemic (1 mU/kg per min) hypoglycemic clamp protocol. Induced platelet aggregation (IAT) in whole blood using thrombin receptor activating peptide 6 (tRaP-6), collagen, arachidonic acid, adenosine-diphosphate was measured during hypoglycemia (plasma glucose 2.3 ± 0.1 mmol/l), normoglycemia (pg $4.4 \pm$ 0.4 mmol/l), and hyperglycemia (pg ≥ 12 mmol/l) by multiple electrode platelet aggregometry (Multiplate). Physiological anticoagulants (Protein S, Protein C, AT-III), von Willebrand factor (vWf) was determined by ELISA. Statistical analysis was performed with SPSS 22.0 for Windows, $P < 0.05$.
Results
Collagen-induced platelet aggregation was significantly increased during 20-min of hypoglycemia 34.0 (25.2;51.7) compared with euglycemia 26.5 (18.0;35.0), $P = 0.027$ and hyperglycemia 23.5 (20.0;23.5), $P = 0.028$. Thrombin-induced platelet aggregation was significantly increased during hypoglycemia 104.0 (88.7;142.2) compared with euglycemia 97.0 (83.2;107.0), $P = 0.046$ and hyperglycemia 96.0 (79.2;110.2), $P = 0.028$. protein S level was significantly increased during hypoglycemia 93.6 (79.2;103.4) compared with euglycemia 77.6 (52.6;90.2), $P = 0.046$ and hyperglycemia 76.3 (61.0;84.5), $P = 0.046$. Protein C level, AT-III, vWf, IAT induced by arachidonic acid ($P = 0.069$) and adenosine-diphosphate ($P = 0.058$) did not differ between groups.
Conclusions
Acute insulin-induced hypoglycemia causes platelet hyperactivity, which may increase the risk of adverse cardiovascular and cerebrovascular events. Hypoglycemia leads to increased free protein S level, which, is probably, due to activation of the endothelium in patients with DM1 without microvascular complications.

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EP562

Biomarkers status and their relation with the presence of type 2 diabetes with and without angiopathy

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Introduction
A useful tool for disease clinical characterization and treatment of type 2 diabetes is the knowledge on the status of several biomarkers. The aim of this study was to evaluate the levels of cardiovascular, oxidative stress and nutritional biomarkers and their relationship with the presence of type 2 diabetes and angiopathy.
Methods
A population-based case-control study in 150 Portuguese type 2 diabetic patients was performed. Group I – 75 diabetics with angiopathy, group II – 75 diabetics without angiopathy and group III – non-diabetic controls. Plasma levels of homocysteine, cysteine, malondialdehyde (MAD), vitamins B_6, C, A and E and carotenoids were measured by HPLC methods. Vitamin B_{12} and folate serum levels were achieved by an electrochemiluminescence method.
Results
The hyperhomocysteinemia prevalence was 20% (group I), 8.7% (group II) and 0.71% (group III). Group I showed the higher prevalence of hypercysteinemia (17%). The MAD serum levels were above the reference value for all groups. The percentage of subjects with ascorbic acid low plasma levels were statistically different in diabetic (I: 55%; II: 47%) compared to non-diabetic subjects (III: 22%). The prevalence of hypovitaminosis B_6 deficiency was at least 30% for all groups. In group I, the probability to have hyperhomocysteinemia was around three times higher ($P = 0.04$) in comparison with group II and 35 times ($P = 0.0006$) with group III. The combined effect of type 2 diabetes and angiopathy is associated with high MAD (OR: 5.33; $P = 0.002$) serum levels compared to group III. Type 2 diabetes predisposes to hypovitaminosis C (OR: 3.10; $P = 0.0002$).
Conclusion
The prevalence of hypovitaminosis C and B_6 were relevant. The presence of type 2 diabetes increases the risk of hyperhomocysteinemia, oxidative stress and hypovitaminosis C. The isolated effect of angiopathy increases the probability to have hyperhomocysteinemia.

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EP563

Severe hypoglycaemias in patients with unnoticed hypoglycaemias: a two-year follow up

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Introduction and objectives
Having frequent hypoglycaemias can enable the appareance of severe and unnoticed hypoglycaemias, as well as favouring vascular damage in these patients. Our objective is to evaluate de incidende of severe hypoglycaemias (SH) in patients with Diabetes Mellitus type 1 and the reduction of perceived hypoglycaemias.
Material and methods
A prospective study was conducted. Patients attending to their Endocrinology appointments between September 2013 and January 2014 were surveyed to evaluate their capacity to perceive hypoglycaemias (Clark's test). Patients with a test result compatible with a diminished capacity to sense hypoglycaemia were tracked 2 years later. The data was analysed using a Chi-squared test (IC 95%) with SPSS 21.0.
Results
104 patients were surveyed, out of which 41 had a diminished capacity to perceive hypoglycaemia (mean age 36.6 ± 11.6 years, 61% women, HbA1c, 26% ± 1.04% and 58.5% had >20 years diabetes evolution). After 2 years, 43.9% referred having had severe hypoglycaemias, out of those 55.6% had had more than 3 episodes and 33.3% had had a loss of consciousness. 19.5% had an insulin pump (21.4% in patients with severe hypoglycaemia). We found a statistically significance between Clark's test results and severe hypoglycaemias ($P < 0.002$).
Conclusions
A pathological Clark's test may be able to identify patients at risk for severe hypoglycaemia, which makes it a useful tool to detect this group of patients. If a high incidence of severe hypoglycaemia is observed, measured should be taken to educate this patients to be able to recognize and interpret the symptoms of low blood glucose as well as developing therapeutic strategies to avoid them, all of which would improve their quality of life.

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EP564

Small for gestational age and gestational diabetes – Should we be more permissive?

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Introduction
Gestational diabetes mellitus (GDM) is a risk factor for large for gestational age (LGA) newborns. The optimization of glycemic control and weight gain restriction during pregnancy according to BMI has contributed to decrease LGA but may increase the risk of small for gestational age (SGA).
Aim
To evaluate the predictors of SGA in women with DGM.
Methods
A cohort of 5271 Portuguese women from the National Registry of GDM was studied. Demographic, anthropometric and analytical data and maternal-fetal outcomes were evaluated.
Results
Women presented a mean age of 33.14 ± 5.4 years, mean BMI of 26.99 ± 5.81 kg/m^2 and mean weight gain during pregnancy of 9.63 ± 5.78 kg. The newborn's growth was evaluated according to Fenton curves in 4727 cases. We identified 3898 (82.5%) newborns appropriate for gestational age (AGA), 180 (3.8%) LGA and 649 (13.7%) SGA. Women with SGA had a significant lower pre-pregnancy weight (66.95 ± 15.20 vs 71.01 ± 16.04, $P < 0.001$) and BMI (26.07 ± 5.75 vs 27.06 ± 5.77; $P < 0.001$). The prevalence of SGA was lower in women with previous GDM (OR = 0.592, 95%CI = 0.466–0.805, $P < 0.001$) or macrosomia (OR = 0.274, 95%CI = 0.145–0.520, $P < 0.001$) and greater number of pregnancies (OR = 0.798, 95%CI = 0.737–0.863, $P < 0.001$) and two-fold higher in twin pregnancies (OR = 2.059, 95%CI = 1.313–3.229, $P = 0.001$). Insufficient weight gain during pregnancy increased the possibility of SGA by 35% (OR = 1.346, 95%CI = 1.127–1.609, $P < 0.001$). A lower value of HbA1c in 3rd trimester was presented in pregnancies with SGA (5.18 ± 0.38 vs 5.25 ± 0.44, OR = 0.662, 95%CI = 0.516–0.849, $P = 0.001$). No significant differences were found regarding age, week of diagnosis and treatment with insulin or oral antidiabetic agents.
Conclusion
In our sample, the prevalence of SGA was 3.5 times higher compared to LGA. Women without previous GDM or macrosomia, with lower BMI before pregnancy, insufficient weight gain during pregnancy, lower HbA1c in 3rd trimester and twin pregnancies had significantly more SGA. Monitoring fetal intrauterine growth, assessing risk-benefits of therapeutic and an individualized approach is required.

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EP565

A case of pulmonary tuberculosis presented with recurrent diabetic ketoacidosis

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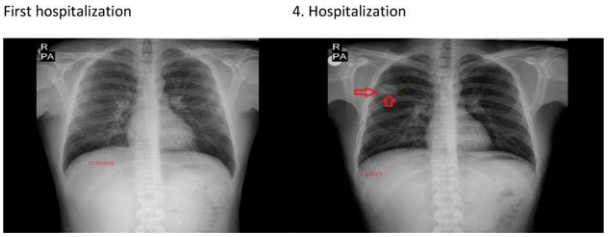
People with diabetes are at increased risk for developing tuberculosis than non-diabetics. We presented a patient with recurrent diabetic ketoacidosis who was later diagnosed with pulmonary tuberculosis.
Case
A 22 year old male with type 1 diabetes for nine years was admitted to the emergency service due to nausea and vomiting. Detecting high anion gap with metabolic acidosis in his blood gas), and ketones in urine analysis,the patient was hospitalized for diabetic ketoacidosis (DKA). Additional analysis of urine, liver, kidney tests, abdominal ultrasound, chest X-ray were within normal limits. Lumbosacral MR imaging based on the low back pain did not reveal any pathology. Serological tests of celiac disease was negative. After receiving intravenous insulin, DKA resolved and he was discharged. 1 week later, the patient admitted to our hospital because of high anion gap metabolic acidosis and hyperglycemia. The cortisol and anterior hypophysis hormones made for the etiology of DKA were within normal range. Recommending outpatient clinic control the patient was discharged. For the third time, after another nausea, vomiting and abdominal pain, the patient was referred to another health center with diabetes ketoacidosis; gastroscopy was performed and esophageal lineer ulcers were detected. Pathology was compatible with non-specific inflammation. After being discharged, the patient was presented again to our emergency department suffering from chest pain, retrosternal burning and weight loss. Again ketoacidosis was detected and hospitalized. During his admission, chest X-ray revealed right upper lobe cavitary lung lesion. With positive sputum acid-fast bacilli(AFB) stains he was diagnosed and treated for pulmonary tuberculosis.
Discussion
The tuberculosis incidence in diabetes is four times higher than general population. Especially in the developing countries like Turkey where the prevalence of type 2 DM is increasing, tuberculosis is an important health problem and patients with diabetes should be screened for tuberculosis.



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EP566

Which one is much more cause in osteoarthritis? Diabetes mellitus Type 1 or 2?

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Osteoarthritis is a great public health problem indiscriminately; ie goanrthritis, coxarthritis or dejenerative spine diseases. Osteoarthritis is focude sixth decades in elderly people, espicially in women. Many studies assingned the efficiancy of Diabetes Mellitus in the etiology of Osteoarthritis. Correlations between bone-destructive characteristics and carbohydrate metabolism errors is now quite accused in this clinical views. A comparing between Diabetes Mellitus Type 1 and 2 is aimed in this study which one cause in much more osteoarthritis. 167 (69 gonarthroisis, 57 coxarthritis and 41 dejenerative spine diseases) patients is joined to this trials for 4 years. All patients were evaluated by endocrinologists and orthopaedists. According to results; there were more counts of Type 2 patients in all groups (51 Type 2 and 18 Type 1 in gonarthrosis; 46 Type 2 and 11 Type 1 in coxarthritis, 32 Type 2 and 9 Type 1 in dejenerative spine diseases). Statistical difference is significiant ($P<0.05$). Many recently clincal and laboratory studies assigned a correlations between Diabetes Mellitus and all rheumatoid diseas. Carbohydrate metabolism is a headstone of all metabolic systems. All defects and errors in carbohydrate metabolism can affect other metabolic systems and bone-soft tissue systems by the metabolits, especially sorbitol. And also presdisposition of Type 2 to Metabolic Syndrome can mark pathophyisology of Osteoarthritis as difference proportions of these types.

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EP567

Prevalence of distal symmetric polyneuropathy in diabetic patients in general medicine wards

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Background
Distal symmetric polyneuropathy (DSPN) is one of the most prevalent chronic complications of diabetes and the most common cause in the pathway to diabetic foot ulceration. Screening for DSPN enables early intervention and prevention of complications. The Semmes-Weinstein Monofilament Examination (SWME) is currently the method of choice to screen DSPN, but ideally two neurologic tests should be used. The Michigan Neuropathy Screening Instrument (MNSI), which evaluates vibratory sensation and ankle reflex, has been proposed as a useful screening test of DSPN. The objective of this study was to determine the prevalence of DSPN in diabetic patients in general medicine wards.
Methods
Diabetic patients admitted within a 5 months period were evaluated with the MNSI and the SWME after exclusion of other causes of polyneuropathy. A score >2 in the clinical examination of MNSI and ≤ 7 positive answers in a total of 10 in SWME were considered positive.
Results
Twenty-three patients were included (75.6 ± 13.7 years; 56.5% male; 9.9 ± 6.1 years of disease duration). Only 2 (8.7%) had previously been diagnosed with DSPN. The SWME was positive in only one of these patients while the MNSI was positive in both. In the remaining undiagnosed 21 patients, 12 patients (57.1%) were positive for the MNSI, while 14 (66.7%) were positive for the SWME. Both MNSI and SWME were positive in 10 out of 23 patients (43.5%) and 19 out of 23 (82.6%) had at least one screening test positive.
Conclusion
In this study, more than half of the diabetic patients without a previous diagnosis were screened positive for either the MNSI or SWME test. Data indicates that using both MNSI and SWME increases the detection of DSPN. This study confirms that DSPN is a prevalent complication of diabetes and that hospitalization is an excellent opportunity to screen for DSPN.

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EP568

Tubular and glomerular biomarkers of kidney injury on glucagon-like peptide-1 (GLP-1) therapy in type 1 diabetic patients

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Background and aims
To evaluate the level of tubular and glomerular biomarkers of kidney injury as potential nephroprorotective effects of GLP-1R agonist (liraglutide) addition in type 1 diabetic patients compared to standard insulin therapy.
Materials and methods
12 T1DM patients with normo-(AER <20 mg/l, $n=7$) and microalbuminuria (AER <199 mg/l, $n=5$) with liraglutide 1.2 mg as add on to insulin for 6 month and 12 patients with normo-(AER <20 mg/l, $n=8$) and microalbuminuria(AER <199 mg/l, $n=4$) on standard insulin therapy. Biomarkers of kidney damage (collagen i.v., nephrin, podocin, cystatin C, kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), uromodulin, osteopontin) were measured by enzyme-linked immunosorbent assay ELISA in the morning urine and fasting plasma; overnight AER by immunoturbidimetry assay; glomerular filtration rate (GFR) by CKD-EPI formula were measured before and after 6-month treatment. Concomitant RAAS blockage-drugs given in stable doses. Differences were examined for statistical significanse ($P<0.05$) using Wilcoxon Signed-Rank Test.
Results
Initially the groups were similar by average age, HbA1c, plazma glucose, BP, lipids, uric acid, C-reactive protein, creatinine, eGFR. HbA1c before and after 6 month treatment. There were no significant differences in BP, albuminuria, creatinine, eGFR, HbA1c in 6 month. BMI decreased from 29 (22;38) to 26.8 (21;34.7) kg/m^2, $P=0.01$ in GLP1 group. Urinary levels of podocin, KIM-1 and collagen did not changed before and after therapy. In GLP1 group observed significant reduction in the urinary levels of NGAL/creatinine 1.48(0.81;2.29) vs 0.65(0.34;0.74) ng/mmol, $P=0.015$; KIM-1/creatinine 115(35;328) vs 47(21;116) ng/mmol, $P=0.02$; cystatin C 881(464;1579) vs 136(91;205) ng/mmol, $P=0.01$; nephrin 0.1(0.09;0.15) vs 0.004(0.01;0.1), uromodulicreatinine rised from 175(82;278) to 458 (235;754); and plazma levels of cystatin and osteopontin after treatment: 1264 (877;1472) vs 722 (672;848) ng/ml, $P=0.007$; 126.8 (45;161) vs 65 (45;74), $P=0.02$, respectively compared to the stable levels of markers in the standard insulin treatment group.
Conclusion
The present data suggest that GLP-1R adding to standard insulin therapy might be effective for the weight reduction and as potential nephroprotective strategy for attenuating the chronic kidney injury in T1DM.

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EP569

Diabetic choroidopathy and renal function

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Objectives
Examine the relationship between choroidal thickness (CT) and renal function tests.
Methods
Cross-sectional study with 42 eyes of 21 ocular treatment-naïve diabetic patients. Demographic and ocular data were analyzed as well as the following renal function tests: microalbuminuria, microalbumin/creatinine ratio and glomerular filtration rate (CKD-EPI and MDRD-4). Choroidal thickness was measured by swept-source ocular coherence tomography (SS OCT).
Results
The mean age was 49.76 ± 17.61 years old (18–74), with a sex ratio of approximately 1:1. 66.7% suffered from type 2 diabetes mellitus, with a mean time of evolution of 12.14 ± 10.08 years. 51.2% of patients didn't present diabetic retinopathy. Among renal function tests, only microalbuminuria positively correlated with CT ($P<0.05$).
Conclusions
The analysis of CT with SS OCT could be a prediction tool of renal function in diabetic patients.

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EP570

Risk factors of diabetic foot complications

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Introduction
Diabetic foot disease is a major health problem. The identification of its risk factors should guide preventive measures. The aim of this study was to determine the factors associated with diabetic foot complications.
Patients and methods
It is a retrospective study including 47 patients admitted at the department of Endocrinology in La Rabta hospital for diabetic foot complications during the years 2015 and 2016. Clinical and para-clinical data were collected.
Results
The mean age was 51 years (27 to 78). There were 39 men (83%). It was a type 2 diabetes in 85% of patients. The mean duration of the disease was 13 years (0 to 30 years). Patients were illiterate or had a primary school level in 73%. Hypertension was present in 23% of the patients, smoking in 61% and dyslipidemia in 29%. Diabetes was complicated with peripheral neuropathy in 81% of the patients, retinopathy in 54% and nephropathy in 53%. Coronary artery disease was present in 15%, stroke in 6% and peripheral artery disease in 46%.
Conclusions
Diabetes foot problems occur more often in men with a long duration of diabetes, peripheral neuropathy and peripheral artery disease.

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EP571

Diabetes mellitus as an important comorbidity in patient with sepsis

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Sepsis represents the host's systemic inflammatory response to a severe infection. It is a common condition in hospital settings and is associated with high rates of morbidity and mortality. Since1992 the knowledge about sepsis epidemiology has clearly improved. There are differences in epidemiologic data about sepsis identification in different countries. The aim of our study is to make a panoramic view of sepsis at the service of Infectious Diseases, University Hospital Center, 'Mother Teresa', Tirane, Albania during January 2009 to December 2013 and to highlight its accompanying diseases.
Material and methods
In our study we included patient over >14 years old, since we are a service for adult patients only. Our study was a retrospective one. A septic patient was defined based on the 2001 sepsis conference definition. Study period was from January 2009 to December 2013.
Results
During our study time from 2009–2013 we had 707 patients with sepsis. The mean age was 50.3879 years old and SDEV resulted ±19.59 years old. The most affected age resulted 55–75 years old. Comorbidities in patients with sepsis were as below: Diabetes mellitus 5.2%, HIV/AIDS 4.5%, malignancies 1.6%, alcoholic cirrhosis 1.2%, autoimmune diseases 0.99%, post-transplant patients 0.84%, and homeopathies 0.7%.
Conclusions
In nowadays sepsis definition is modified. However its concept remains the same. The sepsis cases are increasing. The age and other comorbidities are risk factors that play an important role in the increasing of morbidity and mortality. Diabetes mellitus resulted as a major comorbidity in patient with sepsis.

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EP572

The prevalence of chronic kidney disease and albuminuria in patients with Type 1 and Type 2 diabetes attending a single centre

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Chronic kidney disease (CKD) is an important complication of diabetes and determinant of mortality. Albuminuria represents early diabetic nephropathy, and also indicates generalised vascular dysfunction. Understanding the epidemiology of CKD and albuminuria helps inform health planning and identify opportunities to prevent or delay progression of diabetic kidney disease. The last available serum creatinine and urine albumin/creatinine ratio (UACR) in patients with Type 1 (T1DM) or Type 2 (T2DM) diabetes recorded on the DIAMOND database were used for analysis. Patients were divided into tertiles of age. CKD was defined as eGFR < 90 ml/min; microalbuminuria as UACR > 2.5 mg/mmol (male), > 3.5 mg/mmol (female); macroalbuminuria as UACR > 20 mg/mmol. NA-normal albumin excretion; MA-microalbuminuria; A-macroalbuminuria; ND-not done CKD was common and increased with age. Microalbuminuria also increased with age and was similar in patients with and without CKD. Macroalbuminuria was uncommon. In summary, CKD is common in hospital-based diabetic patients. The low prevalence of macroalbuminuria indicates that this mostly does not reflect classical diabetic nephropathy.

	T1DM, CKD Number/ % (%NA/MA/A/ND)	T1DM, No CKD Number/ % (% NA/MA/A/ND)	T2DM, CKD Number/ % (%NA/MA/A/ND)	T2DM, No CKD Number/ % (%NA/MA/ND)
Age 18–58	271/ 27%	732/ 73%	721/ 42%	978/ 58%
(*n*=2702)	(60/ 13/ 6/ 21)	(51/ 10/ 1/ 38)	(56/ 14/ 4/ 26)	(60/ 13/ 6/ 21)
Age 58–71	106/ 75%	36/ 25%	1736/ 67%	826/ 33%
(*n*=2704)	(56/ 19/ 5/ 20)	(45/ 23/ 6/ 26)	(50/ 17/ 5/ 28)	(50/ 17/ 5/ 28)
Age 71–107	54/ 85%	9/ 15%	2244/ 84%	397/ 16%
(*n*=2704)	(20/ 31/ 6/ 43)	(44/ 22/ 11/ 23)	(40/ 28/ 6/ 26)	(47/ 20/ 5/ 28)

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EP573

Two case reports of diabetic ketoacidosis: as lethal as avoidable

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Diabetic ketoacidosis (DKA) is one of the most serious complications of diabetes *mellitus* (DM). We describe 2 cases of type-2 diabetic patients admitted by a surgical reason/trauma in which DM control was neglected. We present a 74-year-old patient with poor metabolic control (HbA1c 7,6%) treated with metphormin, sitagliptin and glibenclamide, admitted for orthopaedic surgery. During hospitalization, there were noted several episodes of disorientation with hyperglycaemia about 300-350 mg/dl. At day 6, the patient was prostrated and with a glucose over 500 mg/dl and metabolic acidosis (pH 7,34; pCO_2 29 mmHg; pO_2 89 mmHg; HCO_3 15,6 mmol/l; lactate 8 mg/dl). Because of DKA, the patient was transferred to an Intermediate Care Unit (IntCU), where it was begun fluids and insulin perfusion, with great response. Simultaneously, we present a case of a 70-year-old patient, already with diabetic retinopathy, treated with insulin, metphormin and sitagliptin, that was admitted because of a pneumothorax and 3 broken ribs after a fall. She was admitted in Pneumology ward, maintaining hyperglycemias, nauseas and vomiting. At day 8, she was found prostrated, frankly dehydrated and with a hyperglycaemia over 500 mg/dl. After diagnosing DKA with a serious metabolic acidosis (pH 6,97; pCO_2 8 mmHg; pO_2 106 mmHg; HCO_3 3 mmol/l; lactates 31 mg/dl), she was transferred to IntCU, where she was treated with fluids and insulin, with good posterior metabolic control. In both cases, the patients presented had the DM diagnosis, being treated accordingly at home. Although, after being admitted for an unrelated reason, it was neglected all DM control as well as the symptoms that came from its decompensation, ending in an extremely serious state. This reinforces the need of approaching each patient with all its conditions, reassuring the essential role of Internal Medicine in management and orientation of these patients since their admission.

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EP574

Characteristics of patients with cystic fibrosis and hydrocarbon alteration in an adult unit

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Introduction
Hydrocarbon Alteration (HA) is considered as the most common complication in Cystic Fibrosis (CF) and is related to a further deterioration of the lung function and the nutritional status.
Objective
Analyze the prevalence of HA in patients with CF in an adult unit and its relationship with pulmonary complications.
Material and methods
We conducted a retrospective study with 71 patients of our CF unit (age 30+/−9 years, 50.5% women, BMI 22.2+/−3.8 kg/m^2 and CF evolution 22+/−9 years). Patients were classified, according to the glycaemic response to oral glucose overload, in 3 categories: normal glucose tolerance (NGT, 31%), pre-diabetes (preDM, 29.6%) and diabetes (CFRD, 39.4%). The analysis included the variables: age, sex, BMI, lung function, chronic bronchial infection, pulmonary exacerbations and its degree of severity. 32.4% of the patients received some hypoglycaemic treatment (78.6% of them were CFDR): 32% were under bolo-basal insulin, 28% basal insulin, 16% oral drugs and 24% other treatments. Statistical analysis was performed with STATAv12.0.
Results
Lower BMI was observed when comparing patients with CFRD (20.65+/−0.6 kg/m^2) and preDM (23.72+/−0.7 kg/m^2) ($P=0.005$); and a tendency was noticed between CFRD and NTG (22.64+/−0.6 kg/m^2) ($P=0.1$). CFRD patients showed greater frequency of severe pulmonary exacerbations than preDM ($P=0.016$). Higher colonization prevalence by *Staphylococcus aureus* meticilin-resistant (MRSA) (NTG 4.54%, preDM 9.5%, CRFQ 17.86%) and *Achromobacter xylosoxidans* (NTG 4.54%, 19.05% preDM, DRFQ 21.43%) was observed. This trend was not noticed for *Staphylococcus multisensible aureus*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae.*
Conclusions
HA is frequent among our CF patients. Lower BMI is associated with higher degree of HA. CFRD patients show more frequent severe pulmonary exacerbations and higher prevalence of infections by MRSA and *Achromobacter xylosoxidans.* This reinforces the importance of adequate nutritional and endocrine control as well as the need to a multidisciplinary approach for the treatment of CF patients.

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EP575

Management of diabetic ketoacidosis in haemodialysis patient

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Introduction
Diabetes mellitus is the commonest cause of chronic kidney disease leading to end-stage renal failure (ESRF). Fluid replacement is one of the cornerstone treatments of DKA, however anuric dialysis patients are at risk of fluid overload. Information for managing DKA in haemodialysis patients is relatively sparse.
Case report
A 76-year-old gentleman with type 1 diabetes was admitted with drowsiness. He has twice weekly dialysis and on 700 ml/day fluid restriction. Due to recurrent episodes of hypoglycaemia, his insulin dose was reduced. On examination he had dry mucous membranes, cool peripheries and erythematous left below knee amputation stump. Blood pressure was 92/50 mmHg. Blood gas showed pH 7.17, HCO_3 13.2, glucose level 35 and ketones of 6 mmol/l. He was diagnosed with DKA precipitated by inadequate insulin administration and stump infection. He was commenced on fixed rate insulin infusion (FRII) and antibiotics. In total he received 1 litre of fluid. He continued his scheduled haemodialysis sessions.
Discussion
Currently there are no studies available which assess the treatment of DKA in dialysis-dependent patients**.** DKA is uncommon in these patients as ESRF leads to improved glycaemic control due to reduced kidney gluconeogenesis, less insulin clearance and improved insulin sensitivity. Anuric dialysis patients do not have glycosuria and osmotic diuresis, therefore they are less likely to be volume deplete and often have minimal symptoms. Cautious administration of fluid boluses with monitoring is recommended in the presence of intravascular volume depletion. Rarely, DKA can cause pulmonary oedema in these patients due to interstitial hypertonicity from hyperglycaemia, which often responds to insulin treatment alone. If there is inadequate response to maximal medical therapy, earlier haemodialysis is warranted.
Conclusion
Aggressive intravenous fluid resuscitation is a key treatment for DKA. However, cautious fluid administration should be considered in dialysis-dependent patients.

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EP576

Severe diabetic gastroparesis – two cases of challenging treatment

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Introduction
Gastroparesis is defined by a delayed gastric emptying without mechanical obstruction. It can be a debilitating complication of diabetes that is poorly understood and has limited therapeutic options.
Case reports
1st case - We report the case of a 34-year-old woman with type 1 diabetes mellitus (T1DM) with diabetic nephropathy and gastroparesis, and a reasonable glycaemic control (haemoglobin A1c 6.9%) on insulin-pump regimen. Gastric emptying scan revealed 100% contrast retention 2 hours after its ingestion, confirming severe gastroparesis. Repeated vomiting, refractory to oral anti-emetics, led to her hospitalization 8 times in one year in a total of 109 days. She also underwent a medical pregnancy interruption due to hyperemesis *gravidarum*. Due to difficult management of vomits the patient underwent a gastric peroral endoscopic pyloromyotomy (G-POEM). After the procedure she had pronounced symptomatic improvement and reduced need of hospitalization (only 10 days in the 6 months of follow-up). The post-procedure scan showed a near-normal gastric emptying (52% contrast retention at 2 hours).
2nd case - A 23-year-old woman with T1DM with diabetic gastroparesis with no other end-organ damage. She presented a poor glycaemic control with a haemoglobin A1c of 10.3%. Gastric scan revealed severe retention with a half-emptying time of 862.6 minutes (normal time of 80±20). She was severely disabled by vomit episodes that required frequent and prolonged hospitalization periods. She also underwent G-POEM with fair symptomatic improvement and reduced need of hospitalization during her follow-up despite post-procedure gastric scanning still showed a delayed gastric emptying (93% retention at 2 hours).
Conclusions
Diabetic gastroparesis presents a challenging treatment since medical therapy has disappointing results in some patients. In those cases, endoscopic procedures can lead to symptomatic relief and enhanced quality of life obviating the need of more aggressive alternatives like gastrectomy.

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EP577

Predictors of in-hospital mortality in diabetic patients – analysis of 958305 hospitalizations

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Background
Diabetes mellitus is a lifelong chronic disease with higher risk of mortality and morbidity
Objective
To study the risk factors of death in hospitalized diabetic patients
Methods
Data obtained from the database of the National Health Fund (NHF), a public organization financing medical procedures in Poland regarded 958305 hospitalizations of adult ($\geq$18 years old) patients with diabetes in 2014 year. Logistic regression models were performed to identity independent predictors of in-hospital mortality.
Results
There were 573719 hospitalizations in non-surgical wards and 384586 in surgical wards. The mean in-hospital mortality rate was 3,20% (4,52% in non-surgical and 1,23% in surgical wards). In non-surgical wards, odds ratio for in-hospital death increased with patients age, being 52-fold higher in the $\geq$95 years old group compared to the 18–24 years age group; male gender, emergency admission, admission on weekend or other non-working day, hospitalization in county/town, private or regional hospital (vs teaching hospital), were factors associated with greater mortality. In surgical wards odds ratio for in-hospital death started to increase after 75th year of life, being 13-fold higher in the $\geq$95 years old group compared to the 18–24 years age group; female gender, emergency admission, admission on weekend or other non-working day, hospitalization in county/town or regional hospital (vs teaching hospital), were factors associated with greater mortality.
Conclusions
Predictors of in-hospital mortality in patients with diabetes are age, sex, type of hospital admission, admission on non-working day and type of hospital.

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EP578

Gestacional diabetes mellitus: 4 years study case at a tertiary level maternity hospital

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Introduction
Gestational diabetes mellitus (GDM) is a carbohydrate intolerance with onset or recognition during pregnancy. Timely screening and proper management of this condition is essencial to maximize pregnancy and neonatal outcomes.
Methods
Retrospective analysis of all cases of GDM, and the respective new-borns, followed in our obstetrics unit between 2012 and 2015. Clinical and workup parameters were evaluated.
Results
From a total of 644 cases of GDM, median age was 33, median BMI was 27 (overweight/pre-obese) and the most common academic qualifications was a licentiate degree (13 years of school). In terms of risk factors, 51% had a family history of DM and a personal history of: GDM (11%), macrossomia (4%), hydramnios (3%), fetal malformations (5%) and fetal death (0.3%). With respect to pregnancy and maternal complications we verified that 7% had hypertension diagnosis during pregnancy, 4% had one or more urinary tract infection and 11% had preterm birth. The labour was induced in 36% of the times, and we had a 37% caesarean rate, 20% of dystocic deliveries and an eutocic delivery in 43%. Neonatal outcomes consisted of a morbidity rate of 22% and 0.5% mortality rate (3 cases). Pharmacological management was necessary in 38% (35% insulin vs 3% metformin).
Conclusions
There is no denying that GDM is increasing worldwide. From an obstetric perspective this is probably related with the increased mother weight (obesity epidemic) and the delayed age for the first pregnancy (social motives), which are represent at our casuistic. Not long ago, GDM management was a dichotomy that consisted of lifestyle changes (diet and physical exercise) or insulin therapy. Nowadays, for selective cases we can also add to our therapeutic arsenal metformin, which was contraindicated in the past. At our maternity the metformin therapy was implemented in 17 cases on 2014 and 2015, translating this new tendency.

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Diabetes Therapy

EP579

A modelling approach for cost-savings in the elderly ontarian population with type 2 diabetes due to reduction in mild hypoglycemia events for SGLT-2 inhibitor versus sulfonylurea (SU) initiation after metformin

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Background
Mild hypoglycemia in elderly is associated with significant chronic consequences leading to physical and cognitive dysfunction and eventually frailty and disability. Mild hypoglycemia appears to be under-recognized in real-world clinical settings in the elderly and can lead to significant costs for patients.
Objective
To calculate cost-savings due to mild hypoglycemia reduction for SGLT-2 inhibitor versus SU initiation after metformin for elderly Ontarians with type 2 diabetes.
Methods
An economic model was calculated incorporating data from RCTs on SGLT2I for mild hypoglycemia. Data on prevalence of type 2 diabetes and SU utilization for elderly in Ontario were obtained from published data from Institute for Clinical Evaluative Sciences (ICES). Costs per event for mild hypoglycemia were obtained from published studies.
Results
With assumption of only one mild hypoglycemia during the first year of SU versus SGLT2 inhibitor initiation as add-on to metformin for the elderly Ontarian population with type 2 diabetes, the total cost from the patients' perspective would lead to an annual cost-savings of CDN $2 066 224 due to less cost for mild hypoglycemia episodes treatment. Sensitivity analysis resulted in a minimum annual cost-savings of CDN $691 048 and a maximum annual cost-savings of CDN $8 402 373 for SGLT-2 inhibitor versus SU initiation after metformin due to mild hypoglycemia reduction for the Canadian population with type 2 diabetes.
Conclusion
This study illustrates that reduction in mild hypoglycemia episodes (which mostly are not reported in real-world clinical settings) due to SGLT2I utilization instead of SU in elderly Ontarian with type 2 diabetes can lead to a significant cost-savings from patients' perspective.

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EP580

Do adding B vitamins and folate to metformin has beneficial effect on renal function and lipids in type 2 diabetic patients

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Introduction
Metformin is effective in reducing cardiovascular mortality, however may decrease vitamin B12 and folate levels, and increase levels of homocysteine. Hyperhomocysteinemia is associated with adverse impact on lipid parameters and renal function. The present study was designed to determine the effect of homocysteine lowering therapy by using group B vitamins and folate supplementations on lipid metabolism especially HDL cholesterol as well as kidney function assessed by serum creatinine, urine microalbumin (MA), albumin creatinin ratio (MaCR) and GFR in diabetic patients treated with high doses of metformin.
Methods
In a randomized, placebo-controlled study, 60 diabetic patients treated with a high dose of metformin were randomly assigned to receive daily oral supplementation with folate (1000 mcg), vitamins B12 (400 mcg) and B6 (10 mg) (Group 1) or placebo (Group 2). Metabolic parameters were measured at baseline and after 4 months folow-up.
Results
The two groups were similar at baseline in terms of metabolic parameters. After 4-months, HDL cholesterol was significantly greater in patients who received vitamin supplementation than patients in the placebo group ($P<0.0001$). Post-treatment vitamin B12 and folic acid levels were greater in group 1 vs group 2 ($P=0.007$ and $P<0.0001$, respectively). Hcy level decreased significantly in the treatment group from 10.0 ± 4.4 to 7.6 ± 2.5 mol/l, $P=0.002$ and did not change in the placebo group ($P=0.964$). In GLM model, group was significant independent predictor of endpoint HDL choleserol ($P=0.018$), while post-treatment LDL cholesterol did not differ by group after controlling for the other

variables in the model ($P=0.158$). Posttreatment GFR was significantly greater in patients who received vitamin supplementation than patients in the placebo group ($P<0.003$). Plasma creatinine, urine protein and urine microalbumin did not differ significantly by treatment group at baseline at the end of the study. Nevertheless, within the vitamin -treated group, MaCR dcreased from baseline ($P<0.036$) and did not change in the placebo group.
Conclusion
Adding B vitamins and folate supplementations to metformin was associated with beneficial effects on HDL cholesterol and renal function in diabetic patients.

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EP581

The role of sodium-glucose co-transporter 2 inhibitors as add-on therapy in type 2 diabetes

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Objective
SGLT2 inhibitors, have been shown to improve glycaemic control, stabilize insulin dosing and mitigate insulin-associated weight gain in patients whose type 2 diabetes mellitus (T2DM) was inadequately controlled. The objective is to evaluate the real-world efficacy and safety of adding iSGLT-2 therapy in inadequately controlled patients with oral antidiabetic drugs and with or without insulin therapy.
Materials and methods
This observational study assessed the efficacy and safety of SGLT-2 inhibitors used as add-on therapy in a group of 45 T2DM patients from a community endocrinology practice from January 2015 to April 2016. Primary endpoint was HbA1c mean change from baseline at 15 months. Secondary endpoints included change in body weight,other glycaemic parameters,and percentage of patients reporting adverse effects of therapy.
Results
A total of 45 patients met all the study criteria. 60% with oral antidiabetic drugs, 11.1% with oral antidiabetic drugs and basal insulin regimens, 11.11% with basal-bolus insulin therapy and 17.8% with oral antidiabetic drugs and basal-bolus insulin therapy.Baseline patient characteristics were as follows: average age, 60.2 ± 9.7 years; mean duration of T2DM, 11.3 ± 8.3 years**;** 80% male**;** baseline body mass index (BMI), 32.76 ± 4.96 kg/m^2; mean baseline HbA1c, 9.17 ± 2.02%;systolic BP 143.67 ± 15.46 mmHg and diastolic BP 80.44 ± 10.16 mmHg. Mean duration of SGLT2 inhibitors 7.42 ± 4.22 months. HbA1c and weight were significantly reduced by 1.36 ± 1.79%, $P<0.000$ and 3.21 ± 3.52 kg, $P<0.000$, respectively; systolic BP (12.91 ± 10.57 mmHg, $P<0.000$), diastolic BP (6.39 ± 7.34 mmHg $P<0.000$) and triglycerides (45.58 ± 115.65 mg/dl, $P<0.011$). Genital- and urinary tract infections were reported by 6.7% patients.Any diabetic ketoacidosis case was reported.
Conclusion
SGLT-2 Inhibitors added to other oral antidiabetic drugs or insulin in patients with uncontrolled T2DM significantly improved glycemic control, reduced weight, blood pressure and triglycerides,and was generally well tolerated.In conclusion, SGLT-2 inhibitors,appears to be an important addition to the therapeutic options for the management of type 2 diabetes, particularly when used as add-on therapy.

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EP582

Abstract withdrawn.

EP583

Hypoglycemia, weight changes and health related quality of life (HRQoL) instruments for diabetes care

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Background
Diabetes is a chronic disease with significant negative impact on quality of life. Hypoglycemia and weight gain are two important variables that can impact HRQoL negatively in patients with diabetes under treatment with medication.
Objective
The objective of this study was to evaluate HRQoL tools and questionnaires and to explore if the HRQoL instruments address issues related to hypoglycemia and weight gain, which impact HRQoL along other domains.
Methods
A systematic review was conducted utilizing databases on PubMed, Google and Google Scholar to find HRQoL tools that have been utilized in diabetes care. The tools in English language were selected. The construct of the HRQoL tools were analysed by the domains.
Results
In general, three types of HRQoL tools and questionnaires have been utilized in diabetes care (total $N=84$): diabetes specific ($N=27$), domain specific ($N=33$) and general HRQoL ($N=24$). 9.5% ($N=8$) and 2.5% ($N=2$) of tools had domains for hypoglycemia or weight changes, respectively. None of the tools had both domains, simultaneously. 88% ($N=74$) of tools had no domain for hypoglycemia or weight changes.
Conclusion
This study illustrated that few HRQoL instruments incorporated domains related to hypoglycemia and weight gain. This calls for developing more comprehensive HRQoL instruments to measure the impact of hypoglycemia and weight gain on quality of life of patient with diabetes on pharmacotherapy. Addressing such an issue is very timely, in light of recent utilization of newer classes of medications in diabetes care such as SGLT2I and GLP1A which have safer glycemic profile and cause weight loss.

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EP584

Use of an innovative Technology Enabled Care service (TECS) 'Florence' to empower patients and enhance adherence to BP treatments in diabetes

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Background
Social deprivation is high within our large ethnic and diabetes prevalent population. Compliance is a major stumbling block in the achievement of Blood Pressure (BP) targets. Given the above, we took the opportunity to enrol with West Midlands Academic Health Science Network (WMAHSN) Florence (Flo) Exemplar project mobile phone texting service. Flo sends advice and collects patient information which clinicians can access through any device connected to the internet.
Aims
Our aims were to improve adherence to BP treatment via engaging and motivating patients and determine the clinical and cost effectiveness of this simple Telemedicine model.
Method and results
Of the 100 patients enrolled for BP management (April 2015–2016) from diabetes renal clinics:

- BP medications adjusted in 27/100 (27%).
- 46/100 (46%) patients were discharged with good BP control following medication adjustment.

Total outpatient attendances prevented: 107

- 45 (for those we continue to follow up)
- 62 (for those discharged)

This has saved £11 663 (national average £109 per OP attendance) simply from non-face to face BP management against a total cost of £2329 assuming 75% of the 107 patients have used the WMAHSN Hypertension CKD/diabetes protocol for the full 12 weeks (364 texts/patient, cost per patient £29.12 for the service).
Conclusion
Flo's use continues to grow and 5 new teams are ready to join in our Trust. Thus, this clinically and cost effective model of care delivery (with high patient

satisfaction) utilises manpower resources and healthcare professional time effectively to improve outcomes and can be easily replicated in any NHS Trust or CCG.

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EP585

The decreased adiponectin level after the treatment with glibenclamide is associated with deterioration of left ventricular function

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Background and aim
Hyperglycemia is an important pathogenetic factor, which causes abnormalities at the cardiac myocyte level, leading to structural and functional abnormalities and diabetic cardiomyopathy (DCM). It has been proposed that DCM could also occur as a consequence of other metabolic alterations. Adiponectin concentration is negatively associated with obesity, insulin resistance (IR), oxidative stress and endothelial dysfunction. It can be considered as a predictive biomarker of IR and cardiovascular risk. Treatment of diabetic patients with conventional sulfonylurea such as glibenclamide has been reported to be associated with adverse cardiovascular effects and a higher incidence of cardiovascular death. The aim of this study was to assess the effect of glibenclamide on adiponectine level and its impact on left ventricular function in type 2 diabetic patients.
Methods
This single-blind, prospective, randomized controlled study consists of 32 weeks screening period and a 24-weeks treatment period with glibenclamide. From the 167 patients screened, most of whom were treated for hypertension or with metformin, 40 type 2 diabetic patients, were divided in two groups (glimepiride vs glibenclamide) with a body mass index (BMI) >25 treated with glibenclamide for more than 3 months before screening were included in the study. Anthropometric, biochemical and echocardiographic measurements were performed before and at the end of treatment.
Results
In the glibenclamide group significant differences were observed in HbA1C which was decreased from $8.8\% \pm 1.4$ to $8.3\% \pm 1.1\%$ ($P<0.001$), and in the other hand adiponectin was significanty decreased (from 34.3 ± 22.6 to 20.3 ± 11.3 ng/ml, $P=0.011$). From echocardiographic measurements early diastolic (e') and systolic (s') myocardial wall velocity of the septum (from 6.7 ± 1.4 cm/s to 5.6 ± 1.5 cm/s, $P=0.04$, and from 7.0 ± 1.2 cm/s to 6.1 ± 1.2 cm/s, $P=0.03$, respectively); as well as right e' and s' (from 11.7 ± 2.7 cm/s to 7.9 ± 3.8 cm/s, $P=0.01$, and from 12.5 ± 4.3 cm/s to 8.4 ± 3.2 cm/s, $P=0.01$, respectively) were decreased from baseline to the 24 weeks treatment. While DcT time was significantly increased in the group of Glibenclamide, which can explain worsening of diastolic dysfunction in diabetic patients treated with this drug.
Conclusions
The decreased adiponectine level after the treatment with glibenclamide is strongly associated with deterioration LV diastolic and systolic function, in type 2 diabetic patients. This finding highlights the need of further investigations of the impact of metabolic disorders on cardiac function in diabetic patients, beyond hyperglicemia.

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EP586

Effects of inositol on glucose homeostasis: systematic review and meta-analysis of randomized controlled trials

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Aim
To analyze the effects of inositol administration on parameters related to glucose homeostasis.
Material and methods
Systematic review and meta-analysis of articles published in Medline or Web of Science Until February 1, 2016. We included studies that met the following criteria: i) Randomized controlled clinical trials of inositol/inositol isomer supplementation against placebo in parallel design, ii) performed in humans, iii) with information about glycemic control parameters and iv) published as full article. The following parameters were considered: Fasting plasma glucose (FPG), blood glucose at 2 h after an oral glucose tolerance test (OGTT), impaired oral glucose tolerance, need for insulin treatment, body mass index (BMI), insulinemia, HOMA-IR and HbA1c. For the meta-analysis, Revman 5.1 software with a random effects model was used.
Results
The search retrieved 476 publications, of which 22 articles were finally included, with a total of 1533 individuals. Treatment time ranged from 28 days to 12 months. Significant differences were observed in all parameters evaluated except in BMI, HbA1c and % of patients who needed treatment with insulin. Treatment with inositol decreased FPG (mean difference -0.44 mmol/l (-0.65, -0.23)), glycemia at 2 h of OGTT (mean difference -0.69 mmol/l (-1.14, -0.23)), % of patients with impaired glucose tolerance (relative risk 0.28 (0.12, 0.66)), insulinemia (mean difference -38.49 pmol/l (-52.63, -24.36)) and HOMA-IR (mean difference -1.96 mIU/l $\times$ mmol/L (-2.62, 1.30)). No relevant side effects were observed in patients treated with inositol.
Conclusions
Inositol treatment improves glucose tolerance and insulin resistance by a mechanism independent of body mass index.

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EP587

A rare pediatric presentation of type 1 diabetes mellitus with duchenne muscular dystrophy - what to expect in the future?

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Introduction
Duchenne muscular dystrophy (DMD) is a genetic condition caused by mutations in the X-linked dystrophin-gene leading to muscle degeneration and early death in males.Since DMD is characterized by aggressive inflammation it is recommended the use of pharmacological treatment with corticosteroids (CS). Type-1 diabetes mellitus (T1DM) is one of the most common chronic diseases in childhood and is caused by insulin deficiency resulting from the autoimmune destruction of insulin producing beta-cells of the pancreas.
Case presentation
We present the case of a 3-years-old male patient who was admitted in our clinic for episodes of symptomatic hypoglycemia alternating with hyperglycemia. He was diagnosed with T1DM and DMD 1-year prior his admission and had been on Humulin-N and Humulin-R combination and Deflazacort 12mg/daily treatment ever since.His medical history includes upper respiratory tract infection remitted after bronchodilator and expectorant medication in the last month.Clinical examination revealed short stature and overweight patient:height $=90.9$ cm (-2.71 SDS), (5-th percentile); weight $=14$ kg (25-th percentile); BMI $=17.28$ kg/m^2, (88-th percentile); pubertal stage-1 according to Tanner; hypotonic muscular system, hypokinetic, normal thyroid palpation, language deficiency. Lab tests revealed glycemic control with HbA1c $=7.8\%$ (in target for age), hepatic cytolysis (AST $=244$ IU/l, ALT $=583$ IU/l), euthyroidism (TSH $=3.95$ uIU/ml). Funduscopic examination and thyroid ultrasound were normal. During admission the patient is switched from multiple-dose-injection therapy (MDI) to cutaneous-insulin-infusion therapy (CSII) with aspart, well tolerated; basal rates, the correction factor and carbohydrates-ratio are set, followed by glycemic profile evolving favorably. Considering the risks of untreated DMD and the metabolic pathology association, the patient continues treatment with Deflazacort 12 mg/daily under multidisciplinary surveillance. Parents received nutritional counseling.
Conclusion
Possible endocrine complications of DMD with chronic CS treatment consequences regarding growth failure, pubertal disorder due to hypogonadism,

excessive weight gain, diabetes, especially in pediatric patients, and bone health have not been explored in depth. Treating children can be challenging when having such rare presentation because there is a need for better comprehension of metabolic and endocrine implications for DMD with the purpose of developing improved clinical treatments and/or quality of life.

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EP588

Significant effect of a group education program on glycemic control and incidence of hypoglycemia in patients with diabetes mellitus type 1: A case-controlled study

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DM1 constitutes a real challenge in everyday practice for both physicians and patients. Due to the complexity of the disease and its unpredictable nature, structured education and training programs are nowadays implemented that ensure active patient involvement and self-care behaviors to achieve adequate glycemic control, prevent diabetic complications and improve the quality of life of patients. These programs provide patients with the necessary knowledge and skills to self-monitor and self-manage the disease and its associated metabolic conditions.

Aims

To evaluate the effect of a structured 12-month education program that motivated patients to follow a healthy Mediterranean diet and exercise regularly as well as to adjust carbohydrate intake and insulin dose according to their needs.

Methods

The education group (EG) was comprised of 62 patients (45 males) with type 1 DM, mean age 36 ± 4.2 years and BMI: 24.2 ± 3.1 kg/m^2. An age- and BMI-matched control group (CG, $n=25$, mean age 41 ± 6.4 years, BMI: 25.7 ± 4.2 kg/m^2) was composed of patients referred but not enrolled in the project.

Results

At the end of this program, HbA1C levels were significantly decreased (8.5 ± 2.1%vs 7.08 ± 0.79%, $P<0.0001$) as was also the incidence of hypoglycemic episodes ($P<0.05$). Regarding daily glucose fluctuations, significant improvement ($P<0.05$) was observed, as reflected in low, high and daily median glucose values. On the other hand, the above parameters remained stable in the CG.

Conclusions

These results strongly support the need for long-lasting structured education group courses in adult diabetic patients keen to change their habits in order to achieve self-management of the disease.

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EP589

Dapagliflozin induced vulvovaginitis in an atopic patient with type 2 diabetes mellitus

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Introduction

Dapagliflozin is sodium-glucose co-transporter receptor 2 (SGLT2) inhibitor that is recently discovered an oral antidiabetic (OAD) agent that improves glycemic control by increasing the renal excretion of glucose. Vulvovaginal candidiasis (VVC) is the infection of the vaginal vestibuler area. We present a case of VVC accompanied by use of dapagliflozin.

Case

A-48-year-old woman who had T2DM since 8 years was admitted to the endocrinology clinic. Her past medical history was remarkable for atopic dermatitis. Her body mass index was 33.7 kg/m^2. She had been using metformin and sulfonylurea. Her initial laboratory results were; fasting plasma glucose: 131 mg/dl, hemoglobin A1c: 7.8%. Dapagliflozin 10 mg daily therapy added to her therapy. On the 12th day of dapagliflozin therapy she noted vulvovaginal pruritus. Three days later she complained the severity of symptoms. Physical examination revealed wide erythema on vulvar, vaginal and perineal regions of genitourinary area. Positive vaginal culture for Candida albicans was detected. She was diagnosed with VVC. The treatment of VVC was made through topical clotrimazole. Three days later the clinical manifestations become worsened and dapagliflozin was discontinued. Signs and symptoms of VV were regressed two days later.

Summary

Vulvovaginitis is a frequently encountered acute and recurrent complication of diabetes mellitus; tend to be worsened by poor glycemic control. Appropriate diagnosis and management is essential to confirm optimal genital and metabolic health. We consider that this case will be mostly useful among atopic patients who have potential risk for VVC and drug withdrawal may be considered in such of these patients.

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EP590

Efficacy of body weight reduction on SGLT-2 inhibitor in people with type 2 diabetes mellitus

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Objective

Dapagliflozin, sodium-glucose cotransporter-2 (SGLT-2) inhibitor, reduces hyperglycemia and body weight by inhibiting renal glucose reabsorption. However, only a few studies have shown the efficacy of dapagliflozin in type 2 diabetic patients. We evaluated the efficacy and safety of body weight reduction of dapagliflozin in real practice with type 2 diabetes in Korea.

Methods

This is a retrospective, observational study, data from 61 patients with 12 months of dapagliflozin (10 mg once-daily) therapy were analyzed, visited medical center from January 2015 to July 2016. We had divided into three treatment groups: first group taking combination of dapagliflozin and metformin (Group 1); second group taking triple combination of dapagliflozin and metformin with sulfonylurea or dipeptidyl-peptidase IV (DPP-4) inhibitors (Group 2); third group taking quadriple combination of dapagliflozin, metformin and sulfonylurea with DPP-4 inhibitors (Group 3).

Results

After 12 months, mean change from baseline body weight was -3.4 ± 2.6 kg ($P<0.001$) for total, -3.4 ± 3.1 kg ($P<0.001$) for group 1, -2.7 ± 2.0 kg ($P=0.008$) for group 2, -4.0 ± 2.3 kg ($P<0.001$) for group 3. In total, mean change from baseline SBP and DBP were -6.0 ± 14 mmHg ($P=0.001$) and -3.4 ± 7.7 mmHg ($P=0.002$) respectively. Patients who achieved body weight reduction of $\geq5\%$ after 12 months were classified in the responder group and $<5\%$ non-responder group. There were baseline fasting C-peptide level was higher in responder group than non-responder group (3.25 ± 1.07 ng/ml vs. 2.62 ± 1.02 ng/ml, $P=0.023$). In total, reductions in HbA1c and PP2 glucose levels were -0.61 ± 0.82% ($P<0.001$) and -35.4 ± 62 mg/dl ($P<0.001$) respectively. There were no serious adverse event including hypoglycemia in dapagliflozin group.

Conclusions

In patients with type 2 diabetes, SGLT-2 inhibitor improved glycemic control and reduced body weight reduction with safety of dapagliflozin.

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EP591

Modification of lifestyle and influence on leptin and insulin resistance to prevent type 2 diabetes mellitus

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The aim of the present study was to determine the change of fasting serum leptin and insulin levels and insulin resistance in patients with risk factors of diabetes mellitus of type 2 (DM 2) including impaired glucose tolerance/impaired fasting glucose (IGT/IFG), obese and first-degree relatives of patients with diabetes after lifestyle modification.

Material and methods

The study included 100 patients (32 men, 68 female) 25–65 years old at risk factors of DM 2. All patients received recommendations on a balanced diet and physical activity. The average fasting plasma glucose (FPG), 2-h plasma glucose concentrations (2-h PG) following a 75-g oral glucose tolerance test, HbA1c, index HOMA-IR. Fasting serum leptin and insulin levels were detected by sensitive ELISA.

Results

During 18 months our study 56 patients carried out this recommendations (research group) and 44 patients did not (control group). Patients of the research group demonstrated mean reduction of body mass index (-2.6 ± 0.4 kg/m^2) and waist-to-hip ratio (-0.2 ± 0.01) ($P < 0.01$) and persons of the control group had significant increase of these parameters ($P < 0.05$). Among subjects with IGT/IFG at baseline, glucose levels normalized in 56.0% of patients from the research group and 4.5% in control group ($P < 0.001$). Fasting serum insulin and HOMA-IR in research group decreased from 11.9 ± 4.3 to 9.6 ± 4.5 μU/ml and from 3.6 ± 1.1 to 2.7 ± 1.4 accordingly ($P < 0.05$). In control group the specified parameters had increased significantly ($P < 0.01$). The main novel finding was that serum leptin median in research group was decreased from 34.7 to 26.4 ng/ml (-23.9%, $P < 0.001$) and increased in control group from 37.9 to 44.7 ng/ml ($+17.9\%$, $P < 0.01$). The risk reduction of DM 2 development among patients of the research group was 48.0% compared to the control group.

Conclusion

Thereby, lifestyle modification can prevent the development of type 2 diabetes in subjects with risk factors by reduction leptin and insulin resistance.

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Australian women with diabetes survey of contraceptive use and beliefs about safety of contraceptive options

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Introduction

Women with diabetes mellitus (DM) are at increased risk of adverse maternal and foetal outcomes. Preconception planning is required to minimize risks, including good understanding of contraceptive options.

Objectives

To determine in Australian women with DM beliefs regarding safety of various contraceptive methods in DM, information sources regarding contraception, recent and previous contraceptive use, knowledge of pregnancy risks, access to preconception planning and pregnancy history.

Methods

We conducted a cross-sectional 22 item structured questionnaire-based study of Australian women with DM (Type 1 or 2) aged 16–49 years attending Nepean Hospital, a tertiary referral centre. Women were recruited via mail, at scheduled appointments or hospital admission.

Results

107 of approximately 215 (49.7%) women completed the questionnaire. 83% were aware of risks related to DM in pregnancy. However, the majority of women (74%) had not received preconception counselling. The main source of information regarding contraception was the general practitioner (70%). Most women (78%) believed combined oral contraceptive pills (COCPs) were safe in DM. 63% of women were uncertain of the safety of intra-uterine devices (IUDs) in DM and 44% were uncertain of contraceptive implant (CI) safety. The main forms of contraception ever used were condoms (87%) and COCPs (74%), with 34% using long-acting reversible contraception (LARC) of IUDs and CIs. 29% of sexually active women were not using any contraception or planning pregnancy. Amongst 110 pregnancies in 47 women there were 78 (71%) live births, 4 (4%) stillbirths, 16 (15%) miscarriages, 2 (2%) ectopic pregnancies and 10 (9%) terminations.

Conclusion

Despite knowledge of pregnancy risks, preconception counselling is lacking and pregnancy outcomes poor. There was uncertainty regarding safety of LARC, the most reliable contraceptive methods and over a quarter of women used no contraception. Better education of women with DM regarding contraception and preconception planning is needed.

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EP593

Management and control of hospital hyperglycemia in the health area of cuenca (Spain)

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Introduction and objectives

Hyperglycemia is a common problem in hospitalized patients that increases infections, mortality, costs and the hospital stay. The objective of this study is to know the management and control of hyperglycemia in our hospital.

Methods

We designed a cross-sectional observational study. We included patients admitted in the hospital every three days in two months. We excluded patients younger than 15 years, stays less than three days and those of the pediatric, gynecological, emergency and intensive care services. We collected the data from these patients the third day of admission and at discharge. We defined hyperglycemia as two or more capillary glucose values greater than 140 mg/dl.

Results

A total of 328 patients were included. 109 patients had hyperglycemia and 85 were known diabetics. Diabetic patients had the next previous treatments: only oral antidiabetic agents (55.3%), insulin (38.8%), and without treatment (5.9%). During admission 48.5% were treated with insulin sliding scales, 19.2% with insulin bolus-basal regimen, 12.1% with basal insulin, 7.1% with premixed insulin, 2% with only antidiabetic agents and 11.1% without treatment. The glycemic control during admission was considered good in 25% (mean glycemia <140 mg/dl), regular in 45% (140–200 mg/dl) and bad in 29% (>200 mg/dl). Hypoglycemia was diagnosed in 12.5% (2.1% severe). Only 23% patients had a recent HbA1c, with a mean HbA1c of $7.37 \pm 1.4\%$. When the patients discharge from hospital, the antidiabetic treatment for home was not adequately adjusted in 47.4%.

Conclusions

A high percentage of diabetic patients are still treated with insulin sliding scales during hospitalization. Few patients have a good glycemic control. Most of patients hadn't a recent HbA1c. Finally, treatment is not adequately adjusted at discharge in almost half of patients. That's why, we believe it's necessary to create a multidisciplinary protocol to improve the management of the hospital hyperglycemia.

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EP594

Impact of the insulin pump therapy on quality of life children and adolescents with diabetes mellitus type 1

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Objectives
To investigate the changes parameters of quality of life (QoL) in children and adolescents with diabetes mellitus type 1 (T1DM), using different regimes insulin therapy.
Research design and methods
Thirty patients with diabetes mellitus type 1, aged 5–18 years (mean 13.3 ± 3.04 yr), with disease duration from 1 to 10 years (mean 5.4 ± 3.4 yr) took part in paired study. QoL was assessed with the PedsQL (Generic Core Scales and Diabetes Module, Russian version) at two time points: 1st – during multiple daily insulin injection (MDI); 2d – after initiation continuous subcutaneous insulin infusion (CSII). Data were analyzed in subgroups aged 5–7 yr, 8–12 yr, 13–18 yr.
Results
Nevertheless, analysis demonstrated positive dynamic of QoL in patients after initiation CSII. Treatment barriers decreased due to reduction of a number of injections (75.3 vs. 90.0 $P < 0.05$) in preschool-age children. Patients at the age of 8–12 evaluated higher physical function (74.2 vs. 94.0, $P < 0.05$) after initiation CSII. In adolescent's group social activity indicates improved (85.0 vs. 95.0, $P < 0.05$). Further, they were less worried about long-term complications (70.0 vs. 85.0, $P < 0.05$).
Conclusions
Using of insulin pump therapy in children with T1DM allows to improve of quality of life. Preschoolers get used to the necessary of insulin therapy easier, schoolchildren and adolescents have opportunity to increase the level of their physical and social activity.

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EP595

Efficacy of insulin detemir treatment in type 2 diabetes mellitus is associated with a allele od the catechol o-methyltransferase polymorphism

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Introduction
Growing evidence suggests that nutrients and hormonal signals converge and directly act on brain centers, leading to changes in energy metabolism and stable body weight over time. Catechol O-methyltransferase (COMT) is one of the major enzymes involved in catecholamine and estrogen degradation. There is a well-established association between the COMT Val108/158Met polymorphism and abdominal obesity, blood pressure increase and T2DM. Basal insulin detemir besides a low pharmacodynamic coefficient of variability, exhibits anorexigenic features, probably through a complex interplay of its effects on the CNS and on the finely tuned efferent and afferent signals between muscle, brain, liver, renal and adipose tissues.
Aims
To investigate the association of COMT Val108/158Met polymorphisms with effectiveness of insulin detemir in achieving glucose control and body weight control.
Methods
Observational study included 185 T2DM patients inadequately controled with premix insulin analogues, which were replaced with three doses of insulin aspart at mealtime and insulin detemir at bedtime that were followed for 52 weeks. After DNA isolation from blood samples, genotyping of COMT Val108/158Met polymorphism (rs4680) was performed.
Results
The mean age of participants was 67.1 ± 8.01 years, with a mean duration of diabetes 16.1 ± 5.9 years. HbA1c and fasting plasma glucose were significantly decreased after 52 weeks (8.58% vs 7.78%, 11.7 mmol/l vs 8.7 mmol/l, respectively, $P < 0.001$). At the end of the follow up period, 28.1% of patients achieved HbA1c < 7.0%. Insulin detemir had a significant weight sparing effect in overweight patients. The most prominent finding was that A carriers (the combined AG and AA genotype) of the COMT Val108/158Met achieved significantly better HbA1c values compared to patients carrying GG genotype.
Conclusions
Our results showed that the presence of one or two A allele of the COMT Val108/158Met was associated with improved glycemic response, and with a better response to insulin detemir therapy in T2DM patients.

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EP596

A dramatic improvement in metabolic parameters and cutaneous manifestations of insulin-resistance in a type 2 diabetic patient with Congenital Generalized Lipodystrophy (Berardinelli-Seip Syndrome) treated with pioglitazone

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Background
Berardinelli-Seip Congenital Lipodystrophy (BSCL) is a autosomal recessive disorder with only up to 500 reported cases. It is characterized by generalized absence of fat since birth and severe metabolic derangements such as insulin resistance, hyperglycemia and dyslipidemia. Diabetes mellitus generally develops during the second or third decade of life. This is a rare clinical condition, with worldwide prevalence of 1 in 10 million people and incidence of 1:500.000 newborns/year in Portugal.
Patient and methods
11-year-old caucasian boy was referred to the Pediatric Endocrinology consultation because of fasting hyperglycemia detected during routine blood tests. There was no history of polyuria, thirst or weight loss. He was medicated with antihypertensive medication since 6-years-old. Physical examination revealed a thin patient with acromegaloid features and severe acanthosis nigricans involving the posterior cervical region, axillary and periumbilical areas. Subcutaneous tissue atrophy was notoriously evident in the face, trunk and limbs. Secondary sexual characteristics were compatible with stage V of TANNER scale. Blood tests revealed hyperglycemia with hyperinsulinemia, dyslipidemia, low leptin, $HOMA_{IR}$ index indicating insulin resistance, alterations in hepatic function suggesting fatty liver and all autoantibodies searched were negatives. Thyroid function, IGF-1 and Growth Hormone (GH) were within the normal range for age and sex. Abdominal ultrasounds revealed a hepatosplenomegaly.
Results
The presumptive diagnosis of BSCL was admitted and the patient was started on metformin 1000 mg twice daily. Pioglitazone, 30 mg/day in two divided doses was added three months later. After 18 months of treatment, glucose and triglycerides levels were near normal, hepatic enzymes, liver echographic features and cutaneous manifestation of insulin-resistance were improved. Leptin remained undetectable.
Conclusion
Early introduction of pioglitazone in diabetic patients with BSCL may dramatically improve insulin resistance without relevant side effects.

Keywords: Lypodystrophty, Berardinelli-Seip Syndrome, Insulin-resistance
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EP597

Comparison of neonatal outcome in women with gestational diabetes on different pharmacoglogical agents dilevered at term

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Objective
Though many studies have looked at the neonatal outcomes in patients with gestational diabetes on different medications, there is no consensus on the preferred drug for initiation of therapy. We aim to compare the neonatal outcome in a cohort of patients attending our service, to determine if one modality is superior to the other.

Methods
This study is a prospective observational study from 1-07-2015 to 31-04-2016. The data of all gestational diabetic patients referred to the Joint Diabetic Clinic, in a local secondary Hospital, who required pharmacological intervention were entered into an excel spreadsheet. This included their antenatal, intrapartum and postnatal details. *P* values calculated with Student's *t*-test. Statistical significance if $P < 0.05$.
Results
The total number of patients studied was 107. There were 58 patients (54%) who were treated with Metformin only, their BMI at booking was 30 kg/m^2, average HbA1c 5.69%. The average birth weight of the neonates of this group was 3287.78 g and there were 9 (15.51%) Neonatal ICU admissions. 17 patients were commenced on insulin, thier HbA1c was 5.78% and their booking BMI was 32. The average birth weight in this subgroup was 3409.24 g with 2 (11.76%) NICU admissions. 32 (29.90%) of our patients required Metformin and insulin. Their average weight at booking was 35, and thier HbA1c was 5.8%. In this subgroup, the average birth weight was 3494.56 g with 5(15.62%) requiring NICU admission. The least birth weight was observed in the subgroup with Metformin alone (54% of our patients), $P < 0.4$. The subgroups with insulin showed a higher neonatal birth weight. The least NICU admissions were in the insulin only group.
Discussion
The least birth weight was observed in the subgroup with Metformin alone (54% of our patients), with the subgroups with insulin showed a higher neonatal birth weight. However, the least NICU admissions were seen in the insulin only group.
Conclusion
Whether the increase in birth weight seen in patients on insulin, is indicative of uncontrolled blood sugars or due to the direct effect of insulin as shown in some studies, requires further evaluation. Further analysis of the ongoing cohort is needed before we can recommend any one mode of treatment as the preferred choice in our setting.

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EP598

The hypolipidemic and hepatoprotective efficacies of a fixed-dose combination of essential phospholipids with methionine (EPL + M) during atorvastatin (A) therapy in hyperlipidemic patients with cardiovascular diseases (CVD) and type 2 diabetes mellitus (DM) (OLYMP trial)

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Objective
Objective to study the hypolipidemic efficacy, hepatoprotective activity, and tolerance of the fixed-dose combination of essential phospholipids with methionine (EPL + M) - Eslidine in the combination therapy with A in patients (pts) with cardiovascular diseases (CVD) and type 2 DM who suffer from hyperlipidemia (HL) in order to optimize their treatment in daily clinical practice.
Subjects and methods
The trial enrolled 60 pts (mean age 58.1 ± 4.5 years) with type 2 DM. All the pts had essential hypertension, 84.8% were obese; 80% had increased echogenicity in the liver and its enlargement, as evidenced by ultrasound study. The patients received standard therapy appropriate for this disease, other than agents affecting blood cholesterol (Ch) levels. After adherence to a hypolipidemic diet for 2 weeks, the pts were randomized to two groups: i) 30 pts received A in a dose of 20 mg/day; 2) 30 pts had the drug in the same dose in combination with Eslidine (EPL + M). The therapy duration was 12 weeks. The impact of therapy on lipid, lipoproteins, hepatic enzymes.
Results
After 12 weeks, the group of pts receiving A showed a significant reduction in the levels of total Ch by 42.4%, LDL-Ch by 44.9%, and TG by 45.4%; in the A + Eslidine group, these indicators decreased by 37.8, 47.9, and 26.4%, respectively. By the end of a course of therapy, the number of pts with LDL-Ch goals was 26.9 and 36.4% in Groups 1 and 2, respectively. In the pts with significant hypercholesterolemia (LDL-Ch ≥4.2 mmol/l), the LDL-Ch decline was 46.9 and 54.6% in those on A and A + Eslidine, respectively ($P < 0.05$); in the pts with elevated TG levels (1.7 mmol/l or higher), the fall was 36.2 and 47.2%, respectively ($P < 0.05$). A caused a 47% increase in ALT activity ($P < 0.05$), without exceeding the upper normal range. In the pts on therapy A + Eslidine, the activity of ALT was, on the contrary, unchanged, there was a significant decrease in total bilirubin concentrations, glutamyl transpeptidase activity, and bile acid levels.
Conclusion
A 20 mg/day and its combination with Eslidine showed a good hypolipidemic efficacy and tolerability in hyperlipidemic pts with CVD and type 2 DM. Addition of Eslidine to statin therapy resulted in a more reduction in LDL-Ch and TG levels and noticeably improved hepatic functional activity.

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EP599

Pancreas transplantation: experience in a central hospital

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Introduction
Pancreas transplantation is an established treatment for selected patients with type 1 diabetes mellitus (T1DM) and severe chronic kidney disease (CKD), reducing mortality and morbidity.
Methods
We retrospectively reviewed the cases of pancreas transplantation performed at our centre from 1-January-2011 to 30-June-2016.
Results
In this period, 53 transplants were performed: 48 simultaneous pancreas-kidney transplants and 5 pancreas after kidney. Age at time of transplantation was 38 ± 7 years; 34 were male (64.2%). Patients had T1DM for an average of 26 ± 8 years (age at diagnosis: 12 ± 5 years). All patients had severe CKD, 78.4% on hemodialysis and 15.7% on peritoneal dialysis. Major postoperative complications occurred in 23 cases (43.4%): 8 infectious, 8 haemorrhagic, 7 thrombotic. Pancreas graft survival was 86.7% at 1 year (39/45) and 83.3% after 2 years (30/36). Kidney graft survival was 92.7% at 1 year (38/41) and 90.6% after 2 years (29/32). Graft failure ensued in 6 pancreatic grafts and 3 transplanted kidneys. There were 12 acute organ rejections (22.6%). Three patients died (5.9%), 2 from infection, one from haemorrhagic shock. Patients had, on average, 2 hospital readmissions, mainly due to infection. Among those with preserved pancreatic grafts, 93.2% are insulin-free. Over the last 2 years, compared to the first 2 years, there were more transplants performed (23 vs 13), fewer postoperative complications (30.4% vs 61.5%) and higher 1-year pancreas graft survival rate (93.8% vs 69.2%). Young age at diagnosis of T1DM was negatively related to pancreas and kidney graft survival ($P < 0.05$). Duration of dialysis and coronary disease were negatively related to renal graft survival ($P < 0.05$).
Conclusions
Patient and graft survival rates were similar to those described in literature. Better outcomes observed in recent years reflect the experience acquired. Young age of onset of T1DM, duration of dialysis and coronary disease may represent poor prognostic factors concerning graft function.

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EP600

Correlates of health-related quality of life in Bulgarian patients with type 2 diabetes mellitus

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Background
Diabetes mellitus (DM) is one of the greatest threats to global health and development of the 21th Century worldwide. In Bulgaria, it affects 9.6% of residents between ages 18-69 and has a profound impact on healthcare, economy and individuals. Diabetes and its complications are major causes of early death in our country - each year 4 125 women and 4 000 men die of diabetes-related complication. Diabetes not only reduces patient's physical wellbeing but also compromises other aspects of Health-Related Quality of Life (HRQoL). The aim of this study was to investigate the impact of demographic factors and glycaemic control on quality of life in patients with type 2 diabetes.

Material and methods
A cross-sectional survey was conducted in a sample of 540 adult patients under secondary care. Respondents were recruited from nine randomly selected outpatient endocrinology practices, 25% of all practices with contract to the Regional Health Insurance Fund Plovdiv-second largest district in Bulgaria. The survey was administered with disease-specific instrument ADDQoL -19.
Results
A total of 411 diabetic patients with average age of 59.9 + 11.6 years old participated in this study. 'Freedom to eat' was the Audit of Diabetes-dependent Quality of Life domain with the greatest negative average weighted impact (−4.0, on a scale of −9 to 3). In univariate analyses, older age, female sex, low socioeconomic status, cardiovascular disease, microvascular complications, insulin use correlated with decreased quality of life.
Conclusion
Patients with type 2 diabetes have a substantially decreased HRQoL in association with symptomatic complications. The data suggest that prevention of complications have the greatest potential to improve health-related quality of life in type 2 diabetes.
Keywords: Diabetes mellitus, Health-Related Quality of Life, ADDQoL-19, Bulgaria

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EP601

Effects of sitagliptin monotherapy on insulin resistance and immune functions in type 2 diabetic patients

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Background
Sitagliptin, unlike the some major antihyperglycemic drugs, is not associated with weight gain and has neutral effects on body weight. It is unclear whether sitagliptin treatment alters immune functions and insulin resistance in people with type 2 diabetes. The aim of the present study was to assess the effect of sitagliptin on insulin resistance and immune functions in patients with type 2 diabetes mellitus.
Methods
Twenty type 2 diabetic subjects were randomly assigned to receive sitagliptin (100 mg/day; $n=10$) or medical nutrition therapy (MNT) ($n=10$) for 12 weeks. Changes in anthropometric variables, glycemic control, insulin resistance, lipid parameters and immune functions were evaluated at baseline and following 12 weeks of treatment. T lymphocyte subgroups like as CD3, CD4, CD8 and TGF-β1, IL-12 were analyzed to evaluate immune functions.
Results
Significant decreases in body weight and body mass index were observed over the entire study period in MNT treatment group but not in sitagliptin group. HbA1c and postprandial plasma glucose (PPG) levels were decreased in the sitagliptin group compared with baseline values but not statistically significant while they were unchanged in the MNT group. There was a significant decrease c-peptide and insulin resistance (HOMA-IR) in sitagliptin group compared with baseline values but not in MNT group at the end of the 12 weeks. Compared to the MNT group we found a decrease in CD4 lymphocyte count by extension CD4/CD8 ratio in the sitagliptin group though statistically insignificant.
Conclusion
In this study of patients with type 2 diabetes, treatment with sitagliptin was associated with a significant decrease in insulin resistance. The decrease in CD4 lymphocyte count was thought be possibly related to the upper airway tract infection-like side effect described in the literature.
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EP602

Real practice experience: Degludec vs Glargina U300

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Background
In last year, different analogues of very long duration basal insulin have appeared, which favors the flexibility in its use. Both ensure a decrease in the rate of hypoglycemia and improve glycemic control in clinical trials. However, in real practice we have few data in real practice.
Objective
To compare the two ultralente insulin analogues in real practice. To analyze if they are cost effective.
Material and methods
Observational study including patients with type 2 diabetes, referred to Diabetes Day Hospital (DDH) to management diabetes in which we changed the basal insulin regimen to Tresiba® o Toujeo®. We revised them 3–6 months from change.
Results
123 patients were included (68.3% Toujeo® vs 41.7% Tresiba®). Mean age: 52.60 ± 19.67 years; ♂-58.5%. Most patients (83.7%) were with glargina basal insulin regimen. After 3 to 6 months from change in the insulin treatment, basal blood glucose reduced significantly in both groups ((to average of 233.04 ± 87.80 mg/dl down from 132.39 ± 66.03 mg/dl in Toujeo®; $P<0.001$) and (to 238.44 ± 86.28 mg/dl low from 143.11 ± 66.90 mg/dl, in Tresiba®; $P<0.001$)). We also observed a significant reduction in HbA1c levels ((average reduction in Toujeo® of 2.03 ± 2.28%, $P<0.001$) and (average decrease of 1.19 ± 1.46%, in Tresiba®; $P<0.001$)). However, comparatively no differences in efficacy were found between groups (0.49 ± 0.32%; $P=0.185$). At the end of follow-up, the number of units of Toujeo® increased an average of +5.08 ± 18.55 UI ($P=0.014$) while insulin requirements in Tresiba® decreased an average of −4.20 28 ± 7.36 UI (P 0.001). With regard to the cost, an average cost of 436.84 ± 252.57 € per person (Toujeo® group) vs 601.82 ± 419.61 € per person (Tresiba® group), (mean difference: 164.98 €, $P=0.027$).
Conclusion
Both basal insulin analogues are effective in reducing basal glycemia and HbA1c. Although there is an increase in insulin requirements when switching to Toujeo®. Potential economic savings are realized by using Toujeo® instead of Tresiba®.
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EP603

Glycemic control and weight evolution in DM2 patients with canaglifozina

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In the late years ISGLT2 have became an usual choice to treat diabetes. The inhibition of the sodium-glucose co transporters (SLGT2) inhibits also the glucose reabsorption in the proximale tubule and increases the glucose excreted in the urine. Therefore hyperglycemia decreases and so does weight. This is a very convenient side effect since type 2 DM is highly associated with overweight/-obesity. We show the results of HbA1c and weight evolution after starting canaglifozina 100 (added to the previous treatment) in 60 patients. Six of them (four women) had to stop the drug (three because of genital pruritus, one deterioration of renal function and one non related metastatic cancer). We also show the results of canaglifozina 300 in 17 patients. Women represented the 33% and the medium age was 62 ± 7years. We show data after 6 and 12 months on canaglifozina100. We have studied separately people older than 65 years old: 15 patients with medium age of 71 ± 4 years, 10 of them women. This group showed no side effects and no treatment interrumptions. In 30 people we studied uric acid levels, showing a difference of -0.9 mf/dl after 6 months on canaglifozina. Seventeen patients progress to canaglifozina 300, the medium age was 63.2 (±5,6) years. After 6 months they got an additional weight loss of 1.8 kg (±0.5) and decrease on HbA1c of −0.3% (±0.1). There were 18 patients on insuline therapy with an average of 32(±26) daily units one year later the average was 21 (±30) daily units of insulin. 2 patients stopped insulin therapy. Three patients stopped sunfonilurea previously to canaglifoniza 100. Initially HbA1c increased 0.3% (±0.1) and weight decreased 3.3 (±1.7) kg, patients referred decrease or disappearance of hypoglycemia. After one year on canaglifozina HbA1c decreased 0.2 (±0.1)% and weight decreased 4.8 (±2.2) kg. The 96% were satisfied with the new treatment for cana 100 and 100% for cana 300 (Table 1).

Table 1

	A1c	A1c6 months	A1c 1 year	Weight	Weight 6 months	Weight 1 year	Uric	Uric 1 year
All	7.5±1.2	7±0.9	6.9±1.2	89±11	82.8±12	79.5±15	6±1.1	5±1.2
>65	8.1±1.7	7.7±1.4	7.8±1.4	86.8±11	83.2±12	80.8±8	6.6±1.6	5.7±0.8
cana300	73±0.8	xxxxx	7.0±0.2	81.7±16	xxxxxx	79.9±17	xxxxx	xxxxxx

Conclusions
Canaglifozina 100 added to the previous treatment for DM2 improved glycaemic control and produced weight loss. Canaglifozina 300 improved even more this results. A decrease in uric acid levels was showed. The results were the same in the elderly group without increase of side effects. Patients on insulin decrease the dose with an improvement in the glycemic control. Stopping sulfonylurea produced a transient increase in glycaemia with less hypoglycemia. The mail side effect was non complicated urinary infection.

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EP604

Intralesional epidermal growth factor treatment on diabetic foot ulcers

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Objective
Treatment of diabetic foot ulcer is complex and difficult. Blood glucose regulation, debridment and surgical revascularization are used in management of diabetic foot ulcer. Intralesional Epidermal Growth Factor (EGF) is a new treatment approach for diabetic foot ulcer. We report our experience with eight patients with diabetic foot ulcer who were treated by intralesional EGF.
Patients and methods
A total of eight patients whose diabetic foot ulcers did not fully recover with other treatments were included our study (Table 1).
Results
Complete healing was observed all diabetic foot ulcers after the intralesional EGF treatment.
Conclusion
Our diabetic foot ulcers improved with intralesional EGF. Although our results are quite impressive, this treatment is very expensive and caused of some allergic reactions. Relation with malignancies is not known for long-term. In our opinion, intralesional EGF treatment should be used on wounds that did not heal with the other treatments.

Table 1

No.	Age year	Sex	Duration of dm	Lesion place	Wagner Grade	Prior treatment	Numbers of EGF doses
1	74	Male	20	Right 5. Phalanx	4	Amputation from left 4.metatars level	12
2	65	Male	15	Left foot 5th Metatars	3	Debridment+ Negative-pressure wound therapy	9
3	60	Male	22	Right foot First Phalanx	4	Amputation+ debridment	5
4	66	Male	16	Left foot First Phalanx	3	Amputation+ debridment	12
5	56	Male	33	Left heel, 2th and 3th Phalanx	3	Amputation+ debridment	12
6	57	Female	35	Left First Phalanx and heel	3	Debridment	9
7	40	Female	25	Right 3th and 4th Metatars	3	Debridment	9
8	64	Male	20	Left- Foot sole	3	Debridment	5

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EP605

Efficacy and safety of evoglipitin monotherapy in patients with type 2 diabetes

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Background and aims
To evaluate the efficacy and safety of the newly developed dipeptidyl peptidase-4 (DPP-4) inhibitor evogliptin in drug-naïve patients with inadequately controlled type 2 diabetes.
Materials and methods
In randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase III study, 160 patients with type 2 diabetes were randomized to evogliptin 5 mg or placebo for 24 weeks. The primary efficacy outcome measure was mean changes from baseline to endpoint in hemoglobin A1c (HbA1c).
Results
The mean baseline HbA1c levels of the evoglipitin group and the placebo group were $7.2 \pm 0.56\%$ and $7.2 \pm 0.63\%$, respectively ($P > 0.05$). Although the baseline HbA1c was very lower when compared with other phase III clinical trials using DPP-4 inhibitors, evogliptin provided significant placebo-corrected reductions in HbA1c from baseline of -0.23% ($P < 0.0001$) at 24 weeks. Also, the response rate achieving HbA1c $< 6.5\%$ was significantly higher in the evoglipitin group than placebo group ($P = 0.008$). Overall, incidences of adverse event and hypoglycemia were similar between the two groups.
Conclusion
In this 24-weeks study, once-daily evoglipitin monotherapy significantly improved glycemic control and was well tolerated in patients with type 2 diabetes.

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EP606

Rabson mendenhall syndrome-a dilemma to treat in a resource poor country

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Background
Rabson Mendenhall Syndrome (RMS) is a rare genetic syndrome that is caused by the mutation in the insulin receptor gene. Such mutation consequently results in severe insulin resistance. Patients suffering from RMS develop constant hyperglycemia from a progressive decline of endogenous insulin secretion. Drug therapy for RMS includes metformin, pioglitazones, large doses of insulin alongwith recombinant human methionyl leptin or IGF-1. Here we describe a case of RMS who management poses a big dilemma due to unavailabity of these treatment options in a low income country like Pakistan.
Case presentation
A young Pakistani girl of 16 years of age presented in our Endocrine clinic with uncontrolled blood glucose levels. She was diagnosed as case of type i diabetes mellitus (DM) at the age of 4 years due to the complaints of polyuria, polydipsia and weight loss. She was being treated with insulin since then. Initially she attained a good diabetic control but later on, her diabetes worsened. She was never admitted to a hospital as a case of Diabetic Ketoacidosis (DKA). At the time of her visit to our clinic, she was taking 70 units of Humulin-70/30 twice a day. Her fasting insulin level was 589 μU/ml, HbA1C was 16.8% with self-monitoring of blood glucose levels being always recorded as 'High' at home. Examination showed her body mass index of 17, short stature (less than 5th centile), severe acanthosis nigricans, coarse facial features, broad nose, thick lips, dental dysplasia, prognathism, hirsutism, small hands with thick fingersnails and abdominal distension. As genetic testing for RMS is not available in Pakistan, so she was diagnosed as a case of RMS with severe insulin resistance on clinical grounds only. Her insulin dosage was increased gradually to 520 units/day & Metformin+Pioglitazone were added (as insulin sensitizers) to the regimen, but still her blood glucose levels were uncontrolled. At last, she was admitted to hospital for diabetic control. There she received Metformin+Pioglitazone+20 units/day of insulin (regular+NPH) along with continuous insulin infusion @30 units/h bur still her blood glucose levels ranged between 400 and 600 mg/dl. As the 500 U/ml insulin is not available in a resource poor country like Pakistan along with the unavailability of latest treatment options like recombinant leptin or IGF-1, so it becomes a big dilemma for Endocrinologists about how to treat such patient with RMS. Currently the patient is having poorly controlled DM and has started developing multiple bullous, ulcerated lesions all over the body due to poor diabetic control.

Conclusion
Several challenges are encountered by healthcare professionals while treating patients of RMS in resource poor countries of the world. Concentrated insulin (U-500) is not available everywhere to ease the pain of several daily insulin injections and to improve compliance. We hope that future will hold promising horizon for such patients and the global equal access to its available treatment options will result in their better quality of life.

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EP607

Does tolerance develop toward GLP-1 receptor agonists' glucose-lowering effect?

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Background
Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have become a popular tool for the treatment of type 2 diabetes. Unlike many other antidiabetic drug classes, distinct GLP-1 RAs have different therapeutic profiles, mostly due to their different pharmacokinetic properties. Animal experiments and human data indicate that tolerance develops toward at least some of their effects, e.g., gastric motility. Whether tolerance develops toward the glucose-lowering effect of GLP-1 receptor agonists has never been formally tested. We have conducted a series of experiments in mice and a pilot clinical trial in healthy volunteers to address the hypothesis of tolerance development.
Methods
Male C57Bl/6J mice were used. Liraglutide (600 μg/kg once a day s.c.) or exenatide (10 μg/kg twice a day s.c.) were given for 11 days (subchronic group) or 18 days (chronic group). Treatment effects on nonfasting glucose level and during the glucose tolerance test (GTT) were evaluated. Ten healthy volunteers were treated with 0.6 mg liraglutide s.c. once daily for 21 days. The drug's effect was quantified by serial graded glucose infusion tests, with glucose and c-peptide measured every 20 min and insulin secretion rate calculated.
Results (Mice)
The effect of liraglutide on nonfasting glucose was clearly weaker after chronic administration, compared to acute administration ($P<0.01$ Duncan's post hoc test) while exenatide remained equally effective. During the GTT both liraglutide and exenatide, decreased AUC for glucose significantly more after acute administration compared to the chronic groups ($P<0.05$). Moreover, in the experiment with liraglutide the change in insulin-to-glucose ratio was significantly blunted after subchronic ($P<0.05$) and chronic treatment ($P<0.01$) compared to acute effect. Humans: (will be revealed during the presentation).
Conclusions
Prolonged treatment with exenatide and liraglutide induced tolerance in mice.

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EP608

Comparative evaluation the effects of bariatric surgery and exenatide treatment on the clinical and laboratory parameters in obese type 2 diabetic patients

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Background
Obesity and diabetes are major causes of morbidity and mortality that are increasing all over the world. As obesity is a major risk factor for type 2 diabetic patients, weight loss has an important place in the treatment of type 2 diabetic patients. In our study, it's aimed to evaluate the effects of exenatide and laparoscopic sleeve gastrectomy (LSG) in obese diabetic patients on the clinical and laboratory parameters.
Subjects and methods
Twenty-five patients who had undergone bariatric surgery and 25 patients who started exenatide treatment and followed up in our outpatients clinic were included in the study.
Results
At the end of the six month follow-up, weight loss was approximately 35.4 kg in the surgery group and 11.5 kg in the exenatide group. Although postprandial glisemi (PPG) and HbA1c were significantly decreased in both groups, the decrease was significantly higher in LSG group compared to the exenatide group. Although there was no significant change in fasting blood glucose (FBG) in the exenatide group, there was a significant decrease in FBG in LSG group.
Discussion
LSG is a method that should be performed upon indication and much more radical compared to exenatide administration but appears to be a more efficient application that corrects diabetes and obesity related metabolic parameters compared to exenatide treatment in diabetic obese patients. Both treatment options must be evaluated for each patient regarding the advantages and disadvantages and appropriate treatment option for each patient should be decided according to patient's characteristics.

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EP609

Increase in time in target when using a basal-bolus algorithm for insulin dosing with insulin glargine U300 during hospital stay

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Background and aims
Insulin therapy and the use of clinical decision support systems to achieve glycaemic control in hospitalized patients with hyperglycaemia are recommended by clinical guidelines. The aim of this evaluation was to assess time in target by continuous glucose monitoring (CGM) achieved by a basal-bolus insulin algorithm using insulin glargine U300 during hospital stay in patients with type 2 diabetes (T2D).
Material and methods
30 patients with T2D (12 female, age 67 ± 11 years, HbA1c 79 ± 2 6 mmol/mol, BMI 32 ± 6 kg/m^2, diabetes duration 14 ± 11 years) were treated with GlucoTab, a mobile system providing automated workflow support and suggestions for insulin dosing to health care professionals, during hospital stay. Insulins glargine U300 and glulisine were used for basal-bolus therapy. Additionally to blood glucose measurements, blinded CGM (iPro2, Medtronic) was performed throughout the study.
Results
Mean total daily insulin dose was 63.8 ± 39.8 U. A total of 49,846 CGM values were collected. Mean daily sensor glucose was 8.4 ± 1.2 mmol/l. Percentage of CGM values in the ranges was as follows: 5.6–7.8 mmol/l (42.0%), 3.9–10 mmol/l (80.2%), >10 mmol/l (19.0%), >16.7 mmol/l (1.5%). Percentage in the hypoglycaemic range were low: <3.9 mmol/l (0.77%), <3.3 mmol/l (0.35%) and <2.8 mmol/l (0.15%), respectively. When comparing the first vs last full 24-h period, time in target 3.9–10 mmol/l (61.8% vs 85.2%) increased, whereas time in hyperglycaemia >10 mmol/l (37.1% vs 14.2%) and hypoglycaemia $<$ 3.9 mmol/l (1.2% vs 0.6%) decreased.
Conclusions
Basal-bolus insulin therapy using insulin glargine U300 safely establishes glycaemic control as assessed by CGM. Over time percentage of values in target increases without increasing the risk of hypoglycaemia.

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EP610

Intensity of dapagliflozin induced glycosuria correlates with previous glycemic control but not with body weight or duration of type 2 diabetes

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Introduction
Inhibitors of sodium-dependent glucose co-transporter 2 (SGLT2i) reduce circulating glucose concentrations via a renal mechanism. Its metabolic effects have not been fully described and there is a discrepancy on some clinical results found in studies on SGLT2i. Our aims were to detect if there are some predictor factors to identify what patients will have higher response to dapagliflozin, a SGLT2i, and second, to explore whether intensity of glycosuria is correlated to the intensity of metabolic and anthropometric changes.
Methods/design
23 participants with type 2 diabetes (T2D) (age: 53.1 ± 7.6 years; 56.5% males, T2D duration 12.1 ± 6 years) received dapagliflozin (10 mg/day) for 18 weeks in conditions of normal medical practice. Parameters related to glucose metabolism, renal function and anthropometric variables were measured at baseline and at week 18. Glycosuria was quantitatively measured at baseline and at the end of the follow-up.
Results
At week 18, glycosuria increased from 6.4 ± 2.2 to 68.9 ± 50.4 g/24 ($P<0.001$). Significant reductions in body mass index (BMI), HbA1c, fasting plasma glucose (FPG) were observed ($P<0.01$). Quantitative glucose urine levels at week 18 positively correlated with the following variables at baseline: FPG ($r=0.631$; $P=0.001$), HbA1c ($r=0.399$; $P=0.03$), glycosuria ($r=0.397$; $P=0.034$) and inversely correlated with albumin/creatinine ratio ($r=-0.409$; $P=0.037$) but not with age, T2D duration, eGFR or BMI. Intensity of glycosuria correlated with diuresis increase ($r=-0.602$; $P=0.002$) but didn't with and HbA1c or BMI falls.
Conclusions
Glycosuric effect of dapagliflozin is correlated with glycemic control at baseline independently of time of T2D evolution as result of a higher expression of SGLT2 receptors in poorly controlled diabetic patients. The magnitude of glycosuria did not provide higher weight loss or higher falls in HbA1c.

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EP611

How can dapagliflozin affect blood pressure response in a real-life cohort of people with type 2 diabetes and hypertension?

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Introduction
In clinical trials, dapagliflozin has been shown to lower blood glucose, reduce weight and blood pressure in people with type 2 diabetes (T2D). However, there are limited published data on quantitative changes on blood pressure of this drug in routine clinical practice. Our aim was to examine the clinical efficacy of dapagliflozin in patients with T2D and hypertension in a real-life cohort.
Methods/design
Prospective study including patients with poorly controlled T2D and hypertension who were added dapagiflozin in conditions of routine medical practice. Metabolic profile, renal parameters and hemodynamic parameters were measured prior to dapagliflozin intensification and at week 24.
Results
16 patients were evaluated. At week 24, urine volume increased from 1761 ± 693.6 ml/day to 2570.83 ± 758.6 ml/day; $P<0.001$ as well as natriuresis (from 211.6 ± 73.7 mEq/day at baseline to 252.8 ± 94.5 mEq/day; $p=0.009$). No significant differences were observed in eGFR and albumin/creatinine ratio. Systolic blood pressure significantly decreased from baseline (148.9 ± 20.8 vs 141.5 ± 17.9; $P=0.02$) as well as diastolic blood pressure (84.3 ± 11.9 vs 78.8 ± 8.9: $P=0.001$). In five patients, variability of blood pressure was measured showing a significant reduction (15.2 ± 1.9 vs 10.4 ± 2.1; $P=0.02$).
Conclusions
Our results show a higher decrease in blood pressure that observed in clinical trials. Dapagliflozin might potentially improve not only the average blood pressure, but also reduces its variability. We included a little number of patients. Further investigations are needed to verify our observation and determine its potential role on cardiovascular outcomes.

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EP612

Trends in prescription of Sodium-glucose co-transporter-2 inhibitors (SGLT2i) over the last three years in a specialized setting

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Introduction
Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a newly developed class of oral anti-diabetic drugs with a unique mechanism of action and its use is becoming more widespread. Given that dapagliflozin was the first drug of this class used in Spain, available since December 2013, 3 years after its inception, we aimed to investigate whether there have been differences in prescription patterns of SGLT2i (using dapagliflozin as reference) in a Sanitary district from Spain over time.
Methods/design
Using electronic medical records, data of patients with type 2 diabetes who were prescribed dapagliflozin 10 mg/day, were collected at two periods of time: i) between January to June 2013 (consecutive first prescriptions of dapagliflozin in our area) and ii) between June to December 2016 (last prescriptions). Epidemiologic, clinical and metabolic data as well as antidiabetic drugs received were compared between the two periods.
Results
A total of 36 prescriptions of dapagliflozin made in the first period were compared to 32 prescriptions in the second period. Patients in the second period had significantly ($P<0.05$) higher duration of diabetes (13.6 ± 7.4 vs 10 ± 9 years), lower A1C (%; 8.6% ± 1.3% vs 9.1% ± 1.1%) and a lower rate of microvascular (37.5% vs 78%) and macrovascular complications (18.7% vs 33.3%). Also, there has been an increased used as second line treatment (21.9% vs 5.5%; $P<0.001$) as well as combined to basal insulin (62.5% vs 12.5%; $P<0.001$).
Conclusions
Patterns of prescriptions of SGLT2i have changed over the last 3 years in our area. Its use as a second line treatment and combined with basal insulin has increased. Also, patients who are prescribed this class of antidiabetic drug have a better diabetes profile and a lower rate of complications although a higher duration of diabetes.

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EP613

The insulin delivery system and its impact on quality of life and on psychopathological symptomatology

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Introduction
In chronic diseases a good psychological and behavioral adaptation is essential. Concerning diabetes the Insulin Delivery System (IDS) adopted tend to be an important factor of adaptation, global satisfaction and, above all, quality of life (QoL).
Objectives
To analyze the QoL and IDS satisfaction and its relationship with psychopathological symptomatology in patients on continuous subcutaneous insulin infusion (CSII) therapy.
Patients and methods
We gather a convenience sample of 42 type 1 (DM1) patients, with a mean age of 28.4 ± 11.5 years, 61.9% female and with a mean IDS time of usage of 5.6 ± 2 years. We applied the following questionnaires: the Audit of Diabetes Dependent Quality of Life (ADDQoL), o Insulin Delivery System Rating Questionnaire (IDSRQ) e o Brief Symptom Inventory (BSI).
Results
Relatively to QoL, in this sample, the mean values were −1.68 ± 1.37 (results go from −9 to 9). We did not find any relevant psychopathological symptomatology in general in the BSI questionnaire (GSI = 0.10 ± 0.09). Regarding blood glucose monitoring (BGM), 55.3% of patients perform 4–6 blood checks daily and 39.5% more than six times daily. 30% of patients carry out BMG a little more than they would like and 22.5% a lot more than they would like. We noticed a significant statistical correlation between QoL and the level of satisfaction with BGM needed ($r=-0.50$; $P=0.001$) and also with psychopathological symptomatology ($r=-0.53$; $P=0.001$).
Conclusions
Results in this study shows that the chosen IDS has a vital impact in psychopathological symptomatology and in the levels of QoL that patients reveal. This data allow us to conclude that the minor constraints that this IDS has due to its utilization does not contribute negatively to CSII perception, moreover when it is compared with multiple daily dosage.

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EP614

New long-acting insulins in type 1 diabetes: implications for real clinical practice

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The emergence of a new generation of long-acting insulin analogues (insulin degludec -ID- and insulin glargine 300 U/ml -IG300-) has increased treatment options in type 1 diabetes (T1D), demonstrating in clinical trials better metabolic control with lower hypoglycemia rates.
Objectives
To assess characteristics of T1D patients who were given ID and IG300 in clinical practice and to evaluate their effect on metabolic control, weight, insulin dose and hypoglycemia, comparing results obtained.
Methods
Observational, retrospective study. We studied T1D patients whose habitual treatment had been modified. We analyzed anthropometric data (weight, BMI), biochemical parameters (fasting glycemia, HbA1c, lipid profile), insulin dose and number of hypoglycemic events per month (<5; 5–10; >10, initially and after 6 months.
Results
38 patients: 50% women, age 38 ± 12.7 years, BMI 25.8 ± 3.9 kg/m^2, T1D evolution time 14.9 ± 8.6 years and HbA1c 7.4 ± 0.8%. 57.9% initiated ID and 42.1% IG300. They presented: 7.9% hypertension, 13.2% retinopathy, 2.6% history of ischemic heart disease, 2.6% nephropathy and 0% neuropathy. Initially, there were no differences between the two groups, except for higher blood glucose in ID group (189.2 ± 12.1 vs 144.3 ± 22.4 mg/dl, P 0.003). There was a significant decrease in insulin dose with ID (29.05 ± 9.25 vs 24.82 ± 20.8 IU, P 0.010). There was a weight loss of 1.9 ± 4.4 kg in patients with IG300, but not statistically significant. We observed a significant decrease in the number of hypoglycemia events in general (75% with >10 decreased to <5; $P=0.009$). When stratified by comparison groups, the significance is maintained with ID but not with IG300.
Conclusions
1) ID group significantly decreased basal insulin dose. 2) We observed weight loss, not statistically significant, in IG300 patients. 3) There was significant reduction of hypoglycemia rates with both basal insulin analogues. 4) Further studies are needed to distinguish which type of patient benefits more from each insulin analogue.

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EP615

Effect of oral nitrate administration on glucose metabolism and inflammation in obese type 2 diabetic rats

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Introduction
Type 2 diabetes is associated with impaired nitric oxide (NO) bioavailability; nitrate administration might act as a potential therapeutic agent in diabetes through nitrate/nitrite/NO pathway. The aim of this study was to determine the effects of sodium nitrate on glucose tolerance, insulin sensitivity, inflammation, glucose-stimulated insulin secretion (GSIS), and islet insulin content in obese type 2 diabetic male rats.
Methods
Male Wistar rats were divided into four groups: Control, control + nitrate, diabetes, and diabetes + nitrate. Diabetes was induced using high-fat diet and low-dose of streptozotocin. Sodium nitrate (100 mg/l in drinking water) was administered for 2 months. Serum levels of fasting glucose, insulin, and lipid profile were measured and the insulin resistance/sensitivity indices were calculated every 2-weeks. At the end of the study, tissue levels of glucose transporter 4 (GLUT4) protein and serum interleukin-1 beta (IL-1β) were measured as well as glucose and insulin tolerance test were done. GSIS from isolated pancreatic islets and islet insulin content were also determined.
Results
Compared to the control group, diabetic rats had glucose intolerance, dyslipidemia, and higher serum glucose and insulin. In diabetic rats, nitrate significantly improved glucose (area under the curve: 26603 vs. 31947, $P<0.001$) and insulin (area under the curve: 6981 vs 8968, $P<0.001$) tolerance, insulin resistance, insulin sensitivity, lipid profile, and decreased fasting glucose (8%) and insulin (11%), but had no effect on GSIS and islet insulin content. In diabetic rats, nitrate significantly increased tissue levels of GLUT4 by 17% and 22% in soleus muscle and epididymal adipose tissue, respectively. Nitrate also decreased elevated serum IL-1β in diabetic rats (4.7 ± 0.5 vs. 3.2 ± 0.6 pg/ml, $P=0.02$).
Conclusion
Nitrate administration had favourable effects on glucose tolerance, insulin resistance, insulin sensitivity, inflammation, and dyslipidemia in type 2 diabetic rats.
Keywords: Glucose tolerance; Insulin resistance; Insulin sensitivity; Inflammation; Sodium nitrate; Type 2 diabetes.
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EP616

Impact of a universal educational animation movie in an hour workshop on the knowledge of patients with gestational diabetes

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This study assessed the dietary and medical knowledge before and after a group workshop viewing a 5-min animation film in patients with gestational diabetes (GD) (https://www.youtube.com/watch?v=Maf-Uos9oLQ). This animation movie (without speech) explains the course of the patients suffering from GD by emphasizing the stakes, the diet and the medical measures.
Patients and methods
This is a prospective self-assessment study of 10 questions in 100 consecutive pregnant women.
Results
Seventy-four out of 100 subjects were included with their clinical data. Diagnosis was based on the mean blood glucose after a 75 g load charge test: T0 0.92 g/l ($n=47$) T1 1.75 g/l ($n=46$), T2 1.53 g/l ($n=46$). Patients were characterized by a mean age of 32 years, 6% with type 1 or 2 diabetes, G3P1, 91% of foreign origin, predominantly from the Maghreb (59%), mainly unemployed with an average pre-pregnancy BMI of 28 kg/m^2, a mean weight gain of 8 kg during pregnancy, a 42% history of diabetes in the family, a 12% history of personal DG, a 11% history of macrosomia and 24% insulin use. For 71/74, we collected information on delivery accounting for 7% of macrosomia. The analysis of the 100 questionnaires revealed an average correct score of 6.3/10 before and 8.6/10 after the workshop. Before the workshop (99/100), patients were unaware of the presence of sugar in bread, the number of dairy products to be consumed daily, the importance of physical activity, and the possibility of using insulin if blood glucose was too high. After the workshop (98/100), the score improvement was mainly relevant for these four topics.
Conclusion
Our animation film is a simple pedagogical tool that allows us to improve the state of knowledge in an efficient manner.

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EP617

Insulin requirements in pregnant women with DM 1 with different duration of the disease

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Background and aims
To study the need for insulin during pregnancy, depending on the duration of the disease.
Methods
We studied 108 pregnant women with DM 1 receiving insulin with insulin pumps. Patients were divided into three groups: in the 1st group diabetes duration was less than 5 years, in the 2nd – 5 to 15 years, 3rd – more than 15 years. We evaluated the daily need for insulin on 12, 22–25, 30–32 weeks of gestation.

Results
In the 1st group the daily insulin requirement (IU/kg) in the 1st trimester was 0.51, in the 2nd 0.54, in the 3rd 0.79. Significant increase of insulin requirements was identified from the second to the third trimester ($P=0.34$ between 1 and 2 trimester, $P=0.005$ between the 2 and 3 trimester, $P<0.01$ between 1 and 3 trimester). By the third trimester the increase of the daily dose of insulin was on 56% (36; 87). In the 2nd group the insulin requirement was 0.6; 0.73; to 0.87 IU/kg, respectively, dose increased from trimester to trimester ($P<0.01$). By the third trimester, daily dose of insulin increased on 42% (28; 63). Insulin requirements in the 3rd group increased from the first (0.59 IU/kg) to second (0.65 IU/kg) trimester, but in third trimester dose stabilized on 0.74 IU /kg ($P<0.01$ between 1 and 2 trimester, $P=0.17$ between the 2 and 3 trimester, $P<0.01$ between 1 and 3 trimester). However, the daily dose of insulin in this group increased only on 22% (11.5; 32.5).
Conclusions
In pregnant women with DM 1 with disease duration more than 15 years we may not see a significant rise in insulin requirements on the third trimester. This group needs monitoring.

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EP618

Liraglutide restores the hyperglycemia-induced endothelial oxidative stress *in vitro*

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Introduction
Diabetes is characterised by increased oxidative stress and an insufficient antioxidant response, which are crucial for the initiation and progression of atherosclerosis. GLP-1 agonists, used for the treatment of diabetes, are considered as cardioprotective agents but under that concept, there are limited data on their ability to influence the endothelial antioxidant response.
Methods
In order to answer this question we studied the influence of liraglutide, a known long-lasting GLP-1 agonist, on the antioxidant response markers (superoxide dismutase (SOD), catalase, glutathione (GSH) system, endothelial nitric oxide synthase (eNOS), intracellular reactive oxygen species (ROS) and extracellular nitric oxide (NOx)) of Eahy926 macroendothelial cells pre-treated in hyperglycemic (25 mM) environment for 2 h.
Results
Hyperglycemia significantly increased the endothelial intracellular ROS content ($P<0.001$) and decreased eNOS ($P<0.05$), SOD ($P<0.05$) and catalase ($P<0.001$) activity, GSH recycling rate ($P<0.001$) and Nox levels ($P<0.05$). Liraglutide (40 nM) restored the increased intracellular ROS to levels comparable to normal glucose treated cells (control). The elimination of intracellular ROS was accomplished by the activation of SOD ($P<0.05$) and catalase ($P<0.001$) enzymatic antioxidant response and the increase ($P<0.001$) of intracellular GSH recycling rate. Moreover, liraglutide restored also eNOS activity and NOx release ($P<0.05$).
Conclusions
Our results indicate that liraglutide is involved in the redox balance of endothelial cells. Its ability to counterbalance the increased endothelial free radicals induced by hyperglycemia seems to work as a protective mechanism restoring cell function and ameliorating the progression of atherosclerosis process.

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EP619

Incretin-based therapies and pancreatic/biliary tract cancer

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Objective
To study the relation between incretin-based therapies, DPP-4 inhibitors and GLP-1 receptor agonists, and tumor stage at the time of diagnosis of pancreatic and biliary tract cancer.
Methods
Retrospective study of type 2 diabetic patients with newly diagnosed of pancreatic or biliary tract cancer attended consecutively in a tertiary hospital between the years 2012 and 2015.
Results
A total of 37 patients were included. The prevalence of use for DPP-4 inhibitors in our cohort was 37.8% (sitagliptin, linagliptin and vildagliptin). No one patient was under treatment with GLP-1 receptor agonists. Subjects' characteristics are shown in Table 1. Men developed cancer earlier than women (68.4 vs 75.5 years, $P=0.038$). Smoking prevalence and time of diabetes evolution was higher for males. Subjects who were taking DPP4-i exhibited stages more advanced at diagnosis (Table 2). However, this result did not reach statistically significant differences (70 vs 50%, $P=0.250$). Metformin use was not associated with different tumor staging ($P=0.169$).

Table 1. Patients' characteristics

age (years)	71 ± 10.5
sex (male/female)	20/17
A1C levels (%)	7.1 ± 0.8
time of diabetes evolution (median, months)	66.5 (22-127.2)
BMI > 30 Kg/m^2 (%)	50
smoking prevalence (%)	48.1
diabetes therapy: metformin/DPP-4i/insulin/SU/glinides (%)	70.3/37.8/48.6/16.2/5.4
type of cancer (pancreas/ biliary tract)	27/10
cancer stage I-IV (%)	3.3/36.7/3.3/56.7

Table 2. Relation between cancer stage and DPP-4 i consumption

	No DPP-4 i (n=20)				Yes DPP-4 i (n=10)				
Stage TNM	I	II	III	IV	I	II	III	IV	p-value
%	5%	45%	0%	50%	0%	20%	10%	70%	0.250

Conclusions
This study supports DPP4-i safety from the point of view of tumorigenesis in humans. However, the small sample size due to the low incidence of this lethal disease makes us to be cautious in the conclusions. Further research is needed in order to ensure that incretin-based therapies are safe from the oncological point of view.

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EP620

Palpable purpura in an uncontrolled diabetic patient: an uncommon possible side effect of linagliptin

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Introduction
Incretin based therapeutics have commonly been used in the last years for the management of patients with type 2 diabetes mellitus (DM). Linagliptin is a member of "dipeptidyl peptidase 4" (DPP-4) inhibitors and often preferred owing to some advantages over the others. We present a diabetic case developing skin findings after the initiation of linagliptin.
Case
66 year-old woman with a history of type 2 DM for 10 years was admitted to our clinics with the complaints of dry mouth, polydipsia and polyuria. She had also history of coronary heart disease confirmed by coronary angiography. She had been taking metformin, acetylsalicylic acid, and oral nitrate for 10 years. On physical examination; vital signs and examinations of cardiovascular, pulmonary and gastrointestinal systems were normal. She had no skin rash or lesions. Blood

glucose was 319 mg/dl, urine ketone negative, creatinine 0.78 mg/dl; and liver tests and arterial blood gas analysis were in normal limits. Firstly, we initiated intensive insulin regimen together with tight glucose monitoring, to improve uncontrolled hyperglycemia. We increased the dosage of rapid acting insulins gradually to achieve optimal glucose control. Metformin was continued and linagliptin was added to treatment. Lesions like palpable purpura arised on lower legs and upper arms of the patient on the second day of linagliptin therapy. No other drugs, chemicals or herbal preparations were given at this time. After cessation of linagliptin, palpable purpura lesions both on lower and upper extremities regressed gradually.

Conclusion

Due to impact of DPP-4 inhibitors on the other DPP enzymes to some degree, musculoskeletal and dermatological adverse reactions may occur during the treatment with these agents. To our knowledge, palpable purpura lesions were detected with linagliptin therapy in our patient for a first time in the literature.

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EP621

Dulaglutide added on Empagliflozin improves blood pressure, body weight, glycemic control and albuminuria in obese diabetic patients

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Objective

GLP-1 receptor agonists and SGLT2 inhibitors improve glycemic control, body weight, blood pressure and albuminuria by different pathways. However, their combination is not endorsed by ADA-EASD guidelines, and available data are scarce. Our objective in this open observational study was to elucidate the effect of added Dulaglutide in obese type 2 diabetic patients previously treated with Empagliflozin but insufficiently controlled.

Methods

Dulaglutide 1.5 mg/week was added to the treatment of 20 type 2 diabetic patients with BMI >30 kg/m^2 previously treated with Empagliflozin 10 mg/day for at least 3 months but having $HbA_{1C} > 7\%$. They were re-evaluated after 3–6 months without additional medication changes, except for insulin dosage adjustments and iDPP4 discontinuation. Besides clinical routine, 24 h. ABPM were performed before and after. Stats were performed by two-tailed paired t-test, *meaning $P<0.05$. Values are given as mean $\pm$ S.D.

Results

Age was 49 ± 11 and diabetes duration 8 ± 3 years. 53% were women. Baseline BMI was 34.9 ± 2.5 kg/m^2; ABPM: Awake, BP $131\pm8/85\pm8$ mmHg, HR 74 ± 10 bpm; Sleep, $127\pm8/78\pm10$ mmHg, 69 ± 10 lpm. Fasting glycemia was 167 ± 46 mg/dl, HbA_{1C} $8.0\pm0.6\%$, urate 6.9 ± 1.4 mg/dl, Cr 0.91 ± 0.17 mg/dl, GFR (CKD-EPI estimation) 87.1 ± 16.8 ml/min/1.73 m^2, Albuminuria 291 ± 268 mg/gr Cr; median 232, IQR 23-460. At follow-up there were no withdrawals due to side effects, one patient was lost to follow-up and 16% reported mild nausea and/or diarrhoea. Body weight change was -4.0 ± 2.6* kg, BMI -1.37 ± 0.83* kg/m^2. ABPM: Awake SBP -4 ± 4*, DBP -1 ± 3 mmHg, HR 1 ± 4 bpm; Sleep, SBP -6 ± 5*, DBP -4 ± 6* mmHg, HR $+2\pm7$ bpm. Fasting glycemia change -41 ± 23* mg/dl; HbA_{1C} -1.1 ± 0.6* %, urate -0.12 ± 0.24* mg/dl; Cr -0.04 ± 0.11 mg/dl, GFR $+1.9\pm7.3$ ml/min/1.73 m^2, albuminuria -71 ± 105* mg/gr Cr ($-29\pm31\%$).

Conclusions

Dulaglutide added on Empagliflozin in obese type 2 diabetic patients was well tolerated and effective for glycemic control, body weight, blood pressure (particularly nocturnal) and albuminuria.

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EP622

Modern treatment approaches of patients with type 2 diabetes and non-alcoholic fatty liver disease

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Background

One of the most significant complications of type 2 diabetes (T2D) is non-alcoholic fatty liver disease (NAFLD). The search for new effective approaches to the treatment of patients with comorbid chronic condition such as type 2 diabetes and NAFLD is relevant.

Methods

We have observed 118 patients, including 64 patients with T2D and NAFLD, 26 patients with T2D and 28 patients with NAFLD. The control group consisted of 25 healthy individuals. Recommended treatment included individualized diet therapy with energy value of daily ration 1800–2300 kcal/day, a hepatoprotective salt of arginine and glutamic acid at 0.75 mg 3 times a day and alive multistrain probiotic at 10 mg twice a day. Clinical manifestations, echography semiotics, protein, lipid, enzyme and carbohydrate metabolism, the degree of IR, subpopulations of lymphocytes and interleukins, IgG antibodies to LPS, the range of average weight molecules, circulating immune complexes (CIC), dysbiotic disorders of the intestine in patients with T2D and NAFLD were studied.

Results

The application of the developed medical complex that included individualized diet, the salt of arginine and glutamic acid and a multiprobiotic contributed to the normalization of lipid, enzyme, carbohydrate metabolism, improvement of cellular and humoral links of the immune system, reducing levels of CIC 58.3%, reduction of endogenous intoxication (level MCM254 – 30.5%, MCM280 – by 32.4% and the level of IgG antibodies to LPS in 1,6 times), improvement of intestinal microbiocenosis in 84.4% of patients with T2D with NAFLD and normalization of pathological clinical manifestations in 68.8% of patients.

Conclusions

This study revealed the effects of proposed treatment complex on the major lymphocyte subpopulations and cytokine status, reduction of endotoxemia, promotion of the positive dynamics of lipid and carbohydrate metabolism indicators and intestinal microbiocenosis of patients with T2D and NAFLD.

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EP623

The role of diabetic educational programs in glycemic control in patients attending to our day hospital

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Objective

To assess improvement in glycemic control in those diabetic patients who have received structured education in diabetes in our Day Hospital.

Methods

A retrospective observational study was carried out in which 42 diabetic patients who had attended to educational courses in 1 year were included, determining the age of the patient, type of Diabetes, score obtained in the questionnaires at the beginning and end of the course, as well as HbA1c before, at 6 months and at 12 months after the courses.

Results

Of the 42 patients, 25 were diabetic type 1 and 17 diabetic type 2. Mean age 43.64 ± 14.36 years (Type 1 diabetes mellitus (DM1): 36.8 ± 12.17 years; Type 2 diabetes mellitus (DM2): 53.7 ± 11.2 years). Mean HbA1c before the course was $9.14\pm2\%$ (DM1: $8.99\pm1.74\%$, DM2: $9.36\pm2.38\%$). Mean of HbA1c at 6 months of the course was $8.06\pm1.51\%$. (DM1: $8.09\pm1.45\%$, DM2: $8.03\pm1.64\%$). A reduction of HbA1c of $1.08\pm1.87\%$ ($P<0.0001$) was obtained. In the DM1 group the mean reduction of HbA1c was $0.9\pm1.79\%$ ($P=0.014$) whereas in the DM2 group it was $1.34\pm2\%$ ($P=0.008$). Of the 42 diabetic patients in the sample, HbA1c values were determined at 12 months in 27 of them (17 DM1 and 10 DM2). HbA1c at baseline in this group was $9.17\pm2.29\%$; At 6 months $8.13\pm1.58\%$ ($P=0.007$) and at a year $8.05\pm1.25\%$ ($P=0.007$). In DM1 at the beginning $8.64\pm1.47\%$, at 6 months $7.93\pm1.48\%$ and at 12 months $8.06\pm1.1\%$. In DM2 at baseline, $10.07\pm2.72\%$, at 6 months 8.48 ± 1.75 ($P=0.019$), at 12 months $8.02\pm1.78\%$ ($P=0.009$).

Conclusions

Attending courses in Diabetes Education significantly improved glycemic control in all our patients. The type 2 diabetic group showed the greatest improvement in glycemic control, obtaining even greater reduction of HbA1c at one year of the Education course. This is probably because it is the group that most benefits from lifestyle modification.

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EP624

Real-time detection of hazardous changes in blood glucose at the first trimester of pregnancy in women with type 1 diabetes: a pilot study

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Introduction
Type 1 diabetes (T1D) in pregnancy is known to be associated with increased risks of birth defects and miscarriages. Despite the technological improvement and availability of continuous glucose monitoring (CGM), women with T1D who are adequately controlled according to CGM average and HBA1C still face these complications. Glucose variability was suggested as an **explanatory factor** of the difference between actual obstetric outcome and the expected outcome according to currently available monitoring tools.
Aim
To present an algorithm and to verify that it has a practical potential to notify early enough of increased risk of miscarriage or birth defect.
Methods
Change-point detection methods were applied on CGM data of eight pregnant women with T1D during the entire first trimester of pregnancy.
Results
Seven pregnancies ended with good outcome and one pregnancy ended at a late miscarriage (patient H). The average first trimester HbA1C of the pregnancies with good outcome was 6.58 ± 1.2 (range 5.1–8.8), which is similar to the HbA1C of the pregnancy that ended with a late miscarriage (6.6). The daily averages of CGM data were not higher for patient H. Nevertheless, the statistical method (aimed at detection of an increase in the hourly StDev of glucose levels) did detect an exceptional elevation of glucose variability of patient H, at 8 weeks of pregnancy, which was 7 weeks before the actual miscarriage. Namely, we could have predicted this poor outcome early enough to lessen glucose variability.
Conclusions
Analysis of eight first-trimester follow-ups (of more than 1600 hours $\approx$ 20,000 measurements for each patient) showed the change-point detection method to fully discriminate between proper pregnancies and pregnancies with adverse outcome. This approach might serve as an additional tool to detect pregnancies at risk in real-time and to plan better glucose control in order to improve pregnancy outcome.

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EP625

Sense of coherence and glycaemic control among a sample of newly diagnosed type II diabetics in rural Crete

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Aim
Currently there is much discussion on the protective effects of the sense of coherence (SOC) on health. Our aim was to examine possible associations between SOC and glycemic control among 60 newly diagnosed adults with type 2 diabetes.
Methods and results
Thirty males and 30 females diagnosed 3 months before with type 2 diabetes mellitus were included in the study. SOC was measured with the Greek translated and validated version of Antonovsky's 29 item sense of coherence scale. Biochemical tests and blood pressure measurements were also performed in all participants. SPSSv 20 was used for the statistical analysis. Blood pressure has been associated with low sense of coherence levels ($P<0.001$). Remarkably albuminuria presence has been associated with poor SOC ($P<0{,}001$) while good glycemic control presented a statistic significant positive association with SOC ($P<0.001$).
Conclusion
Further future investigations are required in order to address the effect of SOC on diabetic patients

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EP626

Gestacional diabetes mellitus with and without insulin therapy: a case study

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Introduction
Gestational Diabetes Mellitus (GDM) is a pregnancy complication that has experienced a worldwide growth. The use of insulin has to be considered as it may be beneficial for both the mother and the new-born.
Methods
Retrospective analysis of all cases of GDM, and the respective new-borns (NB), followed in our obstetrics unit between 2012 and 2015. Clinical and workup parameters were evaluated in 2 groups: GDM with no insulin therapy (GDMNIT) and GDM with insulin therapy (GDMIT). Data analysed using SPSSv23.0.
Results
We studied 644 GDM and 35% of them were treated with insulin. The BMI was significantly higher in GDMIT ($P<0.001$). Induced labour occurred in 36% of GDMNIT and in 40% of GDMIT, with statistically significant difference ($P=0.027$). The number of C-sections was superior in GDMIT (41 vs 36%), but without significant difference. The need for hospitalization of the NB in the Neonatal Intensive Care Unit (NICU) was significantly higher in GDMNIT. The NB weigh (Fenton) was also significantly different between both group ($P=0.019$), with "large for gestacional age" being higher in GDMIT (7 vs 3%). Postpartum positive screening for Diabetes Mellitus was 0% in GDMNIT and 2% in GDMIT.
Conclusions
One of the indications for induced labour is GDMIT because of the higher risk of fetal complications, which was verified in this study. As the literature states, GDMIT is associated with a difficult blood sugar control during pregnancy. This means that an unsuccessful maintenance of euglycemia may be associated to heavier NB and eventual peripartum complications. However, GDMNIT was associated with more hospitalizations in NICU, and the main causes were prematurity, hyperbilirubinemia and acute respiratory distress syndrome. The results of postpartum screening are in accordance with the literature.

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EP627

Evaluation and descriptive analysis of our type 1 diabetes population and their insulin therapy

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Objectives
To evaluate the different insulin regimens and types of insulin used in our population of type 1 diabetes (DM1) patients in the last revision in our clinic.
Method
A descriptive study was carried out in our population of 535 DM1 patients. They had their initial diagnosis between 1967 and 2014.
Results
In our population, 47.3% were women and 52.3% were men. The mean age of our patients was 33.8 years (s.d. $\pm$12.31 years) and the mean age of diagnosis was 16.67 (s.d. 11$\pm$ years). 17.39% of our population was taking antiplatelet therapy. 17.4% had hypertension, and 36% cdyslipidemia. There were 22.9% smokers and 10.3%. who had given up. The glycated hemoglobin value was 7.8 (s.d. $\pm$1.28%) and the body mass index 27.18 (s.d. 4$\pm$ kg/m^2). 91% had previously received diabetic education assistance, and 32.1% completed the program. Total insulin dose was 40.52 units (s.d. $\pm$29.9 IU) with 0.68 (s.d. $\pm$0.33 U/kg). Insulin regimes used were: basal-bolus 91.3%, basal alone 1.5%, prandial plus mix 2.7% and mix combination 4.5%. In those using basal-bolus regimen, 42.67 (s.d. $\pm$ 25.8%) of total insulin dose (TID) was prandial insulin and basal insulin 54.05 (s.d. $\pm$17.2%):
- Prandial insulins used were: lispro 41%, aspart 46.5%, glulisin 7.7% and regular 4.9%.
- Basal insulin used were: glargine 85.4%, detemir 13.5%, lispro protamine 0.2%, NPH 0.8%.Time of injection was breakfast in 17.9%, lunch 15.8%, dinner 17.6%, before bedtime 34.2%; 14.5% in split doses. In 86%, the split dose regimen was given breakfast and dinner and 14% breakfast and before bedtime. We observed a higher dose of insulin among patients with two daily doses of basal insulin: 35.9 (s.d. $\pm$20) vs 25.54 (s.d. $\pm$12.2) IU ($P<0.05$).
Conclusions
Basal-bolus therapy is the most used regimen in our DM1 population. Those patients using two basal doses per day needed higher TID. The majority of our patients had educational support but less than a half complete the educational program. It is important to aware our patients to finish these activities to better self control of their disease.

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EP628

Effects of dapagliflozin in treatment of gastroparesis considering the state of carbohydrate metabolism in patients with type 2 diabetes mellitus

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Diabetic gastroparesis (DG) is associated with high morbidity and is the most common precipitating factor to decompensation of carbohydrate metabolism. SGLT2 inhibitors are becoming a common and useful drug to treat type 2 diabetes. Principle treatment of gastroparesis considering the state of carbohydrate metabolism in patients with type 2 diabetes mellitus are very limited. The aim of this study was to compare the effects of dapagliflozin for management patients with DG. 16 patients with type 2 DM were randomly allocated into 2 groups: a first group ($n=8$ (3M/5F), mean age was 41.4 ± 6.7 years old, DM during 12.2 ± 5.4 years, body mass index (BMI) was 33.7 ± 1.4 kg/m^2) with gastroparesis, and a second (control) group ($n=8$ (4M/4F), mean age - 45.3 ± 3.9 years old, DM - 13.2 ± 6.2 years, BMI - 32.9 ± 2.5 kg/m^2) to take dapagliflozin (daily doses -10 mg) for 3 months. Gastric emptying rate (GER) measurement with the help ^{13}C-octanoic breath test (^{13}C-OBT), prandial and postprandial glucose levels and glycated haemoglobin (HbA_1C) were performed at entry and at end of treatment period as well. Low gastric motility has been diagnosed in all patients first group with help of ^{13}C-OBT: T ½ - 98.84 ± 4.22 min, in the second group that result is T ½ - 69.82 ± 9.23 min. After the end of 3 months therapy in the first group significantly improved T ½ -83.11 ± 2.31 min ($P<0.05$). In the result after treatment we show that glycemic control to be significantly higher (prandial glycemic-7.81 ± 0.6 mmol/l, postprandial – 8.57 ± 0.88 mmol/l, $P<0.05$) in the patients of the first group than subjects of the second group (prandial glycemic- 8.44 ± 0.34 mmol/l, postprandial – 9.28 ± 0.13 mmol/l, $P>0.05$). After treatment level of HbA_1C significantly decrease in both groups ($P<0.05$).Dapagliflozin is an useful drug for treating type 2 diabetes with and without of gastroparesis. Patients with DG get normalization of gastric emptying rate. It appears that this effect may be due to non-specific mechanisms.

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EP629

Self-monitoring of blood glucose: how are glycemic readers used in practice?

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Introduction
In recent years, the technique of ASG has gained much in simplicity, speed and acceptability, using readers more and more reliable. Despite this, some patients do not acquire the skills needed to achieve it. The aim of this study is to evaluate the technical gestures of use of blood glucose readers in current practice.
Material and method
This is a prospective descriptive study including 369 diabetics for over a year, followed in diabetic consultation in Algiers. A questionnaire was drawn up using the following items: frequency of capillary blood glucose checks, blood glucose readers (choice, number of years of use, rhythm of change), modalities of capillary sampling,, The possible impact on daily life.
Results
Of the 369 diabetics we found 17% type 1 and 83% type 2, sex ratio at 1, the average age is 52.6 ± 15.5 years, with a duration of diabetes of 10.3 ± 8 years. More than half are treated with insulin. Their average HbA1c is $8.25\pm1.8\%$. Patients have more than two readers in 33.9% of cases, the latter are changed with an average rhythm of 4 ± 2.9 years, 22.36% of patients do not systematically wash their hands before capillary blood glucose, and use of alcohol or other antiseptics is observed in 32.5% of patients, 59.2% use recommended sites for stitching, alternative stitch sites are never used, the regular change of the lancets is observed in 2/3 of the cases and the elimination of the lancets is done with the household waste In 86% of cases.
Conclusion
Learning from the GSM must be included in a therapeutic patient education program, as the Haute Autorité de Santé1 has highlighted, practical workshops will help them to master the GSM and easy use of the blood glucose meters.

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EP630

Determinants of patient's adherence and its relation to therapeutic success after hospital admission for decompensated diabetes

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Introduction
Diabetes mellitus (DM) is a chronic disease that requires continuous medical care. Health care providers should adopt approaches that improve patient outcomes and adherence.
Aims
To evaluate the adherence to Endocrinology ambulatory follow-up after elective hospital admission for decompensated DM and to determine the relationship between adherence and therapeutic success after discharge.
Methods
Retrospective study of 86 patients admitted at Endocrinology department in 2014–2015. Two types of assessment were available after discharge: consultation and blood analysis. Adequate adherence was defined by the compliance to $\geq80\%$ of the evaluations. We considered therapeutic success as A1c reduction $\geq1.5\%$ after discharge and persistence of success as no increase of A1c after success achievement.
Results
After discharge, 79 patients maintained ambulatory follow-up, 62 with adequate adherence. Noncompliant patients were younger (52(IQR 39–60) years) than compliant patients (60(IQR 51–67) years) ($P=0.041$). For each year of increase in patient's age at admission we observed a 4% increase in adherence (OR = 1.04, 95%CI 1.00–1.08, $P=0.035$). Hypertensive(HBP) patients showed 88.5% compliance ($P<0.05$). Patients with HBP, compared to those without HBP, showed an adherence of 9.6:1 (OR = 9.60, 95%CI 2.85–32.61, $P<0.001$). Previous treatment with metformin, DPP4i and statins was associated with a 3.9-fold (OR = 3.90, 95%CI, 1.16–13, 46, $P=0.028$), 4.7-fold (OR = 4.70, 95%CI 1.22–17.87, $P=0.025$) and 3.5-fold (OR = 3.50, 95%CI, 1.15–10.6, $P=0.027$) higher adherence, respectively. The degree of adherence to follow-up didn't influence the therapeutic success at 6 ($P=0.547$) nor 12 months(M) ($P=0.611$). Of the compliant patients, 55.4% achieved therapeutic success at 6M, however only 26.9% of these maintained success at 12M. On the other hand, of compliant patients who did not achieve therapeutic success at 6M, only 20.8% achieved it at 12M.
Conclusions
Approximately 80% of our sample showed adequate adherence. Advanced age, HBP and previous therapy with metformin, DPP4i or statin were associated with greater adherence. Therapeutic success was not related to follow-up adherence.

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Endocrine Disruptors

EP631

Study of metabolic and some hormonal aspects among pubertal type 1 diabetic girls

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Background
The onset of type 1 diabetes before menarche was a risk factor for the subsequent development of hyperandrogenic disorders. It has been also suggested that the use of exogenous insulin to treat type 1 diabetes mellitus in those patients may contribute to the development of PCOS. Abnormal lipid levels were also reported in children with type 1 diabetes mellitus during pubertal years.
Aim of work
This study was designed to investigate metabolic and some hormonal changes in relation to puberty among type 1 diabetic girls.
Subjects and methods
The study was carried out on 60 girls, 40 of them were type 1 diabetic patients (the diabetic group), subdivided into two groups (according to age and Tanner breast staging), and 20 of them were normal healthy girls (the control group), also subdivided into two groups (according to age and Tanner breast staging). All girls were subjected to full history taking, thorough clinical examination, estimation of fasting blood glucose and HbA1c (as an estimation for glycemic control), lipid profile, hormonal profile (FSH, LH and free testosterone) in addition to pelvic ultrasound.
Results
There is an increased frequency of dyslipidemia in the form of hypercholesterolemia and increased levels of LDL among type 1 diabetic girls, and pubertal type 1 diabetic girls show higher BMI and cholesterol levels compared to controls, and also show

higher levels of LDL compared to prepubertal type 1 diabetic children. Age at menarche is delayed in pubertal type 1 diabetic girls having PCOS, while not delayed in those without PCOS but positively correlated to the longer duration of diabetes and with the level of HbA1c. Both the frequency of PCOS and the level of free testosterone are higher in pubertal type 1 diabetic girls compared to their normal controls.

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EP632

Bone-to-muscle endocrine axis modulating adaptation to exercise in athletes of mountain cycling in a Portuguese Marathon

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Introduction
Besides the benefits of low-to-high intensity physical activity (PA) on metabolism, it is currently emerging that excessive PA can be deleterious with serious implications not only in muscle but also, bone remodeling. Despite recent findings remains still unclear and controversial, we hypothesize that exercise of impact, like mountain cycling, beyond influencing the metabolic and skeletal profile, represents an important model of profoundly changes in bone metabolism.
Methods
55 participants (mean age 44.8 ± 7.1 years old) of mountain cycling race (TransPortugal) were evaluated at the beginning/basal (M0) and 9-days post-race (M9). Anthropometric/body composition parameters, haematological and liver function were evaluated by conventional methods. Serum Irisin and plasma osteocalcin and IL-6 measurements were evaluated with ELISA (R&D systems and Phoenix Pharmaceuticals-Irisin). Statistical analyses included departure from normality and adequate parametric or non-parametric test to compare the means and the medians. The results were significant for $P < 0.05$.
Results
In the metabolic point of view, we found that this strenuous exercise induced a significant decrease of fasting insulin, triglycerides, total-cholesterol, non-HDL cholesterol, LDL and an increase of glucose, creatinine, uric acid, HDL, HOMA-B ($P < 0.05$). These results reflected the important modifications in muscle, being the myokine/adipokine, irisin, significantly decreased post-race ($P = 0.002$). In terms of bone remodelling, although not statistically significant, osteocalcin was decreased post-race ($P = 0.154$), yet the plasma IL-6, a cytokine involved in osteoclastic proliferation, was significantly increased post-race ($P < 0.0001$).
Conclusions
Our preliminary results, revealed a possible regulation of osteocalcin in glucose and insulin metabolism, being the slowdown in bone formation observed, a prompt metabolic response of bone to the increased energy demands of the muscle.

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Endocrine tumours and neoplasia

EP633

Dumping syndrome post total gastrectomy

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Introduction
Dumping syndrome, also known as rapid gastric emptying, is a relatively rare disorder. It is conventionally due to the brutal flooding of the small bowel by a hyperosmolar food bolus and to the release of various digestive hormones whose real responsibility in the syndrome remains poorly known. It is usually a complication of the gastrectomy (10 to 40% of the cases). Hypoglycemia after surgery for digestive cancer is sometimes severe, but rare, and revealed by the monitoring of blood glucose, and then more frequent. The variability of the definitions in the studies supports a single definition, Whipple, with a blood glucose level below 0.55 g/l.
Observations
We report the case of a patient, aged 32 years with a personal history of total gastrectomy for gastric adenocarcinoma, regularly followed surgery consultation, a family history of diabetes and hypertension. The onset of the disorders dates back to a postoperative month marked by the appearance of signs of adrenergic hypoglycemia without glycogenic signs in late postprandial periods i.e. 2–3 h after a meal. Capillary glucose levels were made with regard to clinical symptomatology Have returned to < 0.50 g/l. Patient in average general condition with a normal BMI of 19 kg/m^2. Remainder of the review is without peculiarities. On the biological level, GAJ: 0.79,. GR 3.6, Hb 10.3, VGM 91, CCMH 31%, GB 5360, Correct renal count: MDRD at 107. Hepatic balance without abnormalities. Malabsorption balance: Normal calcium an 2.28 mmol/l, Phosphoremia: 1.46 mmol/l, Serum iron: 9.65 mmol/l. ECG and Telthorax without abnormality. Glycemic variability is high in our patient, with hypoglycemia and abnormalities in the glycemic Holter (CGMS) or even recording.The symptoms disappeared following a dietary treatment with improvement of the quality of life of the patient, without any medicinal intervention.
Discussions
Hypoglycemia of the syndrome is hyperinsulinic, by histological abnormalities of the pancreas (neisidioblastosis), and/or by stimulation of insulin secretion by incretin, including glucagon-like peptide-1 (GLP-1). The absorption of glucose is both accelerated and exaggerated due to direct communication between the stomach and duodenum. It is an exaggeration after the surgery of a phenomenon of adaptation which exists in the non-operated ones to whom the glucose is infused directly in the duodenum. Patient semiology is not always accompanied by biological abnormalities. However, if hypoglycaemia is severe and neuroglucopenic symptoms, hyperinsulinemia is constant. For the other cases, the possibility that stress and physical exercise increase the semiology. The treatment consists of dietary measures: split the diet into 5 or 6 meals, slow down gastric emptying, reduce glycemic load and glycemic index of food, avoid stress at mealtime. Acarbose is also effective; other treatments (insulin, glucagon, calcium channel blockers, hyperglycaemic sulfamides, somatostatin analogs, GLP-1 analogues) have not been validated on a sufficient number of subjects to be recommended.
Conclusion
It is necessary to educate the patients operated on for gastric surgery, after the resumption of the oral feeding, so that he learns how to manage his functional disorders, that he understands the interest of a supplementation, of fat soluble vitamins and Calcium and accepts the idea of regular clinical, biological and ideally osteodensitometric monitoring, unlimited in time.

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EP634

A case report of insulinoma in a patient with chronic headache

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Introduction
Pancreatic endocrine tumors are rare lesions, with an incidence of 4 cases per 1 million pts-yr. Of these lesions,insulinomas are the most common. The nonspecific symptoms and small sizes of these tumors led to difficulties of diagnosis and localization.
Case report
A 60 year female pts, had history of episodic and repetitive symptoms of strong headaches for the last 5 years; which were relieved with eating or taking glucose water orally. She noticed increased appetite over the past few years. No medications at the time of evaluation. She was obese. Normal visual field exam. On admission serum glucose level 55 mg/dl, insulin, c-peptide in normal range. Prolonged supervised fasting test was applied and produced symptomatic hypoglycemia (33 mg/dl), with slightly elevated insulinemia 26 mU/l(4-23), normal levels of C-peptide, cortisolemia and chromogranina A; interrupted on the first day after 5hours.Abdominal RMN with contrast demonstrated a well-defined hypervascular lesion involving head-body of pancreas measuring about 1.6 cm. Postoperatively the patient was discharged in good health with normal glucose level.
Conclusion
Insulinoma remains a diagnostic challenge to practitioners. This case illustrated the importance of carefully questioning and examining patient for subtle symptoms and signs of hypoglycemia. A chronic headache may hide an insulinoma.
Keywords: insulinoma, headache

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Female Reproduction

EP635

Real-time continuous glucose monitoring during pregnancy in women with type 1 diabetes: glycemic control and key obstertric outcomes

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Introduction
Real time continuous glucose monitoring (RTCGM) has been shown to improve glycemic control. Limited data are available on the effects of RTCGM during pregnancy. The current study assesses glycemic control and obstetric outcomes in women with type 1 diabetes, comparing RTCGM with usual self measurement of blood glucose (SMBG).
Patients and methods
Patients were recruited from two hospitals. All patients were eligible. Glycemic control was assessed by preconception HbA1c and HbA1c during pregnancy. Obstetric outcomes reported are premature delivery (PD, <37 weeks), and macrosomia (Large for Gestational Age (LGA; birth weight $\geq$90th percentile; Very Large for Gestational Age (VLGA; birth weight $\geq$97.7th percentile).
Results
67 women were included; 53 (79%) used RTCGM PD occurred in 22% of the pregnancies, 19.6% with RTCGM, 31% on SMBG ($P=0.5$). LGA occurred in 58% of pregnancies, VLGA in 31%. LGA with RTCGM 61%, with SMBG 46% ($P=0.4$). VLGA with RTCGM 37.5%, SMG 50%, $P=0.9$). Mean HbA1c was significantly lower before pregnancy (52.1 ± 6.1 vs 67.8 ± 18.4 mmol/mol, $P<0.001$) and during the first trimester (6 weeks: 47.9 ± 5.4 vs 58.9 ± 18.1 mmol/mol, $P=0.002$) and 12 weeks (43.9 ± 7.0 mmol/mol vs 53.6 ± 12.8 mmol/mol, $P<0.05$), but not later in pregnancy.
Conclusion
RTCGM was associated with better early HbA1c. Premature delivery occurred less frequently with RTCGM, macrosomia more frequent. Future analysis with this expanding group will assess whether these differences persist; at this moment, better early control is not readily associated with less macrosomia.

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EP636

Differential pattern of insulin signaling in adipose tissue and skeletal muscle in adult female sheep exposed prenatally to testosterone

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Insulin resistance is defined as the incapacity of insulin to increase glucose uptake by peripheral tissues (skeletal muscle and adipose tissue principally). This phenomenon is present in different animal models for PCOS by prenatal exposure to androgens. In the PCOS condition, the metabolic pathway of insulin activity is defective in skeletal muscle and adipocyte whereas the activation of steroidogenesis is maintained. The decreased insulin stimulated glucose uptake is due to impaired signaling and multiple downstream intracellular defects including impaired glucose transport and glucose metabolism. Previous results from our laboratory have demonstrated that female sheep born to mothers receiving testosterone during part of their pregnancy exhibit features from early postnatal life until adulthood resembling those of PCOS women. In the present work, the programming effect of prenatal testosterone on the insulin signaling was explored in adult females born to testosterone treated mothers (testosterone-females), and born to untreated mothers (C-females). Our aim was to define if prenatal exposure to testosterone affects insulin signaling in adipose tissue and skeletal muscle. Adults females (38 weeks of age) were sacrificed and samples of skeletal muscle (*Gluteus superficialis*) and adipose tissue (visceral) were collected. The qPCR assays were performed to analyze gene expression of IR, IRS-1, IRS-2, PI3K, Akt, PKC, GLUT4 and β-actin. Expression pattern of insulin signaling were similar between groups with the exception that in skeletal muscle, IRS-2 showed higher expression in testosterone-females ($P\leq0.05$) than C-females while on the contrary, the GLUT4 RNAm was lower in testosterone-females compared to C-females ($P\leq0.05$). In the visceral adipose tissue, AKT transcript expression was higher in testosterone-females ($P\leq0.05$) than C-females. Results show that prenatal exposure to testosterone affects the insulin signaling, suggesting a change in the type of oxidative metabolism in the muscle tissue and increase in adipogenesis.

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EP637

The evaluation of sexual function of women with type 1 diabetes mellitus

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Aim
The aim of this study was to evaluate the influence of age, disease duration, glycaemic control and diabetic nephropathy for the sexual function of women with type 1 diabetes mellitus (T1D).
Methods
Study subjects – 18–52 year old women with type 1 diabetes. Participants filled the Female Sexual Function Index (FSFI) and questionnaires about T1D, disease duration, glycaemic control and complications. Laboratory tests including glycated hemoglobin (HbA_1C), creatinine, testosterone, Sex hormone-binding globulin (SHBG), estradiol levels and albumin in 24h urine sample were performed. Postmenopausal women were excluded from the study. Female sexual dysfunction (FSD) was diagnosed based on FSFI total score lower than 26.55.
Results
113 women (mean age 34.82 ± 8.34) with T1D were included to the study. Diabetic nephropathy (DN) was diagnosed to 43.4% (mean age 35.24 ± 9.50), 56.6% had no DN (mean age 34.50 ± 7.50). FSD was diagnosed to 42.6% ($N=40$) of participants. Neither age nor disease duration had influence to FSD. Worse glycaemic control had a statistically significant impact to the prevalence of FSD ($P=0.028$). Negative correlations between participant age and FSFI subscales of desire and arousal were observed ($P<0.001$). Lubrication ($P=0.015$) and orgasm ($P=0.027$) subscales were negatively affected by age only in the group of DN. Statistically significant negative impact was found between glycaemic control and lubrication in group without DN ($P=0.009$). There was no statistically significant difference between FSFI scores or sex hormones and disease duration or DN. Free androgen index had impact neither to the FSFI subscale scores nor to total score. Negative SHGB and high glycaemic level correlation was observed only in DN group ($P=0.031$).
Conclusion
Female sexual function is often diagnosed in women with type 1 diabetes mellitus. Sexual function correlates with glycaemic control and age. Worse glycaemic control has negative impact to SHBG levels.

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Growth hormone IGF axis - basic

EP638

GH is related to hepatic mitochondrial activity in humans

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Background
Altered hepatic mitochondrial activity plays a key role in the development of non-alcoholic fatty liver disease (NAFLD). GH has been shown to stimulate mitochondrial function in skeletal muscle. Therefore we hypothesize that the time course of serum GH concentrations during an oral glucose tolerance test might be related to hepatic mitochondrial energy metabolism *in vivo* in humans.
Methods
15 volunteers (male/female: 7/8; 55 ± 8 years; BMI 25 ± 4 kg/m^2) were investigated on two study days; i) oral glucose tolerance tests were performed to assess dynamics of glucose, insulin, C-peptide and GH concentrations and ii) hepatic lipid content was measured by 1H/31P magnetic resonance spectroscopy (MRS). Saturation transfer technique was applied to assess ATP synthesis rate (k).

Results
Basal GH concentrations and GH dynamics strongly correlated with hepatic mitochondrial activity ($GH_{baseline}$&k_{liver}:$r=0.783$; $P<0.001$; GH_{AUC}& k_{liver}: $r=0.676$; $P=0.008$). There was no association between HCL and GH, as well as between HCL and k_{liver}. Six subjects fulfilled criteria for NAFLD (HCL$\geq$5.5%). They presented significantly higher glucose levels and insulin resistance. The strong relationship between GH and k_{liver} did not differ between patients with and without NAFLD.
Discussion
Our data indicate that basal as well as postprandial (oGTT) GH concentrations are directly related to hepatic energy metabolism in insulin sensitive and insulin resistant humans.

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EP639

Modulation of the 22 kD/20 kD growth hormone (GH) ratio by exercise, fasting and glucose load in premenopausal women

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We previously have shown in a cohort of 236 non-fasted women that before and after a short high intensity exercise protocol (HIP) till exhaustion serum concentrations of 20 and 22 kD growth hormone (hGH) are highly correlated ($P<0.0001$). Although the GH response to exercise exhibited huge inter-individual differences, the 20 kD/22 kD-GH-ratio remained unchanged (9.6% vs 11.1%, $P=0.313$). A subgroup of the women was also studied under fasted conditions in a moderate intensity protocol, applying an exercise (70% VO2 peak) over a longer time (mean duration 45 min). In contrast to the HIP under non-fasted conditions, baseline and post exercise 20 kD/22 kD GH ratio were significantly higher in the fasted protocol (mean 15.33% vs. mean 10.85%, $P=0.0021$). To further investigate the impact of fasting and glucose intake on the 20 kD/22 kD-GH-ratio, we analyzed GH isoform secretion before and after an oral glucose tolerance test (OGTT, 75 g glucose) in a subset of the cohort ($n=60$; mean age 36 years (yr), range 20–44yr; BMI: mean 23, 2 kg/m^2). GH isoforms were measured using the IDS-iSYS GH CLIA specific for 22 kD GH and an in-house IFMA for 20kD GH (LoQ 0.025 ng/ml), respectively. 20 kD GH was > LoQ of the assay in all subjects at baseline and in 86% 60 minutes after glucose ingestion. At baseline, fasting 20 kD/22 kD ratio in the subset was 12.9%. Ratio was not changed 60 min after glucose intake (12.3%; $P>0.05$). Due to the expected suppression of GH following glucose intake, after 120 min the 20 kD/22 kD-ratio could only be measured in 18.3% of the subjects, but no significant change in the abundance of 20 kD GH was observed (mean ratio 12.1%; $P>0.05$). In conclusion, the 20kD/22kD-GH ratio is lower in the non-fasted compared to the fasted state, both at baseline and following exercise. However, short-term oral glucose intake per se does not significantly influence the 20 kD/22 kD-GH ratio.

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EP640

Insulin resistance and acromegaly: about 15 cases

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Contexte
Acromegaly is a rare disease, usually caused by hypersecretion of growth hormone (GH) by a pituitary adenoma and very rarely by ectopic secretion of GHRH. It remains a serious disease reduces life expectancy because of its cardiovascular and metabolic impact.
Objective
The objective of this study is to report the glycemic profile in patients followed for acromegaly in the endocrinologic center of CHU Med VI of Marrakech.
Patient – Intervention
We performed a retrospective study over a period of 2 years. Fifteen cases were identified.
Intervention
In terms of methodology, we studied: a family history of diabetes, hypertension and dyslipidemia; Girth, body mass index (BMI), hypertension, diabetes mellitus or impaired glucose tolerance and dyslipidemia in these patients.
Main outcome measure
Glucose intolerance and diabetes with insulin resistance are commonly encountered complications acromegaly. Some studies have shown a direct correlation between the rate of GH and the degree of glucose intolerance. The hyperinsulinemia and insulin resistance may play an important role in the cardiovascular risk of these patients. The role of insulin resistance, but also of pancreatic β dysfunction has been invoked in the pathogenesis of carbohydrate metabolism disturbances secondary to chronic excess GH.
Result
The average age was 43 years (20–63) with a sex ratio (M/F) = 0.33. The duration of the disease at diagnosis was on average 7 years (3–14). Family history were 13.3% diabetes mellitus and heart disease. Pathological BMI was objectified in 52% of cases; 46.6% of these patients had pre-diabetes, 40% diabetic (a total of 84.6% of carbohydrate anomalies) and 46.7% had dyslipidemia. Moreover 26.6% of our patients where hypertensive.
Conclusion
Approximately 84.6% in our series of cases had carbohydrate abnormalities. Diagnostic and therapeutic delay can worsen or even cause the patient's death. After surgical recovery, the evolution of diabetes and/or glucose intolerance is usually favorable.

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Neuroendocrinology

EP641

Comparison of GHRH + arginine vs glucagon test for the evaluation of growth hormone secretion status in a cohort of adults with Prader-Willi syndrome (PWS)

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Background
Prader-Willi syndrome (PWS) is a rare genetic disorder evolving morbid obesity and growth hormone deficiency (GHD). Testing GH-IGF1 axis is required before treatment with rhGH in adults with PWS (1). The most common used tests in these patients are GHRH + arginine (GHRH + a) and insulin tolerance test. There are no prospective data for glucagon test (GT) in comparison to GHRH + a in adults with PWS. Mechanism by which GT causes GH release remains unclear, glucagon-induced GH release via noradrenaline secretion has been postulated.
Objectives
To compare two diagnostic tests to evaluate GH secretion status in a cohort of adults with PWS.
Methods
Twenty-one SPW (8M and 13F, aged 29(17–51), BMI 36.2 +/− 10.2 kg/m^2) participated in the study. After an 8–10 h fast, all patients underwent the two different provocative tests in separate days: GHRH (1 μg/kg, max 100 μg) + arginine (5 g/kg, max. 30 g) and GT (1 mg). We considered GHD according to BMI-specific cut-offs in GHRH + a (2) and when GH peak was <3 ng/ml in GT.
Results
With the GHRH + a test, 14 of 21(66′7%) met diagnostic criteria for GHD and 19 of 21 (90%) with GT. Only two patients did not meet criteria for GHD with both tests. Most patients achieved GH peak at minute 45: 3.31 ng/ml (1.6–9.6), median (interquartile range) with GHRH + a test, whereas GH response was blunted with GT. After the glucagon injection, an increment in plasma glucose levels was observed at 30 min with a peak at 60 min. One patient suffered an asymptomatic hypoglycemia during the test.
Conclusions
Glucagon seems to fail to stimulate GH in adults with PWS. Further studies are necessary to elucidate if the underlying autonomic dysfunction described in PWS could be involved.
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Nuclear Receptors and Signal Transduction

EP642

Dietary intake of linoleic, linolenic, oleic, and arachidonic acid PPAR-gamma gene expression in visceral and subcutaneous adipose tissue among healthy subjects

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Objective
To investigate whether peroxisome proliferator-activated receptor gamma (PPAR-gamma) gene expression in visceral and subcutaneous adipose tissue was related to intake of several fatty acid intakes.
Methods
For the current study 97 subjects (41 non-obese, 18 obese, and 38 morbid obese) were selected. All of the subjects were free of diabetes and cancers and without using anti-lipid medication. Visceral and subcutaneous adipose tissues were obtained during an abdominal open surgery with minimal impact on dietary intake. The PPAR-gamma gene expression was assessed by Real-Time PCR. Usual dietary intake was measured using a validated semi-quantitative food frequency questionnaire. For calculation linoleic (18:2), linolenic (18:3), oleic (18:1), and arachidonic acid (20:4) intakes, the USDA Food Composition Table was used.
Results
The PPAR-gamma expression in visceral adipose tissue among non-obese subjects was correlated with oleic acid ($r=-0.417$, $P=0.007$) and linoleic acid ($r=-0.401$, $P=0.009$). Were seen significant correlations between subcutaneous adipose tissue PPAR-gamma expression and linoleic acid ($r=-0.310$, $P=0.049$) among non-obese subjects. PPAR-gamma expression among obese subjects in visceral adipose tissue was correlated with oleic acid ($r=-0.686$, $P=0.002$) and linolenic acid ($r=-0.699$, $P=0.031$) and also in subcutaneous adipose tissue was correlated with oleic acid ($r=-0.453$, $P=0.048$). Furthermore, among morbid-obese subjects PPAR-gamma expression in visceral adipose tissue was correlated with linoleic acid ($r=-0.336$, $P=0.039$) and in subcutaneous adipose tissue was correlated with linoleic acid ($r=-0.326$, $P=0.046$) and oleic acid ($r=-0.352$, $P=0.030$). Were seen no significant association of dietary intakes of arachidonic acid with PPAR-gamma gene expression.
Conclusions
PPAR-gamma gene expression was negatively correlated with linoleic and oleic acids among non-obese and obese subjects.
Conflict of Interest
None of the authors has any personal or financial conflict of interest.
Funding
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Obesity

EP643

Association between meal intake behavior and body composition/psychological well-being in Japanese adults

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The study aims to evaluate the association between body composition/psychological well-being with meal intake behavior such as eating fast, snacking after dinner, dinner within 2 h before sleep. This cross-sectional study includes $n=3066$ participants aged 19–89 who had participated in an annual health checkup in 2015. BMI, Waist circumference (WC) and the World Health Organization (WHO)-5 Well-Being Index were assessed to determine. The meal intake behavior were assessed with a modified questionnaire based on focused on metabolic syndrome in Japan. In addition, the relation with BMI/WC/psychological well-being and meal intake behavior by controlling age, smoking, alcohol drinking, exercise habit, medication and sleep condition were assessed by multiple regression analysis. Having a short lunch time, preferring salty taste, snacking after dinner and dinner within 2 h before sleep were positively associated with BMI, WC and WHO-5 score after adjusting for all confounders. Although eating vegetable and fruits were not independent of BMI, both are positively associated with WHO-5 score. The present data demonstrate that adjusting meal intake behavior could be helpful in preventing psychological distress as well as obesity.
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EP644

A comparison of the metabolic parameters of obese and non-obese nafld patients with insulin resistance

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Introduction-aim
Non-alcoholic fatty liver disease (NAFLD) is a clinical condition of uncertain etiology, in whose pathogenesis several mechanisms are involved and which is defined by fat vacuoles in more than 5% of hepatic histiocytes in the absence of serious alcohol consumption. It is frequently comorbid with obesity and insulin resistance. However, NAFLD is also seen in non-obese individuals. The purpose of this study was to compare insulin resistance and metabolic parameters in obese and non-obese NAFLD patients.
Materials-method
50 obese (BMI $>=30$) and 50 non-obese (BMI <30) presenting to the Bakırköy Dr. Sadi Konuk Education and Research Hospital Endocrinology, Diabetes and Obesity Clinic with hepatic steatosis determined at ultrasonography (USG) and with no causes such as alcohol use, viral diseases or drug use to account for fat deposition and consenting to participate were included in the study. Patients' demographic characteristics, biochemical tests and insulin levels were investigated. Insulin resistance was determined using homeostasis model assessment (HOMA-IR), a mathematical technique, with the formula fasting insulin (U/ml) $\times$ fasting glucose (md/dl)/405. Insulin resistance was defined as HOMA-IR >2.5.
Results
One hundred patients with NAFLD, 63.3% female, were enrolled in this study. Fifty were obese and 50 were non-obese. Mean age was 44.1 ± 11.1 years. Hepatomegaly accompanied steatosis in 55% of patients. Mean BMI was 37.3 ± 5.63 in the obese group and 28.2 ± 1.35 in the non-obese group. Mean blood sugar values were 99.3 ± 9.78 in the obese group and 103.40 ± 8.3 in the non-obese group, and the difference was not statistically significant (P:0.08). Insulin levels were 10.1 ± 3.3 in the obese subjects and 13.85 ± 12.3 in the non-obese subjects, while HOMA-IR values were 3.48 ± 3.38 in the obese subjects and $2.57\pm.91$ in the non-obese subjects, and the difference was not statistically significant ($P>0.05$). Insulin resistance was determined in 60% of obese patients and 50% of non-obese patients (in 55% of the entire group). The difference was not significant (P:0.3). When the general characteristics and metabolic parameters of the groups with and without insulin resistance were compared (Table 1), significant differences were observed in terms of BMI, waist circumference, insulin level, HOMA-IR, GGT and indirect bilirubin levels, but none between the other parameters.

Table 1

Parameter	With IR	Without IR	P value
Age	46.48 ± 11.77	41.3 ± 9.78	0.072
Sex	F: 52.6%	F: 47.4%	0.098
BMI (kg/m^2)	34.48 ± 6.84	30.71 ± 4.5	0.017
Waist circumference (cm)	103.67 ± 10.72	97.07 ± 10.79	0.022
FBS (mg/dl)	103.88 ± 8.63	98.26 ± 9.17	0.01
Insulin (IU/dl)	15.62 ± 10.99	7.55 ± 1.88	0.000
HOMA-IR	4.03 ± 3.01	1.79 ± 0.42	0.000

Conclusion
We compared metabolic parameters of obese and non-obese patients with NAFLD and insulin resistance. Insulin resistance was present in 55% of the total group. We observed significant differences between insulin levels, HOMA-IR, GGT and indirect bilirubin levels in subjects with insulin resistance. In conclusion, we think that fatty liver disease is by itself a risk factor for insulin resistance independent of obesity, and that GGT and indirect bilirubin levels in particular can show insulin resistance in patients with hepatic steatosis.
Key words: Non-alcoholic fatty liver disease, insulin resistance, GGT

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EP645

Associations between dietary food patterns and metabolic syndrome risk in Albanian adolescents
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Background
Adolescence is a period of rapid body growth and cognitive development, requiring balanced and sufficient nutrient intake. Since dietary habits are usually acquired in this period and could affect dietary practice in later life. It is crucial for adolescents to acquire healthy dietary behaviors for long-term health. However, the prevalence of diet-related metabolic syndrome risks such as obesity, glucose intolerance, elevated blood pressure, and dyslipidemia is increasing worldwide due to unbalanced nutrient intake among adolescents.
Objectives
The main objective of this study is to assess the association between habitual dietary patterns and the MetS risks after adjustments for biological and lifestyle variables in 112 adolescents aged 14–19 in Albania.
Methods
A validated food frequency questionnaire was used to assess dietary patterns, in which three dietary patterns were identified and labeled as ' western –based', 'healthy based' and 'typical food' patterns, whereas MetS risks was determined using multiple indicators such as waist circumference (WC), systolic and diastolic blood pressure (BP), and fasting glucose, triglycerides and HDL cholesterol levels. The outcome variables were statistically normalized and expressed as z-scores. A MetS risk score was computed as the means of these z scores.
Results
Multivariate analyses show that higher intake of western-based diet was significantly associated with the MetS risk scores ($P=0.003$) and WC ($P<0.0001$) and BP compared to those at lower intakes of western-based diet, after adjusting for age, gender,ethnicity, pubertal growth status, total physical activity and sedentary screen-based levels. Similar pattern was found in typical-based diet, whereby adolescents who had higher intake of typical-based diet was significantly associated with higher levels of BP ($P=0.001$) and MetS risk score ($P=0.002$) compared to those at lower intake group. In contrast, high intake of 'healthy' diet pattern was significantly associated with lower WC ($P<0.0001$), BP ($P=0.022$) and MetS risk scores ($P<0.001$) than those at lower health diet pattern.
Conclusion
These findings suggest that high intake of 'healthy' diet that is high in dairy foods, legumes, fruits and vegetables and low-intake of western-based diet and typical based diet were significantly associated with lower risks of abdominal obesity and MetS among adolescents. Hence, effective dietary intervention strategies should emphasize the promotion of healthy dietary practices among adolescents during these critical years of growth in order to prevent the risk of excessive weight gain and metabolic-related disorders.
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EP646

Type 1 diabetes and metabolic syndrome
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Introduction
Contrary to type 2 diabetes, type 1 often occurs in young people, without obesity or cardiovascular or metabolic diseases. The association of type 1 diabetes with an authentic metabolic syndrome including obesity is very rare, though possible, with a mixed clinical picture. The goal of our study is to evaluate the association of type 1 diabetes with the metabolic syndrome.
Material and methods
This is a retrospective cross-sectional study based on the observation of patients admitted for diabetes with insulin deficiency. The positivity of anti-pancreas antibodies testified to the auto-immune characteristic; anti glutamic acid decarboxylase GAD and/or anti tyrosine phosphatase IA2. The goal of the study is to determine the patients' clinical and biological aspects as well as their metabolic profile.
Results
Our series was conducted with 359 patients: 209 men and 150 women, aged between 10 and 69 years with an average of 28.75 years. Metabolic heredity was found in 26 patients (7.2%), Diabetes heredity in 216 patients (60.1%); 147 (40.9%) of whom with type 2 history and 69 (19.2%) with type 1 history. Vascular heredity was found in 27 patients (7.5%). 117 patients (32.6%) were smokers and alcohol consumption was found in 85 of them (23.7%). The clinical picture was ketotic in the majority of cases: 336 (93.6%), with inaugural ketosis in 313 cases (87.2%). Insulin deficiency varied between one week an 36 months, with an average of 3.75 months and a standard deviation of 6.8 months, exceeding 6 months achieving a slow form and a previous oral treatment in 24% of cases. Regarding weight, the average BMI was 22 (extremes: 15 and 39), over 30 in 22 patients. Overweight was more significant in patients over 20 years old, with 6% in the younger population, 14% between the ages of 20 and 40, and 34% in the patients over 40 years of age. Regarding waist size in women, a size over 80 cm was more significant in patients over 40 (38%) against 4% in women younger than 20. Men's waist size over 94 cm was more significant in patients over 40 (19%), against 4% in the ones younger than 20. An obesity previous to the discovery of Diabetes was found in 80 patients (22%). Hypertension was found in 14 patients (4%). Upon admission, average blood sugar levels were 16.40 mmol/l with an average glycosylated hemoglobin HbA1C of 12.32%. Average LDL levels were of 0.912 g/l with a minimum of 0.2 g/l and a maximum of 3.18 g/l.
Conclusion
Even though obesity is often associated with type 2 Diabetes, some type 1 Diabetics present with a metabolic syndrome that could mislead the diagnosis and delay the appropriate management. Obesity in type 1 Diabetes is more correlated with advanced age and metabolic heredity.
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EP647

Intima media thickness of carotid arteries and cognitive function in Georgian nondiabetic obese and overweight hypertensive subjects
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Purpose
Obesity is a serious health problem that has reached very high proportions in our country; prevalence of obesity and overweight together is 56%. Obesity is strongly associated with risk factors for cardio and cerebrovascular disease, AH, type 2 diabetes and cognitive disorders. The aim of our study was to analyze the impact of AH and weight change on carotid artery intima-media thickness (IMT) and cognitive function in Georgian nondiabetic obese and overweight hypertensive individuals.
Materials and methods
We studied 131 patients with mild to moderate AH (89 males/42 females, mean age $53.4\pm3,1$ years, BMI 29.8 ± 3.4 kg/m^2, duration of AH 5.5 ± 2.3 years). Examination included: color triplex carotid artery scanning; 24-h BP monitoring, mini-mental state examination test. 60 overweight patients ($25<$BMI<29.9 kg/m^2) were assigned to group 1 and 71 obese patients (BMI>30 kg/m^2) to group 2.
Results
The groups were comparable by the age, duration of AH, daily mean BP values. Mean values of IMT (gr1:1,04 ± 0.04 mm;gr2: 1.09 ± 0.05 mm) were certainly increased in obese patients compared with overweight ones ($P<0.001$). Prevalence of carotid atherosclerosis was higher in gr2 (78% vs 65%). Occurrence of cognitive disorders was significantly higher in gr 2 (38vs26%)($P<0,05$). BMI positively correlated with IMT ($r=0.25$, $P<0.02$).
Conclusion
Thus, in Georgian obese nondiabetic hypertensive subjects we detected more pronounced and frequent carotid artery affection and cognitive dysfunction

comparing with overweight ones. Data of our study demonstrate importance of more profound examination of cardiovascular system and neurological status in obese hypertensive patients to ensure further more aggressive blood pressure and weight reduction.

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EP648

CGI-58 gene expression profile in individuals with different body mass index

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Background and aim
Although chronic low-grade inflammation is observed in obese subjects, the underlying mechanisms modulating this process are still unclear. The Comparative Gene Identification-58 (CGI-58) is a lipid droplet-associated protein that has an important role in mediating intracellular fat hydrolysis by acting as a coactivator of the adipose Triglyceride Lipase (ATGL). Recent evidence suggests that CGI-58 also has a role in chronic inflammation and insulin resistance (IR). Accordingly, macrophage specific *Cgi-58* knockout aggravated high fat diet-induced inflammation and IR in mice through activation of the NLRP3 inflammasome. However, to date, only few studies have evaluated *CGI-58* expression in obese patients, with inconclusive results. Therefore, the aim of this study was to evaluate *CGI-58* expression in subcutaneous adipose tissue (SAT) from subjects with different BMI. Methods: SAT was obtained from 67 individuals who undergone bariatric surgery or elective abdominal surgery. Twenty-six patients were classified as having morbid-obesity (BMI $\geq$40 kg/m^2), 27 as having moderate-obesity (BMI: 30.0 – 39.9 kg/m^2), and 14 as non-obese subjects (BMI $<$25 kg/m^2). *CGI-58* expression was quantified using RT-qPCR technique. Basal metabolic rate (BMR) was measured by indirect calorimetry and body composition variables by dual-energy X-ray absorptiometry. All subjects underwent complete physical and laboratory evaluations. Results: *CGI-58* expression was decreased in morbid-obese and moderate-obese patients compared with the non-obese group (median 0.59 (minimum 0.18 – maximum 1.39) vs 0.83 (0.28 – 2.15) vs. 1.70 (0.73 – 3.63) *n*-fold change; $P<0.001$). *CGI-58* expression was also negatively correlated with BMI ($r=-0.432$, $P<0.001$), fat mass ($r=-0.380$, $P=0.003$), free fat mass ($r=-0.488$, $P<0.001$), and BMR ($r=-0.373$, $P=0.002$). Regarding lipid profile, *CGI-58* expression negatively correlated with triglycerides ($r=-0.585$, $P<0.001$) and cholesterol levels ($r=-0.305$, $P=0.015$) while positively correlated with HDL levels ($r=0.250$, $P=0.046$). Negative correlations were also found between *CGI-58* expression and HbA1c ($r=-0.421$, $P<0.001$), insulin levels ($r=-0.332$, $P=0.009$) and IR ($r=-0.317$, $P=0.013$). Conclusions: *CGI-58* gene expression is decreased in obese patients compared to non-obese subjects and is inversely correlated with a worse metabolic profile.

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EP649

Fractalkinea as an inflammatory marker in obese subjects

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Background
Fractalkine (CX3CL1) is known to convey its signals through a single G-protein coupled receptor (CX3CR1). It is characterized as a structurally unique chemokine with both membrane-bound and soluble forms. Fractalkine expression has been detected in activated or stressed endothelial, smooth muscle, skeletal muscle, macrophages, neurons, hepatocytes and adipocytes. Inflammation up regulates Fractalkine particularly in adipose tissue of obese individuals.
Aim of Work
This study was designed to assess fractalkine level in obese subjects and its relation with some clinical and laboratory findings. It compares basal plasma fractalkine and hs-CRP in obese patients (with and without metabolic syndrome) and lean healthy controls.
Subjects and methods
The study was carried out on 140 subjects; 70 controls and 70 obese subjects (38 with metabolic syndrome and 32 without metabolic syndrome). All were subjected to full history taking, thorough clinical examination, fasting and post prandial blood glucose, HbA1c, lipid profile, fractalkine level and hs-CRP.
Results
Serum fractalkine level was significantly raised in obese subjects compared to lean controls (being higher in those with metabolic syndrome). There was a significant positive correlation between serum fractalkine level and BMI, WC, WHR, fasting and post prandial blood glucose, HBA1c, total cholesterol, triglycerides and LDL and it was inversely correlated with HDL while there was no significant correlation between serum fractalkine level and hs-CRP.
Conclusions
Fractalkine, like otherknown adipocyte-derived chemokines was increased in obese individuals and associated mainlywith metabolic syndrome. This is a step in the way to understand and explain the exact pathogenesis of metabolic syndrome as well as obesity linked complications.

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EP650

The case of 36 years old obese male patient with high degree of proteinuria and a loosing weight as the major strategy of treatment

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Introduction
Obesity-related glomerulopathy(ORG) is a secondary form of focal segmental glomerulosclerosis (FSGS) occurring in obese patients with a body mass index(BMI) higher than 30 kg/m^2.ORG is typically manifested by nephrotic-range proteinuria without full nephrotic syndrome, and progressive renal insufficiency.
Case presentation
Thirty-six years old male patient (BMI 59.2 kg/m^2) visited endocrinologist with complains of weight gain, hypertension, swollen lower extremities, dyspnea. Laboratory studies revealed: dyslipidemia, primary hypothyroidism and nodular goiter. Liver function- normal. Fasting glucose, postprandial glucose and A1C was normal-diabetes mellitus was excluded. In urine with dipstick proteinuria was found $>$3.0 g/l. The patient was sent to nephrologist. The level of Creatinine-normal, Urea- normal, 24 hour protein urine test: 18872 mg/24 h ($N<150$) and kidney biopsy was recommended. The patient was given low calorie diet (1600 kkal), L-Thyroxine 50 mkg., Simvastatin 20 mg. Because of Heart failure II (NYHA), arterial hypertension III (ESC) AR blockers and diuretics were advised. Despite of strict diet and high doses of diuretics he gained 6 kg in 7 days. Laboratory tests-slightly decreased albumin. Because of no effect of diuretics Albumin transfusion was performed. For 4 days he lost 9 kg. Only moderate edema of lower extremities rested, with AR blockers T/A was within normal range. After month proteinuria decreased till-2641 mg/24 h. He lost nearly 20 kg. He disappeared for 10 months, started to gain weight and whole clinical picture restored. Proteinuria was 4250 mg/24 h. Kidney biopsy was performed-secondary form of FSGS was diagnosed. Treatment strategy remain the same. We concluded that the main reason for proteinuria in this case was obesity.
Conclusion
ORG is in correlation with BMI. With the weight gain the level of proteinuria increases.In the early stage of kidney disease process can be reversible. Loosing weight is one of the most effective strategy of treatment.

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EP651

Mobile and wireless technology to combat obesity. Using on-line program of good nutrition and wright diet: prevention and part of the treatment of diabetes mellitus

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Introduction
It is too much easier and cheaper to combat obesity, than in the future to treat diabetes mellitus and its complications.

Methods
We used an online system for patient education based on the video lessons, full of humor, pictures, and cartoons to convey the necessary information on good nutrition, necessary to do exercises and the need for exposure to the sun to our patients.
Results
Watching the short movies, the patients formed the habits of good nutrition during the first month already, which includes a diet with restriction of fat, digestible carbohydrates and daily consumption of low-fat dairy products, slow carbohydrates, protein and fiber. Were also presented recommendations for compliance with the physical activity, as well as vitamin D consumption. A patient was in touch with a doctor-endocrinologist, if he has any additional questions. We examined data from a survey of 500 patients registered in the online system and 100 patients control group who were given the same recommendations on the appointment. Surprisingly, persistent decrease in body weight by an average of 6.5 kg over 6 months was demonstrated in all patients of the main group, the consumption of milk and dairy products increased by 2.6 times, compared with patients in the control group. The exposure to the sun was observed 15 to 30 minutes daily, compared with the control group 5–10 minutes. Regular physical activity were the main group of 260 minutes per week, in control group 80 minutes per week.
Discussions
Mobile and wireless technology helps physicians to combat obesity and be a part of the treatment of Diabetes Mellitus and we need to improve the quality of information material, including using online technologies to improve the quality and duration of life of our patients.

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EP652

Oligonol supplementation decreases abdominal obesity and the prevalence of metabolic syndrome in a sample of overweight and obese Saudi females without dietary restriction or lifestyle modification

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Background
Obesity, and metabolic syndrome (MS) are highly prevalent in Saudi Arabia, increasing the risk for type 2 diabetes (T2DM), and cardiovascular disease (CVD). Oligonol produced from lychee fruit polyphenols (LFP) has been reported to reduce visceral obesity, and ameliorate MS in Japanese subject.
Aim
To investigate the effect of oligonol supplementation on MS risk factors in overweight and obese Saudi females.
Subjects and methods
Sixty obese and overweight healthy Saudi females were recruited. Blood pressure (BP), height, weight, waist circumference (WC) were measured, and glucose, triglycerides, and HDL cholesterol were assayed in fasting serum samples. Dietary intake, and lifestyle habits were recorded by questionnaire. Subjects were divided into two groups with equal mean body mass index (BMI), in a double-blind /Case-Control study design. Group A (GA) was given placebo, and group B (GB) was given oligonol, and were followed for three months, with all measurements being repeated at the end.
Results
Some subjects were excluded for various reasons, leaving 25 in GA, and 22 in GB. Therefore, the two groups differed significantly in recalculated mean BMI at zero time (29.30 ± 3.97 for GA, and 31.63 ± 4.16 for GB, $P = \mathbf{0.046}$). No side effects or significant differences in diet or lifestyle were found at the end of the study. Mean triglycerides was significantly increased in GA ($P = \mathbf{0.011}$), and decreased in GB ($P = \mathbf{0.008}$). Mean WC increased in GA ($P = 0.027$). Percentage of subjects with high diastolic BP (DBP) in GB decreased significantly from 36% to 9% ($P = 0.031$), and percentage of subjects with metabolic syndrome decreased significantly from 27% to 5% ($P = 0.039$) by the end of the study.
Conclusion
Oligonol supplement succeeded in reversing MS in obese Saudi females by controlling abdominal obesity, and DBP, and decreasing hypertriglyceridemia, thus decreasing cardiometabolic risk without dietary restriction or lifestyle modification.

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EP653

Metabolic and bone effects of high fat diet on adult zebrafish

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Obesity and type II diabetes have been linked to several health issues, including an increased risk of bone fractures. It is well known that an increase of visceral fat affects bone health causing fragility, mechanical strength reduction and increased propensity of fractures because of impaired bone matrix microstructure and aberrant bone cells function. Adult *Danio rerio* (zebrafish) represents a powerful model to study fat and bone metabolism. Then, the aim of this study was to evaluate bone and metabolic effects of high fat diet in adult zebrafish. Fish blood glucose levels have been monitored in time course experiments and glycaemia curve was found altered in fat fish compared to non-fat ones (Figure 1). The adult bone remodeling has been evaluated in fish using the scales as read-out system. The scales of high-fat diet fish shown bone resorption lacunae associated with an intense osteoclast activity. In addition, high-fat fish scales shown a significant decrease of alkaline phosphatase (ALP) activity and increase of tartrate-resistant acid phosphatase (TRAP) activity. These data suggests that an imbalance in fat metabolism leads to an alteration of glucose metabolism and an osteoporotic-like phenotype in adult zebrafish. The zebrafish model of obesity can contribute to elucidate *in vivo* the molecular mechanisms of metabolic changes derived from a high fat diet, which influence the bone tissues regulation and insulin signaling in human obese patients.

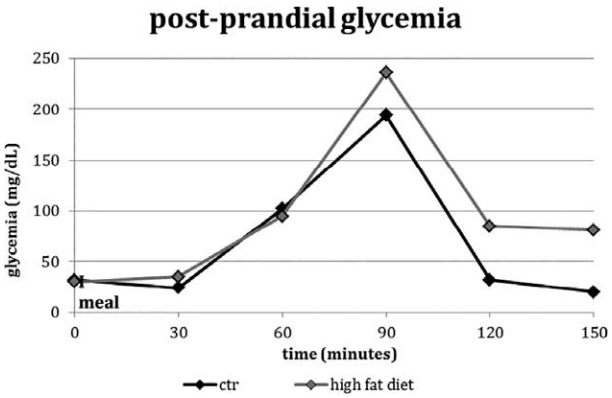

Figure 1

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EP654

Growth hormone signaling and action in obese versus lean human subjects: evidence of increased hepatic GH sensitivity in obesity

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Context
Obesity is accompanied by blunted GH secretion but relatively normal serum IGF-I levels, which suggests increased GH sensitivity. This, however, remains to be tested at the level of GH signaling in human subjects.
Objective
To compare the effects of an acute intravenous GH bolus in obese vs normal weight subjects on GH signaling pathways in adipose and muscle tissue, substrate metabolism and insulin sensitivity.
Subjects and methods
Nine obese (BMI 35.7 ± 0.9) and nine lean (BMI 21.5 ± 0.4) young men were studied twice in a randomized crossover design: (1) After an overnight fast (12 h) ('Control') and (2) After an overnight fast with an intravenous GH bolus (0.005 mg/kg) ('GH bolus'). Each study day consisted of a 4-h basal period ($t = 0 - t = 240$ min) followed by a 2-h hyperinsulinemic, euglycemic clamp (HEC). GH was injected at $t = 0$ and biopsies from muscle and fat were drawn. Muscle and fat biopsies were taken at $t = 60$ min.
Results
Spontaneous serum GH levels were lower in obese subjects, whereas the PK of the GH bolus was comparable. The GH bolus was associated with a BMI-independent increase in STAT5b phosphorylation and CISH mRNA transcription in muscle and adipose tissue. The GH bolus, however, produced a larger relative increase in serum IGF-I levels in obese subjects ($P < 0.01$). GH acutely stimulated lipolysis (ΔFFA in serum, serum palmitate levels and fluxes) to the same extent in both groups. GH significantly reduced glucose uptake during the HEC in both groups ($P = 0.23$), but GH only antagonized insulin-induced suppression of endogenous glucose production (EGP) in the obese ($P = 0.01$).
Conclusions
(1) Acute GH exposure induces pSTAT5b and CISH mRNA and transcription in fat and muscle, and lipolysis to the same extent in obese and lean subjects, (2) A GH-induced relative increase in serum IGF-I levels and suppression of EGP was only recorded in the obese, (3) Our data thus suggest increased hepatic sensitivity to GH in obesity, which in turn may contribute to the blunted endogenous GH secretion.

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EP655

Insulin signaling is involved in the regulation of UCP-1 expression in brown adipose tissue after chronic central leptin infusion

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Background
Brown adipose tissue (BAT) plays a pivotal role in the regulation of energy homeostasis and thermogenesis. This tissue responds to insulin, favoring the expression of uncoupling protein-1 (UCP-1), that in turn is inhibited by insulin-desensitizing cytokines. Leptin may abolish some of the effects of fasting on these parameters through its cross-talk with insulin-related signaling targets.
Objectives
We hypothesized that leptin infusion prevents UCP-1 depletion induced by food restriction through activation of insulin signaling in brown adipose tissue.
Methods
We studied 18 male Wistar rats divided into three groups: rats receiving saline icv (controls, C), those treated icv for 14 days with a daily dose of 12 μg of leptin (L) and a pair-fed group (PF) that received the same food amount consumed by L. We analyzed relative mRNA levels of UCP-1 and glucose transporter 4 (GLUT4) by real time-PCR and changes in the cytokine levels and activation of insulin-related signaling targets by multiplexed bead immunoassay.
Results
Relative UCP-1 mRNA levels were reduced in PF and unchanged in the L group. The mRNA levels of GLUT4 were increased in L rats, as well phosphorylation of insulin receptor substrate 1. Akt phosphorylation on threonine 308 was reduced in PF and increased in L. Among the studied cytokines, fractalkine and TNF-α were decreased in the L group, with no changes in PF rats.
Conclusion
Central leptin infusion could preserve UCP-1 expression in brown adipose tissue through activation of insulin-related signaling.

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EP656

Can night eating syndrome increase basal metabolic rate?

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Introduction
Night eating syndrome (NES) is an eating disorder associated with obesity, characterized by a delayed pattern of food intake in which recurrent episodes of nocturnal eating and/or excessive food consump-tion occur after the evening meal. (1) Studies showed significant weight gain among patients with NES.However, the underlying reason is still controversial.The aim of this study is to investigate the body composition and energy metabolism in patients with NES.
Methods
Obese patients were divided into two groups according to the diagnostic criteria. Diagnostic crite-ria for NES include: (1) recurrent episodes of night eating, as manifested by eating after awakening from sleep or by excessive food consumption following the evening meal, (2) awareness of those eating episodes, and (3) significant distress or impairment caused by the disorder. Patients meeting these three criteria were considered NES(+) (2). 281 women and 46 men, (101 NES(+), 226 NES(−)) were included to study. Body mass index (BMI) and waist to hip ratio (WHR) were measured. Biochemical tests were performed. Total fat mass (FM), fat-free mass (FFM), Body Water (BW), basal metabolic rate (BMR)were measured by Bioelectrical Impedance Analysis (BIA).
Results
BMI and WHR were similar in both groups. There were no significant differences in total cholesterol, triglyceride, LDL, HDL, ALT, GGT, fasting glucose, insulin levels, postprandial glucose and insulin levels. There were significant increase in BMR in patients with NES, and not significant differences in FM, FFM, BW.
Conclusion
BMR is the least amount of energy necessary for life. It accounts for 60–70% of the total energy expenditure in sedentary man and hence forms the basis for human energy requirements. In this study, BMR was found high in patients with NES. Fat distrubution was similar in both groups. There is no study that examines the effects of this syndrome on energy metabolism. There was a need for further work in this regard.

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EP657

Association between cardiometabolic risk indicators and FGF 19 in healthy Saudi individuals of different BMI grades

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Background
Fibroblast growth factor 19 (FGF19) is an enterokine derived from the ileum, and synthesized in response to release of bile acids following food ingestion. It was proposed to be an important regulator of the postprandial adaptive metabolic response. by stimulating glycogen and protein synthesis in the liver, and down regulating glucose production after a meal. There is limited research investigating the association between FG-19 and metabolic dysregulation in overweight and obese Saudi subjects.

Aim
To study association of circulating FGF 19 in healthy individuals of different BMI grades, with some cardiometabolic risk indicators.
Subjects and methods
Healthy adults aged 19–36 years were recruited. Height, and weight were measured to calculate body mass index (BMI). Sixty males and 60 females were included in the study, divided equally between BMI categories (underweight, normal, overweight and obese). Waist, hip, and neck circumference (WC, HC, NC) were measured. Glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), insulin, FGF19 and highly sensitive CRP (hs-CRP) were estimated in fasting serum samples, and low-density lipoprotein cholesterol (LDL-C), Atherogenic index of plasma (AIP), and homeostatic model assessment-insulin resistance (HOMA-IR) were calculated.
Results
No significant correlation ($P=0.457$), or difference in means of FGF19 was noted between different BMI categories ($P=0.905$). A negative significant correlation was found between FGF19 and WC, NC, and LDL-C: HDL-C ratio ($r=-0.203$, $P=\mathbf{0.027}$, $r=-0.297$, $P=\mathbf{0.002}$, $r=-0.187$, $P=\mathbf{0.041}$ respectively).
Conclusions
Serum FGF19 levels do not appear to be related to general obesity expressed as BMI. However, it was found to be associated negatively with indicators of abdominal, and upper torso obesity, reported to be associated with increased cardiometabolic risk, indicating the relationship of FGF19 with this risk. The strong correlation between FGF19 and serum LDL-C:HDL-C;a well established indicator of cardiometabolic risk; validate the link further.

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EP658

The role of pioglitazone and vitamin E for the treatment of NASH with or without metabolic syndrome

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Introduction
Obesity is a global public health problem and is associated with metabolic syndrome and dyslipidemia as well as very often with non-alcoholic steatohepatitis (NASH).
Aim & methods
The aim of the present study was to evaluate the preventive and curable role of vitamin E and pioglitazone (thiazolidinedione-type) in NASH patients with or without metabolic syndrome. 51 patients with NASH were divided into two groups: 26 patients with insulin-resistance (IR) plus obesity and 24 patients without IR. 12 patients from 1-st group (another 14 patients from this group served as a control subgroup) and 12 patients from 2-nd group were treated at least during 3 months with vitamin E (500–1000 mg daily) plus pioglitazone 15–30 mg/d (another 13 patients – control subgroup) as well as put on the low-fat diet. Gender distribution of the patients was equal in each subgroup (26 male, 25-female). Mean age was 46.6 ± 6.4 years. Mean BMI (body mass index) - 34.6 ± 4.1 kg/m^2. HOMA-IR of patients from 1-st group was 2.7 ± 0.8.
Results
The concentration of the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels ($P<0.01$) as well as cholesterol and triglycerides ($P<0.05$) were found to be higher in the both subgroups without pointed treatment. HDL level, however, was comparable in both groups ($P>0.05$). Results also indicated that this therapy reduced BMI ($P<0.05$) and HOMA-index ($P<0.05$) in both subgroups.
Conclusions
Insulin resistance appears to be the underlying pathophysiological defect leading to NASH. The data from this study demonstrate the possible mechanism by which pioglitazone and vitamin E mediate their beneficial clinical and metabolic effects in patients with NASH. To prevent this condition is to maintain a healthy diet and rigorous exercise regimen.

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EP659

MicroRNAs, associated with coronary heart disease in patients with obesity and diabetes mellitus type 2

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Introduction
Obesity and diabetes mellitus type 2 (T2DM) are considered as one of the major risk factor for coronary heart disease (CHD) development, but the mechanisms beyond this relationship still need to be clarified. miRNAs are supposed to be involved in regulatory mechanisms in this relationship.
Aim
To determine miRNAs expression in patients with obesity and T2DM.
Methods
MiRNAs were detected in peripheral blood of 43 patients, aged 48–65 years with obesity and T2DM. Patients were divided in two groups: 1st group – 21 patients with CHD, 2nd group – 22 patients with excluded CHD after Tredmil-Test. All patients from the 1st group underwent coronary angiography (CAG).
Results
Nine CHD-related mRNAs were selected as candidates for the investigation: miRNA-1, miRNA-21, miRNA-26a, miRNA-27a, miRNA-33a, miRNA-33b, miRNA-133a, miRNA-133b and miRNA-208. Expressions of these miRNAs were compared in studied groups. Expression of miRNA-21 (3.44 vs. 0.37; $P=0.007$) and miRNA-27a (0.86 vs.0.31; $P=0.013$) in patients with CHD were higher than that in 2nd group, while expression of miRNA-26a (1.06 vs. 2.14; $P=0.022$) was lower in patients with CHD. Spearman correlation analyses showed that miRNA26a was positively associated with cholesterol level ($r=0.316$, $P=0.042$). MiRNA-21 and miRNA-27a were negatively correlated with HbA_{1c} in both groups ($r=-0.363$, $P=0.042$ and $r=-0.420$, $P=0.036$, respectively). MiRNA-208 was positively correlated with hypertrophy of the interventricular septum ($r=0.61$, $P=0.027$) and number of significantly affected coronary vessels according to CAG ($r=0.65$, $P=0.034$), negatively – with left ventricular diastolic dimension ($r=-0.52$, $P=0.029$).
Conclusion
1) Expression of miRNA-21 was increased by 9 times, miRNA-27a in 2.5 times in patients with CHD, while miRNA26a compared with patients with type 2 diabetes and obesity was lower in 2 times.
2) We revealed correlations of miRNA-208, 27a, 21 with pathological angiogenesis, and heart remodeling processes in patients with obesity and T2DM.
3) Increased expression of miRNA-208 can determine the severity of cardiovascular disease in patients with obesity and T2DM.

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EP660

The surgical approach to obesity in numbers

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The prevalence of obesity has greatly increased worldwide in the last decades, particularly in Europe and Portugal. It is associated with many health problems, including cardiovascular diseases, cancer and diabetes.
Methods
Revision of the clinical records of all 61 patients who underwent bariatric surgery between 2013 and 2015. Analysis of their metabolic profile prior to surgery and its evolution after the operation.
Results
61 patients were reviewed, namely 90.2% females and 9.8% males. The mean age was 43.6 years. All patients had class II or III obesity according to their BMI, with an average score of 46.4 kg/m^2. The associated cardiovascular risk factors include: hypertension (47.5%), total cholesterol >200 mg/dl (35.8%) and type 2 diabetes mellitus (10.6%). 60% had an apnea–hypopnea index great than 5/h. Most patients underwent gastric sleeve surgery (93.4%) and only 6.6% received a bypass surgery. Six patients were treated with an endoscopic intragastric balloon prior to surgery. Weight was evaluated at 3 months' intervals in the first 1.5 years, and then every 6 months. 13.6 months was the mean follow-up time after the procedure. The average weight loss prior to surgery was 9.6% of the initial body weight. After the operation, weight loss was more pronounced between the first and third months (7.4% of the initial body weight). The trend of weight loss remained until 9 months, stabilizing afterwards. The mean BMI reduction was 27.1% at the end of the follow-up time. Both HbA1c and triglycerides were reduced by 11% and 15%, respectively, after surgery. HDL increased by 16%.
Conclusions
The majority of patients eligible for bariatric surgery were young females with class II or III obesity. Many had other cardiovascular risk factors, particularly hypertension and dyslipidemia. Gastric sleeve was the preferred technical procedure and only a few patients received an endoscopic intragastric balloon to aid weight loss prior to surgery. Weight loss was more pronounced in the first 3 months after surgery, but that tendency was mitigated after only 9 months.

Nevertheless, body mass index was reduced by a quarter at the end of follow-up. These results show the importance of the multidisciplinary approach to obesity and the potential benefits with bariatric surgery. However, we emphasize the short follow-up time and the need to maintain evaluation of these patients in the future.

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EP661

Decreased HDL cholesterol efflux capacity in morbidly obese individuals as a surrogate marker for increased cardiovascular risk

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Background
Obesity has become a worldwide epidemic and carries excess cardiovascular morbidity and mortality. HDL efflux capacity (HEC) was shown to be inversely correlated with cardiovascular risk (CVR), both in the acute and the chronic phases. Our aim was to understand if decreased HEC can serve as a surrogate marker for the increased CVR in this population.
Methods
Forty patients: 10 obese diabetic (OD), 10 obese non-diabetic (OND), 10 with stable Coronary Artery Disease (sCAD) and 10 healthy controls were blindly selected from another cohort and their HECs were studied using radioactive cell-based assays.
Results
The mean age of the cohort was 50 ± 12 years, with 72.5% men. Mean BMI for the obese groups was 46.8 ± 7.03 kg/m^2, for the sCAD group 27.7 ± 3.3 kg/m^2 and for the controls 24.2 ± 2.26 kg/m^2. Mean HEC (adjusted to ApoA1 mass) was 14.18 ± 0.95% for the OD group, 14.73 ± 3.18% for the OND group, 19.11 ± 1.6% for the sCAD group and 16.01 ± 1.6% for the controls. A linear regression model adjusted for age, sex, BMI and TG has found that both OD and OND have significantly lower HEC in comparison to controls ($P < 0.05$ for both), whereas the sCAD did not.
Discussion
In the current study, we found that morbidly obese individuals have significantly lower HEC in comparison to controls. Given that HEC has an inverse correlation with CVR, these finding may explain, at least in part, the increased CVR in morbidly obese patients. It is unclear if bariatric surgery improves HEC, but it is reasonable to speculate it does, given the other metabolic effects the surgery exerts.
Conclusion
HDL function is compromised in morbidly obese individuals and contributes to progressive atherosclerosis and increased CVR in this population. If HEC does improve post-metabolic surgery, decreased HEC might serve as another indication for bariatric surgery.

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EP662

The association of anthropometric measurements and PPAR-γ gene expression among healthy adult subjects

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Introduction
Peroxisome proliferator activated receptor-γ (PPAR-γ) is a distinguished transcription factor abundantly expressed in the adipose tissues and plays a key role in the regulation of adipocyte differentiation and development of obesity. In the current study, we aimed to investigate the association of PPAR-γ mRNA expression in omental and subcutaneous adipose tissues with anthropometric indices and blood pressure (BP) among healthy adults.
Methods
97 subjects (41 non-obese, 18 obese, and 38 morbid obese) were eligible for the study. Omental and subcutaneous adipose tissues were obtained during open abdominal surgery. The PPAR-γ mRNA level was evaluated in omental and subcutaneous adipose tissues using Real-Time PCR assay. Height, weight, BMI, waist, hip, and neck circumferences, and BP were determined according to standard protocols.
Results
The mean of BMI was 24.8, 34.9, and 46.8 kg/m^2 in morbid obese, obese and non-obese subjects, respectively. PPAR-γ gene expression was not significantly different between omental and subcutaneous adipose tissues in each group. However, PPAR-γ mRNA expression was down-regulated in omental adipose tissues of non-obese subjects compared to obese subjects and up-regulated compared to morbid obese ones ($P < 0.05$). Among morbid obese subjects, diastolic and systolic blood pressures were positively correlated with omental PPAR-γ expression ($r = 0.409$, $P = 0.020$ and $r = 0.371$, $P = 0.037$, respectively); waist and neck circumferences were positively correlated with both adipose tissues ($P < 0.05$). Among obese subjects, PPAR-γ expression in both tissues had significant positive correlation with waist circumference ($P < 0.05$).
Conclusion
Our study suggested that several obesity-related indices have a positive correlation with PPAR-γ expression in omental and subcutaneous adipose tissues.

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EP663

Results of computer-assisted intravital microscopy in overweight and obesity

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Rationale
Obesity, prediabetes and diabetes are strongly associated with microcirculation (MC) abnormalities. It is known that pathological changes in microvessels predispose to CHD, CKD and retinopathy. Also it is widely recognized that biochemical and immunological changes accompanied with obesity and overweight lead to MC damage.
Objective
Of the study was to assess changes in MC in patients with overweight and obesity.
Materials and methods
Computer-assisted intravital microscopy (CAIM) was used to assess intra- (six scores), extra- (three scores) and vascular (11 scores) changes of bulbar conjunctiva and vascular indexes were calculated. We included 91 patients with overweight (group 1), 103 patients with obesity (group 2) both with concomitant prediabetes and diabetes and 58 almost healthy person (group 3).
Results
Overweight and obesity are characterized by progressive changes in MC. A significant difference was observed in perivascular edema in patients with overweight (0.5 (0.0;1.0) as well as in patients with obesity (1.5 (0.5;1.0) ($P_{1-3} = 0.025$, $P_{2-3} = 0.012$) compared to group 3. There were no any significant intravascular changes between groups. Vascular changes included inequality in vessels size (1.0 (1.0;1.0) in groups 1 and 2 vs 1.0 (0.0;1.0) in group 3) $P_{1-3} = 0.012$, $P_{2-3} = 0.010$), meandrous tortuosity of venules (1.0 (0.0;1.0) in groups 1 and 2 vs 0.0 (0.0;1.0) in group 3) $P_{1-3} = 0.002$, $P_{2-3} = 0.001$) and meandrous tortuosity of capillaries (0.0 (0.0;1.0) in groups 1 and 2 vs 0.0 (0.0;0.0) in group 3) $P_{1-3} = 0.001$, $P_{2-3} = 0.004$). Calculating of partial vascular indexes and total vascular index optimizes results of CAIM. Vascular index was significant higher in patients with overweight (10.0 (8.0;11.0) compared to patients with obesity (10.0 (9.0;11.0) ($P_{1-3} = 0.001$, $P_{2-3} = 0.001$).
Conclusion
Overweight and obesity are associated with MC abnormalities and mostly expressed in extra and vascular changes. Use of partial and total vascular indexes optimizes evaluation of MC changes.

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EP664

Assessment of adipose tissue distribution in youg women with polycystic ovary syndrome

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PCOS is characterized by abdominal obesity along with conventional diagnostic features.
Objective
To assess body composition in women with PCOS and normal body weight.
Materials and methods
35 women (24±1.1 years old) with confirmed diagnosis of PCOS according to Rotterdam criteria, 27 almost healthy women (25±1.2 years old), both groups wotn normal weight. Whole Body Dual-energy X-ray Absorptiometry (DEXA Total Body) scans were carried out using 'Prodigy Lunar' machine (USA).
Results
Registered differences included increase of total fat accumulation, fat accumulation in android compartments as well as android-gynoid fat ratio index. Basic antropometric measurements and DEXA of patients with POCS and control group. 29 (82.86%) patients in study group demonstrated significantly higher waist circumference (77.1±11.2 cm) and higher percentage of adipose tissue in android area (37.9±3.0%) correspondingly compared to control group (R – 0.846176 at P <0.05).
Conclusion
Abdominal fat accumulation is attributable to patients with PCOS. Lack of significant differences between BMI and total fat accumulation is apparently explained by age, dietary habits, patient's disease awareness as well as reasonable life style modification and physical exercises modification.

Table 1

Measurements	Study group, n=35	Control group, n=27
Total fat content, g	34.257±5.763	17.737±2.393
Total fat content by DEXA, %	37.3±6.7. P<0.05	29.2±4.9
Trunk fat accumulation, g	11.315±3.400	6.326±1.592
Trunk fat accumulation, %	31.2±4.7	29.3±2.7
Fat accumulation in android compartments, %	37.9±3.0, P<0.05	30.9±3.1
Fat accumulation in gynoid compartments, %	40.5±4.3	39.3±2.8
Android-gynoid fat ratio index (A/G)	0.91±0.1, P<0.05	0.76±0.1

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EP665

Decreased muscle strength is associated with vitamin D and albumin levels after bariatric surgery

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Bariatric surgery patients are at risk of decreasing in muscle mass, vitamin and protein deficiency. The aim of this study is to asses muscle strength, serum protein and vitamin levels after bariatric surgery.
Methods
264 patients underwent bariatric surgery who completed 6 th month policlinic visits were included in the study. Patients were followed appropriately supplemented protein and vitamins as suggested; all study parameters were assessed before and after 3rd. mo. and 6th mo. of bariatric surgery. Handgrip dynamometry was used to measure static muscle strength. Serum Albumin, 25OH vitamin D (25OHD), Vitamin B12, ferritin and creatinine levels were measured by immune- chemiluminecanse method.
Results
Postoperatively, all patients showed a significant decrease in the BMI in 3 mo and 6 mo compared to preoperative levels (P:0.0001). Biochemical measurements are shown in Table 1. Serum ferritin and, creatinine levels were in reference range and not change during the follow-up. In a multivariate regression model showed that 25OH D and creatinine levels were independent risk factor for muscle strength (r^2:16.2, P<0.0001). Serum albumin and handgrip measurements showed a positive correlation (r:0.23, P<0.001).

Table 1 BMI, handgrip and biochemical measurements before and after surgery in obese patients

	Before surgery	3rd mo. After surgery	6th mo.fter surgery	P
BMI (kg/m^2)	48.3±8.9	40.4±7.9	38.1±11	0.0001
Handgrip (kg)	28.1±9.2	21.6±7.5	21.3±6.4	0.001
25OHD (ng/dl)	14.4±20	25.6±15.7	31.9±49	0.0001
Vitamin B12 (ng/dl)	284±154	339±219	326±208	0.004
Albumine (mg/dl)	4.42±0.2	4.30±0.3	4.07±0.9	0.0001

Conclusion
Although appropriate vitamin and protein supplementation bariatric surgery patients are at risk of decreased muscle strength related complications.

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EP666

Comparison between mathematical indexes and histopathological findings in the diagnosis of nonalcoholic fatty liver disease in mexican population

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is an emerging disease in Mexico, comprising a spectrum of histopathological findings ranging from simple steatosis to steatohepatitis and cirrhosis. The gold standard continues to be the liver biopsy, but several mathematical indices have been proposed, such as non-invasive techniques, however there are very few studies in our population.
Objetive
This study aims to compare mathematical indexes and histopathological findings for the detection of NAFLD in Mexican population.
Methods
A cross-sectional study was performed at the 'Hospital General León' between November 2016 and January 2017. Patients aged 18 years or above that underwent laparoscopic cholecystectomy were recruited. No history of alcohol consumption habit or hepatic diseases characterized the patients. The fatty liver index (FLI) and the lipid accumulation product (LAP) were calculated. Demographics, blood samples, and a liver biopsy were obtained. Results between FLI, LAP and livery biopsy were compared.
Results
A total of 59 patients were included (80.1% women and 19.1% men). The mean age was 39.6±14.8 years, BMI 29.7±10.11 kg/m^2. The FLI identified 31 patients with NAFLD of which 11 were corroborated with biopsy, whereas the LAP identified 26 patients of which 17 were corroborated with biopsy. From the patients with negative FLI index (n=26), a total of 11 (42%) were diagnosed with steatosis by histopathology. For LAP, 31 patients (54.3%) were negative, four of which (7.01%) presented positive for NAFLD by histopathological diagnosis.
Conclusion
According to our results, at least in our population these two mathematical indices are not useful for the diagnosis of NAFLD, so liver biopsy remains to be the gold standard for the detection of NAFLD. Future studies should be performed in order to continue looking for other non-invasive markers for NAFLD.

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EP667

Obesity and infertility among Tunisian women of reproductive age: about 40 cases

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Obesity is on the increase worldwide and mainly in women of reproductive age. In turn, it is associated with various reproductive complications. To assess the detrimental effect of obesity on reproductive health and the means of its management, this retrospective cohort study of 40 obese and infertile women has been conducted in the department of endocrinology and diabetology of Hedi Chaker hospital in Sfax-Tunisia from 2009 to 2014. These patients have a mean age of 34 years and a mean BMI of 37.29 kg/m^2. They were to suffer from infertility for a mean period of 5,7 years. The polycystic ovary syndrome was the most common cause of infertility diagnosed in 52.5%. Classic morbidities of obesity were dominated by metabolic (52.5%) and cardiovascular (37.5%) complications. Ovulation disorders were identified in 77.5% of cases and serious complications during pregnancy were observed. These complications affect the obese mother as well as the child: abortions (52.5%), delivery by caesarean section (35%), gestational diabetes (20%), foetal malformation (12.5%), neonatal death (7.5). Though the management of the combination of obesity and infertility was quite difficult, a weight loss of 5–8% has resolved 61.2% of menstrual irregularities and improves the chances of pregnancy in 20% of cases. Insulin resistance and hyperleptinemia are the main mechanisms linking obesity to infertility. Thus the establishment of a healthy lifestyle since a young age is the best therapeutic solution for obesity-induced infertility. Obese women have a higher prevalence of infertility, maternal morbidity, mortality and foetal anomalies. For these reasons it's necessary to raise the public awareness on the detrimental effects of obesity on reproductive health.

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EP668

Mindfulness-oriented weight management course in a tier 3/tier 4 obesity service

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Overeating contributes to obesity epidemic and has many causes. Evidence shows that problematic eating behaviours can be modified with mindfulness. In the UK the use of mindfulness in management of obesity has been studied only once before. We aimed to pilot a new weight management course that would improve patients' skills and confidence in ability to lose weight, and reduce patient waiting time. The course covered mindful eating, compassion and self-esteem, managing relapses and weight loss orientated marketing. Four interactive sessions were delivered by dietitians and psychologists over 8 weeks, resulting in frequent contact with participants. Patients were invited to participate in this course following their first appointment, and received normal follow-up regardless of their participation. Ten patients were included in the final analysis. Anonymized feedback and eating style questionnaires were collected before and after the course. The average weight and age were 120 kg and 45 respectively, and eight were women. 90% of patients lost weight (0.4–5 kg). Average weight loss was 1.54 kg. Patients were seen more frequently in the initial phase of their treatment pathway, leading to improved experience.30% of participants heard of mindful eating prior to our course, with 90% finding it a useful concept for weight management on completion. Patients became more confident, compassionate and felt more in control. Eating styles were assessed by a validated questionnaire. Paired t-test was applied to analyse results. Statistically significant improvement was found in emotional eating ($P=0.010$), food fretting ($P=0.022$), unappetizing atmosphere ($P=0.042$) and overall eating style ($P=0.017$). This holistic course equipped patients with new skills to change eating behaviours, coping strategies and changed their mindset and will be incorporated into the standard service for all bariatric patients. However, the results of this project have global implications as management of obesity should incorporate holistic approach and utilize mindfulness in future.

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EP669

Menopause is a major determinant of endocannabinoid 2-arachidonoylglycerol plasma level and of its relevance as biomarker of dyslipidemia and insulin resistance in lean women

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Context
The endocannabinoid system (ECS) hypertonicity contributes to obesity development and maintenance. Excess circulating levels of ECS mediator 2-arachidonoylglycerol (2AG) were reported in obese humans, however, unstandardized experimental settings (i.e. analytical conditions, sample size, concurrent diseases/medications, statistics, gender, body mass index (BMI) and age), clouded its role in dysmetabolism and its usefulness as biomarker. The study aimed at describing 2AG associations with visceral obesity, dyslipidaemia, insulin resistance and hypertension in females according to BMI and menopausal status.
Methods
Adult, unmedicated, disease-free premenopausal (preMP, $n=103$) and menopausal (MP, $n=81$) females were stratified in normal weight (NW, BMI:18.5–24.9kg/m^2), overweight (OW; BMI: 25.0–29.9kg/m^2) and obese (BMI $\geq$30.0kg/m^2) classes. Plasma 2AG, anthropometric and metabolic parameters were assessed.
Results
Menopause ($P<0.001$) and BMI ($P=0.001$) independently increased 2AG levels. NW ($P=0.001$) and OW ($P<0.001$), but not OB, MP women, displayed higher 2AG than preMP counterparts. 2AG increased with BMI in preMP ($P<0.001$), but not in MP cohort. 2AG displayed BMI-independent relationships with triglycerides in both preMP ($P=0.006$) and MP ($P=0.005$) and with glucose in MP ($P=0.036$). When analyzed within preMP BMI classes, only in OB class 2AG significantly associated with total cholesterol (TC, $P=0.040$) and triglycerides ($P=0.020$). In MP cohort, 2AG associated with TC ($P=0.006$), glucose ($P<0.001$), HOMA-IR ($P=0.035$) and triglycerides ($P=0.001$) within NW, with triglycerides in OW ($P=0.034$) and with none of the parameters in OB class. Moreover, increasing BMI significantly reduced 2AG associations with TC ($P=0.037$) and glucose ($P=0.002$) in MP cohort, while 2AG associations with TC, glucose and HOMA-IR significantly distinguished NW MP from NW preMP women ($P=0.036$, $P=0.005$ and $P=0.027$, respectively). No 2AG associations were found with waist circumference and blood pressures.
Conclusions
Plasma 2AG is a valuable biomarker of clustering insulin resistance and dyslipidemia in lean menopausal women, and may play a causative role in menopause-related metabolic worsening.

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EP670

Genetical predictors of neuroendocrine disturbances in children with severe obesity

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Objectives
Neurogenetical predictors of psychological disturbances in children with severe obesity.
Methods
We examined 254 pubertal obese children: group1 (simple obesity) 187 children, 14.3$\pm$2.0 yrs, 30.4$\pm$2.8 kg/m^2; group2 (severe obesity) 67 children, 14.7$\pm$2.1, 39.1$\pm$3.8. Control 80 children, 14.4$\pm$2.0 yrs, 19.7$\pm$1.7 kg/m^2. Dopamine levels were determined. Genotyping was performed on polymorphic genes COMT, MAOA, A1 Tag 1A allele of DRD2/ANKK1 polymorphism (rs1800497).
Results
A statistically significant difference between dopamine levels were in patients with simple (8.8(4.8; 20.7)) and severe obesity (48.8(29.8, 163.9)) ng/ml and AA genotype ($P=0.05$). We found the significant increasing of dopamine levels (82.5 [61.3; 116.3]) in boys with severe obesity and 3-3 MAOA genotype comparison

to 4-4 genotype (35.7 [23.2; 54.9]) (U = 4.0; $P = 0.03$). We determined more frequent occurrence of GA (Val/Met) genotype COMT gene in children with severe obesity (54.3%) compared to simple disease (32.7%) ($\chi^2 = 6.9$; $P = 0.03$). AA genotype frequency was 21.7% in patients with severe obesity, which were higher than control (16.6%) ($\chi^2 = 14.6$; $P = 0.006$). We revealed significantly higher BMI in children with severe obesity and the presence of GA genotype (41.3 ± 4.5 kg/m^2) compared to GG (37.4 ± 3.1) ($P = 0.006$) and AA (38.6 ± 2.8) ($P = 0.04$) genotypes. The more frequent presence of A1 allele, associated with low dopamine D2 receptors density (A1A1 and A1A2) was detected in children with morbid obesity (17.9%) in comparison with alimentary obesity (4.8%), ($\chi^2 = 9.7$, $P = 0.008$). The positive reliable correlation was found between A1A2 genotype and BMI ($r_s = 0.8$, $P = 0.001$).

Conclusions

A large frequency of AA genotype were found in children with severe and simple obesity. Higher BMI levels were in children with severe obesity and genotype GA. The more frequent presence of A1 TaqIA allele, associated with low dopamine D2 receptors density was found in children with morbid obesity.

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EP671

Endocannabinoid 2-arachidonoylglycerol plasma level is a BMI-independent biomarker of cardiometabolic risk in adult males with higher relevance in lean and aged conditions

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Context

Ageing and obesity are similarly characterized by metabolic impairment in terms of visceral fat, dyslipidaemia, insulin resistance and hypertension. Obesity is featured by endocannabinoid system (ECS) hyperactivation. Increased levels of endocannabinoid 2-arachidonoylglycerol (2AG) found in obesity were variously associated to dysmetabolic features, however, it is not clear whether such associations exist in normal weight conditions. Moreover, ageing contribute in modulating 2AG tone and involvement in worsening metabolic profiles was not addressed. The study aimed at defining 2AG relevance as BMI-independent biomarker of metabolic impairment in males and whether its relevance is modified by ageing.

Methods

Unmedicated, disease-free male volunteers ($n = 144$) aged 18-84yo were stratified in normal weight (NW, BMI:18.5–24.9 kg/m^2, $n = 61$), overweight (OW; BMI: 25.0–29.9 kg/m^2, $n = 61$) and obese (BMI ≥ 30.0 kg/m^2, $n = 22$) classes. Plasma 2AG, anthropometric and metabolic parameters were assessed.

Results

Age did not influence 2AG levels in the overall cohort nor within BMI classes. 2AG levels increased with BMI ($P = 0.019$), however, significance was lost after adjustment for each metabolic parameter. 2AG displayed age- and BMI-independent positive relationships with SBP ($P = 0.020$), insulin ($P = 0.011$), HOMA-IR ($P = 0.006$), total cholesterol ($P = 0.001$) and triglycerides ($P < 0.001$) and negative with HDL-cholesterol ($P = 0.046$). 2AG correlation with triglycerides was confirmed in each BMI class (NW and OW: $P < 0.001$; OB: $P = 0.029$). Positive 2AG correlation was found with SBP ($P = 0.023$) and DBP ($P = 0.048$) within OB, and with total cholesterol within OW ($P < 0.001$) class. Finally, within the NW class, 2AG negatively associated with HDL-cholesterol ($P = 0.004$) and positively with glucose ($P = 0.015$), insulin ($P = 0.003$) and HOMA-IR ($P = 0.001$); notably, the last two correlations were positively influenced by age (both $P = 0.004$). No associations were detected between 2AG and waist circumference.

Conclusions

Plasma 2AG is a valuable biomarker of clustering hypertension, insulin resistance and dyslipidemia in male gender. Results in lean males may suggest a causative role for 2AG in age-related insulin resistance.

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EP672

Unfavourable blood pressure and lipid levels in obese individuals from the general population

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Background

Early diagnosis and treatment of high blood pressure (BP) and high cholesterol is important to reduce cardiovascular mortality risk.

Methods

We assessed actual BP and LDL-cholesterol (LDL-C) levels in 88,029 participants (36,122 men), aged 18-80 yrs, without diabetes, from the Dutch Lifelines Cohort study. Participants were categorized according to degree of obesity (normal weight, overweight, obese) and age decade group. BP measurement was rigorously standardized. Mean systolic and diastolic BP were calculated depending on BP-treatment status for the three BMI classes, and for each age group. We repeated these evaluations for LDL-C levels.

Results

In total, 13.3% of men and 15.6% of women were obese. BP increased gradually in each age group, with mean levels of 124/68 mmHg in the youngest and 142/77 mmHg in the oldest male participants, and was significantly higher in obese vs. non-obese and overweight individuals in all age groups ($P < 0.01$). The largest difference (10-11 mmHg) between obese and non-obese was observed in males below 50 yrs. Despite the use of BP-lowering medication (5.1–6.2% in non-obese, 21% in obese), still 20–50% had elevated systolic BP ≥ 140 mmHg. Overall mean LDL-C was 3.5 ± 0.9 mmol/l in obese vs. 3.2 ± 0.9 mmol/l in non-obese men ($P < 0.001$), and 3.3 ± 0.9 vs 2.9 ± 0.8 mmol/l in women ($P < 0.001$). More untreated obese than non-obese participants had an LDL-C ≥ 3.5 mmol/l (men: 56% vs 37%, women: 41% vs 24%, both $P < 0.001$). Only 37% of obese men and 28% of obese women treated with statins reached an LDL-C target < 2.5 mmol/l. A small percentage of obese individuals treated with BP-lowering drugs also were using statins (33% in men, 16% in women).

Conclusions

Obese individuals have higher BP and LDL-C compared to non-obese, and especially obese men younger than 50 yrs have elevated BP levels. There is considerable undertreatment of elevated BP and elevated LDL-C in the general population.

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EP673

Relation of insulin resistance to neurocognitive function and electroencephalography in obese chıldren

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Background

This study aimed to investigate neurocognitive functions and electroencephalography (EEG) parameters in normoglycemic obese children.

Method

A total of 73 obese children (38 male and 35 female) and 42 healthy children (21 male and 21 female) were recruited. Biochemical disturbances and insulin resistance (IR) were investigated. The Wechsler Intelligence Scale for Children-Revised (WISC-R) and EEG were performed for all children. Obese participants were classified according to the presence of IR. Data were compared between these subgroups.

Results

Verbal scores on the WISC-R of the IR + Group were significantly lower than the control group and the IR– Group. There were no differences between groups with respect to other parameters of the WISC-R and EEG. Verbal and total scores of the WISC-R were negatively correlated with HOMA-IR values. In the EEG study, slowing during hyperventilation was seen significantly more frequently in obese children than non-obese children.

Conclusion

Neurocognitive functions, particularly verbal abilities, were impaired in obese children with IR. On the other hand, EEG results did not differ in terms of obesity and IR. IR may be associated with neurocognitive abnormalities in obese children.

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EP674

Abstract withdrawn.

EP675

Lipid profiles and vitamin D receptor polymorphisms in overweight/obese dialysis patients

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Background
Vitamin D receptor (VDR) is present on adipocytes, and many studies were carried out to investigate the association between single nucleotide polymorphisms (SNPs) in VDR gene with obesity. However, little is known about the role of VDR gene polymorphism with obesity in dialysis patients. Therefore, we aimed to investigate lipid profile and VDR gene TaqI, ApaI and FokI SNPs in overweight/obese dialysis patients.
Methods
Seventy one normal weight and 68 overweight/obese patients were included in study. PCR-RFLP method was used for genotyping.
Results
For all three SNPs, no significant association was found between normal and overweight/obese patients ($P>0.05$). The level of LDL, total cholesterol and triglycerides was found significantly high, and HDL level was found significantly low in overweight/obese patients compared to normal weight patients ($P<0.05$). In overweight/obese patients, patients carrying ApaI CC genotype have higher triglyceride levels compared to AA and AC genotype (CC vs AA $P=0.001$; CC vs AC $P<0.001$) and CC $=627\pm653$; AC $=193\pm85$; AA $=233\pm156$). No significant association was found between other SNPs and lipid profiles.
Conclusions
Our results suggest that ApaI polymorphism are associated with high triglyceride levels in overweight/obese dialysis patients.

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EP676

Bone mineral density and bone turnover markers after bariatric surgery

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Although bariatric surgery has beneficial effects on obesity related complications, rapid weight loss might have negative effects on skeletal health. The objective of our study was to evaluate changes in bone mineral density (BMD) and bone biochemical markers in patients, before and 1 year after bariatric surgery.
Methods
One hundred and two morbidly obese subjects (mean 43 ± 15 years, BMI 48,5 g/cm^2) performed either Roux en Y gastric bypass (n:9) or sleeve gastrectomy (n:93) were included in the study. Serum vitamin D, calcium, parathyroid hormone (PTH), C-terminal telopeptide (CTX), osteocalcin levels were measured with immunochemiluminescence method. BMD measured with Dual X ray absorbsiometry (DEXA) before and after first year of the surgery.
Results
BMI decreased significantly after surgery compared to baseline ($30,5\pm8.5$kg/m versus 48.5 ± 9.08 $P:<0.0001$). Serum CTX levels were significantly higher at 1 year ($P:<0,0001$). Changes in calcium, PTH, 25 OH vitamin D, CTX and osteocalcin at baseline and first year of the surgery. Lumbar BMD was 1,284 versus 1.260 g/cm^2 (P:0,32), femoral neck BMD was 1.034 versus 1.030 g/cm^2 (P:0,85), before and after surgery, respectively. We didn't find any correlation between BMI and BMD but there was a negative correlation between 25-OH D and PTH (r: $-0,298$ P:0,0003)

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EP677

Effects of mediterranean diet in obese patients with metabolic syndrome and depression

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Introduction
Central obesity is the source of inflammatory factors, causing endothelial dysfunction. In central nervous system, inflammatory factors mediate neurotransmitter metabolism promoting excitotoxicity and increase oxidative stress, and a major clinical symptom is depression. Mediterranean diet (MD) resulted as a good prevention method for depression.
Aim
To examine the relationship of depression with abdominal obesity and metabolic syndrome (MS) criteria, blood pressure, lipids, glycaemia and inflammation factors. Analysing effects of MD on weight correction, abdominal obesity and consequent less score points in Hamilton scale for depression.
Methods
Study included 36 adolescents and youth (16–30 years) and 22 adults over 30 years, overweight and obese patients with MS, diagnosed with depression using Hamilton scale. MS was diagnosed using ATP III classification criteria. The following parameters were observed: BMI, waist circumference (WC), blood pressure, lipids, CRP and basal glycaemia and insulin. Seven day scheduled MD was used by patients.
Results
Correlation is found between Hamilton's scale score and body weight, BMI, WC ($P<0.01$) and CRP ($P<0.05$) in adolescents and youth. Implementation of MD resulted in reduction of body weight and WC ($P<0.05$), Hamilton's scale score ($P<0.001$), insulinemia, HOMA-IR and CRP ($P>0.5$). Hamilton's scale and Hamilton's scale score correlated with insulin ($P<0.05$) and glycaemia ($P<0.05$), basal insulin correlated with CRP ($P<0.05$). After MD values of Hamilton's score, WC, insulin and CRP were lower ($P>0.5$).
Conclusions
Mediterranean diet resulted with reduced values of Hamilton's scale score, waist circumference, insulinemia and CRP in patients with MS and depression. Positive correlation of Hamilton's scale score with glycaemia and insulinemia suggest importance of insulin resistance and glucoregulation disorder on occurrence and stage of depression in obese patients with metabolic syndrome. CRP is useful marker for low grade inflammation in obese patients with MS, hence depression.
Keywords: metabolic syndrome; obesity; depression; Mediterranean diet; hyperinsulinism

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EP678

Visceral obesity in youth followed by decreased testosterone leading to erectile dysfunction and risk of early atherosclerosis

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Background
Abdominal obesity, which in fact is a metabolic syndrome (MS), is related to decreased testosterone, insulin resistance (IR), increased inflammatory factors,

non-alcoholic fat liver disease (NAFLD) and risk of early atherosclerosis. Elevated inflammatory markers (CRP) may interfere with insulin signal transduction at the neuronal level inducing hypogonadotropic hypogonadism.
Objective
To examine testosterone relationship with abdominal obesity, lipid status, blood pressure, IR and NAFLD in obese young males with pre-MS and MS.
Methods
The study included 52 obese male individuals with pre-MS or MS (age16–30) classified in two groups: I-with low testosterone <12.0 nmol/l; II-with testosterone $\geq 12,0$ nmol/l. The following parameters were observed: waist circumference (WC), blood pressure, lipids, microalbuminuria. SGOT, SGPT and γ-GT were liver function parameters. ATP III classification was applied for diagnosing MS. Patients with less than three above criteria were considered pre-MS. IR was determined by HOMA IR. OGTT was used to evaluate glycoregulation disorder. Testosterone was determined by radioimmunoassay.
Results
BMI:I-35.7$\pm$35, II-33.0$\pm$4.9 kg/m^2; WC:I-117.3$\pm$15.5, II-109.9$\pm$14.2 cm; HDL:I-0.96$\pm$0.18, II-1.04$\pm$0.2 mmol/l; triglycerides: I-2.74$\pm$1.6, II-1.8$\pm$1.0 mmol/l; insulin 0':I-113$\pm$128. II-40.1$\pm$61.2 IU/l; insulin 30':I-199.8$\pm$124.II-124.1$\pm$90 IU/l; insulin 120':I-119.8$\pm$114. II-53.9$\pm$70.8 IU/l; HOMA IR:I-26.8$\pm$31, II-9.1$\pm$14 µmol/mU/ml; SGOT:I-50.5$\pm$39.3, II-26.8$\pm$7.8;SGPT:I-81.8$\pm$48.2, II-40.2$\pm$18.0 U/l; γ-GT:I-49.8$\pm$19.3 U/l, II-39.7$\pm$21.9 U/l.CRP:I-5.2$\pm$2.5, II- 5.25$\pm$5.8 mg/l.
Correlations
Testosterone negative with body weight, BMI and WC ($P<0.05$). Decreased testosterone (<12.0 nmol/l) was found in 13.5% obese young males (8.5$\pm$2.6 nmol/l), with normal FSH, LH and estradiol. A statistically important difference between groups was found for 0, 30 and 120 minute insulin values ($P<0.05$) and for liver function parameters SGOT and SGPT ($P<0.001$).
Conclusion
Low testosterone is characterized by obesity, MS parameters, hyperinsulinism, IR and NAFLD. Negative correlation of testosterone with WC and statistical importance of insulinemia and liver function parameters differences confirm the important effect of visceral obesity and IR on the occurrence of erectile dysfunction, NAFLD and risk of early atherosclerosis in obese adolescents and youth.

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EP679

The prevalence of obesity and related factors: An urban survey study

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Objectives
Obesity is a chronic and progressive disease that limits physical activity, causes psychological problems, and finally leads to social isolation of the person. Detecting the factors affecting obesity and its prevalence in the populaton are important steps in dealing with the problem. In this study, we aimed to evaluate the obesity prevalence and the factors affecting this prevalence in randomly selected volunteers from residents of the city of Bursa.
Methods
A questionnaire consisting of 40 questions evaluating the sociodemographic aspects, healthy nutrition and exercise habbits and comorbidities of the subjects was performed face to face to 528 volunteers (414 females, 114 males) participating in our study. Height, weight, waist, hip, neck and wrist circumferences and random blood glucose levels were measured. BMI and waist to hip ratio were calculated for each participant.
Results
The mean age of the whole study population, female and male participants were 39.6$\pm$12.8, 40.2$\pm$12.7 and 37.1$\pm$12.9 years, respectively. According to BMI values 23.5% of the whole study population, 25.8% of females and 14.9% of males were obese. For the female subjects, the obesity prevalence was found to be increasing with age, being married, being housewife and having lunch at home and decreasing with higher education level and income. When we investigated the male subjects, the only factor related to and found to be increasing the obesity prevalence was having lunch at home.
Conclusions
Obesity is a worldwide problem. Its prevelance is increasing in our city and country. Education level of the subjects seems to be the most important factor in controlling body weight. It is possible to prevent most of the morbidities and mortality related to obesity by preventing weight gain. Every effort should be made to increase the level of education about healthy nutrition habbits and importance of regular physical activity.

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EP680

Effect of Vitamin D supplementation on body composition in overweight men: A randomized controlled trial

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Introduction
The prevalence of vitamin D deficiency is higher in obese individuals but it is unclear whether vitamin D deficiency impacts body composition or if body composition impacts the vitamin D status. The research regarding vitamin D supplementation and weight loss in obese individuals is ambiguous. One hypothesis for the presumed fat reductive effect of vitamin D is that vitamin D inhibits adipocyte differentiation.
Aim
To investigate if treatment with vitamin D can reduce fat mass in obese men with vitamin D deficiency.
Methods
This study was designed as a randomized prospective, placebo controlled, double blind intervention. Thirty eight overweight men (BMI $>$ 25 kg/m^2) with vitamin D deficiency (25(OH)D $<$ 55 nmol/l) were randomized to receive 2000 IU Cholecalciferol drops or the equivalent amount of placebo drops for 6 months. At baseline and after 6 months body composition and BMI was measured and blood samples were obtained; body composition was measured using bioelectrical impedance analysis (BIA).
Results
The mean change in body fat percentage for the vitamin D group and the placebo group was a 0.6%-units (baseline compared to follow up; $P=0.222$) and a 0.1%-units ($P=0.857$) increase, respectively. The mean change in BMI in the vitamin D group was a 0.2 kg/m^2 decrease ($P=0.272$) and for the placebo group a mean decrease in BMI of 0.5 kg/m^2 ($P=0.049$). There was no statistically significant difference between the placebo group and the intervention group regarding change in fat percentage or BMI ($P=0.544$, $P=0.256$, respectively). Moreover no statistically significant difference was observed between the groups regarding change in any of the metabolic laboratory values.
Conclusion
We conclude that treatment with 2000 IU vitamin D daily for 6 months does not impact BMI or fat percentage in overweight men with vitamin D deficiency.

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EP681

Intensified telematic treatment for obesity using the web platform PREDIRCAM2, descriptive basal characteristics and preliminary results

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Background
PREDIRCAM2 is a web platform for obesity treatment and follow-up. It contains modules for: dietary prescription and registry with nutritional analysis based on individualized and mediterranean dietary goals, physical activity prescription and tracking with individualized targets, and anthropometric tracking. An ongoing multicenter randomized clinical trial evaluates the intervention's effectiveness in obesity treatment and cardio-metabolic-risk prevention.
Methods
Inclusion criteria: 18–65 years-old, BMI 30–39.9 kg/m^2, no medication for type-2 Diabetes Mellitus (DM), dyslipidemia (DLP) or hypertension (HT). Randomization to intensified technological intervention (TI) supported by PREDIRCAM2 platform, or traditional non-technological face-to-face intensified treatment intervention (NTI). Both groups receive one year follow-up through 12 appointments with health-care professionals, 4 of which are exclusively telematic in the TI group.
Basal characteristics
183 participants have been included, BMI 34.74 $\pm$ 2.74, age 44.27 $\pm$ 10.62, 84% female (31% postmenopausal, 6.5% history of gestational DM), 54% high education level, 54% married. Comorbidities: 2.2% type-2 DM, 5.5% HT, 11.5% DLP, 6.5% Depression, 2.7% diagnosed eating disorders. 56% received medication, most frequently antidepressants (24.5%) followed by vitamin D supplements (11.8%). 68% reported anxiety towards food, overeating in the form of: pecking 84.7%, binge-eating 35.5%, binge-and-vomiting 3.2%.
Preliminary results
119 participants have completed 3-month follow-up: 60 TI, 59 NTI. Both groups have lost weight significantly ($P < 0.0001$). 26.7% TI, and 25.4% NTI have achieved at least a 5% weight-loss ($P = 0.88$). 81 participants have completed 6-month follow-up: 41 TI, 40 NTI. Both groups have lost weight significantly ($P < 0.0001$). 46.3% TI, and 32.5% NTI have achieved at least a 5% weight-loss ($P = 0.20$). Both groups have achieved a reduction in HbA1c levels ($P < 0.0001$), TI $-0.81 \pm 1.9\%$ and NTI $-1.36 \pm 2.2\%$ ($P = 0.24$).
Conclusion
Our study population is mostly composed of highly educated females who report a high frequency of anxiety towards food and eating. PREDIRCAM2 shows to be a promising tool for obesity treatment and cardio-metabolic-risk prevention.

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EP682

Suboptimal prediction of advanced fibrotic liver disease by standard non-invasive scoring systems in obese patients undergoing bariatric surgery

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Introduction
Non-Alcoholic Fatty Liver Disease (NAFLD), is present in over 90% of obese patients undergoing bariatric surgery. It is a spectrum of pathology ranging from steatosis through to inflammation (Non-Alcoholic Steatohepatitis, NASH) and fibrosis. Bariatric surgery is currently the most effective treatment for NAFLD, but post-operative hepatic decompensation can occur and therefore pre-operative stratification of liver disease severity is beneficial. Several non-invasive scoring systems have been developed to stage NAFLD, but validation in the bariatric surgical population has been limited.
Methods
135 consecutive patients who underwent bariatric surgery in a tertiary referral unit from November 2014 to December 2016 were identified and the following NAFLD risk scores calculated: AST/ALT, APRI, BARD, Fib4 and NAFLD Fibrosis Score (NFS). All patients had an intraoperative liver biopsy performed for accurate histological staging of disease. Logistic regression analysis was used to determine their efficacy in detecting NASH (NAFLD Activity Score ≥ 5), advanced fibrosis (Brunt F3/4) and cirrhosis (F4) identified on liver biopsy using R software.
Results
BARD and AST/ALT were independent predictors of NASH on multivariate logistic regression analysis. However, only AST/ALT ratio was significant in the final model (AST/ALT $P = 0.04$, BARD $P = 0.08$). AUROC for the regression model which included AST/ALT and BARD was 0.75. BARD and APRI were significant factors ($P = 0.03$, $P = 0.04$) on stepwise regression for F3/4 cirrhosis and they were included in the final model, which had AUROC 0.73. Only Fib4 scoring was independently associated with cirrhosis (F4) on multivariate regression analysis ($P = 0.04$) and AUROC for the final model incorporating this factor was 0.70. In contrast to observations in non-bariatric patients, the NFS was of limited value and not an independent factor in predicting NASH, advanced fibrosis or cirrhosis.
Conclusion
Currently used non-invasive serum-based scoring systems have only a modest predictive value for staging the severity of NAFLD in patients undergoing bariatric surgery. Intra-operative liver biopsy to detect and subsequently manage advanced liver disease therefore remains of value. There is a need to develop and validate non-invasive biomarkers of disease that offer better predictive value in the bariatric population.

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EP683

Discussion with cases: Could we achieve the goal with non-surgical treatments in morbid obese patients?

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Objective
Diet, lifestyle changes, medical agents and surgical approaches are treatment options in obese patients. We reported two morbid obese patients who lost 25 and 21% of their previous weight respectively with only lifestyle changes and orlistat therapy.
Case 1
Forty nine year-old woman had type 2 diabetes mellitus for 20 years. She took premix insulin twice a day. Her height was 157 cm, her weight was 120 kg, body mass index was 48.6 kg/m^2. One month later, she lost 3 kg with diet and exercise and then orlistat was started. After seventh month of orlistat therapy, her weight reduced to 85 kg and body mass index was 34.4 kg/m^2.
Case 2
Fifty-four year-old man has type 2 diabetes mellitus and took metformin for 10 years. His height was 168 cm, his weight was 118 kg, BMI was 41.8 kg/m^2. One month later, he lost 2.5 kg with diet and exercise and then orlistat was started. After seventh month of orlistat therapy, his weight reduced to 93 kg and body mass index was 32.9 kg/m^2. Both patients lost their weight 35 and 25 kg respectively with lifestyle changes and orlistat therapy. First year of treatment, patients maintain their weight without any gain.
Conclusion
The number of patients undergoing obesity surgery has increased at the present time. Patients prefer surgery instead of lifestyle changes. Our results of patients with morbid obese emphasize importance of lifestyle changes and orlistat therapy.

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EP684

Body compositions in obesity may corralete the minimal change of tyhroid functions within normal range

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Introduction and aim
Overt thyroid dysfunction is well recognized to affect weight, but the influence of minor perturbations of thyroid function remains unclear. There is ongoing debate regarding the influence of minor changes in thyroid hormones status within the normal range and BMI. The aim of this study was to investigate the association between thyroid function within normal ranges and obesity via BMI and body compositions analyzed by bioelectrical impedance.
Materials and methods
One hundred twenty persons with normal thyroid functions were included in our study. According to the BMI, the patients were divided into 5 groups. Group1; normal weight ($n=40$), group 2; overweight ($n=20$), group3; classI obesity ($n=20$), group4; class II obesity ($n=20$), group 5 morbid obesity ($n=20$). Measurements of serum TSH, free T3, free T4 and lipid profile were recorded. Body compositions and BMI were evaluated by bioelectrical impedance (TANITA).
Results
In group 1, TSH was negatively correlated with BMI ($r=-0.430$, $P=0.006$). On the contrary, TSH was positively correlated with percentage of body fat (BF%) ($r=0.391$, $P=0.014$). Free T3 was positively correlated with BF% ($r=0.333$, $P=0.038$). In group 2, free T3 was positively correlated with BF% and fat mass ($r=0.657$, $P=0.010$, $r=0.751$, $P<0.001$ respectively). In group 3, free T3 was positively correlated with BF%, fat mass, HOMA-IR and LDL ($r=0.521$, $P=0.018$; $r=0.543$, $P=0.013$; $r=0.512$, $P=0.021$; $r=0.469$, $P=0.037$, respectively). Similarly, TSH was positively correlated with BMI ($r=0.553$, $P=0.011$). In group 5, free T4 was negatively correlated with LDL ($r=-0.485$, $P=0.030$).
Conclusion
We demonstrated that differences in thyroid function within the normal range may correlate with differences in BMI and body compositions in subjects within different BMI categories. Further large scale data from the population is required to confirm our findings.

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Association of Transforming growth factor β and Fibroblast growth factor 21 with cardiovascular diseases in obese patients

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Introduction
Obesity and type 2 diabetes mellitus (T2DM) are associated with cardiovascular diseases (CVD). Fibrotic changes in obesity include several molecular processes, including activation of Transforming growth factor β (TGF-β). Recent data indicate the involvement of Fibroblast growth factor 21 (FGF-21) as an important metabolic regulator, and even biomarker of metabolic changes in obesity and T2DM.
Aim
To determine TGF-β and FGF-21 level in patients with obesity and T2DM.
Methods
TGF-β and FGF-21 were identified in peripheral blood of 66 patients, aged 48–65 years with obesity. They were divided into 3 groups. 1st – 21 patients with coronary heart disease (CHD) (confirmed by coronary angiography (CAG)) and T2DM, the 2nd – 22 patients with T2DM, in the 3rd – 23 patients without T2DM and CHD. CHD was excluded in the 2nd and 3rd groups by Tredmil test. Control (4th) group included 14 healthy person matched by age and sex.
Results
TGF-β was significantly different in the studied groups ($P=0.046$). We found that TGF-β was significantly lower in patients with CHD (group 1) compared with the group of "metabolically healthy" obesity ($P=0.02$). TGF-β negatively correlated with. atherogenic fractions of cholesterol – LDL ($r=-0.426$, $P=0.043$) and with the degree of internal carotid artery 0stenosis ($r=-0.426$, $P=0.039$) in patients with T2DM. In contrast, patients with verified CHD demonstrated a negative correlation with the duration of obesity ($r=-0.395$, $P<0.033$), and the processes of heart muscle remodeling (thickness of the left ventricular posterior wall ($r=-0.386$, $P=0.029$) and interventricular septum ($r=-0.335$, $P=0.031$). FGF-21 and TGF-β in the 1st group showed a negative correlation with the number of significantly affected vessels according to CAG ($r=-0.73$, $P=0.041$ and $r=-0.52$, $P=0.036$, respectively). All patients with obesity had significantly increased level of FGF-21 compared with the control group ($P=0.03$) and FGF-21 positively correlated with BMI ($r=0.47$, $P=0.021$)
Conclusions
1. FGF-21 and TGF-β reduction were associated with CHD in patients with obesity.
2. Increased TGF-β may play a protective role in atherosclerosis in patients with diabetes and obesity.

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EP686

The dynamics of anthropometric data in fertile age women by various types of the treatment

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The aim
To study efficiency of pathogenetic therapy and dynamics of anthropometric indexes for women with obesity of fertile age at different endocrinopathies to and through 6 months after treatment.
Material and research methods
On the etiologic factor of patient with obesity were up-diffused on three groups: 1 g. are patients with obesity at the polycystic syndrome of ovaries (PCOS) – 30 patients, 2 g. are patients with hypothalamic obesity – 21 cases and 3 g – patient with endocrine obesity (at a primary hypothyroidism) – 20 patients. Age of patients in a 1th group hesitated 39 from 20 to and 28.3 ± 0.64 averaged year. To all patients have been conducted spectrum of investigations, which include clinical, biochemistry, hormonal analysis of the blood. Besides of this, electrocardiography, ultrasound investigation of uteri and ovarium during 11–14 days of periods, and MRY of pituitary. For the 1 g. we administered combination of Syofor 1000 mgs + spironolacton 100 mgs + yodmarinum 100 mgs +L-thyroxine 50 mgs in the morning + antiandrogens + antidepressants. For the 2 group: combination of Syofor 1000 mgs + spironolacton 100 mgs + Yodmarin 100 mgs +L-thyroxine 50 mgs i+ methaboliks + Reduxine (Sibutramin) 15 mgs + antidepressants. For the 3 groups: combination of Yodmarin 100 mgs +L-thyroxine 50 mgs.
The results
In 1 and 2 groups of patients marked reliable decline of BMI 1 and 2 degrees after 6 months of treatment, while for patients 3 groups of reliable changes of BMI through 6 months of treatment were not attained at none of degree of BMI Thus, for patients 1 and 2 groups with BMI 3 degrees through 6 months a tendency was attained to the decline of BMI. In addition, renewal of fecundity and pregnancy was attained for the patients of a 1 group – in 19.5% cases (at 10 patients).
Conclusions
Optimization of treatment of obesity for the women of reproductive age is based on drafting of the individual programs, the choice of that is determined by the values of anthropometric indexes, state of hormonal and metabolic status, features of food behavior and personality-emotional sphere, state of menstrual and reproductive function.

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EP687

Effects of IL-1β on the hypothalamic-pituitary-gonadal axis in men with obesity and metabolic syndrome – A randomized, double-blind, placebo-controlled trial

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Background
Low testosterone levels in men appear to be an independent cardiovascular risk factor closely associated with the metabolic syndrome. Reciprocally, the metabolic syndrome leads to a decrease in testosterone levels, suggesting a bidirectional relationship. It has been hypothesized that increased inflammation is causative for the development of obesity-associated hypogonadism. However,

clinical evidence supporting this hypothesis is lacking. The aim of the present study was to determine whether anti-inflammatory treatment may restore endogenous testosterone production in obesity-associated hypogonadism.
Methods
This is a randomized, placebo-controlled, double-blind, trial including 70 hypogonadal men with the metabolic syndrome. Patients were randomly assigned to either receive 100 mg of a recombinant human interleukin-1–receptor antagonist subcutaneously twice daily for 4 weeks or to receive placebo. The primary endpoint was the change in total testosterone levels between baseline and 4 weeks. Predefined secondary end points included a change by week 4 in insulin resistance, body composition, muscle strength, hypogonadal symptoms and hemodynamic parameters.
Results
From April 2016 to January 2017, 66 patients have been enrolled at two tertiary care centers in Switzerland. Median age was 51 years (IQR 41–65) and patients had a median BMI of 37 kg/m^2 (34–39 kg/m^2). Patients had hypogonadotropic hypogonadism with median baseline testosterone levels of 8.8 nmol/l (231 ng/dl) (7.6–10.1), median LH levels of 3.7 IU/l (3–5.2 IU/l), and median C-reactive protein levels of 2.9 mg/l (1.4–4.0 mg/l) mirroring a low-grade inflammatory state. Final results will be available in March 2017 and will be presented first at the ECE 2017.
Significance
This study will show whether there exists causality between obesity-associated inflammation and hypogonadism.

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EP688

Demographic and baseline characteristics of an obese population admitted for bariatric surgery in a secondary care centre

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Obesity has become one of the greatest public health concerns and is known to be a major risk factor for cardiac, respiratory and metabolic diseases. Bariatric surgery is the most effective treatment for morbid obesity. According with guidelines, surgery is indicated for treatment of patients with BMI greater than 40 kg/m^2 or above 35 kg/m^2, with at least one obesity-related comorbid condition, such as as type 2 diabetes, hypertension, dyslipidemia, sleep apnea, osteoarthritis. Nowadays, sleeve gastrectomy is one of the most common techniques, able to cure metabolic disorders, allowing a shorter convalescence and fewer complications. We herein describe the baseline characteristics of 38 adults (35 women, mean age 41 $\pm$ 13 years), suitable for surgery. Patients were referred by Surgeons or other Specialists such as Cardiologists, Pulmonologists, Nephrologists or Orthopedicians. Three patients were admitted for the conversion of laparoscopic adjustable gastric banding, to achieve additional weight loss. In keeping with guidelines, BMI was 43.3 $\pm$ 6 Kg/m^2 (71% $\geq$40 kg/m^2, 23.5% 35–39.9 kg/m^2, 5.3% $<$35 kg/m^2), with a visceral pattern of obesity (waist circumference 123 $\pm$ 11 cm). Half of the patients suffered from metabolic syndrome, defined according to IDF/AHA/NHLB harmonized definition. Actually, 29% had diabetes, 37% hypertension and 53% dyslipidemia. Among the others, arthropathy was the most frequent comorbidity (21%), followed by respiratory diseases (chronic obstructive or restrictive pulmonary disease, 19%), chronic venous insufficiency (11%) or heart diseases (5.3%). We observed gastric diseases in almost half of the population (44%), and, as expected, 24% had hiatal hernia. Beyond these, 71% of patients emerged to have thyroid disease, with a high prevalence of non-toxic goiter and Hashimoto's thyroiditis. During the screening, papillary thyroid cancer was disclosed in two patients (5.3%). According to the literature, these data underscore the high prevalence of obesity-related morbilities and the need for an effective and urgent treatment.

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Clinical and metabolic markers of X-syndrome

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We identified factors that significantly influenced the development of the X-syndrome. A significant influence on the development of X-syndrome have increase the level of total cholesterol (b = 0.65; P = 0.036; Exp (b) = 1.92 (1.04 ÷ 3.54)). Increases the risk of X-syndrome increase the level of apo-B-protein (b = 4.79; P = 0.014; Exp (b) = 12.69 (2.68 ÷ 54.41)). The increase in linear dimension of preperitonialy fat increased the risk of developing X-syndrome (b = 1.14, P = 0.036; Exp (b) = 3.14 (1.08 ÷ 9.16)). By reducing the level of free thyroxine was a consistent trend of formation of X-syndrome (b = $-$0.25; P = 0.09; Exp (b) = 1.08 (0.57 ÷ 1.10)). When using the ROC analysis were obtained by the cut-off point, allowing to calculate the relative risk. The critical cut-off point for preperitonealny fat figure was more linear size 2.1 sm (P < 0.02); total cholesterol – more than 6.36 mmol/l (P < 0.02), apo-B-protein – more than 1.15 g/l (P < 0.001), free thyroxine – less than 13.40 pmol/l (P < 0.001). If the linear dimension preperitonealny fat more 2.1sm RR X-syndrome was 3.00 [0.87 ÷ 10.39]. When total cholesterol level of more than 6.36 mmol/l RR X-syndrome was 16.50 [2.05 ÷ 33.05]. When damage apo-B protein over 1.15 g/l RR X-syndrome was 22.00 [2.49 ÷ 94.44]. By reducing the thyroxine levels below 13.40 mmol/l RR X-syndrome was 13.00 [1.53 ÷ 110.51].

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EP690

Impact of weight changes on the incidence of diabetes mellitus: a Korean nationwide cohort study

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Objective
Obesity is a well-known risk factor for type 2 diabetes, but few data exist on the association between weight changes and future diabetes risk in non-obese subjects. This study aimed to investigate the effect of weight changes on the incidence of type 2 diabetes in Korea, using prospective nationwide data.
Research design and methods
A total of 51 405 non-diabetic subjects were included who had undergone health examinations in 2002 and completed follow-up in 2006.
Results
Individuals who developed type 2 diabetes were more likely to be older and male, to have high BMI, blood pressure, fasting plasma glucose, and total cholesterol, to be a current smoker, to consume larger amounts of alcohol, to be hypertensive and hyperlipidemic, and to have a family history of diabetes, compared to those without type 2 diabetes. Compared with the consistently non-obese group, there was a higher hazard ratio for incident diabetes (95% confidence interval) in subjects becoming obese (1.50 (1.27–1.78)), losing weight (1.89 (1.61–2.22)), and remaining obese (2.60 (2.56–3.05)), over 4 years, after adjustment for confounding factors. When stratified by BMI categories, risks for incident diabetes were significantly decreased with lower BMI and the trends were more evident in the non-obese group. However, there was no significant association of high BMI with incident diabetes.
Conclusions
Weight loss was significantly associated with decreased diabetes risk both in non-obese and obese Koreans, but particularly in the non-obese. Further long-term studies are needed to establish weight reduction as a preventive strategy for type 2 diabetes.

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EP691

Metabolic profile reversal after bariatric surgery

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Bariatric surgery is the most-effective treatment for morbid obesity, superior to medical treatment. Metabolic syndrome (MS) is a condition characterized by multiple major risk factors for coronary heart disease, diabetes, fatty liver, and several cancers; the main, diagnostic, components of MS are low HDL-cholesterol (<40 mg/dl in man, <50 mg/dl in woman), raised triglycerides (>150 mg/dl), blood pressure $>130/85$ mmHg, fasting plasma glucose >100 mg/dl and waist circumference >94 cm in man and >80 cm in woman. Indeed, in addition to weight loss, changes in metabolic profile after bariatric surgery could improve long-term outcomes. Complete demographic, clinical and laboratory data from 38 people (35 women, mean age 41 ± 13 years) undergoing bariatric surgery and followed by a dedicated clinical team were analyzed. Descriptive statistics detailed clinical characteristics of the cohort of patients. Paired *T*-test compared baseline clinical parameters, lipid and glycemic profile index at three (T3) and six (T6) months after surgery. General Linear Model for Repeated Measure compared the five conditions defining MS over time. Weight, BMI, waist circumference and systolic blood pressure decreased significantly at T3 and T6, compared to baseline [all $P<0.05$]. Triglycerides and LDL cholesterol decreased at T3 and T6, HDL notably raised at T6 [all $P<0.05$]. Fasting plasma glucose and HbA1c decreased at T3 and T6; HOMA index improved over time [all $P<0.05$]. Prevalence of MS according to IDF/AHA/NHLB harmonized definition in our population was 50% at baseline, 10 times higher for age than average prevalence in literature; at 6 months such prevalence decreased to 16%. In conclusion, in our population of patients undergoing bariatric surgery and a dedicated follow-up program, we observed a trend towards a noticeable improvement of the metabolic profile in the mid-term.

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Hydroxysteroid (17beta) dehydrogenase 13 knockout mice present with inflammation associated liver steatosis

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Hydroxysteroid (17beta) dehydrogenases (HSD17Bs) form a group of enzymes that are characterized by their sequence similarity at the active site, and their ability to catalyze the conversion between the weak 17keto- and the highly active 17beta-hydroxysteroids. To study the physiological role of HSD17B13, a lipid droplet associated protein, we characterized the phenotype of knockout (KO) mice deficient in HSD17B13 (HSD17B13KO). The data revealed normal serum sex steroid concentrations and proper reproductive performance in both male and female HSD17B13KO mice, indicating a minor role for HSD17B13 in sex steroid metabolism and reproduction. In line with the strong expression in the liver, histological analysis showed the presence of liver steatosis in HSD17B13KO mice that was associated with inflammation. The phenotype was more pronounced in males than females. The severity of the phenotype progressed with aging, and accumulation of triglycerides was observed in the livers of the male mice from 3 months onwards. Furthermore, metabolic profiling showed a tendency for increased hepatic phospholipid content in the 9 month-old HSD17B13KO males with two acylcarnitines (C16:0 and C18:1) showing the most profound increase ($\sim$2-fold). Additionally, presence of microgranulomas (Kupffer cell aggregations) with increased portal inflammation and ductular proliferation was observed in liver specimens from HSD17B13KO mice. This was associated with increased expression of immune response genes in the HSD17B13KO male liver. In conclusion, the lack of HSD17B13 impairs hepatic lipid metabolism in mice, resulting in liver steatosis and inflammation. The data, thus, indicate that HSD17B13 is involved in fatty acid metabolism in the liver, while the enzyme does not play a major role in the regulation of reproductive functions.

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Visceral vs subcutaneous white adipose depots response to insulin treatments in rats

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White adipose tissue (WAT) has an important role in the regulation of metabolic homeostasis. It is well known that two distinct WAT depots in mammals, subcutaneous WAT (sWAT) and visceral WAT (vWAT) display different metabolic roles and it could be presumed that exert different response to various hormones. Numerous studies revealed leading role of insulin in both fat accumulation (lipogenesis) and adipocyte differentiation (adipogenesis) although it is not clear is there a difference in response among these two depots. The aim of this study was to reveal effects of insulin treatments on sWAT and vWAT morphology. Male Wistar rats were treated acutely (1 day) or chronically (3 days) with low (0.4 IU/kg bm) or high (4 IU/kg bm) dose of insulin. Saline-treated animals served as controls. The portions of retroperitoneal, epididymal and subcutaneous WAT (rWAT, eWAT, sWAT, respectively) were removed and prepared for microscopic and Western blot analyses. Tissue components (adipocytes, blood vessels and stroma) volume density and cell profile density per unit area were determined. To establish adipogenic origin of multi-locular/paucilocular cells PCNA immunoexpression was examined, while protein expression and cell presence of phosphorylated form (phospho-IR) of insulin receptor (IR) was used to analyze insulin signaling. Our results demonstrate slightly higher number of adipocytes and adipogenic cells and increased capillarization in vWAT depots. A stronger response of vWAT to insulin treatment in comparison to sWAT is due to higher phospho-IR expression in endothelial and multilocular/paucilocular cells of analyzed vWAT depots. Namely, in hyperinsulinaemia canonical insulin-signaling pathway favors adipogenesis and capillary remodeling in vWAT to a greater extent than in sWAT depot. Our results suggest that insulin-induced differences in remodeling of sWAT and vWAT depots may contribute to visceral obesity and development and progression of insulin resistance and diabetes type 2 among other visceral obesity-associated metabolic diseases.

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Association between obesity and glomerular hyperfiltration: impact on metabolic risk factors

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Abstract
Glomerular hyperfiltration has been suggested as a possible mechanism linking obesity and chronic kidney disease, independently of classical risk factors such as diabetes. In terms of determining the creatinine clearance has numerous drawbacks, in clinical use are predictors of glomerular filtration rate (GFR) which show varying degrees of accuracy in obese patients. The aim of our study was to determine whether it is in our group of obese patients without type 2 diabetes, glomerular hyperfiltration associated with metabolic disorders. This cross-sectional study included 30 obese patients at the beginning of treatment in Center for Obesity. Excluded were patients with type 2 diabetes, moderate/severe hypertension and cardiovascular comorbidity. We analyzed metabolic parameters (fasting glucose and insulin, HOMA-IR, HbA1c, liver enzymes and renal function (GFR, proteinuria and albuminuria). According to the degree of GFR determined by: 1. the creatinine clearance (CCR); 2. The use of predictors GFR - MDRD and Cockcroft-Gault (CGO) equation, patients were divided into two groups: with hyperfiltration and with normal levels of glomerular filtration rate. According to the level of GFR, 44.4% (CCR), 25.9% (MDRD), 66.7% (CCE) had hyperfiltration, while 55.6% (CCR), 74.1% (MDRD) 33.3% (cGO) patients had normal filtration. Patients with hyperfiltration had significantly higher fasting glycemia (CCR: 4.9 ± 0.8 vs 4.7 ± 0.5, $P = 0.038$; MDRD: 5.1 ± 0.3 ± 0.9 vs 4.9, $P = 0.039$; cGO: 5.2 ± 0.9 vs 4.7 ± 0.5, $P = 0.049$) and HbA1c (CCR: 6.1 ± 0.4 vs 5.6 ± 0.6, $P = 0.015$; MDRD: 5.8 ± 0.9 vs 5.3 ± 0.3, $P = 0.022$; cGO: 6.1 ± 0.4 vs 5.3 ± 0.3, $P = 0.038$) compared to patients with normal filtration. The value of gamma-GT was significantly higher in the group of patients with hyperfiltration compared another group [CCR: 30 (18–80) vs 24 (15–58), $P = 0.080$; MDRD: 29.5 (19–80) vs 24.5 (15–58), $P = 0.006$; CGO: 41 (15–80) vs 18 (15–27), $P = 0.003$]. In our group of patients has been shown that obese patients with glomerular hyperfiltration had significantly higher values of the parameters of glycemic control and gamma-GT compared to those with normal levels of filtration, regardless of age and BMI, which could suggest important interrelationship among the initial development of chronic kidney disease with rediabetes and nonalcoholic fatty liver disease in obesity.

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EP695

Characteristics of cellular immunity in men with obesity and hypogonadism

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Abstract
There are few studies of the cellular immunity in men with obesity and hypogonadism. The aim was to study the parameters of cellular components of the immune system in patients with obesity and hypogonadism.
Materials and methods
The study included 120 men aged 40–65 years with obesity (mean BMI – 35 ± 5.6 kg/m^2). Patients were divided into two groups depending on the level of total testosterone (T). The first group included 56 patients with T level > 12.1 ng/ml (mean T – 16.3 ± 3.8 ng/ml), the second group – 64 patients with T level ≤ 12.1 ng/ml (mean T – 8.3 ± 1.9 ng/ml). The control group consisted of 25 healthy men with BMI up to 25 kg/m^2. Levels of CD3+,CD4+,CD8+, CD16+,CD25+ lymphocytes were analysed. Statistical data were analysed using Mann–Whitney *U*-test.
Results
Level of CD4+T helper cells was significantly lower in the 1st group as compared to the control group (41[38; 45]% vs 46[44; 47]%, $P < 0.005$). Level of cytotoxic lymphocytes CD16+ was higher in the 1st group as compared to the control (12.0[9.0; 15.0] vs 9.0[9.0; 10.0]%, ($P < 0.005$). Significant changes in other parameters were not found. Changes in T-cell immune system, namely in reduction of CD4+ lymphocytes (32[28; 39] vs 41[38; 45]%, ($P < 0.001$) and increasing of CD8+ lymphocytes (28[26;30] vs 24[20; 29]%, ($P < 0,05$), were detected in patients with obesity and hypogonadism as compared with the 1st group. There were a significant activation of CD16+ lymphocytes (19.0[16.0; 23.0] vs 12.0[9.0; 15.0]%) and reduction of the CD25+ cells number (1.4[1.0; 1.7] vs 1.9[1.8; 2.11]%), which reflects the early T-lymphocyte activation, in patients of the 2nd group ($P < 0.0001$).
Conclusion
The excessive accumulation of adipose tissue leads to dysfunction of the helper-cell immunity. Hypogonadism with obesity aggravates the imbalance of cell immunity, which could contribute to the formation of additional metabolic and immunological disturbances.

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EP696

GLP-1 therapy and the immune system – can we predict responders from non-responders?

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Abstract
Obesity has reached epidemic proportions globally. At least 2.8 million people die each year as a result of being overweight or obese, the biggest burden being obesity-related diseases. Glucagon like peptide 1 (GLP-1) targeted therapies show the greatest potential for intervention and are approved as weight loss agents. However not all patients respond to GLP-1 therapy. Understanding the mechanisms of bodyweight regulation and their role in GLP-1 responders vs. non-responders is essential to better serve our patients. We have previously shown that invariant natural killer T (iNKT) cells, which resides in adipose tissue, and acts as adipose tissue regulators are required for the full weight loss effect of GLP-1, a licensed weight loss therapy. In the absence of iNKT cells, GLP-1 therapy is 30% less effective at inducing weight loss, due to a loss of FGF-21 and thermogenic reprogramming. In the current project we have extended our findings from murine models into humans investigating the adipose tissue metabolic pathways induced by GLP-1 therapy in patients who display significant weight loss and a subset who fail to lose weight. We have also investigated if two immune cell derived proteins associated with obesity and insulin resistance (soluble CD163 and Galectin-3) could be used to predict responses to intervention (GLP-1 therapy or RYGB). We show that sCD163 but not Gal-3 is elevated in obesity from childhood through to adulthood, and within 1 week of RYGB and 8 weeks of GLP-1 therapy sCD163 levels are significantly reduced. Overall this project sheds light on novel mechanisms of bodyweight regulation and highlights the possible use of sCD163 in mapping the progression of obesity and predicting responders from non-responders to intervention.

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EP697

An assessment of the relationship between abdominal obesity and the severity of upper extremity lymphedema

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Abstract
Obesity is one of the well-known initiating and aggravating factor of lymphedema. BMI is typically used to define obesity, but in Asian populations, health risks are elevated at lower BMI levels and abdominal fat may be a better obesity metric. Thus, we assessed the potential association between abdominal obesity and lymphedema severity in postoperative breast cancer patients. Thirty-three women with breast cancer-related lymphedema participated in this study. Arm circumference was measured at four locations per arm to identify the maximal circumference difference (MCD) between the affected and unaffected sides. All patients underwent lymphoscintigraphy and we calculated the quantitative asymmetry index (QAI) of both arms. A computed tomography (CT) was also performed to assess abdominal obesity after lymphedema. Abdominal obesity was classified as a visceral fat cross-sectional area larger than

70 cm^2. Fourteen women (42%) were obese (BMI $\geq$ 25 kg/m^2) and 18 women (54%) had increased abdominal fat. BMI obesity and abdominal obesity were significantly correlated, but five patients were classified with abdominal obesity despite a BMI below 25 kg/m^2. There were no significant differences in age, time after surgery, cancer stage, history of axillary lymph node dissection, chemotherapy, or radiotherapy between patients with and without obesity. The mean arm circumference difference was 2.8 $\pm$ 2.4 cm. Decreased axillary QAI was significantly correlated with obesity, and increased arm edema (MCD $\geq$ 2 cm) was significantly correlated with abdominal obesity. Abdominal obesity was significantly correlated with increased MCD and should be considered along with obesity as an aggravating factor for lymphedema severity.

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EP698

Associations between the dysregulation of splicing machinery components and the development of hepatic steatosis in obese women

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Hepatic steatosis is a common obesity-associated pathology characterized by the accumulation of fat within the liver, which can progress to liver fibrosis, cirrhosis and ultimately lead to hepatocellular carcinoma. Remarkably, obesity and cancer course with a profound dysregulation of the genetic expression patterns and, particularly, with the aberrant expression of splicing variants that could contribute to the aggressiveness and comorbidities of these pathologies. Since the appearance of alternative splicing variants could be related to a dysregulation of the cellular machinery responsible for this process ((spliceosome core elements and splicing factors (SFs)), the objective of the present study was to determine the association between the expression pattern of the components of this machinery and hepatic steatosis of obese patients. To this end, we collected clinical and demographic data and liver biopsy samples from obese women (IMC > 30) with (n = 32) and without (n = 9) hepatic steatosis. RNA from liver samples was extracted and retrotranscribed to determine the expression levels of selected components of the major (n = 13) and minor spliceosome (n = 4), and associated SFs (n = 28) using a qPCR-based array. Results revealed that the liver of steatotic patients exhibit a profound dysregulation of certain spliceosome components and SFs compared to non-steatotic patients (e.g. RNU6, SF3b1, etc.). Although these alterations were not associated with the hepatic steatosis level, the expression pattern of the components of this cellular machinery could define discrete groups of steatotic patients that presented similar alterations in certain spliceosome components and SFs. Interestingly, these groups of patients were also characterized by particular hepatic and clinical-metabolic alterations (e.g. ALT, hyperglicemia, hyperinsulinemia, etc.). Therefore, although further confirmatory studies are needed, these results could suggest that the development of hepatic steatosis and its associated comorbidities could be linked to the dysregulation of certain components of the splicing machinery, which may provide novel diagnostic/therapeutic tools for this pathology.

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EP699

Irisin and cardiovascular risk

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Aims
Irisin is a recently discovered myokine that has been implicated in the pathogenesis of type 2 diabetes (T2D) and metabolic syndrome (MS). Its involvement with cardiovascular disease (CVD), however, has not yet been elucidated. The aim of the current study was to shed light on the potential association with irisin and cardiovascular risk.
Methods
Eighty patients with obesity (BMI $\geq$ 30 kg/m^2) and mean age 50,4 $\pm$ 10,6 years were included in the study which was realized in a third level university endocrine department. Biochemical measurements consisted of fasting plasma glucose, serum immunoreactive insulin, serum uric acid, lipid profiles, liver enzymes. Measurements of weight, height, waist circumference and arterial blood pressure were performed. Cardiovascular risk was estimated by means of Framingham Risk Score calculation and a measurement of mean carotid intima media thickness (CIMT) as measured by an automated software via B-mode ultrasound. Ankle-brachial index (ABI) measurement was also performed. Circulating serum irisin was measured by a commercially available ELISA kit.
Results
Among parameters of interest, circulating irisin correlated positively with BMI (r=0, 246, P<0,05) and negatively with age (r=−0,457, P<0,001), total cholesterol (r=−0,246, P<0,05), LDL-cholesterol (r=−0,234, P<0,05), ABI (r=−0,272, P<0,05). CIMT (r=−0,353, P<0,01) and with Framingham Risk Score (r=−0,400, P<0,01). Associations with CIMT, Framingham Risk Score and ABI persisted after adjustment for age and sex. In a ROC-curve analysis circulating serum irisin was of use (AUC=0,665, 95%CI: 0,525-0,804, P=0,037) for distinguishing subjects with CIMT $\geq$ 75th percentile, which was found in 32,5% of the study participants
Conclusions
Circulating irisin levels were negatively associated with established CVD estimates. Irisinaemia could be useful for distinguishing subjects with increased CIMT. Larger, prospective studies are required to establish the particular mechanisms for these observations.

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EP700

Circulating adipomyokines, inflammatory marker, insulin resistance, and physical fitness among severely obese Korean children and adolescents

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Background
Associations between obesity and adipomyokines, inflammatory marker, and level of physical fitness have not been well evaluated in severe obesity in children and adolescents.
Method
Data on leptin, irisin, FGF21, hsCRP, glucose, insulin, physical fitness measured by arm curl test for upper extremity)and wall sit test for lower extremity were obtained in 266 participants who were recruited for ICAAN study, community-based multidisciplinary weight control program in severely obese Korean children and adolescents. Participants were classified into 3 groups according to their BMI status based on sex and age-specific BMI percentiles: severely obese (SO, $\geq$ 120% of the 95th percentile), overweight or obse (OB, 85th- < 120% of the 95th percentile), and non-obese (NW, < 85th). Levels of circulating adipomyokines, inflammatory marker, insulin resistance (HOMA-IR), and physical fitness were compared across the groups adjusted for sex and age. Cross-sectional associations between obesity status and biomarker levels and physical fitness were assessed.
Results
Participants in SO group tended to have higher levels of leptin(NW, 12.19 $\pm$ 1.05: OB, 25.64 $\pm$ 1.05: SO, 40.77 $\pm$ 1.09), hsCRP (NW, 0.37 $\pm$ 1.09: OB,1.18 $\pm$ 1.09: SO,1.82 $\pm$ 1.16), and HOMA-IR (NW, 1.78 $\pm$ 1.06: OB, 3.55 $\pm$ 1.06: SO, 6.28 $\pm$ 1.10) compared to participants in NW or OB(all P for trend <0.001). Levels of physical fitness tended to be significantly decreased across the BMI groups (P for trend, arm curl test 0.03: wall sit test <0.001). Circulating levels of irisin showed overall significance (P for trend 0.04), but did not show significant difference between groups. FGF-21 did not show significant difference across the BMI groups.
Conclusions
Severe obesity in children and adolescents compared with NW or OB is associated with higher levels of leptin, inflammatory marker and insulin

resistance and lower levels of physical fitness, which implies problems with further weight gain and cardio-metabolic health risks.

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EP701

Genetic variants of the adiponectin gene and its association with adiponectin level in metabolic syndrome women

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Background
Adiponectin is an adipocyte-derived adipokine, down-regulated in obesity linked disorders. Here, we investigated the genotypic variability of adiponectin (at position; +T45G and +G276T) and its association with circulating adiponectin and metabolic syndrome in North Indian adult women.
Methods
We compared metabolic syndrome (MetS; 269) women to without metabolic syndrome (wMetS; 272) women of North India. Genotype frequencies of the adiponectin gene were performed using PCR-RFLP method and circulating adiponectin estimated by sandwich ELISA method.
Results
Low level of adiponectin ($P<0.001$) and high HOMA-IR were found ($P<0.001$) in MetS women. Gene frequency of combined mutant genotype (TG+GG) at position +45T/G of adiponectin was found to be significantly less ($P=0.017$) while mutant G allele was significantly high ($P=0.008$) in MetS women as respective to wild type. However, frequency of mutant T allele in MetS women was found to be significantly ($P=0.027$) less as compared to wMetS at position +276G/T of adiponectin gene. The mutant genotype GG of +45T/G and TT of +276G/T of adiponectin were significantly associated with lower adiponectin level and higher HOMA-IR (all $P<0.001$) in adult metabolic syndrome.
Conclusions
Results suggest that adiponectin gene variants might be associated with lower adiponectin level and metabolic syndrome.

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EP702

Obesity, cardiomyopathy and anabolic hormones

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Obesity is associated with hemodynamic alterations that may lead to heart failure (HF), through the development of cardiac structural abnormalities and impairment of ventricular function. Obesity-related neurohormonal and metabolic disturbances may predispose to HF, even in the absence of comorbidities. Excess adipose tissue and in particular visceral adiposity contributes to the altered production of a number of anabolic hormones also involved in the regulation of the cardiac function. The aim of the present study was to evaluate cardiac morphology and function by echocardiography and the relationships between echocardiographic parameters, BMI and hormonal status in a population of obese patients. 1821 patients (mean age 46.94±13.62 yrs, 1331 females and 490 males) were studied. 157 were normal weight (BMI 22.14±1.83), 247 overweight (BMI 27.76±1.45), and 1417 obese (BMI 39.39±6.88). Anthropometric data, blood pressure, lipid and glycemic parameters and a complete hormonal status were recorded. Two-dimensional echocardiography and carotid intima/media thickness measurement were performed. Total testosterone in males and SHBG in both sexes were significantly and inversely correlated with epicardial fat thickness (EFT) ($r=-0.33$ and $r=-0.44$, $P<0.001$). Circulating levels of DHEAS were positively related with E/A ratio ($r=0.26$ $P<0.001$) and inversely with left ventricular mass index (LVMi) ($r=-0.20$ $P<0.01$) and carotid intima-media thickness (cIMT) ($r=-0.24$ $P<0.005$). Urinary free cortisol was positively related with EFT ($r=0.22$ $P<0.001$). Circulating IGF1 levels were positively related to E/A ratio ($r=0.27$ $P<0.001$) and negatively correlated with EFT (r-0.14 $P<0.001$), LVMi ($r=-0.16$ $P<0.001$), end diastolic left ventricular diameter ($r=-0.16$ $P<0.001$), cIMT ($r=-0.25$ $P<0.001$), and left atrial diameter ($r=-0.14$ $P<0.001$). All the echocardiographic and hormonal parameters evaluated showed significant correlation with the degree of weight excess and the duration of obesity ($P<0.001$). In conclusion, cardiac function and morphology associate with weight excess, duration of obesity and anabolic hormones deficiencies.

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EP703

Are there any associations between vitamin D levels and insulin resistance in obese patients?

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Introduction
Most of the human studies suggested an association between obesity and low 25(OH)D3 0levels. It has been proposed that co-existence of vitamin D deficiency may have a role in the development of IR in obesity. We aimed to reveal whether any association was present between IR and 25(OH)D3.
Materials-methods
223 obese patients referred to our clinics were evaluated for the study. 24 patients with known diabetes mellitus were excluded. Finally, 199 patients were included and anthropometric (height, body weight, body mass index) and biochemical (fasting blood glucose, HbA1c) and hormonal (fasting insulin, C-peptide, 25(OH) D3) measurements were assessed. We evaluated IR by 'homeostasis model assessment of IR' (HOMA-IR). The patients having HOMA-IR value of equal to or greater than 2.5 were accepted as insulin resistant. The patients were grouped according to body mass index (BMI), HOMA-IR, and 25(OH)D3.
Results
25(OH)D3 levels were significantly lower in the groups of BMI >50 kg/m^2 and BMI 40–50 kg/m^2 in comparison to the group of BMI <40 kg/m^2 (mean 25(OH) D3 levels 12.0, 12.12, 17.02 ng/dl; respectively) ($P=0.042$, $P=0.025$; respectively). BMI levels were significantly lower in the group of 25(OH)D3$>$ 30 ng/ml in comparison to the group of 25(OH)D3 <10 ng/ml (mean BMI 42.27 vs 45.59 kg/m^2; respectively) ($P=0.05$). Likewise, there was significant negative correlation between BMI and 25(OH)D3 ($P=0.045$, $r=-0.142$).There was no difference between 25(OH)D3 levels in patients with IR (HOMA$\geq$2.5) and not IR (HOMA$<$2.5) patients ($P=0.071$). Similarly, there was no significant correlation between HOMA-IR values and 25(OH)D3 levels ($P=0.98$).
Conclusion
Our study showed that 25(OH)D3 levels decreased in obesity; and 25(OH)D3 levels were not different in patients having IR or not. These findings suggest that decreased vitamin D levels in obesity may be result of increasing BMI rather than IR.

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EP704

Elevated serum adiponectin in Alzheimer's disease as neuroprotective strategy

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Background
Several studies have highlighted the contribution of adipose tissue dysfunction to the development and progression of Alzheimer's Disease (AD), which may depend on alterations in adipokine secretion. Leptin and adiponectin are the most abundant adipokines in circulation, with recognized systemic effects, but also able to cross the blood-brain barrier and influence cognitive-related structures, such as the hippocampus.
Objective
To determine if serum and CSF adiponectin and leptin/adiponectin ratio are correlated with AD biomarkers and can constitute predictors of progression.
Methods
A total of 53 AD and 71 aMCI subjects (mild cognitive impairment amnestic type) were included and underwent a thorough clinical and neuropsychological evaluation (MMSE, MoCA, ADAS-Cog). Serum and CSF adiponectin and leptin, serum insulin and AD biomarkers (CSF $A\beta_{42,}$ t-tau, p-tau and hippocampal formation volumetry) were also performed. Sixty-seven MCI patients had clinical and neuropsychological follow-up in order to identify progression to AD.
Results
Serum adiponectin was 33% higher in AD when compared to MCI. In CSF, leptin and t-tau showed a negative correlation in AD patients ($\rho = -0.597$, $P = 0.026$) while adiponectin was positively correlated with $A\beta_{42}$ ($\rho = 0.590$, $P = 0.002$), but only in women. A robust association between CSF adiponectin and hippocampal volume was observed in a subgroup of patients with CSF-based AD diagnosis. However, no correlation was found with total cognitive scores. Twenty-seven MCI progressed to AD upon a mean follow-up of 38.2 ± 18.83 months, whereas 40 maintained the diagnosis. Baseline serum and CSF adipokine levels were similar in both groups. Only serum adiponectin positively correlated with time of progression ($\rho = 0.484$, $P = 0.049$), though incapable of predicting progression to dementia.
Conclusions
Higher CSF adiponectin levels are associated with less $A\beta_{42}$ deposition and higher hippocampal volume. Accordingly, higher adiponectinemia observed in AD could be looked as a strategy to maintain its central levels and, consequently, its beneficial effects.

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EP705

Late dumping syndrome in pregnant women after ROUX-EN-Y gastric bypass (RYGB) surgery

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Introduction
Dumping syndromes are common after bariatric surgery and can present diagnostic and therapeutic challenges in pregnancy.
Case report
A 23-year-old female who underwent a RYGB surgery because of morbid obesity in 2013. She had no medical history of diabetes nor any other comorbidity related to obesity. Two years later, her weight had reduced from 128 to 76 kg and also her body mass index (BMI) from 43.8 to 26 kg/m^2. She was treated with multivitamins, iron vitamin B12 and calcium. She remained clinically asymptomatic. In 2016, she got pregnant and on the 24th gestational week she checked herself post prandial capillary blood glucose (CBG) that confirmed hypoglycemia, with glucose levels from 55 mg/dl to 30 mg/dl, accompanied by clinical intense asthenia. Fasting plasma glucose was 71 mg/dl and insulin 5 mIU / ml (2.6–24.9). Dietary modification with frequent intakes every 3 hours, with low glycaemic index food and avoidance of physical activity immediately after oral intake were recommended. At the beginning, the episodes were reduced, but on the 35th gestational week hypoglycemia episodes had increased in severity and frequency, raising concerns of the risk of maternal neuroglycopenia and fetal hypoglycemia, that's why it was decided to treated with Diabetes-specific Oral Nutritional Supplement *(*low in carbohydrates with no added sucrose, high in protein and contains soluble fiber) twice a day between the main meals. Finally, on the 39th gestational week an induced birth was planned of a healthy 31oo-g infant, with a nearly complete remission of the dumping syndrome after giving birth.
Conclusions
Dumping syndromes in pregnant women that have gone through a RYGB surgery need to be distinguished from common symptoms of a normal pregnancy. Its therapeutic use gets more difficult, because it was restricted to dietetic modifications and not having medicines that have indication by FDA during pregnancy.

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EP706

Folate: a new player in metabolic syndrome?

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Introduction
Bariatric surgery (BS) candidates display several nutritional deficiencies that can aggravate after surgery. Metabolic syndrome (MS) is a cluster of cardiovascular risk factors with several disturbed metabolic pathways. Therefore, individuals with MS submitted to BS are probably more prone to nutritional deficiencies.
Objective
To evaluate the prevalence of nutritional deficiencies and eventual differences between BS candidates with and without MS.
Materials and methods
Retrospectively, databases of 385 patients who underwent BS between 01/2011 and 07/2015 were analyzed. Nine subjects were excluded due to missing data on MS parameters. Subjects with ≥ 3 criteria according to the NCEP ATP III report were classified as having MS.
Results
A total of 181 individuals with MS (150 females, body mass index (BMI) 44.56 ± 6.4, mean age 45.14 ± 10.9) and 195 without MS (174 females, BMI 42.98 ± 5.9, mean age 39.44 ± 9.3) were included. No significant differences were found in iron metabolism (iron/ferritin/hemoglobin), vitamin B12, vitamin D, albumin and homocysteine between males and females with and without MS. However, both males and females with MS had significantly higher levels of folate than individuals without MS. Males with MS exhibited significantly lower levels of magnesium comparing to males without MS. In females, folate was positively associated with glucose ($r = 0.206$; $P < 0{,}001$), glycated hemoglobin (A1c) ($r = 0.294$; $P < 0{,}001$), total cholesterol ($r = 0.153$; $P = 0.006$) and low-density-lipoproteina cholesterol ($r = 0.117$; $P = 0.037$). In males, folate was positively associated with glucose ($r = 0.402$; $P = 0.003$), A1c ($r = 0.362$; $P = 0.012$) and triglycerides ($r = 0.372$; $P = 0.007$), whereas magnesium was negatively associated with glucose ($r = -0.437$; $P = 0.01$) and A1c ($r = -0.298$; $P = 0.042$).
Conclusion
There were no significant differences in nutritional deficiencies between individuals with and without MS. However, in our study individuals with MS presented significantly higher folate levels than individuals without MS. Interestingly enough, folate levels positively associated with lipid and glucose metabolism. The metabolic and clinical significance of our results warrants further investigation.

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EP707

Evolution of body composition 3 years after sleeve gastrectomy

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Background
Sleeve gastrectomy (SG) has effective results on weight loss, which should result from fat mass loss and efforts should be made to preserve lean mass. Few studies have evaluated body composition (BC) changes after SG for periods > 2 years.
Objective
To investigate the impact of SG on weight and BC, comparing by gender.
Materials and methods
Retrospectively, databases of patients who underwent SG between 2011 and 2013 were analyzed. Data was obtained before and 1, 2 and 3 years after SG. BC was measured by bioelectrical impedance.

Results
Fifty-five females, mean age 42.11 ± 10 years, mean body mass index (BMI) 44.59 ± 4.9 Kg/m^2 and 11 males, mean age 39.55 ± 10.9 years, mean BMI 44.66 ± 5.4 Kg/m^2 were included. One year after SG, males had lost 36% of weight, 67% of fat mass and 18% of lean mass. In females, 1 year after SG, weight decreased 32%, fat mass 52% and lean mass 12%. Two and 3 years after surgery, males had lost 33% and 30% of weight, 59% and 53% of fat mass and 20% and 19% of lean mass, respectively. In females, 2 and 3 years after surgery weight decreased 33% and 30%, fat mass 52% and 48% and lean mass by 14% and 13%, respectively. Males presented the lowest weight and fat mass 1 year after surgery; females had the lowest weight and fat mass 2 years after SG.
Conclusion
Despite both genders show a weight loss of 30% 3 years after SG, males initially lose more weight that is regained after the first year. Males also present a greater loss of lean mass. Our results highlight the need to develop strategies to avoid weight regain, which seems to start 1 and 2 years after SG, respectively for males and females. Efforts should be also made in order to avoid lean mass loss.

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EP708

Comparative study between laparoscopic gastric bypass and laparoscopic sleeve gastrectomy

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Introduction
Bariatric surgery is currently considered the most effective treatment for morbid obesity. Laparoscopic gastric bypass (LGB) and laparoscopic sleeve gastrectomy (LSG) are the most widely used bariatric procedures today.
Objectives
In this study we compared LGB and LSG in order to establish whether there is any superiority of one or the other in effectiveness and complications.
Methods
We included all the patients who underwent bariatric surgery in Hospital Universitario Virgen de la Arrixaca during one year ($n = 101$) of which 62 received LGB and 39 LSG. Both groups were comparable in age, body max index, rates of hypertension (HT), type 2 DM (T2DM), hypercholesterolemia (Hchol), hypertriglyceridemia (HTG) and obstructive sleep apnea syndrome (OSA). A higher percentage of women was present in the LGB group. We retrospectively compared postoperative complications and excess weight loss (EWL) and comorbidity resolution (HT, T2DM, Hchol, HTG and OSA) at one year after surgery.
Results
LGB was superior to LSG in HT remission (75% vs 43.8%, $P = 0.046$) and Hchol remission (96.3% vs 33.3%, $P < 0.001$). We found no significant differences between LGB and LSG regarding EWL (77.7% ± 23.3 vs 76.9% ± 17.8), T2DM remission (78.6% vs 75%), HTG resolution (86.7% vs 75%) and OSA remission (55.6% vs 16.7%). Also, both techniques were comparable regarding rate of postoperative complications (17.7% vs 10.3%).
Conclusions
At one year postsurgery, LGB was superior to LSG in HT and Hchol remission. However, both techniques are comparable in terms of safety, weight loss and resolution of other comorbidities (T2DM, HTG and OSA).

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EP709

Prevalence of mono-ethyl-hexyl phthalate and mono-ethyl phthalate in Serbian population and their influence on leptin and thyroid function in obesity

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Introduction
Phthalates are ubiquitous endocrine disruptors (EDs). EDs induce obesity. MEP and MEHP affect thyroid function.
Aim
Estimation of burden of MEP and MEHP in our population, evaluation of leptin in obese MEP and MEHP positive and negative subjects and evaluation of connection between leptin, MEP, MEHP and thyroid indicators in that subgroup.
Materials and methods: a cross-sectional study, with 201 subjects divided into MEP/MEHP positive and negative, subdivided in obese and lean. Anthropometric parameters done: body height, weight, waist and body mass index. Laboratory tests: morning urine sample for MEP/MEHP and venous sample for free thyroxine (FT_4), free tri-iodothyronine (FT_3), thyroid stimulating hormone (TSH) and leptin. Statisycal analysis was done in SPSS. Results: Mean age of participants was 36.74 (±8.55) years, 86 (42.8%) males and 115 (57.2%) females. There were 64 (31.2%) MEP+, and 44 (22%) MEHP+ participants, and 5 (5.05%) positive for both. There were 93 (46.3%) participants in obese subgroup, MEHP- 64 (68%), MEHP+29 (32%; MEP− 58(62%), MEP+38%). Independent *t*-test and Mann Whitney *U* test did not show statistical significance in leptin level neither in MEP+ and MEP− (t −0.316, $P < 0.753$; Z −0.242, $P < 0.809$), nor in MEHP+ and MEHP− obese participants (t −1.049, $P < 0.297$; Z −1.377, $P < 0.169$). Pearson correlation for leptin and FT_4 in obese MEP+ subgroup was statistically significant (r −0.347, $P < 0.041$). No significant correlations were found for leptin with FT3 (r −0.123, $P < 0.48$) and TSH (r 0.078; $P < 0.655$). In MEHP+ obese patients we did not find any significance (FT_4: r 0.189, $P < 0.25$; FT_3: r −0.023, $P < 0.897$; TSH r 0.062, $P < 0.928$).
Conclusion
Half of our population is exposed to MEHP and MEP. In obese subjects higher leptin correlates with lower FT_4.

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EP710

Using diaserein on the patients with glucose intolerance

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Diaserein is used in the spesific and long-term treatment of degenerative joint diseases (as osteoarthritis). *In vitro* studies have showed that Diaserein and its active metabolyte Rheinin inhibate production and activity of interleukin-113 (IL-113), some proinflamatuar and pro-catabolic cytokines. Interleukin-113 play important role to trigger production of more pro-inflamatuar factors as cytokines, cyclo-oxygeneas, prostogalandines, nitric oxide, matrix metalloproteinases in chondrocyte degradation, snobial enflamation, remodelling of subchondral bone. Diaserein stimulates Transformic Growth Factor 13 (TGF-13) even if IL-113 exists. Diaserein stimulates synthesis of chondral matrix components as proteoglicans, glicoseaminoglicans, hyaluronic asids. After all Diaserein decreases the lost of chondral components continuously. We present 41 case series of patients that is used Diaserein on the treatment of osteoarthritis in various joints (gonarthroisis, coxarthritis, dejenerative lomber diseases). 41 patients have followed up clinically in 2014–2016. 17 patients in this serie have show intolerance to medicine by diarrhea, vomitting and some clinical compliants. At the research of these intolareted patients 16 patients have glucose intolerance as Diabetes Mellitus Type 1 and 2. At the researching of literature, Diaserein were not advised severe renal insufficiency, gastrointestinal disorder (Chrone, Ulserative Colit…), hepatic insufficiency and also glucose intolerance. Diaserein must be used carefully on the patients that have renal and hepatic insufficiency and failure. And also it must not be preferred on the patients which have glucose intolerance because of seein severe side effects.

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EP711

Bone mineral density in obese patients

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Background
Obesity and osteoporosis are two public health problems with an increasing prevalence and high impact on morbidity and mortality which, during the last two

decades, have become major health threats worldwide. However, obesity has long been considered as a protective factor against osteoporosis. The purpose of our study was to evaluate the bone mineral density in obese patients followed at Mohammed VI university hospital.
Methods
Our study has included 35 patients followed for obesity. Bone mineram density was ordered in all patients.
Results
The mean age was 40 years, ranging between 21 and 69 years, 94.2% of our patients were female, mean body mass index was 43.9 kg/m^2 with an average waist circumference of 120 cm, over two thirds of the patients were morbidly obese, 31.4% had diabetes and 14.2% had hypertension, 18.1% of our female patients were postmenopausal. One female patient had osteopenia with a *T* score of -1.2 at the spine. The rest of our patients had normal bone mineral density with a mean T score at the spine and the femur of 0.65 and 1.39 respectively.
Conclusion
Obesity is associated with normal bone mineral density even in postmenopausal obese women, suggesting a protective effect of obesity against osteoporosis that was highlighted in several literature studies. That said, this beneficial effect should always be weighed against its adverse effects especially the metabolic and cardiovascular ones.

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EP712

Role of cognitive-behavioral therapy in the treatment of obesity

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Dietary therapy, programmed physical activity and cognitive-behavioral therapy are basic measures in the treatment of obesity. Cognitive-behavioral therapy applies methods which change eating habits of obese persons, aiming to remove barriers relating dietary therapy and programmed physical activity. The goal is to try efficiency of applying cognitive-behavioral therapy in the program for the reduction of body mass of obese persons, versus the application of dietary therapy and programmed physical activity alone. The study included 60 obese persons, who were divided into two groups with 30 patients in each group, 20 to 58 years of age with the body mass index $\geq$30 kg/m^2 and hyperlipidemia (LDL cholesterol $\geq$ 4.2 mmol/l). Patients from both groups were on hypocalorie diet, individually designed and had programmed physical activity every day. Patients in group II underwent group cognitive-behavioral therapy under the supervision of psychiatrist once a week with the duration of 120 min. Both groups also went to see an endocrinologist 6 times, on which occasions their body weigh, blood pressure, parameters of lipid status serum and level of glucose in serum were mesured. Results showed that in group II the medium value of body mass reduction after twelve weeks of treatment was 9.5 kg (8.9%) and in group I 4.4 kg (4.1%). In group II, LDL cholesterol decreased for 34.5% and in group I for 5.0%; HDL cholesterol increased for 2.7% while in group I it decreased 2.5%; total triglycerides decrased for 15.3% and in group I for 5.4%; values of glicaemia decreased for 14.8% while in group I they remained unchanged. Cognitive-Behavioral therapy affected the improvement of motivation and readiness of patients to stick to the dietary regime and programmed physical activity. In designing the program for the reduction of obesty it is necessary to include cognitive-behavioral therapy, which brings significantly better therapy outcomes.

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EP713

Dynapenic obesity and myosteatosis in women with and without the metabolic syndrome

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Introduction
Insulin resistance is a well-known hallmark of the metabolic syndrome (MetS), and it detrimentally affects also protein metabolism, favoring to the decline of lean body mass. The aim of the present study was to explore muscle strength (as a functional consequence of sarcopenic obesity) and muscle quality (namely, myosteatosis) in women with and without the Metabolic Syndrome (MetS).
Methods
Study participants were enrolled at the Sapienza University, Rome, Italy. Body composition was assessed through DXA. The Handgrip strength test (HGST) was performed to assess muscle strength using a dynamometer (Dynex, Akern). HGST was normalized to arm lean mass; intramuscular adipose tissue (IMAT) and intramyocellular lipid content (IMCL) were measured by magnetic resonance spectroscopy, and used as indicators of myosteatosis. The MetS was diagnosed according to the NCEP-ATPIII criteria. HOMA-IR was calculated; C-reactive protein (CRP) levels were measured. The International Physical Activity Questionnaire (IPAQ) was administered to assess the physical activity level (PAL).
Results
54 women (age: 48$\pm$14 years, BMI: 37.9$\pm$5.4 kg/m^2) were included. MetS was diagnosed in 54% of subjects. HGST/arm lean mass was lower in women with the MetS compared to their counterparts without the MetS (6.3$\pm$1.8 vs 7.8$\pm$1.6, $P=0.03$). HGST/arm lean mass was negatively associated to HOMA-IR (beta: -0.37, S.E.:0.16, $P=0.02$), after adjustment for age, body fat, CRP levels, and PAL. IMAT (2655$\pm$1710 vs 1614$\pm$642 mm^2) and IMCL (25.0$\pm$21.4 vs 23.1$\pm$20.6%) were not different in obese women with the MetS compared to women without the MetS ($P>0.05$). No association emerged between HGST/arm lean mass and IMAT or IMCL.
Conclusion
Insulin resistance, and not muscle fatty infiltration *per se*, may play a role in the decline of muscle strength in subjects with obesity, leading to the phenotype of dynapenic obesity.

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EP714

Concern about body image, impulsiveness and personality traits in the morbidly obese before bariatric surgery and in patients who have undergone surgery

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Objectives
To analyse the levels of anxiety, depression, impulsiveness, bulimic behaviour, concern about body image and the quality of life of patients included in the care process following bariatric surgery, in our field.
Methods
Observational study of the patients included in the care process for bariatric surgery at University Hospital Puerta del Mar. Two cohorts were identified according to their situation before or after surgery. Studies were made of variable antropometrics, clinics, personality traits and quality of life. The instruments used were: Anxiety inventories (BAI) and Depression (Beck); Body Sharp Questionnaire (BQ21); BULIT-R test of bulimic behaviour, impulsiveness (BIS) and SF12 questionnaire on quality of life.
Results and conclusions
A total of 198 patients were studied, women constituted 69.2% of the subjects; the average age was 45 without differences in the cohorts before/after 12 months; the BMI in patients before surgery was 48 (S.D. 7) and in patients post surgery, 34 (S.D. 6). The patients on waiting lists presented higher levels of concern with regard to their body image (BQ21: 65), bulimic behaviour (BULIT: 62) and depression (BECK: 15). The SF12 reflected good mental health but scored lower on points for physical health. The levels of impulsiveness were not high (BIS: 53), so no patient reached the cut off point (104). The cohort of post-surgery patients presented high levels of concern about body image (BQ21: 65) and anxiety (BAI: 34). Impulsiveness was moderate (BIS: 58). It was noted that the proportion of patients with extreme concern about their body image (BQ21 $>$ 105) was higher in patients who had already undergone surgery (12.5 vs 6.5%). Attending to the depressive state of patients (BECK) prior to surgery required professional care for 35.9% for the morbidly obese, against 16.7% of post-surgery patients; severe depression was detected in 11.7% and 4.8% of patients respectively.

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EP715

Lifestyle of morbidly obese patients awaiting bariatric surgery and in the cohort of patients who have undergone surgery

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Objectives
To determine the habits and lifestyle of the morbidly obese before and after bariatric surgery.
Material and methods
Transversal study of two groups of morbidly obese patients attending the Endocrinology Unit of Puerta del Mar, Cádiz: one group before and the other after bariatric surgery. Clinical and analytical data of the patients was collected: socio-demographic and lifestyle characteristics, Bulit-R Questionnaire (Bulimia), BIS (impulsiveness), BQ1 (body image), BAI (anxiety), BECK (depression) and quality of life through questionnaire SF12.
Results
111 morbidly obese were studied before surgery (31.5% men, 68.5% women) and 87 morbidly obese post-surgery (29.9% men and 70.1% women). Before surgery mean weight was 133.4 (S.D. 24.4) and BMI 48.6 (S.D. 7.0), and post-surgery 94.9 (S.D. 19.8) and BMI 34.5 (S.D. 6.5). In both groups there was a predominance of primary and lower secondary education (25.8% of total); the greater proportion of subjects with a higher level of education was in the post-surgery group (3.6% vs 13%). Only 25% were actively in work before surgery, rising to 36.5% in the post-surgery group. Significant differences were observed between the two groups in relation to habits and lifestyle sucha as tobacco consumption (21.1 vs 7.1%), alcohol consumption (21.1 vs 17.4%), physical exercise (55 vs 82.6%), hours of physical exercise (4.75 hours/week vs 5.9) and increase in meals per day from 3 to 5. Family support is greater for the post-surgery group (90 vs 83.8%), excluding differences in professional support services (14%).
Conclusions
Significant differences were observed in patients' habits and lifestyle before and after bariatric surgery; factors which could contribute to the care, prognosis and evolution of the patients. Social and family support is greater for post-surgery patients.

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EP716

Thyroid hormone treatment reduces inflammatory cytokines in mesenteric adipose tissue improving insulin sensitivity of obese rats

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Thyroid hormone plays an important role on carbohydrate and lipid metabolism. In hypothyroidism is observed reduction of glucose transporter-4 expression and insulin sensitivity and in hyperthyroid states the key enzymes of gluconeogenesis and glycogenolysis are induced, and both conditions lead to glucose intolerance. It has been reported an increased prevalence of thyroid dysfunction in obese and diabetic patients. Recently we have demonstrated a hypothyroid state in alloxan-induced diabetic rats, in which the treatment with triiodothyronine (T3) improved glycemia control and insulin sensitivity. These alterations were accompanied by reduction of inflammatory cytokines in white adipose tissue and skeletal muscle. The present study aimed at evaluating the thyroid function of cafeteria diet-induced obese rats and the effects of thyroid hormone treatment on their glycemia control, insulin sensitivity and subclinical inflammation.
Methods
Obesity was induced in male Wistar rats by cafeteria diet. A subset of the obese rats was treated with T3 (1.5 μg per 100 g body weight) for a 28-day period (DT_3). Thyroid function was evaluated by molecular (TG, NIS, TSHR and TPO expression in thyroid gland) and biochemical parameters (serum TSH, T4 and T3 concentrations). Cytokines concentration was measured in mesenteric white adipose tissue (MWAT) (MILIplex assay kit).
Results
Obese rats exhibited decreased insulin sensitivity, thyroid function and serum TSH concentration, and increased MWAT inflammatory cytokines, NIS and TSHR expression in thyroid gland. Thyroid hormone treatment improved insulin sensitivity, glucose tolerance and reduced MWAT inflammatory cytokines content, which are known to induce insulin resistance.
Conclusions
The present data provide evidence that thyroid function is reduced in obese rats and reinforce the role of T3 treatment on improvement of insulin sensitivity by its negative modulation of inflammatory cytokine expression in metabolic disorders as obesity or diabetes mellitus.

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EP717

Predictive factors of outcome in bariatric surgery

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Introduction
Bariatric surgery is currently considered the most effective treatment for morbid obesity, although rates of weight loss and comorbidities resolution differ among bariatric techniques and depending on preoperative factors.
Objectives
In this study we analyse possible factors that influence the outcome of bariatric surgery (weight loss and improvement in metabolic comorbidities) in order to identify those patients most likely to benefit from surgery.
Methods
We included all the patients who underwent bariatric surgery in Hospital Universitario Virgen de la Arrixaca during one year (n = 101) of which 62 received LGB and 39 LSG. We retrospectively analysed which preoperative factors were related to percentage of excess body mass index (BMI) loss (%EBMIL), type 2 diabetes remission (T2DM), and higher rates of hypertension (HT) and hypercholesterolemia (Hchol) persistence one year after surgery.
Results
%EBMIL one year after surgery was significantly higher ($P = 0.016$) in patients with preoperative BMI $\leq 50\ kg/m^2$ vs BMI $> 50\ kg/m^2$ (79.4 ± 21.3 vs 65.6 ± 15.4). Age, sex and presurgery T2DM were not associated with %EBMIL one year after surgery. Absence of insulin treatment at baseline (89% vs 50%, $P = 0.03$), less than five years after diagnosis of T2DM (100 vs 53.8% $P = 0.017$) were associated with higher T2DM remission one year post surgery. Age, sex, presurgery BMI, HbA1c and smoking status were not associated with higher remission rates. HT persistence one year after surgery was significantly associated to age > 50 (30.3% vs 8.2% $P = 0.005$) and baseline T2DM (30.8% vs 10.3%, $P = 0.015$). HChol persistence one year after surgery was significantly associated to age > 50 (28.1% vs 8.5%, $P = 0.013$) and baseline T2DM (28% vs 10.6%, $P = 0.04$). Sex, baseline BMI nor smoking status were not associated with HT nor HChol persistence.
Conclusions
There is a heterogeneous pattern of presurgical factors that predict the outcomes of bariatric surgery.

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EP718

Prevalence of obesity in Algeria

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Introduction
The epidemiological transition has resulted in a major increase in the prévalence of obesity in our country. Obesity is closely associated with chronic diseases such as type 2 diabetes, hypertension and dyslipidemia. The aim of our study is assessing the prevalence of general obesity, central obesity (OA), associated risk factors (D2, HTA and dyslipidemia) and tries to provide information on determinants of obesity in Algerian adult.

Methods
This was a cross sectional study conducted among 2210 subjects (1583 women and 627 men) aged 18 to 64 years old, living in Algiers (Algeria). Subjects were randomized, anthropometric parameters, socio demographique situation; informations about food habits and physical activity were collected using a questionnary. Fasting blood glucose, cholestrol, triglycerids and blood presure were mesured.
Results
The prevalence of obesity (BMI $>$ 30 kg/m^2) was 24, 9% (12, 7% for males and 66, 4% for females). The prevalence of central obesity (WC $>$ 80 cm for women and 94 cm for men) was 66, 4%, 41% for males and 76, 4% for females. Multi variable logistic regression showed that elderly, female gender, low educationnal level, a history of familial or personnal obesity and menopause were at risk of obesity classified by BMI or WC. Wheras a young age, a higher level of education, male gender, current smoking, celibacy and hight physical activity were at low risk of obesity. Obeses subject's definied by BMI or Waist circumference had an increased risk of type 2 diabetes, hypertension and dyslipidemia.
Conclusion
The caracterization of these factors will contribute to defining more effective and specific strategies to screen and control obesity.

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EP719

Testosterone deficiency in obese males: is insulin resistance the one to blame?

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Introduction
Obesity is a growing worldwide public health issue and it is associated with multiple comorbidities, namely the so called Male Obesity-associated Secondary Hypogonadism (MOSH). However, the mechanisms that explain this association are not fully understood.
Methods
Cross-sectional study of 163 obese men that were evaluated for several clinical and analytic parameters. Testosterone deficiency was defined as: total testosterone $<$2.8 ng/ml and/or free testosterone calculated by the Vermeulen formula $<$50 pg/ml.
Results
The studied population had a mean age and BMI of 40.8 $\pm$ 10.5 years-old and 45.8 $\pm$ 6.7 kg/m^2, respectively. Testosterone deficiency prevalence was 47.2%. The majority (96.1%) of these men had hypogonadotropic dysfunction and 2.9% presented high gonadotrophins. When only calculated free testosterone was considered, the deficiency prevalence was 18.1%. Higher BMIs correlated with lower levels of SHBG (sex hormone binding globulin): $r=-0.19$; $P<0.05$. BMI ($r=-0.26$; $P<0.001$), age ($r=-0.21$; $P<0.05$) and HOMA-IR ($r=0.39$; $P<0.001$) had a negative correlation with calculated free testosterone levels, while SHBG levels exhibited a positive correlation ($r=0.18$; $P<0.05$). There was no significant correlation between oestradiol levels and free/total testosterone or BMI. When the aforementioned significant variables were included in a linear regression model, HOMA-IR ($\beta=-0.33$; $P<0.001$) and SHBG levels ($\beta=0.20$; $P<0.01$) could predict the free testosterone levels, while age ($P=0.07$) and BMI ($P=0.23$) lost their significance after the adjustment. In accordance, males with normal glucose tolerance had higher free testosterone levels than those with pre-diabetes or diabetes even after adjusting for age and BMI ($\beta=0.22$; $P<0.01$).
Conclusions
Testosterone deficiency is frequent in obese males, with most of them presenting hypogonadotropic dysfunction. SHBG levels and mainly insulin resistance, and not obesity *per se*, seem to be the true mediators of this interplay. We found no correlation between oestradiol and testosterone levels suggesting that androgen aromatization in adipose tissue is not a key determinant as previously thought.

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EP720

Anthropometric and metabolic effects of a milk-based intensive lifestyle intervention in severely obese adults

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Therapeutic options for patients with severe obesity are limited. Low energy meal replacement regimes can induce significant short-term weight loss and improvements in metabolic variables. We sought to estimate the effect size on adiposity and cardiovascular risk factors of a relatively inexpensive 24-week regime based on meal replacement with semi-skimmed milk in severely obese adults. A retrospective cohort analysis showed that of 206 patients in our hospital-based bariatric medicine service who started, 112 (54%) completed the programme and underwent an initial milk-based weight loss phase, followed by weight stabilization and weight maintenance phases, each lasting 8 weeks. Patients were seen every two weeks by the bariatric physician, nurse and dietitian. We compared outcomes in completers (who had similar baseline characteristics to non-completers) at time 0, 8, 16 and 24 weeks, with repeated measures ANOVA. 50.9% of completers were female, 40.2% had diabetes, mean age was 50.9 $\pm$ 10.3 years. BMI decreased from 52.7 $\pm$ 9.3 to 46.9 $\pm$ 8.7, 44.8 $\pm$ 8.6 and 43.8 $\pm$ 9.2 kg/m^2 at 0, 8, 16 and 24 weeks, respectively ($P<0.001$ with repeated measures ANOVA), equivalent to 24.8 kg weight loss and a reduction in excess body weight from 110.6 $\pm$ 37.2 to 75.2 $\pm$ 36.9%, $P<0.001$ over 24 weeks. In patients with diabetes, HbA1c decreased from 63 $\pm$ 18.3 to 48 $\pm$ 14.5 mmol/mol, $P=0.01$. There were very significant reductions in all diabetes medications, except for metformin. These preliminary findings suggest that a 24-week milk-based meal replacement programme can have large effect sizes on important outcomes in severely obese. However, attrition was high. A more formal assessment of the efficacy of the intervention as well as its safety, feasibility and cost-effectiveness seems warranted.

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EP721

Association of cortisol, DHEA-S and cortisol/DHEAS ratio with insulin resistance in overweight and obese women

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HPA axis that plays important controlling and modulating functions in organism is also linked with insulin resistance and weight control. The number of evidences linking cortisol secretion with obesity and other metabolic complication increase, but still there is a lack of definitive results. Therefore the aim of our study was to compare adrenal function parameters between high and normal insulin resistant overweight and obese women. This retrospective analysis was performed on the group of 70 adult polish Caucasian overweight and obese women with the mean age of 40 years. Mean BMI for the whole group was 38 kg/m^2. Exclusion criteria were: pregnancy or breastfeeding, history of any pituitary or adrenal gland disorders, current or previous usage of any glucocorticoid-containing medications, other drugs known to affect cortisol level and patients with diagnosis of severe liver or kidney dysfunctions and acute or chronic inflammatory disorder at the time of measurements. Patients were divided into two groups according to HOMA-IR value (cut-off point of 3.8). Statistical analysis was performed using Statistica software. Differences between lower HOMA-IR and higher HOMA-IR groups were determined by student t test and Mann-Whitney U test when appropriate. To analyze correlations between measured values Spearman correlation coefficiency was calculated. P value <0.05 was considered statistically significant. Patients with higher HOMA-IR have higher morning cortisol concentration (504.36 vs 425.82 nmol/l) and lower DHEA-S concentration (170.18 vs 227.49 µg/dl), although these differences were not statistically significant. There was statistically significant difference between higher and lower HOMA-IR groups in evening cortisol concentration (248.28 and 186.02 nmol/l, respectively, $P=0.007$) and cortisol/DHEA-S ratio (5.73 vs 2.73, $P=0.003$). For the whole group studied there was statistically significant positive correlation between cortisol/DHEAS ratio and HOMA-IR ($r=0.39$, $P=0.001$). There is a significant association between evening cortisol secretion and HOMA-IR and between cortisol/DHEA-S ratio and HOMA-IR.

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EP722

Obesity and fruit and vegetables consumptions in children

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Introduction
Obesity is associated with the low consumption of fruit and vegetables.
Objective
Evaluate the obesity and the fruit and vegetables consumptions in children after an intervention of school food education program.
Methodology
It was implemented a food education program in three classes ($n=55$) of 1st cycle, on school year (2016/2017) and the evaluation of this action was done comparing fruit and vegetables consumptions and nutritional status of this children between beginning and the end of the program (after 12 weeks). Fruit and vegetables consumptions were assessed through the application of a food frequency questionnaire and the nutritional status was determined by BMI. Weight and height were assessed in all children and BMI was calculated. To determine the obesity was used CDC criteria. The educational intervention consisted in promoting fruit and vegetables consumptions at school environment, involving formative and recreational activities, as well as a greater supply of fruit and vegetables in school.
Results
This sample had between 6 and 8 years old and 54.5% were girls. Fruit consumption increased and considering the 3–5 pieces of fruit per day recommended by the Portuguese Food Wheel, the consumption in these students evolved from 16.3% to 41.8%. Vegetables consumption also increased. At beginning 54.5% ate two or more servings per day of vegetables, and at end 74.5%. In nutritional status, it was observed that obesity decreased from 20% to 16.4%.
Conclusions
This type of educational intervention in schools increased fruit and vegetables consumptions and reduce the prevalence of obesity in children.

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EP723

Neuromedin B receptor: role in adipogenesis and a possible target for obesity treatment

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Neuromedin B (NB) is a peptide highly expressed in adipose tissue (AT) but its function remains unclear. We showed that NB receptor (NB) knockout mice (NBR-KO) are resistant to diet-induced obesity compared to wild type (WT) and now we aimed to analyze NBR influence in adipocytes. Mesenchimal cells from perigonadal AT of WT and NBR-KO mice were isolated and maintained in growth medium (GM) as control group or in differentiation medium (DM) as induced group. After 2 weeks cells were fixed and lipid accumulation was evaluated by Oil Red O staining. NBR-KO cells accumulated 56% less lipids than WT cells in DM. To analyze NBR antagonist intervention during adipogenesis 3T3-L1 cells were cultured in GM (GMC), or in DM in the absence (DMC) or presence of 3 μM of NBR antagonist (DMA), during 21 days. In parallel NBR antagonist was added to DMC group for 6 days after 21 days in culture to verify its influence after differentiation. Cells were fixed and stained with Dapi and Bodipy for cell and lipid measurements. After 21 days DMC group exhibited 2.7 times more cells number than GMC but DMA group presented similar cell number as GMC. DMC group reached 83% of well area as lipid while DMA did only 7% although it was corrected by cells area. When NBR antagonist was added for 6 days to DMC it decreased cells number by 40% and lipid accumulation diminished 10%. In conclusion NBR-KO AT cells have impaired induced-adipogenesis and NBR antagonist promoted less adipogenesis, reduced adipocytes number and decreased lipid accumulation. Data demonstrate, for the first time, a role for NBR in adipocyte differentiation, suggesting it is a possible target for obesity treatment. Presently, we are analyzing hormones and factors involved in adipogenesis, lipogenesis and cell death to clarify mechanisms.

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Paediatric Endocrinology

EP724

Intracranial lesions in children and adolescents with morbid obesity; results of long-term follow-up

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Introduction
Childhood obesity has become an important health problem nowadays. Intracranial lesions (IC) can affect the hypothalamic - hypophyseal axis depending on the localization of the lesion and lead to hypophyseal hormone deficiencies, especially growth hormone. Although IC lesions are important in the etiology of obesity, There's limited data in the literature about this subject. Aim of this study is to evaluate the incidence of IC lesions and their role in clinical symptoms and etiology in cases with morbid obesity (MO) in childhood.
Materials and methods
One hundred twenty cases admitted with the complaint of MO in 13 years (2002–2015) were included in this study. Anthropometric evaluation and detailed physical examinations were performed. Biochemical and hormonal parameters (glucose, lipid metabolism, adrenal steroids and diurnal cortisol) were evaluated. Contrast-enhanced dynamic magnetic resonance imaging (CDMRI) technique was used to assess the hypothalamo-hypophyseal field. Height of hypophysis was evaluated according to age and sex.
Results
In our study, 16.6% of the MO patients had an IC lesion. Most of the cases had adenoma of the hypophysis (55% of the cases with IC lesion.) Six of the patients with IC lesion had high prolactin levels. Prolactin levels were increased in the 6 patients but front hypophyseal hormone levels were in between normal range in the rest of the patients. None of the patients had decreased growth velocity.
Conclusion
In this long-term study, the important result is that; IC lesion frequency was significantly higher in children and adolescents with MO than those of the normal population. Moreover, these lesions show no other endocrinological or neurological symptom besides obesity. Furthermore; due to this study; we suggest that cranial imaging with CDMRI in these cases, even if the physical-neurological examination is normal, will contribute greatly to the early diagnosis and treatment of lesions without causing other symptoms.

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EP725

Congenital hyperinsulinism in two siblings due to the same ABCC8 mutation: the clinical importance of an early diagnosis and treatment

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Introduction
Congenital hyperinsulinism (CHI) is a heterogenous disease caused by insulin secretion regulatory defects, being ABCC8/KCNJ11 the most commonly affected genes. It can present as focal or diffuse pancreatic disease, which is mainly determined by the genotype. Diazoxide is the first-line medication in diffuse cases, however many do not respond satisfactory. Second-line options include somatostatin analogues and surgery, which is curative in case of focal CHI.
Case report
We report the case of two siblings that presented with hypoketotic hyperinsulinemic persistent hypoglycemias during neonatal period. The diagnosis of diffuse CHI due to an ABCC8 compound mutation (c3576delG and c742C > T) was concluded. They did not benefit from diazoxide therapy (or pancreatectomy performed in patient no 1 when he was 3 months old) yet responded to

somatostatin analogues. Patient no 1 developed various cognitive deficits and epilepsy, however patient no 2 experienced an entirely normal neurodevelopment.
Conclusion
We report the case of two siblings with diazoxide-resistant CHI caused by the same compound *ABCC8* mutation (which was never before described, to the best of our knowledge). Their phenotype and therapeutic management had some differences and this could offer a potential explanation for the distinct neurological outcomes, despite the same genetic basis for the disease. Molecular diagnosis and better knowledge of the disease behaviour seemed to contribute to a better medical care in patient no 2, which ultimately resulted in a better outcome. This highlights the importance of early recognition and diagnosis of this disease.

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EP726

Association between oxidative stress and bone turnover markers in the obese children

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Background
Recent data have been showed that free radicals are involved in either bone resorption and atherosclerosis development in adults. In paediatric population the important risk factor for the early atherosclerosis development is obesity, which can be also associated with the disturb bone turnover.
Objective and hypotheses
The aim of the study was to evaluate the interrelationship between oxidative stress and bone turnover markers in obese children vs lean controls and correlated them with the anthropometrical status and metabolic activity of adipose tissue.
Method
Bone turnover markers (osteocalcin (OC), N-terminal telopeptide of type I collagen (NTx)), oxidative stress markers (TAC – total antioxidative capacity, glutathione peroxidase, oxLDL) and leptin were determined in 50 obese children and 79 healthy controls. Anthropometrical status by BMI calculation and body composition parameters as: fat mass (FAT), fat-free mass (FMM), predicted muscle mass (PMM) and total body water (TBW) were evaluated using bioelectrical impedance analyzer (BIA) in all children.
Results
OC was significantly lower in obese children and correlated significantly (negatively $P<0.01$) with BMI in the lean group. There was also significant positive correlation between OC and TAC in obese children. NTx correlated significantly with oxy-LDL (positively) in either, obese and lean group ($P<0.05$ and $P<0.01$ respectively). In the lean group only, there were significant relations between NTx vs leptin and body composition parameters ($r=0.245$ vs leptin, $r=0.245$ vs FAT%, $r=-0.252$ vs PMM%, and $r=-0.245$ vs FFM% respectively).
Conclusion
Bone turnover seems to be disturbed in the obese children and pathophysiological factor with can be involved in that mechanism may be an increase oxidative stress level. Osteocalcin and NTx levels seem to be related to the anthropometrical status and adipose tissue activity (leptin level).

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Steroid Metabolism + Action

EP727

In vivo porcine and *in vitro* HepG2 models with 11β-HSD1 overproduction

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Introduction
11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) has been associated with several human metabolic disorders and is converted from inactive 11-keto form to glucocorticoid (GC or cortisol). GC overproduction or hypercortisolism is a major diagnostic factor of Cushing syndrome and Anorexia. GCs regulate carbohydrate, fat, and protein metabolism.
Materials and methods
Previously we established porcine fibroblasts overexpressing 11β-HSD1. Based on these, transgenic piglets overexpressing 11β-HSD1 were born through somatic cell nuclear transfer (SCNT) and re-cloning methods. Transgenic piglets were identified by PCR methods using specific primers for the targeting cassettes from the genomic DNA of piglets. HepG2 cell line overproducing 11β-HSD1 (11β-HSD1-HepG2) was established for *in vitro* model. *In vivo* porcine and *in vitro* hepatic models were analyzed by real-time PCR, immunohistochemistry and Western blotting methods.
Results
Six live piglets were born. Integration of target gene into the genomic DNA was confirmed from all of them. Excessive expression of 11β-HSD1 induced up-regulation of gluconeogenesis (*G6PT, G6Pase, PEPCK and etc.*) and lipogenesis related genes (*FASN, ACC, and SCD*) in *in vivo* and *in vitro* models. To compensate for energy loss by anabolism, it stimulates AMPK and SIRT signaling, which controls energy balance and mitochondrial biogenesis.
Conclusions
These results suggest that the overproduction of 11β-HSD1 induce activation of complementary energy gaining processes through mitochondrial respiration. Our *in vivo* and *in vitro* models will be useful for further study and potential application in metabolic diseases.

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EP728

Hepatic and adipose tissue insulin resistance as a consequence of intermittent hypoxia are exacerbated by glucocorticoid receptor antagonism in man

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Introduction
Obstructive sleep apnea (OSA) affects up to 20% of a Western population and is associated with non-alcoholic fatty liver disease and type 2 diabetes (T2D). OSA is characterized by intermittent episodes of hypoxia (IH) that occur during sleep. It is not yet known if IH is directly linked to insulin resistance within key metabolic target tissues (adipose; liver and skeletal muscle) and what the potential underlying mechanism may be. It has been suggested that individuals with OSA have high circulating glucocorticoid levels which may be linked to the development of IR and T2D.
Methods
17 healthy male volunteers were recruited and underwent detailed metabolic phenotyping in a fasted state including a hyperinsulinaemic-euglycaemic clamp, incorporating the use of stable isotopes of glucose and palmitate to measure fatty acid partitioning. Initial assessments were made in normoxic conditions; volunteers were then randomised either to no treatment ($n=9$) or treatment with the glucocorticoid antagonist Mifepristone (600 mg once a day) ($n=8$). After 1 week of treatment, assessments were repeated under conditions of IH (12 desaturations/h to arterial saturations of 85-91%).
Results
Global insulin sensitivity as measured by M/I values was unchanged by IH or by IH + Mifepristone (control: 8.65 ± 4.1; IH: 9.13 ± 5.4; control (pre_drug): 8.9 ± 3.7; Mifeprisone + IH: 10.13 ± 3.3). However, IH impaired the ability of insulin to suppress TAG, an effect that was worsened by Mifepristone ((insulin mediated suppression of TAG: control: -449 ± 124; IH: -218 ± 131 ($P=0.0034$); control (pre_drug): -339 ± 201; Mifeprisone + IH: -76 ± 128; ($P=0.008$). In addition, adipose tissue IR, as measured by a reduction in the ability of insulin to suppress circulating NEFA, was worsened by Mifepristone under conditions of IH (insulin mediated change in plasma NEFA control: -501 ± 164; IH: -411 ± 187 ($P=$ns); control (pre_drug): -549 ± 130; Mifeprisone + IH: -367 ± 109; ($P=0.03$)).
Conclusion
Acute IH causes insulin resistance in liver and adipose tissue. These effects are worsened rather than improved by antagonism of the glucocorticoid receptor, highlighting the importance of understanding tissue specific glucocorticoid

actions and suggesting activation of the HPA axis is not the link between OSA and metabolic risk

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EP729

Dexras1 regulates MSC-derived adipogenesis and osteogenesis

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Mesenchymal stem cells (MSCs) are multipotent stromal cells that can differentiate into various types of cells including chondrocytes, osteoblasts and adipocytes. Since these types of cells are simultaneously derived from the same precursor cell, adipogenesis and osteoblastogenesis are thought to be counter-related. It is well-known that chronic treatment of steroid can induce Cushing's syndrome which has phenotypes like visceral adiposity and osteoporosis. Cell fate of differentiation into either adipocytes or osteoblasts is one of the critical factors of these symptoms, but the molecular mechanism of cell fate decision of MSCs under the streroid treatment is unclear. Recently, we showed that Dexras1 mediates glucocorticoids and IGF-I signaling followed by MAPK activation and results in increased adipogenesis while its abolishment decreases adipogenesis. Now we established that lack of Dexas1 exhibited increased osteogenesis in mesenchymal stem cells including both bone marrow derived stem cells (BMSCs) and mouse embryonic fibroblasts (MEFs). Corroborative to our previous data, decreased adipogenesis in MSCs was also observed in the absence of Dexras1. Despite less dramatic change in differentiation, it is also shown that lessened mature osteoblasts in Dexras1-overexpressing preosteoblast cell line, MC3T3-E1, down regulating Smad signaling in the early period of differentiation. Furthermore, we found that Dexras1 is involved in increased central obesity associated with chronic treatment of steroids but rescued steroid-induced osteoporosis in mouse model treated with dexamethasone for 8 weeks followed by increased gene expression related to osteoblast in the murine bone. Above all these results, we suggest that Dexras1 is a key molecule which stimulates adiposity and down regulates osteogenesis via counter regulating action.

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EP730

Gender specific metabolic phenotype in the 5β-reductase knockout mouse

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Steroid hormones and bile acids are potent regulators of metabolism. The enzyme 5β-reductase (AKR1D1) has a crucial role in bile acid synthesis and also generates 5β-reduced dihydrosteroid metabolites, regulating intra-cellular steroid availability though the clearance of cortisol, testosterone, androstenedione, and progesterone. As AKR1D1 sits at the interface of bile acid synthesis and steroid metabolism, we have hypothesised that it plays a key role in metabolic homeostasis and have generated and characterised an entirely novel, global AKR1D1 knockout (KO) mouse. As expected AKR1D1 KO mice had altered hepatic steroid (*in vitro* cortisone clearance: 100% (WT), 70% (KO); *in vitro* 5α-cortisone/cortisol metabolite generation increased 3.9-fold (KO)) and bile acid metabolism (hepatic bile acid concentration males: 1164±626 pmol/mg (WT), 122±42 pmol/mg (KO) $P<0.05$; females: 310±67 pmol/mg (WT), 113±23 pmol/mg (KO) $P<0.01$). At 30 weeks male, but not female, AKR1D1KO animals were lighter than wildtype (WT) littermates (males: 35.6±0.9 g (WT), 33.2±0.6 g (KO) $P<0.05$; females: 25.3±0.6 g (WT), 24.9±0.4 g (KO) P=ns) with lower total (9.7±0.7 g (WT), 7.4±0.5 g (KO) $P<0.05$) and % (29±1.4% (WT), 24±1.5% (KO) $P<0.05$) fat mass, as determined by DEXA. At termination, male AKR1D1 KO mice had smaller subcutaneous adipose depots (1.0±0.1 g (WT), 0.7±0.1 g (KO) $P<0.05$) and, despite no difference in body weight or composition, female KO animals had smaller gonadal fat depots (0.5±0.1 g (WT), 0.3 g±0.03 g (KO) $P<0.05$). Both male and female AKR1D1KO mice had enhanced insulin sensitivity (ipITT AUC males: 793 mMol min (WT), 647 mMol min (KO); ipITT AUC females: 663 mMol min (WT), 568 mMol min (KO)), without changes in glucose tolerance. AKR1D1 KO mice display a sexually dimorphic metabolic phenotype. Whereas both male and female AKR1D1 KO mice have increased insulin sensitivity, only male AKR1D1 KO mice have a lean phenotype. Although the underpinning mechanisms remain to be fully defined, AKR1D1 may represent a future novel therapeutic target for the treatment of metabolic disease.

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Eposter Presentations: Environment, Society and Governance

Cardiovascular Endocrinology and Lipid Metabolism

EP731

Measuring of quality of life and health characteristics among 40–79 old population in Hungary

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Introduction
Life expectancy is increasing in most developed countries, in part due to improved socio-economic conditions and in part to advances in healthcare. It is widely acknowledged that the promotion of healthy ageing by delaying, minimizing or preventing disabilities or diseases is one of the most important public health objectives in this century.
Methods
243 Women and 181 men aged 40–79 years were recruited in Szeged (Hungary) Subjects were recruited from population registers and those who agreed to take part completed a detailed questionnaire including aspects of personal and medical history, lifestyle factors. Objective measures of body size, cognition, vision, skeletal health and neuromuscular function were obtained. Internal consistency of the questionnaire was also investigated (Cronbach alfa: 0.715).
Results
Mean age of participants was 59.17 S.D.:10.71 years. There were significant correlation between the quality of life and systolic blood pressure of the right & left hand ($P=0.007$ and $P=0.013$) and smoking use ($P=0.002$) The cardiovascular risk was significantly higher in the 40–50 age groups compared to the older age groups ($P=0.002$).
Conclusion
We provide new data among the health characteristics of older population in South Hungary. Such information is an important prerequisite to develop effective strategies to reduce age-related disabilities and optimise health and well-being into old-age.

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Clinical Case Reports - Thyroid/Others

EP732

Does standardising the dynamic endocrine testing process improve patient communication and safety?

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Background and objectives
Ineffective communication is one of the leading causes of medical errors and patient dissatisfaction. We implemented an initiative for dynamic endocrine tests to enhance communication with primary care colleagues and patients.
Methods
We introduced a comprehensive system of organising dynamic tests, structured documentation, weekly endocrine meeting to discuss the results and standardised escalation process for suspected abnormal results. We retrospectively analysed 50 tests prior to and 50 after the initiative was introduced ($n=100$). Most were routine short synacthen tests (SST) with a small proportion of other tests including urgent/semi-urgent SST, dexamethasone suppression tests, TRH and GnRH stimulation tests, prolonged oral glucose tolerance test and prolonged supervised fast.
Results
The mean time from the date of test and the letter to general practitioner/patient of routine tests reduced from 22.07 days to 13.92 days for normal SSTs and 5.16 days to 4.83 days for abnormal SSTs, although the latter was not statistically significant. The other test numbers were too small to establish significance. There was no significant difference in time taken for organising the tests and no patient harm was reported in both groups. Anecdotal reports from trainees suggested that there were more training opportunities with the introduction of the new process.
Discussion
Our data suggests that streamlining the dynamic endocrine function test system reduces the delay in communicating normal routine dynamic endocrine test results and can increase the training opportunities for trainees. We aim to perform another analysis with a larger sample and analyse patient satisfaction data and consider confounding factors such as time taken from the dictation of letters to typing and postal delays, and observer effect from trainees. The endocrine meeting is not happening every week, and trainees are not attending it consistently due to other clinical commitments. We are actively looking to rectify these issues.

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Developmental Endocrinology

EP733

Endocrinology training programs in member countries of the International Society of Endocrinology (ISE): a pilot survey evaluation comparing regions and cultures

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Background
Endocrinology is a relatively young subspecialty of internal medicine. No consensus on international standards for training has been established, and hence the variability between training programs and endocrinologist qualifications may be great.
Methods
A standardized questionnaire was constructed to explore individual national standards for endocrinology training, evaluating the responding programs for physician entry criteria for each program, medical content, duration of the programs, procedural competency, and qualification and re-qualification requirements. Representatives from member societies of the ISE were solicited to provide specific characteristics of their respective national training programs via a questionnaire on SurveyMonkey.
Results
Sixteen of 54 (30%) ISE member countries responded regarding training program characteristics. Spanish-speaking (SS) countries were more likely to have an entrance exam compared with non-SS countries (80 vs 27%, $\chi^2=3.88$, $P=0.049$). On average 62–85% of programs included all general endocrinology knowledge content with the exception of endocrine surgery (15%) and genetics (31%). Genetics was included more frequently in SS vs non-SS countries (60 vs 13%, $\chi^2=3.26$, $P=0.071$) and less frequently in European Union (EU) vs non-EU countries (17 vs 43%, $\chi^2=3.61$, $P=0.057$). Pediatric endocrinology was included more frequently in SS vs non-SS countries (100 vs 43%, $\chi^2=4.29$, $P=0.038$). Endocrinology research was included less frequently in EU vs non-EU countries (50 vs 86%, $\chi^2=3.26$, $P=0.071$). Thyroid procedures were taught only 33–38% of the time across programs while diabetes-related procedures and DEXA were required by 62–69% of the programs, and both were included more frequently in the SS vs non-SS countries ($\chi^2=8.70$, $P=0.003$, $\chi^2=5.08$, $P=0.024$, respectively). While 100% of countries required certification to practice endocrinology, only 38% had a certifying examination, with significantly lower administration in EU vs non-EU (17 vs 57%, $\chi^2=5.08$, $P=0.024$).
Conclusion
The questionnaire identifies differences in endocrinology training, which can be addressed by ISE member countries in the hope of an overall improvement in the quality of training and international harmonization of the discipline of endocrinology.

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EP734

The basic characteristics of delivery of endocrinologic care in Slovakia from outpatients care perspective

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The prevalence of endocrinologic diseases in Slovak Republic in 2015 was about 390 000 patients e.g. the prevalence was about 7.1%. The objective of this study was to find out the basic relevant characteristics of delivery of endocrinologic care based on data from General Insurance Company with covering cca 63% of all inhabitants.
Methods
The combined analysis from the GIC data was used.
Results
246 195 patients, 212 977 women and 33 597 men, were examined in this study. The patients visited 150 endocrinologic outpatients departments (EOD). The number amounted from 1100 to 2800 patients per one department. The prevalence

of endocrinologic diseases differed from 6.1% to 9.3% compared 8 administrative regions. The ratio of EOD varied between 2.9% and 6.7% per 100 000 inhabitants. The migration of patients among regions varied from 3% to 10%. The thyreoid diseases represented 88.4% of all patients, metabolic diseases – 8.3%, bone diseases – 6.5%, all other diseases – 5.4% (1 patients had one and more diseases). The prevalence of benign tumors in patients was cca 1.85% and malignant tumors about 1.7%. Some endocrinologic diseases were treated by more than 50 other specialists like internal specialists etc. In this thyreoid diseases represented about 21.9%, bone diseases – 686%, metabolic diseases – 18.6% and all others diseases – 65.4%. From 2013 to 2015 y. was observed an increase of patients with thyreoid diseases in 7.0%, bone diseases – 4.5%, other diseases 5.3%. Together 21 activities from daily practice were observed and evaluated. The most often were: first and followed examination, blood taking, evaluation of laboratory exams, ultrasonography, advice to the patients, densitometry, biopsy, etc.

Conclusions

The prevalence of endocrinologic diseaseas in Slovakia is high. There are some non explanable differences among administrative reasons in access to endocrinologic outpatients care and high level of overlapping among endocrinology and other medical specialties.

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Diabetes (to include Epidemiology, Pathophysiology)

EP735

Gestational diabetes risk in three Israeli population subgroups

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Objective

Israeli Ethiopian Jews (EJ) and Arabs have at reproduction age higher incidence of diabetes than other Israeli Jews. We aimed to compare gestational diabetes (GDM) risk among these population subgroups.

Methods

The study cohort included age-matched EJ, non-Ethiopian Jews (NEJ) and Arab women age 20–45 years. GDM diagnosis was based on the two step screening method of 50 and 100 g oral glucose load tests. Univariate comparisons and the association between population subgroups and the risk for GDM were tested in multiple logistic regression analysis, adjusted for age, parity and pre-gestational levels of the metabolic syndrome components.

Results

The study included 13 943 women (2938 EJ, 5156 NEJ and 5849 Arabs). During the years 2008–2011, birth rate was 0.358, 0.475 and 0.526 ($P<0.001$), diabetes screening was performed in 84, 81, 85 and GDM prevalence was 4.3, 2.2 and 2.9% among Ethiopian, non-Ethiopian and Arab women respectively. The multivariate odds ratios (OR) for GDM were age 2.9-per 10 years (95% CI 2.1–4.1), BMI 1.12 (95% CI 1.1–1.2), triglycerides 1.05-per 10 mg/ml (95% CI 1.0–1.1), systolic blood pressure 1.05-per 10 mmHg (95% CI 1.02–1.1), parity 0.8 (95% CI 0.7–0.9) and Ethiopian ethnicity 2.55 (95% CI 1.6–4.1). Arab-ethnicity 1.4 (95% CI 0.95–2.15) and HDL-c 0.99 (95% CI 0.91–1.08) were not associated with risk for GDM.

Conclusions

Ethiopian ethnicity is an independent risk for GDM. The higher GDM prevalence in Arab women is mainly explained by higher obesity rates.

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Diabetes Complications

EP736

Improvement of specialised help to patient with diabetic foot syndrome in Uzbekistan

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Goal

Decrease a number of lower limb amputations in PDM in Uzbekistan by improvement of specialised help given to patients with DFS.

Materials and methods

Prior to 2010 there were only 2 'Diabetic foot' rooms in Tashkent, Uzbekistan. In 2010–2012, CPA 'UMID' jointly with Uzbekistan Ministry of Health and Research Centre for Endocrinology implemented a project 'Prevention of lower limb amputations in people with diabetes mellitus in Uzbekistan' granted by the World Diabetes Fund (WDF).

Results

Within the framework of the project for the first time in Uzbekistan, 288 'Diabetic foot' rooms were set up under 14 endocrinological dispensaries and in 274 rural district clinics which were also equipped with a medical armchair for feet examination, a tuning fork, monofilament, percussion hammer, kit of dressing materials. To work in these rooms, 615 podiatrists were trained who render a qualified medical help to PDM and teach them rules of foot care. Annually over 28 800 PDM undertake feet examination and training in these rooms. A twofold decrease in a number of amputations and increased awareness of PDM in foot care proves improvement of specialised help to people with DFS. Within the framework of the project, 288 multidisciplinary teams (surgeon + endocrinologist + podiatrist) were trained throughout the country and now they render a specialised help to patients with DFS.

Conclusions

Implementation of the project 'Prevention of lower limb amputations in people with diabetes mellitus in Uzbekistan' improved a specialised help to people with DFS due to launching a network of 'Diabetic foot' rooms and an effective work of podiatrists and multidisciplinary teams trained on sites and that lowered a number of amputations in PDM by two times; increased awareness of people with diabetes on prevention of DFS.

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EP737

Assessment of the prevalence of type 1 diabetes microvascular complications in young adults in the repablic of Belarus with regard to the duration of the disease

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Background and aims

According to current recommendations of the American Diabetes Association expedient screening of microvascular complications in all patients with type 1 diabetes (T1D) with a duration of 5 years of the disease. Therefore, the aim of study was to assess the prevalence of microvascular complications in T1D patients aged 30−45 years with regard to the duration of the disease 5−10 years and over 10 years.

Materials and methods

We examined 360 patients with type 1 diabetes, 196 (54.4%) men and 164 (45.6%) women. The average age of the patients was 37.9±4.5 (37.4−38.4) years, the age of onset of diabetes – 28.1±6.2 (27.5−28.8) years, duration of the disease – 9.0 (7.0−12.0) years, BMI – 24.8±3.95 (23.6–25.2) kg/m^2, Hb_{A1c} – 8.37±1.83 (8.18−8.56). In the study, carried out a detailed clinical examination of patients with medical records analysis.

Results

Diabetic peripheral neuropathy (DPN) was diagnosed in 133 (36.9%) patients; diabetic retinopathy (DR) − 78 (21.7%) patients, diabetic nephropathy (DN) − in 146 (40.6%) patients, albuminuria was detected in 137 (38.1%) persons. In general, microvascular complications of diabetes were set at 270 (75%) patients. With increasing duration of the disease for more than 10 years showed a significant increase in microvascular complications: DPN 30.6 vs 47.1% (χ^2=9.91; P=0.002); DN − 34.2 vs 50.7% (χ^2=9.60; P=0.002); albuminuria − 31.9 vs 47.8% (χ^2=9.06; P=0.003); DR – 40.1 vs 71.7% (χ^2=34.2; $P<0,005$); any microvascular complications − 67.6 vs 86.9% (χ^2=17.06; $P<0,001$). However, no significant differences in Hb_{A1c}: 8.32±1.83 vs 8.45±1.82% (P=0.539).

Conclusions

Patients with type 1 diabetes with disease duration 5−15 years microvascular complications recorded in 75% of cases. The increase in the prevalence of microvascular complications associated with the duration of the disease, but not with the level of Hb_{A1c}.

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Endocrine Disruptors

EP738

Endocrine disrupting chemicals exacerbate type 1 diabetes mellitus model

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It has been proposed that cellular Ca^{2+} signals activate hormone secretion. In pancreatic β cells, which produce insulin, Ca^{2+} signals have been known to contribute to insulin secretion. In previous study, demonstrated that endocrine disrupting chemicals (EDCs) such as bisphenol A (BPA) and Octylphenol (OP) could cause increase in insulin level and insulin transcription factors. But in regulations of plasma glucose level were not decreased as much as insulin increase. For identifying this phenomenon, we evaluate the HOMA-IR which is used for calculating insulin resistance, trace that EDCs has ability to increase insulin resistance. We hypothesized that EDCs disrupts calcium homeostasis and the altered intracellular calcium levels may induce insulin resistance. The expression of genes involved in transporting calcium ions to the endoplasmic reticulum (ER) was decrease while the expression of those affecting the removal of calcium from the ER was increased. Depletion of calcium from the ER leads to ER-stress and can induce insulin resistance. Taken together, these results imply that the disruption of calcium homeostasis by EDCs induces ER-stress and leads to the insulin resistance. Additionally, findings from this study suggest that imbalances in calcium homeostasis due to EDCs such as BPA and OP could promote insulin resistance and its harmfulness especially to the Type I diabetes mellitus patients.

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EP739

Stimulating effect of 17β-estradiol and TCDD and on the protein expression of cytochrome P450 1A1 gene in cellular and xenografted models of breast cancer

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Cytochrome P450 (CYP) 1A1 plays a major role in the metabolic activation of procarcinogens to carcinogens via aryl hydrocarbon receptor (AhR) pathway. Especially, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) is known as an agonist of AhR. In estrogen responsive cancers, 17β-estradiol (E2) may influence on AhR dependent expression of CYP1 family via the interaction between estrogen receptor (ER) and AhR. In the present study, the effect of E2/ER on the expression of AhR and CYP1A1 genes was investigated for MCF-7 clonal variant (MCF-7 CV) breast cancer cells expressing ER. In reverse transcription (RT)-PCR and western blot analysis, mRNA level of AhR was not altered, but its protein level was increased by TCDD or E2. The transcriptional and translational levels of CYP1A1 appeared to be increased by TCDD or E2. The increased expression of AhR and CYP1A1 induced by E2 was restored to the control level by the co-treatment of ICI 182,780, indicating that E2 induced the protein expression of AhR and CYP1A1 like TCDD via an ER dependent pathway. In an *in vivo* xenograft mouse model transplanted with MCF-7 CV cells, the protein levels of AhR and CYP1A1 of tumor masses were also increased by E2 or TCDD. Taken together, these results indicate that E2 may promote AhR dependent expression of CYP1A1 via ER dependent pathway in MCF-7 CV cells expressing ER in the absence of TCDD, an agonist of AhR. The relevance of E2 and ER in CYP1A1 activation of estrogen responsive cancers may be targeted for developing more effective cancer treatments. (This research was supported by a grant (14182MFDS977) from Ministry of Food and Drug Safety in 2016.)
Keywords: Dioxin, 17 β-estradiol, breast cancer, xenograft models, CYP1A1

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EP740

Abstract withdrawn.

EP741

24 hrs chronomics of BP/HR in terms of double amplitude, acrophase, hyperbaric index and its relation with circadian rhythm of 6-sulfatoxy melatonin in night shift nursing professionals: A Case-control study

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The present study was aimed to investigate the 24 hours chronomics of BP/HR in terms of Double amplitude, Acrophase and Hyperbaric index and its relation with circadian rhythm of 6-sulfatoxy melatonin in night shift nurses and actual day workers. 56 night shift nurses, aged 20–40 years, performing day and night shift duties were recruited from the Trauma Center, KGMU, India, and 56 age sex matched actual day workers were also enrolled as controls. BP and HR were recorded by ABPM at every 30 min intervals in day time and each hour in night time synchronically with circadian rhythm of 6-sulfatoxy melatonin during shift duties. Highly significant difference was found in double amplitude (2DA) of SBP between night (23.10 ± 14.68) and day shift (34.27 ± 16.44) ($P < 0.0005$). In night shift, hyperbaric index (HBI) of mean SBP was found to be increased at 00-03 am (midnight) while during day shift, peak was found at 06-09 am. HBI of mean HR was found to be increased at 18-21 pm during night shift while in controls, peak was found at 09-12 & again 15-18 pm of SBP, DBP & HR. Alterations in Acrophase of BP/HR were very common among night shift workers and Ecphasia was found in few night shift workers. Alteration in morning and night melatonin level was also found during night shift as compare to their day shift and in actual control group. Reverse pattern of Acrophase and HBI of BP & HR along with 6-sulfatoxy melatonin during night shift represents desynchronization. It indicates that the circadian rhythm was disrupted during night shift and recovery occurs during day shit.

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EP742

The effects of halogenated-hydrocarbon uron herbicides, as endocrine disruptor compounds on the oxytocin (OT) hormone regulation in vitro

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The biological organisms are complex systems regulated by the homeostatic back-end network. In these days the growing environmental loads (from industry, household, etc.) contain chemical exposure eg. halogenated hydrocarbons (monuron: MU ($C_9H_{11}ClN_2O$), diuron: DU ($C_9H_{10}Cl_2N_2O$)), which can be endocrine disruptor compounds (EDCs). Synthesis, release of hormones and cell processes of endocrine cells, and the biochemical properties of hormones can be changed by these agents. The disturbance of endocrine regulation by the EDCs can induce different diseases for example in the reproductive-, neurological, and/or psychical, and/or immunological system. In this study the aim was to investigate the effects of uron herbicides (fenuron: PU ($C_9H_{12}N_2O$); MU, DU) on the monoamine activated ocytocin (OT) release from neurohypophysis (NH) cells. The primary monolayer NH cell cultures were prepared from the evidenced Wistar rats (♂) for the experiments. The separated NH tissues were dissociated by enzymatic (trypsine, collagenase, DNA-se I; II) and mechanic methods. The 14 days old cultures were standardized for cell-viability and OT content. The NH cells were tested for functionally OT hormone volume by aspecific stimulus (30 mM $[K^+]$). The untreated cultures were the controls, and the treating system was the consequential: **A:** 1 hour 0.1 μg/ml EDCs; **B**: 10^{-6}M monoamines (epinephrine, norepinephrine, dopamine, histamine, serotonine) alone; **C**: combined the monoamines agents with EDCs. The OT content was measured from supernatant media by RIA method. The results showed that the uron herbicides alone did not have significant effects on the OT release in the primary monolayer NH cell cultures. The EDCs caused alteration of the monoamine activated hormone release. The uron herbicides can play as strong environmental stress factors in the homeostatic system regulation. This work was supported by: TÁMOP-4.2.2.D-15/1/KONV-2015-0010, TÁMOP-4.2.4.A/2-11-1-2012-0001.

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EP743

The protective role of *Zingiber officinale* extract against methyl thiophanate induced toxicity in male rats

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In this study, we attempted to assess the toxicity of Methyl Thiophanate (MT) on the biochemical and reproductive parameters in male Wistar rats as well as the possible protective role of *Zingiber officinale* (Ginger, Ging) extract against MT-induced toxicity. Hence, forty adult Wistar rats were allocated into four groups of 10 rats for each; the first group served as control, groups 2, 3 and 4 were treated orally (5/week) for 8 weeks by MT (150 mg/kg bw), Ging (100 mg/kg bw) and MT plus Ging respectively. At the end of experiment, blood samples were collected under anesthesia for measuring the biochemical parameters and testosterone level, while, the reproductive organs were excised and used for semen quality analysis and histopathological examinations. Results indicated that MT exposure increases the level of blood glucose, cholesterol, triglycerides, urea, uric acid, AST, ALT and total protein, whereas, no clear impact on testosterone level was noted compared to the control. Semen analysis showed a decrease in spermatids number, sperm count, motility and viability. Moreover, a marked histopathological damage in testis and epididymis was detected which reflect a poor semen quality. Ginger extract co-treatment with MT alleviates and/or repairs all adverse toxic effects caused by MT on the reproductive, biochemical and hispathological parameters. This amazing preventive role may be related to its potential antioxidant properties. In conclusion, ginger extract supplementation plays crucial protective role against MT-induced toxicity in male rats.

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EP744

Systematic screening for environmental and behavioral determinants identifies factors detrimental to skeletal health

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Background
An increasing amount of biomedical data is becoming available, and methods are needed to tackle these "big data".
Methods
We performed a systematic evaluation of 138 environmental and behavioral factors in relation to bone mineral density (BMD) in the National Health and Nutrition Examination Survey (NHANES). Dual energy X-ray absorptiometry (DXA) scans were available for total body, head, pelvis and lumbar spine for 27,259 participants from NHANES surveys 1999–2000 (A), 2001–2002 (B), 2003–2004 (C) and 2005–2006 (D). A discovery Environment-Wide Association Study (EWAS) was performed on cohorts B and D, and replication was sought in cohorts A and C.
Results
Higher serum levels of a-tocopherol (per s.d. $\beta = -0.25\%$ for lumbar spine) and of g-tocopherol ($\beta = -0.54\%$ for total body), forms of vitamin E, were associated with decreased BMD. In contrast, retinol serum levels were related to higher BMD (per s.d. $\beta = +0.21\%$ for total body). Serum lead levels had a negative relationship to BMD of the lumbar spine (per s.d. $\beta = -0.43\%$) and head (per s.d. $\beta = -0.87\%$). Higher levels of physical activity were associated with higher BMD (total body: per MET $+1.2\%$). Being a current or past smoker was associated with decreased BMD of the total body, pelvis and head.
Conclusion
In conclusion, our study demonstrates consistently that several behavioral traits and fat-soluble vitamins may have detrimental effects on BMD, while reinforcing the benefit of physical activity for skeletal health.

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EP745

Quantitative image based analysis of endocrine disruptor effects on mitochondria morphology-function in prostate cancer cells

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Persistent organic pollutants (POPs) are environmental contaminants that interfere with normal hormonal homeostasis and act as endocrine disrupting compounds (EDC). These molecules can mimic hormone effects on metabolism. The links between metabolism and cancer are now well established. Metabolism generates reactive oxygen species (ROS), which contribute to mutations and induces oncogenic transformation. In turn, cancer cells display high metabolic flexibility allowing them to grow in various cellular environments and favoring their proliferative and invasive capacities. Mitochondria are key players in this complex interplay since they produce ROS, generate energy, and participate in nucleotide synthesis and in glutamine metabolism of cancer cells. Regarding the importance of hormones on prostate cancer risk and outcomes, we are developing a multiple parameters *in vitro* assay conducted in a high-throughput screening format relevant for prostate cancer metabolism and aggressiveness. This screening method includes, *inter alia* a microscopy based analysis of mitochondria structure and function. We analyzed the effects of five EDCs (Aldrin, BDE28, TCDD, PCB153, PFOA) identified in the plasma of patients on two prostate cancer cell lines, 22RV1 (androgen-responsive) and DU145 (androgen-unresponsive). Each compound was tested in a dose dependent manner to determine its effects on ROS production, mitochondrial membrane potential, mitochondrial biogenesis and mitophagy. In addition, we performed an image based computational analysis of the mitochondrial network morphology and dynamics. This strategy allows us to extract some quantitative parameters on the mitochondrial network as fragmentation index, compactness, average volume, *etc*. When combined, morphological and functional parameters allow us to discriminate subtle perturbations of the mitochondrial structure-function induced by EDCs in prostate cancer cells. We are confident that this multiparameter analysis strategy could represent a new perspective in identification and characterization of EDCs based on their effects on cell metabolism (phenoscore) in order to estimate their potential risk on human health.

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Endocrine Tumours and Neoplasia

EP746

NENs, NETs, NECs: Accessing expert care

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Endocrine tumours are a heterogenous group of tumours, that are frequently described as "complex", "diverse"and, with few exceptions, "rare". According to the Giwice Position Statement (as issued by the European Task Group for Endocrine Tumours): Endocrine Tumours are defined…as malignant tumours arising from endocrine organs including thyroid, adrenal, parathyroid, as well as

neuroendocrine tumours in general. The research supported recommendation, to improve care, experience and outcomes, is for patient-centric endocrine cancer care in specialist centres, by multidisciplinary teams (Box: MDT members), with access to enrolment into clinical and translational research. Specialism being determined by patient volume (geographical prevalence and incidence) and centre/MDT experience in disease subtype. The Taskforce points to the ENETs Centre of Excellence Programme as an exemplar of specialist accreditation. Neuroendocrine neoplasms (NENs) can be found in endocrine glands and more diffusely throughout the body, including respiratory, digestive and urinary tracts, breast, skin and nerve structures. They display a variety of functional and infiltrative behaviours, and growth patterns. Nomenclature varies but in general is based on site of origin, grading (utilising morphology and proliferation), functionality then staging – though determining malignancy for some types is based predominantly on the presence / absence of metastases. The global incidence of NENs is rising. However despite expert recommendations and European guidelines, NET Patient experience reports suggest ongoing care deficits related, amongst other issues, difficulty in accessing clinically appropriate diagnostics, treatment and psychosocial care, including information and support.

1. http://www.endocrinecancer.eu/en/pages/statement
2. http://jgo.ascopubs.org/content/early/2016/06/03/JGO.2015.002980.full
3. http://www.netpatientfoundation.org/2016/10/npf-patient-experience-survey/

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Female Reproduction

EP747

The accuracy of lifestyle management information on websites for the management of PCOS

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Background
Lifestyle approaches (diet, physical activity and/or behavioural) play an integral part in Polycystic Ovary Syndrome (PCOS) management. The internet is widely used as a resource for health information. However, the accuracy of lifestyle information on PCOS websites is unknown. This study aimed to assess the accuracy of lifestyle recommendations on PCOS websites.
Methods
The internet search was conducted through three search engines across different web browsers and countries. Keywords "PCOS", "Polycystic Ovary Syndrome" and "Polycystic Ovarian Syndrome" were used to identify websites using a previously defined internet search protocol. Websites providing lifestyle information in less than 10 sentences were excluded. The accuracy of the information was assessed through a checklist of 29 questions developed based on National and International guidelines for diet, physical activity or weight management for the general population and PCOS with higher scores indicating greater accuracy. Websites were scored by two independent reviewers.
Results
Fifteen websites were eligible from 72 websites in total (20%). The total accuracy score was 56 ± 13 (potential range -29 to 87) comprising 23 ± 6 for diet (potential range -11 to 33), 15 ± 5 for physical activity (potential range -9 to 27) and 14 ± 3 for weight management (potential range -8 to 24). A moderate proportion of websites provided general information on appropriate diet (40–80%) or weight management strategies (47–60%) but only 10–40% of the websites provided information on aspects such as core food, discretionary foods, exercise quantity/intensity, specific energy deficits or behavioural strategies.
Conclusion
A limited number of Internet sites for PCOS contain information on lifestyle management. Of these, the majority provided information on general diet, physical activity and weight recommendations but less information on a healthy lifestyle implementation. These findings suggest that PCOS-related websites need to be improved to provide more detailed and practical information for consumers to apply to their PCOS management.

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Pituitary - Clinical

EP748

Learning from adult growth hormone deficient patients' advisory panel

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Introduction
Adult Growth Hormone Deficient (AGHD) patients have often a difficult path from diagnosis to treatment. A patient advisory panel was conducted to better understand the AGHD patient journey and how this could be supported. This format was chosen to allow for direct patient to patient interactions and discussions and for physicians to learn.
Findings
A total of nine patient advisors (three childhood-onset; six adult-onset, age 33–67 years; 4M: 5W) were invited through different US endocrinology offices for a one day meeting. All had multiple pituitary hormone deficiencies (MPHD) and received daily GH. Six HCPs attended the meeting to learn from the interactions. An independent moderator facilitated the meeting and discussion. All patients reported that their journey was challenging regardless of age at diagnosis or MPHD. They felt that there is a lack of AGHD knowledge, and unawareness among physicians and patients. Symptoms went unrecognized for years prior to-diagnoses/treatment: and included: weight gain, arthralgia, social withdrawal/apathy and extreme fatigue (labelled 'laziness'). The majority was misdiagnosed: mainly with depression and treated with antidepressants for variable period of time. The patients felt their 'life caving in'. Some were too fatigued to go to the doctor. After diagnosis, it sometimes took months to get on GH replacement therapy due to insurance issues and finding a physician who would treat. Support was very limited without the opportunity to learn about AGHD or connect with other patients. The advisors proposed several ideas to improve their experience, i.e. education of HCPs, and patients, patient ambassador programs, patient panels etc.
Conclusions
Hearing live from patients is an innovative way of learning outside the traditional clinical setting. We identified a major need for more education, awareness, and resources for AGHD patients as well as physicians to improve their care.

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Thyroid (non-cancer)

EP749

Iodine supplementation in children and pregnant women from rural areas of Belarus in 2015–2016

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The efficiency of the Belarusian model for iodine deficiency elimination based on obligatory use of iodized salt in the industrial food production and bread baking has been often challenged in other countries. In support the facts are presented evidencing of insufficient iodine intake in groups of increased risk of iodine deficiency in children and pregnant women from the rural areas of Belarus. The goal of the recent study is to compare the dynamics of iodine supplementation for the period of 2015–2016 in groups of increased risk in Brest region. The iodine status of the body was determined by the iodine urine concentration. The study included 30 pregnant women examined in 2015 and 40 pregnant women examined in 2016 aged 23–32 years, and 51 children examined in in 2015 and 44 children examined in 2016 aged 8–14 years. Statistical processing was performed by nonparametric statistics.In 2015 in the rural area ioduria median was 165.7 μg/l in children and 107.5 μg/l in pregnant women. Iodized salt was used by 86.2% of schoolchildren and only 66.7% of pregnant women. In 2016 ioduria median in children of the same region increased to 233.0 μg/l, and in pregnant women to 152.4 μg/l. Iodized salt in 2016 was used by 89.4% of schoolchildren and 78.8% of pregnant women. Thus, the Belarusian model of iodine deficiency elimination having been used since 2001 has demonstrated its long term efficiency even in the risk groups of iodine deficiency development.

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Eposter Presentations: Interdisciplinary Endocrinology

Adrenal Cortex (to include Cushing's)

EP750

Comparison of 17-OH-Progesterone results by a radioimmunoassay and a chemiluminescent assay

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Introduction
The major clinical importance of 17-OH-Progesterone is related to the diagnosis and therapeutic monitoring of Congenital Adrenal Hyperplasia (CAH). Radioactive assays are widely used in clinical laboratories for measuring 17-OH-Progesterone. The appearance of a non-isotopic, chemiluminescent automatic assay, may be an interesting alternative if the performance of the assay remains the same or higher.
Obective
To compare the 17-OH-Progesterone results by a radioimmunoassay (RIA) and a chemiluminescent assay (CLIA) and to analyze the clinical impact taking into account the % concordance.
Material and methods
We studied 74 patients, aged 6 months to 83 years old, observed at CHLC endocrinology appointments, in Lisbon. The serum samples were analyzed by '17α-Hydroxyprogesterone (17-OHP)-RIA-CT', DIASource (wr: 0.04–12.5 ng/ml) and 'Maglumi 17-OH Progesterone (CLIA)' Snibe (wr: 0.1–20 ng/ml). An excel tool was used for statistical treatment and the clinical concordance of patients was analyzed according to the reference values of both. For statistical comparison nine patients were excluded and to analyze the clinical impact we divided patients into groups according to age and gender.
Results
Pearson correlation coefficient $r=0.90$ and the equation of linear regression was:$y=0.46x+0.17$. Group 1 = 24 both gender (6m-11y); Group 2: 12 male (12 y-47y); Group 3: 38 female (13y–83y). For the group 1 and 2: % agreement was 62.5 and 66; It was impossible to classified 25% of group 1 because CLIA has no reference values for age. Group 3 had insufficient clinical data.
Conclusion
There is a good correlation but in order to become an alternative to RIA it is fundamental to have reference values between 3 months and 3 years for a further reassessment since its main usefulness is the diagnosis and monitoring of CAH.

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Calcium and Vitamin D Metabolism

EP751

The effect of parathyroidectomy on graft function in kidney transplant recipients with persistent hypercalcemia

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Although serum calcium (Ca), phosphorus and parathyroid hormone (PTH) levels tend to normalize after successful kidney transplantation (KT), persistent hyperparathyroidism (PHPT) can have deleterious effects on graft function. We aimed to evaluate the effect of parathyroidectomy (PTx) on graft function in recipients after KT.
Methods
This retrospective study conducted in 319 adult KT recipients. PHPT is defined as serum corrected Ca level >10.2 mg/dl (at least twice in a 6 month period) and PTH >150 pg/ml at 6th month of KT.
Results
The mean follow up time was 49.4 ± 1.4 months. Mean serum PTH levels before and at 12th month of KT and prevalence of hyperparathyroidism were 529 ± 474 and 212 ± 236 pg/ml, and 83.9% and 51.9%, respectively. Fifteen recipients with PHPT received cinacalcet for an average of 14.2 ± 5.7 months. After cessation of cinacalcet therapy, serum Ca levels increased within 6 month. Mean serum Ca levels at 1st, 6th and 12th months of 12 recipients who underwent PTx before KT were 9.3 ± 1.2, 9.6 ± 0.8 and 9.2 ± 1.2 mg/dl, respectively. The duration between PTx and KT in 16 recipients who underwent PTx after KT was 17.1 ± 8.9 months (range 5–41 months). Two of 16 had operation at 5th and 1 at 7th month of KT because of severe hypercalcemia. Mean serum Ca levels of 16 recipients at 1st, 6th and 12th months of KT were 10.5 ± 0.9, 10.8 ± 0.9 and 10.6 ± 0.9 mg/dl, respectively. There was no significant difference in graft function between post-transplant follow-ups in both groups.
Conclusion
In recipients who underwent Ptx before and after KT, PTx provided sustained decrease in serum Ca and PTH levels without affecting graft function.

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EP752

The effect of corticosteroids on development of femoral head osteonecrosis in patients after kidney transplantation

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Corticosteroid-induced osteonecrosis is seen in 3–4% of patients undergoing kidney transplantation (KT), especially at the head of the femur. The use of corticosteroids for any reason is responsible for approximately 41% of total hip arthroplasty performed due to osteonecrosis. In this study, we investigated factors affecting osteonecrosis development after KT
Methods
Among 205 recipients who underwent KT, 32 (15.6%) had symptomatic femoral head osteonecrosis (FHO group). Fifty patients who were similar in terms of age, sex, and posttransplant follow – up period constituted the non-FHO group.
Results
The gender, age and pre-transplant BMI of both groups were similar. In patients who developed FHO, the onset of symptom was median 6 months (range: 1–40). In patients who developed bilateral FHO, the mean duration of symptomatic change in the other hip was 2.1 months (range: 0–6). The median value of the patients' diagnosis time was 9 months (range: 1–40). The serum creatinine, calcium, phosphorus, ALP and PTH values at 1st, 6th and 12th after KT in both groups did not differ. There was no significant difference in hip and lumbar DEXA values between the groups in terms of osteonecrosis development. Three patients (9.4%) in the FHO group and seven patients (14%) in the non-FHO group had steroid treatment before KT. Cumulative steroid doses taken after KT the FHO and non-FHO groups were 6366 mg (range: 3230–10947) and 5664 mg (range: 3717–13887) at 12th month ($P=0.068$). A total of 17 hips total hip prosthesis were performed in 11 patients (six female, five male, mean age 45.2) who developed FHO.
Conclusion
We did not find any association between post-transplantation FBO development, lumbar and femoral bone density measurements, and steroid doses.

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Cardiovascular Endocrinology and Lipid Metabolism

EP753

Resveratrol increases hepatic *SHBG* expression through human constitutive androstane receptor: a new Contribution to the French Paradox

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Sex hormone-binding globulin (SHBG) carries sex steroids in blood regulating their bioavailability. Red wine consumption increases plasma SHBG levels, and we have discovered that resveratrol, a polyphenol enriched in red wine, acts specifically through the human constitutive androstane receptor (CAR), a drug/xenobiotic detoxification gene regulator, to increase hepatic SHBG production. Chromatin immunoprecipitation and luciferase reporter gene assays show that human CAR binds to a typical direct repeat 1 nuclear hormone receptor-binding element in the human SHBG proximal promoter. Resveratrol also increased hepatic SHBG production in humanized SHBG/CAR transgenic

mice. Moreover, SHBG expression correlated significantly with CAR mRNA levels in human liver biopsies. We conclude that the beneficial effects of red wine on the metabolic syndrome and it associated co-morbidities, including cardiovascular disease and type 2 diabetes, may be mediated in part by resveratrol acting via CAR to increase plasma SHBG levels.

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EP754

Therapeutic potentials of small molecular weight allosteric agonist of relaxin receptor

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The anti-fibrotic, vasodilatory, and angiogenic therapeutic properties of relaxin peptide have been shown in several animal models of human diseases and in clinical trials. Using high-throughput screening of small molecule library, structure-activity relationship (SAR) studies, ligand-receptor interaction modeling, site-specific mutagenesis, and transgenic animal studies we discovered the first series of small molecule agonists of relaxin GPCR, RXFP1. The lead compound ML290 is a selective RXFP1 agonist with low cytotoxicity, preferred *in vitro* ADME and *in vivo* pharmacokinetic properties. ML290 displays efficacy similar to the natural hormone in several functional assays *in vitro*. ML290 activates human, macaque, pig, and rabbit RXFP1, but not rodent receptors. Computational modeling of small molecule binding with human RXFP1 and related receptors in combination with site-directed receptor mutagenesis studies indicated that the small molecules activated RXFP1 through an allosteric site and did not compete with relaxin binding to RXFP1. To test agonist activity *in vivo* we produced mice with knock-in of human RXFP1 into mouse gene. The analysis of transgenic mice showed that the human receptor fully complement the deletion of mouse gene. Intravenous injection of relaxin led to a rapid increase in heart rate in unconscious WT and humanized mice, but not in *Rxfp1* deficient animals. The ML290 injection increased heart rate in humanized but not in WT animals suggesting specific target engagement by small molecule agonist *in vivo*. Similar to relaxin IV injections of ML290 caused increased blood osmolality. Therapeutic potentials of the small molecular weight relaxin receptor agonist can be now tested in various preclinical cardiovascular and fibrotic models of human diseases.

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EP755

PCSK9 inhibitors effects on lipid profile in familial hypercholesterolemia in a specific Lipid Unit: experience in first year commercialization

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Objective
Analyse the features of first patients treated with PCSK9 inhibitors in a specific Familial dyslipidemia Unit and the effects on lipid profile in first months of treatment.
Material and methods
Data from patients with heterozygous familial hypercholesterolemia treated with PCSK9 inhibitors were reviewed. Clinical data, physical examination and analytical data were collected at baseline, one month and 3 months.
Results
Data were obtained from 13 patients, 45.5% male. Mean age: 49.5 years (26-74). Mean follow-upin our Unit:12 years. Diagnosis by DLC: 100% score higher than 6. 54.6% had been detected with family cascade screening, 45.5% cases with mutation detected in LDL-R. Initial levels in our clinic: CT: 313.5 mg/dl, TG: 102 mg/dl, LDL 228 mg/dl, HDL: 52 mg/dl, non-HDL C: 202 mg/dl, despite 45.5% had already started treatment. 72.7% had a family history of premature CVD, Diabetes 18.2%, smokers 18.2%,HTA 36.4%, high lipoprotein(a) 45.5%, early CVD 54.6%. 72.7% treated with statins (73.6% rosu and 9.1% atorvastatin) and ezetimibe. 44.4% had elevated transaminases with at least two statins and 27.3% did not tolerate any statin. Patients performed regular physical exercise (at least 180 min per week) and diet (100% BMI $<$ 30).100% of the subjects had LDL levels at least 60 mg/dl above therapeutic target. The mean pre and postreatment levels were: TC: 243.8 $\pm$ 27.7 vs 148.5 $\pm$ 47.4 mg/dl (*P* 0.01), LDL-C: 159 $\pm$ 23.9 vs 69.9 $\pm$ 39.3 (*P* 0.01), 100% in therapeutic objective, HDL-C 58.5 $\pm$ 14.4 vs 56.6 $\pm$ 16.1 (*P* 0.7), non-HDL-C 185.3 $\pm$ 21.5 vs 91.8 $\pm$ 32.7 (*P* 0.01), 100% on therapeutic target, TG 130 $\pm$ 46.2 vs 109 $\pm$ 54.8 (*P* 0.3), Apo B 136 $\pm$ 19.9 vs 64.3 $\pm$ 11.04 (*P* 0.01), lipoprotein (a) 133.1 $\pm$ 9.9 vs 112.5 $\pm$ 5.1 (*P* 0.04). Only 2 patients had mild side effect: one patient with pseudogripal syndrome that spontaneously disappeared in 2 days and another patient with injection site reaction.
Conclusion
PCSK9 inhibitors were well tolerated and significantly reduced levels of TC, LDL-C, ApoB, non-HDL C and lipoprotein a, with 100% of patients achieving therapeutic goals after 3 months of treatment.

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EP756

Non-lipidic effects of PCSK9 inhibitors in real life

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Objective
Analyse possible effects on physical examination, blood count, liver and kidney function, and steroidogenic hormones synthesis. Know the satisfaction of patients with the first injectable treatment for hypercholesterolemia approved in our country.
Material and methods
Data were collected from patients with heterozygous familial hypercholesterolemia treated with PCSK9 inhibitors. Clinical, physical and analytical data were collected at baseline, 1 month and 3 months. Satisfaction test (TQ21M-9) was performed 3 months after treatment.
Results
Data were obtained from 13 patients, 45.5% male. Mean age: 49.5 years (26-74). Mean pre and postreatment levels were: TC: 243.8 $\pm$ 27.7 vs 148.5 $\pm$ 47.4 mg/dl (*P* 0.01), LDL-C: 159 $\pm$ 23.9 vs 69.9 $\pm$ 39.3 (*P* 0.01), non-HDL-C 185.3 $\pm$ 21.5 vs 91.8 $\pm$ 32.7 (*P* 0.01), Apo B 136 $\pm$ 19.9 vs 64.3 $\pm$ 11.04 (*P* 0.01), lipoprotein (a) 133.1 $\pm$ 9.9 vs 112.5 $\pm$ 5.1 (*P* 0.04). HbA1c 5.9 $\pm$ 0.4 vs 5.70.3 (NS), creatinine 1.01 $\pm$ 0.3 vs 0.92 $\pm$ 0.2 (NS), GOT 34.7 $\pm$ 34.2 vs 34.6 $\pm$ 21.9 (NS), GPT 29.8 $\pm$ 18.7 vs 28.2 $\pm$ 13.9 (NS). Weight: 70.9 $\pm$ 11.2 vs 73.5 $\pm$ 11 kg (NS). No effects were detected in blood count, systolic, diastolic BP or heart rate. The mean levels of hormones were: Testosterone 4.3 $\pm$ 1.4 vs 4.04 $\pm$ 1.8 ng/ml (NS), TSH 2.2 $\pm$ 0.8 vs 2.14 $\pm$ 0.8 mU/l (NS), T4l 16.3 $\pm$ 1.1 vs 14.8 $\pm$ 0.4 (NS) ACTH 24.2 $\pm$ 17.7 vs 30.2 $\pm$ 25.2 (NS), Cortisol 14 $\pm$ 2.9 vs 16.6 $\pm$ 2.1 (NS) Vitamin D3 41.5 $\pm$ 49.1 $\pm$ 18.2 ng/ml (NS). Patients showed a high level of satisfaction with treatment, with mean scores of 75.9% for effectiveness items, 80.2% convenience items and 85.2% overall satisfaction.
Conclusion
Despite the decrease in TC and LDL C levels, there were no significant changes in the levels of stereogenic hormones or vitamin D levels. Treatment with PCSK9 inhibitors did not change hemogram, hydrocarbon metabolism, kidney, liver function, or physical examination parameters. Patients show a high satisfaction with this injectable treatment for hypercholesterolemia.

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EP757

Renal function preservation with Manidipine vs Amlodipine in type 2 diabetic hypertensive patients with persistent microalbuminuria

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Objectives
The AMANDHA randomized study (PROBE design) showed that the addition of Manidipine 20 mg vs Amlodipine 10 mg for 2 years in 91 hypertensive type 2 diabetic patients with persistent microalbuminuria, uncontrolled with a renin-angiotensin system inhibitor (given full-dose for at least the 6 previous months) was more effective in reducing albuminuria in spite of similar blood pressure control. Patients with significant renal impairment (PlCr >1.4 mg/dl in women and >1.5 in men) had been excluded. However, no data were published on the progression of renal dysfunction, with only PlCr values reported, which were not significantly different. We undertook to establish if there were differences in glomerular filtration rate (GFR) progression.
Methods
Post-hoc analysis of AMANDHA. GFR was estimated by the MDRD-4 equation for each individual measurement. Point-to-point GFR were compared by unpaired *t*-test and progression was compared by the Kruskal-Wallis test. (non-parametric ANOVA). Values are given as mean ($\pm$S.E.M).
Results
Baseline GFR were 67.3 ($\pm$5.2) and 70.2 ($\pm$5.0) ml/min/1.73 m^2 with Manidipine and Amlodipine, respectively; at 6 months they were 68.6 ($\pm$5.6) and 69.5 ($\pm$5.3), and at two years 66.9 ($\pm$4.7) and 65.5 ($\pm$5.0). During follow-up, patients treated with Manidipine lost 0.4 ($\pm$3.9) ml/min per 1.73 m^2 of FGR vs 4.7 ($\pm$5.2) with Amlodipine. Point-to-point GFR were not significantly different between the groups, but GFR loss after two years was lower with Manidipine ($P=0.032$).
Conclusions
The previously published data of AMANDHA showed a markedly greater albuminuria reduction (about 40% more) with Manidipine vs Amlodipine, which was attributed to efferential arteriole dilatation. The present *post-hoc* analysis also shows a better preservation of renal function with Manidipine. These results strengthens the case for combined treatment with Manidipine and a renin-angiotensin system blocker in hypertensive type 2 diabetic patients with persistent microalbuminuria.

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EP758

Effects of calcineurin inhibitors on abdominal obesity in kidney transplant recipients

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Calcineurin inhibitors (CNI, cyclosporine A: CsA and tacrolimus: Tac) cause posttransplant diabetes mellitus, hypercholesterolemia and hypertension. Post-transplant weight gain can be related to the type of CNIs. Distribution of obesity is one of the major predictors of cardiovascular diseases. Several indices assessed upper body obesity such as waist circumference (WC) and waist to hip ratio (WHR) are more accurate than whole body obesity (body mass index: BMI). This study aimed to compare the effects of CNIs on obesity after kidney transplantation.
Methods
The 133 consecutive transplant patients were randomized into 2 groups: CsA ($n=62$) and Tac ($n=71$) for two years. In all patients, BMI, body fat percentage, WC, hip circumference (HC) and WHR were measured.
Results
The weight, BMI, body fat percentage, WC and HC were significantly increased up to month 24 in both groups. There was no significant difference in increases of BMI, WC, WHR and body fat percentage between both groups. The ratio of diabetics in CsA group was higher than Tac group (21% vs 1.4%, $P<0.001$). The ratios of de novo diabetics (4.8% vs 12.7%) and hypertensives (29% vs 26.8%) were similar in the CsA and Tac groups, respectively. Although the abdominal obesity ratios in the CsA and Tac groups increased, the ratios were comparable in the preoperative (17.7% vs 23.9%), after 12 (37.3% vs 39.3%) and 24 (40% vs 45.9%) months of transplant, respectively. There was no significant difference in glucose and lipid profile between CsA and Tac groups.
Conclusion
The type of calcineurin inhibitor used did not affect anthropometrical measurements throughout two years although both of them caused weight gain after transplant.

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EP759

Anthropometric measurements, nutrition and exercise habits in kidney transplant recipients

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After a successful kidney transplant, the nutrition of patients is improved and they gain weight. Increased appetite due to medication, age of transplant, gender, race, pre-transplant obesity story and dialysis type increase the obesity frequency. We aimed to evaluate the effect of gender on nutrition and exercise habits on transplant recipients.
Methods
Stable patients were divided into two groups according to gender: 29 males and 33 females. Their nutrition and exercise habits of recipients were questioned by a survey. The 3-day dietary regimen of all patients was studied using the BEBIS™ programme.
Results
Charateristics of groups similar. BMI, blood pressure, hip circumference, suprailiac and suprascapular fold thicknesses of the groups were not different. The waist (90.3 vs 98.2 cm, $P=0.01$), mid-arm (27.2 vs 28.9 cm, $P<0.05$), triceps (16.1 vs 11.8 cm, $P<0.01$) and neck (36.6 vs 41.5 cm, $P<0.001$) circumferences in female recipients were lower than those of males. The body fat percentage of females (30.9 vs 23.8, $P<0.01$) were lower. HDL levels in males are significantly lower among lipid and apolipoprotein levels. The ratios of eating at home, using oils and exercising in both groups were similar. When recipients' daily diets were evaluated, intake of fat in males was higher than that of females (63.3 ± 4.1 vs 70.1 ± 3.1 g, $P<0.05$). There was no difference in total energy (1645 ± 68 vs 1681 ± 62 kcal), water (1590 ± 79 vs 1665 ± 76 ml), protein (70.4 ± 4 vs 75.8 ± 3.5 g), carbonhydrate (197.7 ± 9 vs 191.8 ± 11.4 g), fiber (25.7 ± 2.4 vs 24.1 ± 1.7 g) and polyunsaturated fatty acid (12.8 ± 1 vs 13.4 ± 1) intakes between females and males, respectively. Also vitamin intake of both groups were comparable except carotene intake of females (5.3 ± 0.4 vs 4 ± 0.3, $P<0.05$).
Conclusion
We observed no difference in nutrition and exercise habits between male and female recipients. Although the percentage of body fat in males was lower, the amount of fat consume in their diets was higher. The waist and neck circumferences, which is important for the risk of cardiovascular disease, were higher in males.

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EP760

Hyperglycemia as a factor changing the level of the patient's rehabilitation after ischemic stroke

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The aim of the study was to defined the level of rehabilitation after the stroke depending on the type of hyperglycemia.
Materials and methods
The retrospective analysis of 122 (54 female and 68 men) cases of ischemic stroke (IS) has been done. The diagnosis of IS was confirmed by computer tomography. According to the level of hyperglycemia at the debut of IS the patients were divided into three groups. Group 1 (60 patients) – with normoglycemia, group 2 (27 patients) – with stress hyperglycemia and group 3 (35 patients) with chronic hyperglycemia. At the beginning and the end of hospitalization the level of neurological deficit was determined according to NHSS scale. The comparison of averages was carried out using the Kruskal-Wallis test (a posteriori pairwise comparisons were made using the method of Niemen), program R Foundation for Statistical Computing, Vienna, Austria (Version 3.2).
Results
The patients with normoglycemia and stress hyperglycemia have had the same level of rehabilitation (50% (CI: 45–75%) and 50% (CI: 32–73%) respectively). The statistical significant difference has been found between groups 1 and 3. In patients with chronic hyperglycemia the average relative level of rehabilitation was 33% (CI: 22–50%, $P=0.023$). The level of rehabilitation of patients 60 years old was 57% and between 60–75 years old and older this level was 50%.

Conclusion
The negative influence of chronic hyperglycemia has been revealed. The stress hyperglycemia does not influence on the level of rehabilitation The age exerts on the regress of neurological deficit regardless of the hyperglycemia kinds.

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EP761

An investigation into role of circulating concentrations of vitamin D and calcium in the development of hypertension and related cardiovascular diseases

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Vitamin D plays a key role in the control of cardiovascular diseases (CVDs), acting as negative regulator of renin-angiotensin-aldosterone-system (RAAS), whereas calcium directly affects central blood pressure (BP) control center, nucleus tractus solitarus. We investigated associations between plasma concentrations of vitamin D and calcium and BP in 100 hypertensive CVDs patients and 100 normotensive subjects of 21–60 years. Vitamin D concentrations were measured using ECLIA system, whereas calcium concentrations were determined using spectrophotometric system. Data were analyzed using Student's *t*-test, ANOVA and Pearson correlation *r*. Out of 10 RAAS inhibitors (RAASi) treated patients, nine were vitamin D deficient and one was vitamin D insufficient. Of 29 non-RAASi treated patients, 28 were vitamin D deficient and one was vitamin D insufficient. Among 36 patients treated with combination of RAASi and non-RAASi, 35 were vitamin D deficient and one was vitamin D insufficient. Out of 25 untreated patients, 22 were vitamin D deficient and three were vitamin D insufficient. Ninety one control subjects were vitamin D deficient, eight were vitamin D insufficient and one was vitamin D sufficient. In patients treated with RAASi, calcium concentrations were at lower limit of normal range in 7 and at upper limit in 3. In non-RAASi treated patients, calcium concentrations were at lower limit in 13 and at upper limit in 16. In both RAASi and non-RAASi treated patients, calcium concentrations were at lower limit in 27 and at upper limit in 9. In untreated patients, calcium concentrations were at lower limit in 15 and at upper limit in 10. In control subjects, calcium concentrations were at upper limit in 21, at lower limit in 77 and below lower limit in 2. There were weak correlations between vitamin D and calcium concentrations and mean BP and systolic and diastolic BP in all patients.

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Clinical Case Reports - Thyroid/Others

EP762

Multiple autoimmune syndrome: about six observations

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Introduction
Autoimmune disorders are known to be more frequent in women and often associated each others, but it is rare to see multiple autoimmune diseases in a single patient. Multiple autoimmune syndrome (MAS) is defined as the combination of at least three autoimmune diseases in the same patient. The pathogenesis of MAS is not known. Genetic, infectious, immunologic and psychological factors have all been implicated in its development.
Observations
We report six new observations of MAS.
Results
Observation 1: A 24-year-old female patient followed for Hashimoto's thyroiditis, Addison disease and celiac disease. The patient was explored for cytolysis. The diagnosis of autoimmune hepatitis was retained and the patient was treated with oral corticosteroid and azathioprine. *Observation 2*: A 61-year-old woman without special history who was diagnosed to have autoimmune hepatitis, celiac disease, autoimmune pancreatitis and sclerosing cholangitis. The patient was put on a gluten-free diet, corticosteroid therapy, azathioprine and ursodeoxycholic acid. *Observation 3*: A 37-year-old man, with a history of vitiligo and Hashimoto's thyroiditis, presented asthenia and normocytic normochromic anemia. Biermer's disease and celiac disease have been diagnosed. *Observation 4*: A 41-year-old woman with a history of Hashimoto thyroiditis presented a dry syndrome and asthenia and liver cytolysis. The anti-nuclear, anti-SSA and anti-SSB antibodies were positive and labial biopsy showed a lymphocytic sialadenitis stage III of Chisholm confirming the association autoimmune hepatitis and syndrome of Gougerot Sjogren. *Observation 5:* A 29-year-old female patient with a history of Type 1 diabetes, Basedow and Addison diseases was diagnosed to have a celiac disease revealed by diarrhea and abdominal pain. *Observation 6*: A 31-year-old woman follwed for Systemic erythematosus lupus and Gougerot Sjogren syndrome presented a persistent anemia. Anti-transglutaminase antibodies were positive and duodenal biopsies showed subtotal villous atrophy confirming celiac disease.
Conclusion
Patients with autoimmune diseases have a tendency to develop additional autoimmune disorders indicating the need for continued surveillance for the development of new autoimmune disease in predisposed patients.

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EP763

Endocrine complications in a female patient with β-thalassemia major following bone marrow transplantation

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We report the case of a 14-year-old female patient with β-thalassemia major (β-TM) that presented numerous endocrine complications following bone marrow transplantion (BMT). The patient was admitted in our department for endocrine evaluation 3 years after BMT. She was diagnosed with β-TM at 1 year of age and received chronic blood transfusions and oral chelating therapy until 2012 when BMT was performed. The patient developed acute skin and intestine graft-versus-host-disease remitted with glucocorticoids and suffered severe convulsions as a result of cyclosporine administration with two subsequent vertebral fractures appearance (T5–T6). At first admission in our department she complained of irregular menses. The physical exam revealed H = 148.4 cm (− 2.33 S.D.), BMI = 20.17 kg/m^2, Tanner P5B5. The laboratory tests were normal, except for low normal estradiol (34.4 pg/ml) with elevated FSH (57.9 mIU/ml), low 25-OH-vitamin D and high titre of thyroid antibodies with normal thyroid hormones level. The thyroid ultrasonography showed a hypoechoic, heterogeneous thyroid with increased vascularity. DXA whole-body revealed low bone mineral density (*Z* score = − 2.2 S.D.) and the vertebral MRI showed reduced vertebral height at T6–T8 and L3–L5. She started treatment with Duphaston and vitamin D. At 1 year follow-up, she presented normal menses, both FSH and estradiol normalized (FSH = 5.11 mUI/ml, E_2 = 76.37 pg/ml) and no further fractures occurred.
Conclusion
Endocrinopathies are a common late effect of both β-TM and BMT, resulting in thyroid dysfunction, impaired growth, ovarian insufficiency and decreased bone mineral density. Because of the possible endocrine complications, lifelong endocrine follow-up is necessary in these patients.

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EP764

Association of Basedow disease with pernicious anemia: a case report

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Introduction
Immunologic background often present different association of two or more autoimmune diseases. However the coexistence of Basedow disease (BD) – the prototype of these disorders - with pernicious anemia (PA), sometimes as a component of pancytopenia, is rarely described. Between 50 patients operated on immunologic hyperthyroidism in a 20 years period only one case related this uncommon combination.

Case report
AB, a 46-year-old woman with a long standing BD treated from 1 year with antithyroid drugs (propylthiouracil) and β-blockers (propranolol) recorded a notable clinical improvement but with stationary or even increase size of her diffuse goiter. In addition she charged in the last three months palled skin, giddiness, tiredness, anorexia and coldness of the extremities. Laboratory workup showed TSH = 4.6 mU/l, fT_4 = 38 pmol/l, fT_3 = 9 pmol/l, TRAB = 1.8 = 1.8 UI/l. Current thyroid scan and US objectifies a diffuse 8×6 cm homogeneous, hypervascularised gland with uniform uptake. Though full blood count indicate pancytopenia with normochromic, normocytic anemia (Hb = 9 g/dl, MCV = 88 fL, MHCH = 34 q/l). Also total white count was 3400 μ/l, platelet count was 48 000 μ/l and reticulocyte count was 1%. Peripheral smears show oval macrocytes, hypersegmented granulocytes and anisopoikilocitosis so a diagnosis of megaloblastic anemia secondary to Vitamin B12 deficiency was established. The standard treatment with intramuscular cyanocobalamin obtained substantial resolution of woman's symptomatology. However maintained thyroidomegaly prompted our patient to undergo surgery. An adjusted near total thyroidectomy (Dunhill technique) was practiced followed by a smooth postoperative course. Histological examination of the operative piece (150 g) showed all stygma of thyrotoxicosis. Astoningshly endocrine equilibration was obtained together with positive hematological response occuring gradually within few months and maintaining further.
Discussions and conclusion
1–3% of patients with immunogenic hyperthyroidism (BD) have associated hematological disorders as single-cell lineage abnormalities like pernicious anemia and related troubles or pancytopenias. In all cases BD precedes the blood disease. Causes of these pathologic coincidences reside unlikely as pure coincidence but rather from reciprocal influence, immune-mediate effects, outcomes of antithyroid therapy or vitamin B12 deficiency. Appropriate surveillance of all cases of untreated or treated BD is mandatory, recommended for early detection of pernicious anemia as for other autoimmune disorder.

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EP765

Chronic hyponatremia caused by Thiazide diuretic: A case report

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Introduction
Hyponatremia (defined as a serum sodium level <135 mmol/l), is seen in in 15–30% in hospital setting, especially in intensive care units. Certain drugs (e.g.Thiazides diuretics) used in everyday clinical practice, may induce hyponatremia, more frequently in elder women.
Case report
A 76-year-old woman presented at emergency unit with complaints: physical weakness, nausea, vomiting, extreme fatigue and abdominal pain. She was under arterial hypertension treatment with Valsartan/Hydroclortiazide 160/25 mg 2 pills/day for 4 years. She was presented many times at emergency unit, during last 4 years with the same complaints, but she was never evaluated about the cause of hyponatremia. Her life quality and cognitive performance were getting worse during this time. Objective examination: Overall condition poor, pale face, stupor, incoherent answers to different questions, TA 170/80 mmHg, Fc 80/min, SO_2 97%, lungs normal, abdomen soft, liver, spleen, kidneys were normal, legs free of edema. Laboratory examinations revealed: Severe hyponatremia, hypokalemia, hypochloremia and metabolic alcalosis (Na + 102 mmol/l; K + 2.8 mmol/l; Cl-71 mmol/l,Ph = 7.49), others biochemical blood test and hemograme were normal. Urine analysis: density 1007,pH 7. Imagery examination: Head CT: showed no acute lesions, hypodens areas, cortical subatrofi. Chest CT: normal. EKG normal. She was treated for 2 days in Intensive unit care with 3% NaCl sol, KCl 7.5%, $MgSO_4$ 25%iv, correcting Na +, 10 mmol/l daily. After initial improvement, she was transferred to Endocrinology Unit for further treatment. After normalization of blood electrolytes, we looked for the cause of hyponatremia. In literature treatment with Hydrochlortiazide was reported as the cause of hyponatremia and hypokalemia especially in elder women. She was informed about the drug adverse effect and the importance of never using it again. She dehospitalized with overall improved conditions. During follow up, blood electrolytes resulted normal and her life quality and cognitive performance were improved.
Conclusion
Our case confirms that, Thiazides can induce hyponatremia, especially in elderly female patients. Chronic hyponatremia, must be seriously evaluated, to find out the cause and to be corrected if possible. Correction of hyponatremia can improve cognitive performance and life quality. We must be careful while treating an older female patient with Thiazides.

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EP766

Raynaud phenomenon in a young PCOS patient

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Polycystic ovarian syndrome presents in 4–8% of women worldwide, making it the most common reproductive age endocrinopathy. Rheumatological concomitant diseases are extremely rare in PCOS patients, especially Raynaud's phenomenon. Condition that, lowers the quality of life in patients, suggesting hormonal imbalances despite years of treatment. Studies show that oestrogen plays a role in the vasculature, it is exogenous administration increases the endothelium dependent dilation. Treatment of the phenomenon is symptomatic, wearing gloves, avoiding triggering factors, and lastly pharmacotherapy or sympathetic blockade in severe cases to avoid digital ischemia. We are presenting a rare case of dermato-rheumatological involvement in a PCOS patient. 24-year-old woman, diagnosed with PCOS in 2010 was treated with multi drug therapy including: Metformin up to 1500 mg daily, oral contraceptive pill, spironolactone up to 150 mg daily, Topiramate 50 mg daily for migraine headaches and Liraglutide 0.6 mg with varying regimens throughout the years. In winter 2014 she presented with the first symptom of Raynaud's phenomenon (RP). However that has been ignored until 2016; – 1 year after the discontinuation of oral contraception, the patient reported; pain upon dishwashing, hand washing, and increased frequency of the phenomenon despite wearing double winter gloves. She was then referred to a rheumatology department, underwent capilaroscopy exam, which revealed dilated capillary nail beds. The following laboratory tests; ANA-HEp2 was elevated – 1:640 (<1:80 norm) of a granular type. Antibody panel characteristic for connective tissue diseases was all negative except for – DFS 70 being mildly elevated. The antibody is typical for an autoimmune rather than rheumatological ethology. No other abnormalities were found in the blood morphology, rheumatoid factor nor erythrocyte sedimentation rate. Syndrome as common as PCOS should be of a concern across different hospital departments, the complexity of the pathomechanism and treatment regime should alert us for further clinical consequences.

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EP767

Polyglandular autoimmune syndrome type III-case report

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The term polyglandular autoimmune syndrome (PAS) is used when there is a dysfunction of two or more endocrine glands associated with circulating antibodies directed at organspecific included glands. Neufeld and Blizzard classified PAS into two categories: type I and type II with the newly added category, type III, which does not include the adrenal cortex. PAS III includes several autoimmune diseases (autoimmune thyroiditis, immune-mediated diabetes mellitus, pernicious anemia, vitiligo, alopecia areata, and many others) and is divided into four sub-categories. We report a 44-year-old patient who was hospitalized in August 2016 at our department with suspected polyglandular autoimmune syndrome. In 2013 he was repeatedly evaluated at gastroenterology department where were established the diagnoses of primary hemochromatosis (homozygous mutation in the gene p C282Y HFE), Crohn's disease and celiac disease, as well as candidiasis in May 2016. In our department, the endocrinological testing establish the existence of autoimmune thyroiditis (anti -TG 207.1 IU/ml; antiTPO 141.0 IU/ml) without disorders of thyroid function and the presence of insulin resistance.

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EP768

Resistance of SIAD to tolvaptan despite initial control in progressive small cell lung cancer

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A 58-year-old male was admitted through the emergency department with symptomatic severe euvolemic hyponatremia. Biochemistry was consistent with SIAD (plasma sodium (pNa) 107 mmol/l, plasma osmolality 230 mOsm/kg, urine sodium 36 mmol/l, urine osmolality (UOsm) 638 mOsm/kg, 0900 h plasma cortisol 484 nmol/l and thyroid function tests normal). Chest X-ray was normal but CT thorax confirmed a lung mass suspicious for malignancy. As the patient had symptoms of cerebral irritation, including drowsiness and confusion, he was treated with hypertonic (3%) saline infusion; pNa rose by 13 mmmol/l over the 48 h and symptoms resolved. Water deprivation caused no further rise in pNa so the patient underwent tolvaptan challenge; pNa rose from 121 to 125 mmol/l over 12 h, associated with a rise in plasma vasopressin (pAVP) from 4.4–9.3 pmol/l. Tolvaptan 7.5 mg daily was commenced on day 5 and pNa rose gradually to 130 mmol/l with an eventual tolvaptan dose of 15 mg daily. Over 6 weeks, the patient developed persistent hyponatremia despite escalating doses of tolvaptan to 60 mg daily. UOsm while on tolvaptan was >800 mOsm/kg and AVP levels between 8 and 16 pmol/l indicating unopposed action of AVP. Systemic chemotherapy led to temporary improvement in plasma sodium and tolvaptan dose was reduced to 15 mg over the subsequent three months. Six months after initial presentation, pNa fell again and tolvaptan dose was increased to 60 mg; noncompliance was excluded by supervised tolvaptan challenge, during which pAVP rose to 178 pmol/l, and UOsm remained >909 mOsm/kg, suggesting renal resistance to tolvaptan. Imaging confirmed progressive liver and bony metastases and the patient died 10 months after presentation, due to metastatic malignancy. This is the first report of escape of SIAD from tolvaptan therapy, despite increasing doses. With progression of malignancy, and rising pAVP conentrations tolvaptan may have been insufficient to compete with tumour associated AVP for renal receptors.

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EP769

Overestimation of HbA1c by an unusual hemoglobin variant

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Glycosylated haemoglobin (HbA1c) is considered the Gold Standard parameter for evaluating long-term glycemic control in individuals with Diabetes Mellitus (DM). The presence of hemoglobin variants or others conditions that modify its glycosylation, can affect the veracity of its measurement. The detection of these hemoglobinopathies and his knowledge by the clinicians is very important for the correct diagnosis and follow-up. We present the case of a patient who presented a hemoglobinopathy that interferes with the determination of HbA1c by HPLC, one of the methods most used in laboratories. The case is about a man of 17 years old referred for evaluation by Endocrinology because in the context of a study of syncopal episodes and possible hypoglycaemia presents HbA1c of 6.5% with repeated blood fasting glucose between 70 and 75 mg/dl. A new HbA1c with a result of 7.0% and other exams were requested, which were normal: oral glucose tolerance test, negative autoantibodies (GAD, IA-2 and insulin), plasma C-peptide and insulinemia. Blood count parameters were also normal. He had no family history of DM to suspect Monogenic Diabetes. Levels of fructosamine (alternative marker for assessing glycemic control of the last 2–3 weeks, based on glycoproteins measurement) were requested, resulting in 240 µmol/l, which correlated with a calculated HbA1c of 5.6%. In addition to the incongruity between the HbA1c values and the rest of the study, an abnormal peak in the HbA1c chromatogram (HPLC assay) was observed. HbA1c was measured again by a different method (boronate affinity chromatography) resulting in a very different result (HbA1c 5.3%). Due to the suspicion of hemoglobinopathy that overestimates HbA1c, it was sent to the reference laboratory for molecular characterization. Finally, the patient presented hemoglobin J-Camagüey heterozygous (Arg$>$Gly; HBA1: c.424C$>$G). The mother also presented the same hemoglobinopathy in heterozygous.

Conclusions

Many patients may present simultaneously a hemoglobinopathy and DM. Some hemoglobinopathies, without clinical repercussion are detected incidentally during the measurement of HbA1c. It is important for clinicians to be aware of its existence, because some may falsify the results (underestimating or overestimating HbA1c, such as J-Camagüey). The use of alternative glycemic markers may be helpful in these cases.

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EP770

Myasthenia gravis associated with Graves' disease and adrenal insufficiency

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Introduction

Multiple autoimmune syndrome (MAS) is a rare condition, first described by Humbert and Dupond in 1988 and characterised by three or more autoimmune disorders in the same individual.

Case description

Here we present a case of 14-year-old female patient diagnosed with ocular myasthenia gravis. The diagnosis of Graves' disease was suspected on the basis of hyperthyroidism symptoms and confirmed by undetectable TSH level (<0.01 mUI/l) with high FT_4 level (27.8 pmol/l). The adrenal insufficiency was suspected also clinically (extreme fatigue, weight loss, hyperpigmentation and low blood pressure) and accepted with a low cortisol level (37.4 ng/ml). The patient has improved after taking an anticholinesterase agent and corticosteroid replacement therapy. For the hyperthyroidism, a radical treatment is recommended and the Beta-blockers should be avoided.

Conclusion

The MAS-3 in our case is characterized by the association of myasthenia gravis, Graves' disease and adrenal insufficiency in which every condition has a different treatment and prognosis in addition to a multidisciplinary care.

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EP771

Incidental asplenia in a patient with presumed type 2 autoimmune polyglandular syndrome (APS-2): misclassification or overlap?

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Introduction

Asplenia has been reported in 10% of patients with type 1 APS (APS-1), but has never been reported in APS-2. We describe a patient with presumed APS-2 and aplenia.

Case report

A 69-year-old woman was diagnosed with B12 deficiency with severe anemia at age 21 and insulin dependent diabetes mellitus at age 33, following routine testing. At 59, she was hospitalized with salt wasting and a diagnosis of Addison's disease was made, which was subsequently confirmed by an inadequate response to tetracosactide stimulation. The diagnosis of subclinical Hashimoto's thyroiditis was concurrently made. The patient had chronic onychomychosis of one fingernail and multiple toenails, but never of the mucous membranes and has never reported tetany. The diagnosis of APS-2 was made, based on the presence of the complete tri-glandular syndrome. The patient was under active surveillance for other autoimmune manifestations, but none has so far been detected. Her past history is negative for serious illnesses or infections and has never had abdominal surgery. Of note, she had never received a pneumococcal vaccine. Her family history is negative for autoimmune disorders. An abdominal CT scan was requested for complaints of non-specific abdominal discomfort and an incidental observation regarding the absence of an orthotopic spleen was made. An abdominal ultrasound found evidence of a hypoplastic splenic vessel. Functional imaging of the spleen using 99mTC-colloid failed to reveal a functional spleen. Relevant laboratory investigations including peripheral blood smear revealed Howell-Jolly bodies. Parathormone and electrolytes were normal. Quantitative measurements of major immunoglobulin classes and T lymphocyte subpopulations were normal. HLA II haplotypes DQB1*05 and DQA1*01 were indentified. *AIRE* sequencing is pending.

Conclusion

Asplenia in the context of well-defined APS-2 and in the absence of clinical immunodeficiency, is a novel finding that challenges our current understanding of APS and needs to be further investigated.

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EP772

Immune checkpoint inhibitors related thyroiditis – a report of two cases

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Introduction
Immune checkpoint inhibitors (ICPIs) are recent approved drugs used in malignant melanoma, non-small-cell lung cancer and renal cell cancer. They act by activating host T cell against malignant antigens. Immune checkpoint blockade can lead to breaking of immune self-tolerance, thereby inducing autoimmune/autoinflammatory side effects, such as endocrinopathies. It may affect thyroid, adrenal and pituitary. We present two ICPIs induced thyroiditis cases.
Case 1
Sixty-eight-year-old female diagnosed with a conjunctival malignant melanoma at the age of 64. She was first surgery treated and then submitted to radiotherapy. Due to bone, lung and hepatic metastasis she started Ipilimumab 3 mg/kg on 21-day cycle. Eleven days after the third Ipilimumab administration she was asymptomatic but was found to have thyrotoxicosis (TSH 0.04 μUI/ml; FT_4 1.31 ng/dl). Thyroid peroxidase and thyroglobulin antibodies were elevated and thyroid stimulating immunoglobulin was low. Four months after suspension of Ipilimumab a spontaneous recovery of the thyroid axis was seen.
Case 2
Sixty-two-year-old female diagnosed with a foot malignant melanoma one year before. She was first surgically treated. Due to lung, breast and lymph node metastases she started Nivolumab 3 mg/kg on 15-day cycle. Before starting this drug she had a diffuse thyroid uptake on PET-scan with normal thyroid function. Twelve days after the first administration of Nivolumab she described a painless increase of anterior cervical volume, fatigue and had thyrotoxicosis on the blood test (TSH 0.02 μUI/ml; FT_4 2.50 ng/dl). One month after she was found to have asymptomatic hypothyroidism (TSH 9.96 μUI/ml; FT_4 0.49 ng/dl). Thyroid ultrasound showed a thyroiditis pattern. She started levothyroxine therapy and one month after stopping Nivolumab she was still on hypothyroidism.
Conclusions
ICI may induce autoimmune thyroiditis or may worsen a pre-existing one. These patients should be monitored for signs and symptoms of thyroid dysfunction, since it can cause significant morbidity if not promptly recognized and treated.

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EP773

Nivolumab-associated pituitary, adrenal and thyroid autoimmune disorders

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Background
Nivolumab is a monoclonal antibody specific for human PD-1 (programmed cell death protein-1), a checkpoint molecule highly expressed in several cancers. Nivolumab is an immunotherapeutic strategy for human cancer, but it can interfere with endocrine system.
Case reports
We report four cases regarding nivolumab-associated endocrinopathies: (i) Male, 55-year-old, with previous normal cortisol and adrenocorticotropic hormone (ACTH) levels, treated with nivolumab for metastatic lung epidermoid carcinoma. After 14 cycles, he developed asthenia, anorexia, weight loss, hypotension and hyponatremia, resulting in hospital admission. Adrenal insufficiency was confirmed by morning cortisol <1.0 μg/dl; hydrocortisone treatment was started with clinical improvement. (ii) Male, 78-year-old, with previous normal cortisol and ACTH levels, treated with nivolumab for stage 3B lung epidermoid carcinoma. After 15 cycles, he developed adrenal insufficiency with morning cortisol <3.0 μg/dl and ACTH <5.0 ng/l. He had recent weight loss, but was hemodynamically stable, without electrolyte imbalance. He started hydrocortisone with clinical improvement. (iii) Male, 70-year-old, without previous thyroid disease, treated with nivolumab for metastatic clear cell renal carcinoma. After 2 cycles, he developed thyrotoxicosis with thyroid-stimulating hormone (TSH) 0.01 μUI/ml (ref:0.35–4.94), free thyroxine (FT_4) 1.82 ng/dl (ref:0.70–1.48), free triiodothyronine (FT_3) 3.68 pg/ml (ref:1.71–3.71), positive thyroglobulin antibody (TgAb), negative peroxidase (TPOAb) and TSH-receptor antibodies (TRAb). He was treated with methimazole for 3.5 months. He maintains normal thyroid function since antithyroid drug withdrawal. (iv) Male, 64-year-old, without previous thyroid disease, treated with nivolumab for metastatic lung adenocarcinoma. After 5 cycles, he developed thyrotoxicosis with TSH 0.003 μUI/ml and normal FT_4 and FT_3. He had spontaneous remission of thyrotoxicosis within 2 months and then developed hypothyroidism with TSH 7.78 μUI/ml, FT_4 0.48 ng/dl, FT_3 2.19 pg/ml and positive TPOAb and TgAb. Levothyroxine was initiated, compatible with the possible diagnosis of nivolumab-associated thyroiditis.
Conclusion
Health providers must be aware of endocrine disorders that may be associated with immunomodulatory therapies for a timely diagnosis and correct treatment.

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EP774

Meigs' syndrome in a 63 year-old woman – case report

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Introduction
Meigs' syndrome is defined as the presence of a benign ovarian tumour (fibroma), in association with ascites and hydrothorax. The characteristic feature of this condition is the resolution of the effusions once the tumour is surgically removed.
Case report
A 63 year-old female patient was admitted to the Surgery Clinic with metroragia, abdominal distention, and a recent history of minor breath shortness. Pulmonary clinical examination showed all the signs of right pleural effusion, which was also confirmed by the chest X-ray. The abdominal examination revealed a round irregular mass arising from the right pelvic cavity. Abdominal ultrasound showed a large pelvic mass (23 cm in diameter) more on the right pelvic cavity, a polyfibromatous uterus, and a small quantity of ascites. A complete blood count was carried out, with normal results. Surgical intervention was decided and the laparotomy confirmed a large pelvic mass which was part of the left ovary, dislodged in the right side of the peritoneal cavity. Also, 100 ml of ascitic fluid and a polyfibromatous uterus were found. The ovarian mass was removed and also a hysterectomy with bilateral adnexectomy was performed. The macroscopic appearance: giant polynodular tumoral mass (23 cm in diameter), with compact structure, microcysts, and haemorrhagic areas. No residual ovarian tissue was observed in the subcapsular portion of the tumour. Microscopically, a compact tissue, consisting of pleomorphic fusiform cells, and discrete mitotic activity (less than 3 divisions/10 fields) was described. The cells were arranged in fascicles, with hyaline and myxomatous areas. Dilated vessels with thrombotic material were noted. The absence of malignancy of the tumour and of the ascitic and pleural effusions was confirmed by cytomorphologic study. In conclusion, the histopathological examination demonstrated an ovarian tumour with a fibroma aspect. Postoperative evolution was favorable and the patient was discharged after 12 days. The controll chest X-ray revealed the resolution of the hydrothorax.
Conclusion
Even though Meigs' syndrome mimics an aggressive malignant ovarian tumour, in the presence of pleural and peritoneal effusions, after surgical removal of the tumour the patient has a good prognosis and the life expectancy is similar to normal healthy population, even if recurrence was also reported.

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Developmental Endocrinology

EP775

GH influences plasma fasting adropin concentration in patients with turner syndrome

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Background
Increased adiposity and insulin resistance are conditions frequently observed nowadays. Many hormones are involved in the pathogenesis of the condition but

therapeutic options we can offer to the patients are still scant. Each newly discovered peptide give us hope. Adropin (Ad) is a newly discovered metabolic hormone involved in energy homeostasis. This homeostasis is frequently disturbed in patient with Turner Syndrome (TS). Patient with Turner syndrome are unique model for studies of an effect of the treatment with supraphysiological doses of growth hormone (GH).
Objective and hypotheses
We studied adropin dependance and response in a group of TS patients treated with supraphysiological doses of growth hormone (rGH).
Method
The study group consisted of 36 TS patients aged 3.2–16.07 years (mean 8.2 years) diagnosed by karyotyping. The rGH was applied in a dose 0.05 mg/kg per day Prior to and following the treatment anthropometrical data were recorded as well as biochemical parameters were measured: adropin, OGTT, insulin, lipids, IGF-1, and IGFBP-3.
Results
The increase of IGF-1 concentration at the end of observation was significant (from 119.4 ± 62.46 to 413.37 ± 204.38 ng/ml, mean $\pm$ S.D., $P = 0.000$). The GH treatment influenced insulin resistance revealed by increased HOMA values (median 0.64 ± 0.45 before and 0.92 ± 0.97 after, $P = 0.02$). rGH treatment cause a significant rise in Ad level. The correlation between adropin and IGF-1 and IGF-1 SDS levels was not significant neither before nor on the treatment ($r = 0.17$ and $r = 0.004$ respectively). Adropin concentration correlated with IGFBP3 level before rGH treatment but not on rGH therapy. Ad also correlated with insulin level before GH applying. Correlation with glucose levels at 30' of OGTT was stable and even rise on GH treatment ($P = 0.33$ vs $P = 0.48$). Similar observation was noticed for lipids, but close correlations between Ad adropin and total cholesterol, LDL cholesterol, triglycerides (TG) before GH applying changed on rGH therapy. The only correlation noticed in GH treated patients was between Ad adropin and TG ($P = 0.34$).
Conclusion
Result of the study showed an increase in adropin level following rGH application is not mediated by IGF-1. rGH treatment changes adropin influence on lipid metabolism, but ameliorates insulin action.

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Diabetes (to include Epidemiology, Pathophysiology)

EP776

Diagnosis of cystic fibrosis related diabetes

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Aim
To describe the prevalence of abnormal glucose tolerance and diabetes in patients with cystic fibrosis (CF) depending on the diagnostic criteria.
Methods
Observational, cross-sectional, clinical research on patients with CF evaluated at Hospital Universitario Reina Sofía (Córdoba).
Results
Twenty-eight patients were selected for the study. Age: 31.85 ± 8.78 years, with a CF evolution time of 21.77 ± 9.37 years. 64% women. 55.6% of the subjects presented with the deletion of phenylalanine in position 508 (DF508), known to be a severe one. Most patients (85.2%) suffered from pancreatic insufficiency. We compared the three ADA classical diabetes diagnostic criteria. With the fasting plasma glucose 3.6% of patients were diagnosed with impaired glucose tolerance (IGT) and 3.6% with cystic fibrosis-related diabetes (CFRD). Using the glycated haemoglobin (HbA1c) 28.6% of patients had (IGT) and 3.6% CFRD. After the oral 75g-glucose test (OGTT) with intermediate blood glucose measurements, 25.1% were diagnosed with IGT and 7.1% with CFRD. We found different prevalence of abnormal glucose tolerance depending on the diagnostic criteria used. OGTT with intermediate blood glucose measurements is the most sensitive criteria for IGT and CFRD compared to fasting glucose ($P = 0.002$) and HbA1c ($P = 0.289$).
Conclusions
- In our series, there are statistically significant differences among the criteria used to diagnose the abnormal glucose tolerance and CFRD
- OGTT was the most sensitive test to establish the abnormal glucose tolerance and CFRD in our series, in agreement with published evidence.

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EP777

Erk- and Akt-mediated osteocalcin signaling in human pancreatic β-cells does not directly involve GPRC6A activation

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Osteocalcin (OC) is the main non-collagenous protein of the bone and it has a regulatory role in mineralization. Extra-skeletal roles have been recently hypothesized for OC (e.g., modulation of glucose-induced insulin secretion by interacting with GPRC6A in β-cells). However, OC-mediated GPRC6A activation has been demonstrated only in rodents and heterologous systems. In this study we aimed at evaluating the dose-dependent response to OC and the eventual activation of the GPCR-dependent pathways in a physiologic-like model of human pancreatic β-cells. 1.1B4 cell line, derived from electrofusion of PANC-1 cell line and primary human β-cells, were treated for 5 and 30 min with different concentrations of OC (20 to 100 ng/ml) either alone or in combination with 10 μM NPS2143, a non-competitive antagonist of GPRC6A. mRNA and protein expression were evaluated in order to assess the expression of GPRC6A and the activation profile of Erk and Akt pathways. As for human β-cells *in vivo*, which physiologically express nearly undetectable levels of GPRC6A, 1.1B4 cells displayed undetectable levels of GPRC6A protein. On the contrary, GPRC6A mRNA was slightly detectable. A slight increase (1.5 fold) of pErk/tErk was induced by OC 40 ng/ml at 30 min. Instead, pAkt was dose-dependently induced within 5 min with a 2-fold peak with OC 80 ng/ml; at 30 min a residual activation was evident for OC 20 and 40 ng/ml. NPS2143 did not affect the activation profile of Erk and Akt if not for a slight peak activation of both pathways with OC 60 ng/ml, instead of 40 ng/ml for Erk and 80 ng/ml for Akt. In summary: i) GPRC6A is not expressed (or it is expressed at very low levels) by human pancreatic β-cells; ii) the common OC signaling pathways, identified in heterologous expression systems, are only slightly induced in human pancreatic β-cells; iii) the inhibition of GPRC6A do not affect the activation profile of Erk and Akt and, hence, GPRC6A may not be involved in physiological OC signaling in human β-cells.

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Diabetes Complications

EP778

The comparison of cardiovascular events in kidney transplant recipients with and without type 2 diabetes mellitus

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Diabetes melliuts (DM) presents particular challenges after kidney transplant (KT). These challenges contribute to cardiovascular disesases among diabetic recipients. We assessed frequency of posttransplant cardiovascular events in diabetic patients.
Methods
This retrospective study conducted in 399 kidney recipients at our center. The patients were divided into two groups: DM (n:59, 52.5% females) and non-DM (n:340, 46.5% females).
Results
The median KT duration was 4 years. The median age and BMI of DM group were higher than those of non-DM group (51 vs 42 years and 28.6 vs 25.8 kg/m^2, respectively, $P < 0.001$). The mean creatinine levels of both groups were similar. Hypertension (76.3 vs 62.4%, $P = 0.04$), coronary artery disease (15.3 vs 4.1%, $P = 0.001$), obesity (39.7 vs 20.9%, $P = 0.007$) and dyslipidemia (32.3 vs 15.4%, $P = 0.002$) co-morbidities in DM were more frequent than those of non-DM groups. There was no significant difference between the ratios of myocardial infarction (3.4 vs 2.6%), cardiac arrhythmia (3.4 vs 9.4%), congestive heart failure (3.4 vs 1.2%), stroke (1.7 vs 0.6%), transient ischemic attack (1.7 vs 4.1%) and peripheral vascular disease (3.4 vs 0.6%) in DM and non-DM groups. The ratio of patients underwent angioplasty was higher than that of non-DM group (23.7 vs 12.1%, $P = 0.016$) while the ratios of patients underwent coronary stenting (1.7 vs 1.8%) and coronary by-pass operation (3.4 vs 1.2%) were similar. The graft loss and mortality rates in DM and non-DM groups did not differ (5.1 vs 5.6% and 5.1 vs 1.8%, respectively).
Conclusion
We observed that there was no difference in new cardiovascular events, graft loss and mortality between recipients with or without DM after KT.

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Endocrine Disruptors

EP779

The adrenal gland after diosgenin application in a rat model of the menopause

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Diosgenin, a steroidal sapogenin of natural origin, demonstrated some therapeutic effects when it comes to the treatment of cardiovascular issues, malignancies and the menopausal symptoms. In this study, we have investigated histological changes and corticosterone secretion of the adrenal gland after diosgenin application in a rat model of the menopause. Middle-aged, acyclic female Wistar rats were divided into control (C; $n=6$) and diosgenin treated (D; $n=6$) groups. Diosgenin (100 mg/kg b.w./day) was orally applied for 4 weeks, while C group received the vehicle alone. Our approach considered using the design-based stereology, histochemistry and the hormonal assay. The adrenal cortex volume decreased in D females by 15% ($P<0.05$) while the volume of adrenal medulla increased ($P<0.05$) by 64%, compared to the same parameters in C group. Volume density of zona glomerulosa (expressed per absolute adrenal gland volume) in D rats increased ($P<0.05$) by 22% in comparison with C animals. Diosgenin treatment decreased ($P<0.05$) volume density of zona fasciculata (expressed per volume of adrenal cortex) by 15% and caused vasodilatation within this zone, when compared to C females. Circulating corticosterone was also decreased by 16% compared to the C group. Absolute volume of zona reticularis in D group decreased ($P<0.05$) by 38% in comparison with the same parameter in C rats. Also, after diosgenin application, volume density of zona reticularis (expressed per absolute adrenal gland volume) and zona reticularis cell volume were decreased by 40% and 20% ($P<0.05$) respectively, compared to C animals. Our results, reflecting a decrease of the numerous adrenocortical stereological parameters, indicate that diosgenin took over the role of corticosteroid precursors and got incorporated into the steroidogenesis.

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EP780

Association of autoimmune endocrinopathies and celiac disease

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Introduction
Celiac disease (CD) is an immune-mediated small intestinal disorder that occurs in genetically susceptible people. It is significantly associated with other autoimmune disorders represented mainly by type 1 diabetes and autoimmune dysthyroidism.
Material and methods
We report 23 observations of patients with autoimmune endocrinopathies associated with celiac disease.
Results
There are 23 patients with an average age of 31 years. All patients had chronic diarrhea associated with abdominal pain in 15 cases and malabsorption syndrome in five cases. The diagnosis of celiac disease was made on serological (Anti-transglutaminase, anti-endomysium and anti-gliadin antibodies positive respectively in 20, 18 and 15 cases) and histological criteria (Partial villous atrophy in 13 cases and total villous atrophy in 10 cases). Autoimmune endocrinopathies associated to celiac disease were: type 1 diabetes in 14 cases, Hashimoto thyroiditis in seven cases and Addison disease in one case. One patient had type 1 diabetes, Basedow disease and Addison's disease associated to celiac disease. All patients were treated with gluten-free diet and specific endocrinopathy treatment with favorable evolution.
Conclusion
In the presence of autoimmune endocrinopathies the search of associated autoimmune diseases in particular celiac disease is necessary in order to avoid any therapeutic delay which can alter the prognosis of the patient.

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EP781

Characterization of murine Leydig cell lines as tools to study androgen synthesis disruption by xenobiotics

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Mammalian Leydig cells produce the majority of the systemic levels of the primary male sex hormone testosterone. Testosterone plays a crucial role during development of male reproductive tissues, onset of puberty, and maintaining health state. The final step of testosterone synthesis is catalyzed by 17β-hydroxysteroid dehydrogenase 3 (17β-HSD3). Disruption of testosterone synthesis is associated with many diseases. Due to the lack of a human Leydig cell line, two different murine Leydig cell lines (MA10, BLTK1) were studied for their suitability as screening tools for testosterone synthesis disruption by xenobiotics. The endogenous expression and activity of murine 17β-HSD3 was studied in both cell lines. Further, cells were stimulated using br-8-cAMP and forskolin to study testosterone production. Cell supernatants were analyzed using LC-MS. Unstimulated cells showed no or very low endogenous 17β-HSD3 activity. Stimulated MA10 cells showed low but concentration-dependent increases of testosterone levels in supernatants after 24 h. BLTK1 cells did not produce any testosterone. This study emphasizes the necessity of analyzing steroid using sensitive MS-based methods and shows that MA10 and BLTK1 cells produce a variety of steroids but only low amounts or no testosterone.

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EP782

Identification of chemicals disrupting adrenal steroid production by steroid profiling in H295R cells

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Human adrenal H295R cells are applied according to the validated OECD test guideline 456 to identify potential endocrine disrupting chemicals. Testosterone and estradiol production serves as read-out although these are not steroids typically produced by the adrenals. The current study attempted to optimize conditions for using H295R cells to detect chemicals disturbing the synthesis of key adrenal steroids. Culture supernatants of H295R cells were analysed by LC-MS-based steroid quantification. The impact of experimental conditions including time and serum content on steroid profiles was assessed. Steroid profiles were measured before and after incubation with reference and test compounds for potential disruption of adrenal steroidogenesis. The results revealed that H295R cells cultivated according to the OECD test guideline produced progestins, glucocorticoids, mineralocorticoids and adrenal androgens but only very low amounts of testosterone. However, testosterone contained in Nu-serum was metabolized during the 48 h incubation. Therefore, inclusion of positive and negative controls and a steroid profile of the complete medium prior to the experiment was needed to characterize steroid synthesis and indicate changes occurring upon exposure to chemicals. Among the test chemicals, octyl methoxycinnamate and acetyl tributylcitrate resembled the corticosteroid induction pattern of the positive control torcetrapib. Gene expression analysis revealed that octyl methoxycinnamate and acetyl tributylcitrate enhanced CYP11B2 expression; however, less pronounced compared with torcetrapib. In conclusion, the extended profiling and appropriate controls allow detecting chemicals that act on steroidogenesis and provide initial mechanistic evidence for prioritizing chemicals for further investigations.

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EP783

Endocrine dysfunctions associated with Hodgkin Lymphoma treatment

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Introduction
Hodgkin lymphoma (HL) survivors may develop a range of long-term complications that arise years after therapy. Among these, the endocrine dysfunctions are a major concern. Aim: To investigate the long-term endocrine effects of HL treatment.
Methods
Revision of the HL patients' medical files who were followed at our Endocrine Late-effects Clinics.
Results
We studied 178 patients (86 (48.3%) were female), whose mean age at HL diagnosis was 18.07 ± 10.79 (2–56) years. Chemotherapy was offered to 177(99.4%) patients and radiotherapy to 157 (88.2%). Hypothyroidism was identified in 76(42.7%) patients; women were not more affected than men ($P = 0.083$). Mean time between radiotherapy and hypothyroidism diagnosis was 7.76 ± 6.96 (1–39) years. Seven patients who developed hypothyroidism did not receive directed cervical radiotherapy and only 3 of them evidenced positive thyroid antibodies. Thyroid nodules were present in 41 (23%) patients. Mean time between radiotherapy and thyroid nodules development was 13.41 ± 7.90 (1–35) years. Although women were more affected ($P = 0.01$), they were not diagnosed earlier ($P = 0.842$). Six (3.4%) patients developed thyroid cancer. Mean age at thyroid cancer diagnosis was 24.4 ± 8.36 (17–34) years. Patients who developed thyroid cancer were significantly younger when they underwent radiotherapy (10.2 ± 2.9 vs 20.3 ± 9.8/$P = 0.024$). Mean time between radiotherapy and thyroid cancer diagnosis was 16.25 ± 5.5 (11–21) years. Ten (11.63%) women developed breast cancer, 16.7 ± 6.03 (7–25) years after HL therapy. Hypogonadism was observed in 32 women and 12 men; mean age at hypogonadism diagnosis was 28.07 ± 8.92 (13–48) and 40.5 ± 17.19 (14–66) years, respectively. Women ($P < 0.001$) and men ($P = 0.001$) who developed hypogonadism were older when they received HL therapy. Median time between HL therapy and hypogonadism was significantly shorter in women (1(0–18) vs 11.5 (3–39) years; ($P < 0.001$)). Women who recovered their gonadic function were younger when they received lymphoma therapy (17.5 ± 7.0 vs 20.46 ± 9.8/$P = 0.026$).
Conclusion
Given the high relevance of endocrine dysfunctions in these patients, in order to early identify and manage them, a long-term endocrine follow-up is needed, with adequate protocols.

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Endocrine Tumours and Neoplasia

EP784

Multidisciplinary committee on endocrine tumors: an analysis of 6-year experience

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Aim
Multidisciplinary approach is mandatory in the management of endocrine tumors. Herein, we summarize the healthcare activity performed during the last 6 years at the multidisciplinary committee for endocrine tumors of a tertiary and University Hospital.
Methods
A search of clinical-care activity of the endocrine tumors committee of our hospital from 2011 to 2016 was performed. Clinical and demographic data of all patients were recorded. The committee's decisions were analyzed by tumor type and the type of decision (diagnostic or therapeutic). Clinical protocols approved by the committee were quantified.
Results
Two hundred and sixty seven decisions, affecting 205 patients (72.2% women, mean age 53.3 ± 16.9 years) with endocrine tumors, were made. Thyroid tumors accounted for the main workload of the committee, with 61.8% of all decisions, a percentage that has not substantially changed over the years. The rest of decisions dealt with neuroendocrine (14.6%), pituitary (13.5%), adrenal (6.0%) and parathyroid tumors (4.1%). Most cases came from the Departments of Endocrinology (52.8%) and General Surgery (18.0%). 75.7% of the committee's decisions were therapeutic and 15.7% diagnostic. The committee developed 29 clinical protocols for local use. 65.5% of them were therapeutic and 34.5% diagnostic. When studying the relationship between the department of origin and tumor type, we found a statistically significant difference between the cases presented by the department of Endocrinology and the surgical departments (General Surgery and Otolaryngology) and the remaining departments (χ^2 46.55; $P < 0.001$). No significant association between the type of decision and tumor type was found (χ^2 9.79; N.S.).
Conclusion
Multidisciplinary teams are feasible and needed to make reliable, shared, patient-centered and evidence-based decisions. Endocrinology department remains the cornerstone that allows the flow of patients across the team.

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EP785

ER status heterogeneity in breast cancer: role in response to endocrine treatment

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Tumor heterogeneity affects diagnosis, prognosis and response to therapy. Heterogeneity is found in both normal and neoplastic human mammary gland. For example, luminal estrogen receptor (ER)-negative cells can give rise to various phenotypes, including ER-negative and ER-positive mammary tumors, suggesting that the cell-of-origin does not necessarily reflect the tumor type. Regarding ER status, heterogeneity can challenge endocrine therapies; elimination of responsive clones can increase resistance of the survived ones and ultimately reduce treatment efficacy leading to tumor relapse. The aim of our study is to investigate breast tumor heterogeneity and its role in endocrine resistance onset. For this purpose, we co-cultured ER-positive (T47D, CAMA1) and triple negative breast cancer (TNBC) (MDA-MB231, HCC70) cell lines, using 2D and 3D models. CAMA1 were sensitive to tamoxifen in term of cell viability, however this sensitivity was reduced when CAMA1 were co-cultured with TNBC cells. Interestingly, following co-culture with TNBC cells, the expression of ER in CAMA1 decreased while the anti-apoptotic protein Mcl-1 increased. On the other hand, T47D are slightly sensitive to tamoxifen; however, this sensitivity was completely abolished when T47D were co-cultured with TNBC. In addition, the expression of ER in T47D was significantly increased following co-culturing with TNBC cells, while the doubling-time of T47D was significantly reduced, suggesting an increase in cell proliferation rate. Our results demonstrate that ER status appears to be modulated when ER positive cells are co-cultured with TNBC cells, leading to a different response to endocrine therapy. In addition, ER positive cells' doubling time is modified after exposure to TNBC cells. Further experiments are needed to fully understand the molecular mechanisms behind these findings.

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EP786

Potential role of vitamin D in restoring sensitivity to mTOR inhibitors in hepatocellular carcinoma (HCC): 1,25(OH)vitamin D (VitD) reverts everolimus (EVE) resistance in a hcc cell line

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HCC is a difficult-to-treat- cancer with poor prognosis. Despite EVOLVE-1 trial demonstrated that EVE did not improve overall survival in molecularly and clinically unselected patients with advanced sorafenib resistant HCC, in selected patients, the established antitumor effect of EVE could make this drug a potential adjuvant therapy. Unfortunately, the acquired EVE resistance due to the tumour adaptation to chronic drug use is a current challenge. VitD has been deemed as potential regimen to treat a variety of cancers alone or in combination with other drugs. The aim of this study was to assess the antiproliferative effect of the combined treatment with EVE and VitD in JHH-6, a model of HCC cell line, and to explore the role of VitD pre-treatment in the re-sensitization to EVE in JHH-6 cell line resistant to EVE (JHH-6 EveR). JHH-6 EveR were obtained after 4 months of EVE 10-8M treatment. Messenger and protein VitD receptor (VDR) expression was confirmed by RT-qPCR and immunofluorescence. DNA assay

was established to evaluate the proliferation rate in parental and EveR cells after EVE treatment (from 10–14 M to 10–8 M) alone or in combination with VitD (10–7 M). In parental cells, EVE significantly reduced the proliferation index in a dose-dependent manner after 6 days of treatment and VitD did not improve EVE effect. JHH-6 EveR cells no longer responded to EVE treatment but 12h and 24h of VitD pre-treatment was sufficient to significantly restore the efficacy of EVE at concentration ranging from 10–14 M to 10–8 M with a maximum effect of 3.3% at 10–8 M ($P<0.001$). Moreover, the liver miRNA PCR Array study demonstrated that VitD treated JHH-6 EveR showed an increased expression of miR-375 compared to JHH-6 EveR, suggesting a role of miR-375 in EVE re-sensitization. These preliminary data suggested the use of VitD to overcome the acquired resistance to EVE in HCC.

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EP787

Comparisson of subtraction and two-phase parathyroid scintigraphy conserning histological type of hyperfunctioning parathyroid tissue

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The aim of this study was comparison of sensitivity of subtraction parathyroid scintigraphy (SBPS), vs. two-phase parathyroid scintigraphy (2FPS), related to histological type of hyperfunctioning parathyroid tissue.
Materials and methods
Fifty patients, thirty with primary hyperparathyroidism and twenty on dialysis and secondary hyperparathyroidism underwent parathyroid scintigraphy (PS) before surgery. Static scintigrams of neck and chest were performed, fifteen minutes and two hours after iv. injection of 740 MBq of Tc99m-MIBI. Four hours latter, after iv. injection of 185 MBq Tc99m, thyroid scintigraphy was performed. After normalization and motion correction, subtraction Tc99m from Tc99m-MIBI scintigrams was done. Scintigraphic results of both PS methods were graded from one to five: grade 1-normal finding, grade 2-probably normal finding, grade 3-suspicious finding, grade 4-probably abnormal finding and grade 5-abnormal finding. Scintigraphic findings graded 3, 4 and 5 were considered as pathologic. Pathohistological analyses were done microscopically on standard haematoxylin-eosin stained slides to determine the substrate: adenoma and type of hyperplasia.
Results
Postoperatively 96 hyperfunctioning paratiroid glands (PG): 24% adenomas, 62.5% with nodular hyperplasia (NHPL) and 13.5% with diffuse hyperplasia (DHPL), were found. Overall sensitivity of SBPS was 74%; 91.3% for adenoma, 70% for NHPL and 61.5% for DHPL, with no statistically significant difference in sensitivity between groups of PG. Overall sensitivity of 2FPS was 67.7%; 100% for adenoma, 61.5% for NHPL, and 38.5% for DHPL. Statistically significant difference was found in sensitivity of 2FPS findings between these three groups, $P<0.0001$. SBPS had statistically significantly higher sensitivity of 61.5% for diffuse hyperplasia, comparing to 2FPS, with sensitivity of 38.5%, $P<0.0001$.
Conclusion
SBPS and 2FPS showed similar sensitivity in detection of PG adenoma and nodular hyperplasia of parathyroid glands. Superiority of subtraction parathyroid scintigraphy in detection of PG with diffuse hyperplasia is important finding, knowing that these glands are the smallest one and often remain undetected prior surgery, both in secondary, and importantly in primary hyperplasia.

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EP788

Endocrine health problems detected in 764 patients evaluated in a late effects clinic

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Context
Many pediatric cancer survivors have endocrine conditions. After alkylating agents, steroids, methotrexate and radiation, several endocrine dysfunctions may appear. Surveillance for late effects is recommended by worldwide guidelines.
Objective
The objective of the study was to describe the endocrine outcomes of 764 patients followed during a 20 years period in our out-patient clinic.
Design
The design was a retrospective medical records review.
Patients
The study included 764 patients whose oncological or hematological dangerous diseases appeared before 18 years old. Larger groups were constituted by Leukaemias, Central Nervous Tumors and Lymphomas.
Outcome measures
The frequency and types of endocrine conditions were measured.
Results
One thousand and ninety one endocrine conditions were observed in all groups. The most common types of endocrine conditions were problems with growth and thyroid. We found puberty abnormalities and bone problems in third and fourth places of frequency. ACTH insufficiency was found in seventh place.
Conclusion
Endocrine dysfunctions are very common in survivor's population. Endocrinologists should be aware of international guidelines and to make an effort to optimize screening and treatment of endocrine effects of cancer therapy. The crucial period is the pubertal with growth spurt failure and acceleration puberty maturity wisch of them can bring future social and professional difficulties.

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EP789

Magmas modulates chemoresistance in endocrine-related cancers

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Magmas, a gene encoding for the mitochondrial import inner membrane translocase subunit, Tim16, protects different cell lines from the antitumoral effects of several pro-apoptotic stimuli (i.e. chemicals and chemotherapeutic agents). The synthetic Compound 5 is capable of sensitizing chemoresistant tumor cells overexpressing Magmas to proapoptotic stimuli, indicating that this molecule may be useful to overcome tumor chemoresistance. The aim of our study was to evaluate whether Compound 5 targets Tim16 and is cytotoxic *in vivo*. We found that Compound 5 enhances the antiproliferative effects of doxorubicin in MCF7 cells, while it fails to do so in two independent MCF7 cell clones where Magmas was silenced by specific shRNA. Then, the normal breast MCF12 cells were transfected with two differently tagged vectors, tim16-ddktag encoding for Tim16 and tim14-hatag, encoding for its partner Tim14. We found that Tim16 co-immunoprecipitates with Tim14 and that their interaction is reduced in the presence of Compound 5. However, Tim16 levels appear to be reduced in cells treated with Compound 5. The toxicity of this molecule was then tested *in vivo* by the Fish Embryo toxicity assay, employing Zebrafish eggs: Compound 5 is not toxic *in vivo* at the concentrations employed *in vitro* (5 and 10 μM), while its toxicity increases dose-dependently at higher concentrations. These data support the hypothesis that Compound 5 targets Tim16 and that Tim16 levels modulate the chemosensitizing effects of Compound 5, that need to be confirmed by *in vivo* studies.

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EP790

Altered expression of the components of the splicing machinery is associated to increased malignancy and expression of aberrant splicing variants in prostate cancer

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Prostate cancer (PCa) is the most common cancer among men in developed countries. Unfortunately, the heterogeneity of this malignancy hinders the finding of new biomarkers and therapeutic tools. A potential factor contributing to PCa is alternative splicing, which can generate the appearance of oncogenic variants involved in PCa aggressiveness. Thus, we hypothesized that the alteration of the splicing machinery (spliceosome components and splicing factors (SFs)) could be associated to the expression of tumorigenic splicing variants and malignancy of PCa. Accordingly, we characterized the expression pattern of key components of the major ($n=13$) and minor spliceosome ($n=4$) and associated SFs ($n=28$) in 51 PCa biopsies and 15 normal prostates, by using a microfluidic-based qPCR-array. The results revealed a downregulation of two key components of the spliceosome responsible for the recognition of and binding to the branching site of the target introns (RNU2 and RNU12) in PCa samples compared to controls, which might explain the prevalence of intron retention events found in PCa. In addition, expression of other components of the minor spliceosome (i.e. RNU11, RNU4atac or PRPF8) was also significantly reduced in PCa, suggesting a profound dysregulation of the minor spliceosome function and a consequent alteration in the processing of U12-introns. Furthermore, this analysis also revealed a marked alteration of certain SFs (i.e. SRSF5, SRSF9, MAGOH or TIA1) in PCa, whose expression was associated with the expression of relevant splicing variants (i.e. In1-ghrelin variant) and with malignancy features (metastasis, PSA levels, etc.). Finally, functional assays (proliferation, migration, etc.) with PCa cell lines confirmed the pathophysiological role of some of these SFs. Altogether, these results indicate that the splicing machinery is drastically dysregulated in PCa, which could help to explain the predominance of intron retention events and the appearance of tumorigenic splicing variants in this pathology, providing novel tools to develop diagnostic markers or therapeutic targets.

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EP791

Polyglandular autoimmune syndrome type III b

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We report the case of a 57-year-old female diagnosed with Grave's disease fifteen years before (TSH <0.001 U/ml; FT4 2.3 ng/dl; FT3 7.2 ng/dl, TSAbs 17 U/l). Persistency of hyperthyroidism despite antithyroid therapy led to total thyroidectomy three years after the diagnosis. Thereafter, thyroid function remained normal under hormonal replacement with levothyroxine. The patient had also been diagnosed with Pernicious Anemia at 47 years of age after investigation for complaints like fatigue and shortage of breath. Hemoglobin levels were 10.2 g/dl and Intrinsic Factor antibody titer was positive. She was treated with cobalamin and folic acid and hemoglobin levels became stable in the low-normal range. A year ago, the patient presented with left upper quadrant abdominal pain and asthenia, raising the suspicion of gastric disease. Specific blood tests were performed and the presence of high titers of gastric parietal cells antibodies (PCA), elevated gastrin (>1000 pg/ml; normal range: 13–115 pg/ml) and chromogranin A (936 ng/ml; normal range <102 ng/ml) confirmed the hypothesis of autoimmune gastritis. Furthermore, an elevated NSE level of 13.2 ug/l was detected. Endoscopy of the gastrointestinal tract found a pedunculated polypoid lesion in the stomach fundus which was resected. Histological results revealed a well differentiated neuroendocrine tumor (NET) with no evidence of vascular invasion or necrosis and Ki-67 index $<2\%$; immunohistochemical studies for gastrin, somatostatin and serotonine were negative; atrophic gastritis was also documented. The association of Graves' disease, pernicious anemia and gastrointestinal neuroendocrine tumor suggests the diagnosis of the very rare type IIIb polyglandular autoimmune syndrome. Gastric NETs associated to chronic atrophic gastritis (Type 1) are often small (<1–2 cm) multiple in 65% of cases and polypoid in 78% of cases, often G1 and with an excellent prognosis.

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EP792

Chronic stress and somatotroph axis in breast cancer more than a simple association

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Introduction
Epidemiological and clinical studies have proven direct correlations between chronic stress, inflammation and cancer progression. The inflammatory environment preexisting the malignant change and elevated IGF-1 levels are associated with higher cancer risk, especially through GH effects on cell proliferation and inhibition of apoptosis.
Aim
To evaluate the relationship between biological and hormonal stress markers, growth factors and breast cancer (BC).
Patients and Methods
Biological markers (fibrinogen, C-reactive protein (CRP), ESR), endocrine stress markers (urinary free cortisol, ACTH and urinary metanephrines) and somatotroph axis: growth hormone (GH), insulin-like growth factor-1 (IGF1) were determined in a population-based sample of 79 female patients diagnosed and treated for breast cancer.
Results
Among the inflammatory markers the increase of fibrinogen has been connected to high levels of IGF1 ($r=0.231$, $P=0.045$), low GH ($r=-0.220$, $P=0.062$) and low cortisol ($r=-0.226$, $P=0.058$); elevated ESR correlates with the increase in GH secretion ($r=0.243$, $P=0.039$) and high CRP was directly linked to higher values of ACTH ($r=0.417$, $P=0.00$). Both cortisol ($r=-0.265$, $P=0.025$) and urinary metanephrines ($r=-0.311$, $P=0.016$) have proven to negatively correlate to IGF-1. While advancing in age, both ACTH levels ($r=-0.225$, $P=0.052$) and IGF1 ($r=-0.223$, $P=0.051$) tend to decrease.
Conclusion
The chronic inflammatory status, frequently found in patients suffering from breast cancer, seems to be linked to the increase of the endocrine stress and growth markers. This augmentation of IGF1 levels could be a negative predictive factor for the further evolution and prognostic for the disease. However, our study has shown that high levels of stress hormones correlate to lower IGF1.

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Female Reproduction

EP793

Cynicism and common endocrine diseases in pregnancy

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Introduction
Cynicism (or cynical distrust) is described as a state of mind and belief that most people are selfish. Cynicism is an attitude characterized by general distrust of the motives of others, and some experts describe it as a form of chronic anger. Negative emotions, especially cynicism, may be harmful to physical health.
Aim
The assessment of cynicism in pregnant women with common endocrine diseases.
Subjects – Methods
We examined 54 Greek pregnant women (mean age + S.D.: 35+5 years), 18 with hypothyroidism diagnosed during pregnancy (HT), 18 with gestational diabetes mellitus (GDM) treated with medical nutrition therapy and 18 with HT+GDM. They all responded to the validated Greek version of the Cook-Medley questionnaire (by T Anagnostopoulou & G Kioseoglou) (minimum possible score: 8, maximum: 40). The validity of the responses was assessed by calculating Cronbach's alpha and the differences between the three groups of women, taking into account their age, were assessed with analysis of covariance (ANCOVA).
Results
The validity of the questionnaire was satisfactory (Cronbach alpha $=0.77$). Women with HT had mean cynicism score+SE: 19.4+1.3, with GDM: 21.6+

1.3 and HT + GDM; 24.7 + 1.3 ($P = 0.02$ for HT vs HT + GDM). The cynicism score had no correlation with age ($P = 0.34$).
Discussion
In our study we found that coexistence of HT + GDM acted cumulatively in cynicism score. It has been found that cynicism raises the risk of developing DM type 2, and so does GDM. Given such negative consequences, we discern the need of women with GDM to reassess their life attitudes and possibly to seek help to improve their life and their prognosis.

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EP794

Thyroid ultrasonography findings in patients with polycystic ovary syndrome

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Polycystic ovarian syndrome (PCOS) affects 6–10% of women of childbearing age. The pathophysiology of PCOS is related to increased insulin resistance (IR). Obesity, the leading cause of high IR, is present in 50% of women with PCOS, but lean women with PCOS also have higher IR than women with the same BMI without PCOS. Recent studies have correlated high IR with presence of thyroid nodules (TN), which motivated us to evaluate the occurrence of TN in patients with PCOS. 50 women with 18–45 years with PCOS according to the Rotterdam criteria were submitted to: evaluation of BMI and presence of acanthosis nigricas (AN): laboratory tests for blood glucose and thyroid hormones; and thyroid ultrasound (made by the same examiner with the same device). Laboratory and imaging results were compared between patients with (group 1) and without (group 2) TN through the Student's *T*-test. The prevalence of TN was 36%. We observed that weight, BMI and glycemia were significantly higher in group 1 with the following p-values, respectively: 0.003; 0.01; and 0.028. The prevalence of AN was also higher in group 1 (50 × 37.5%). Among patients with TN, 13 had a single nodule and only 5 had multinodular disease (2 patients with 4 and 3 with 3), totalizing 30 nodules identified. 13 of these were ≤1 cm and 7 were suspicious, indicating that further investigation would be necessary. Our prevalence of TN was higher than that found by other authors in obese women at the same age without PCOS (21.4%). Although prevalence of TN increases with age, a Finnish study evaluating healthy middle-aged women (49–58 years) also showed a lower prevalence (30.69%). These data suggest that patients with PCOS have a higher risk of developing TN.

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EP795

Comparison of free testosterone results by a radioimmunoassay and a chemiluminescent assay

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Introduction
Radioactive assays are widely used in clinical laboratories for measuring free testosterone. The appearance of a non-isotopic, chemiluminescent automatic assay, may be an interesting alternative if the performance of the assay remains the same or higher.
Objective
To compare the free testosterone results by radioimmunoassay (RIA) and chemiluminescent assay (CLIA) and to analyze the clinical impact taking into account the % concordance.
Material and Methods
We studied 76 patients, aged 13–73 years old, and observed at CHLC medical appointments, in Lisbon. The serum samples were analyzed by "Free TESTO-RIA-CT", DIASource (0.2–22.1 pg/ml) and "Maglumi Free Testosterone (CLIA)" Snibe (1.52–40.62 pg/ml). An excel tool was used for statistical treatment and the clinical concordance of the results were analyzed according to the reference values of both.
Results
A strong correlation was observed $r = 0.95$ and linear regression was calculated: $y = 1.51x + 0.072$. The % concordance found was:

	n	Age	Agreement	Disagreement	% concordance
Female	50	16–73	49	1	98
Male	26	13–60	19	7	73.1

Conclusion
There is a good agreement between the two methods. The absence of age-stratified reference values by CLIA' method may explain the discordant results. Despite the small sample size, Maglumi free testosterone may be considered a good alternative to the RIA assay, although it is fundamental to have reference values according to age and gender since the concentration of free testosterone varies throughout life from childhood to adulthood.

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Growth Hormone IGF Axis – Basic

EP796

Impact of new standardization on IGF-I assay IMMULITE 2000

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Introduction
IGF-I is a clinically relevant protein in the diagnosis and monitoring of treatment of growth disorders. The Growth Hormone Research Society and the International IGF Research Society have encouraged the adoption of a universal calibration for immunoassays to improve standardization of IGF-I measurements.
Objectives
Comparison of new standardization IGF-I assay with IGF-I assay currently used in CHLC, Lisbon; To study whether the introduction of the new assay would lead to different clinical interpretations, verifying the concordance of results.
Material and Methods
A random sample of 186 patients regularly assisted at CHLC, mostly in Endocrinology Departments, comprising both genders, ages 2 months–85 years. Determinations on IMMULITE 2000 (Siemens). Chemiluminescent assays: new standardization (1st IS WHO, 02/254 NIBSC) and old (1st IRR WHO, 87/518 NIBSC); An Excel tool was used for statistical treatment. For comparison statistics we excluded 9 patients.
Results
Comparison statistics: $r = 0.994$; Slope = 0.63; interception (ng/ml) = 22.4; $n = 177$; range 27.2–938.0 ng/ml. According to assay and age-specific reference values specified by the manufacturer, we found concordance between 78.3 and 90.4%, regardless of gender, with the exception of 0–3 year age group, in which concordance fell below 33.3 and 50%.
Conclusions
Comparison statistics revealed data overlapping with those of the manufacturer. Although there was a good agreement between assays results, caution should be exercised in the interpretation of a single IGF-I value and of the impact of the new standardization. Discrepancies require posterior evaluation in the evolution of the disease, mainly in group 0–3 years. Clinicians should be aware of the tendency to reduce IGF-I values with the new calibration, so that they do not attribute it to a change in patient status.

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Male Reproduction

EP797

Rare case of manifestation of erectile dysfunction soon after thyroidectomy because of thyroid cancer in 56-year-old man with diabetes mellitus type 2 and diabetic neuropathy

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Introduction
Erectile dysfunction (ED) is common among men with diabetes mellitus (DM). Early diagnosis for such patients is essential in case of other multiple serious

endocrine disorders like thyroid cancer (TC). The aim of our presentation is to demonstrate the case of 56-year-old male with DM and TC when the manifestation of ED had been observed only after thyroidectomy.
Clinical presentation
A 56-year-old man attended our clinic with complains of ED and loss of libido. He also represented the complains characteristic to diabetic neuropathy. The symptoms of diabetic neuropathy appeared approximately 10 years ago. The patient is diagnosed with diabetes mellitus type 2 since the age of 46. So diabetes mellitus and diabetic neuropathy was diagnosed at the same time. In November 2016, total thyroidectomy was performed because of papillary microcarcinoma. After several days of surgical intervention the patient represented complaints of ED. Laboratory investigations were performed: HbA1c-6.0%, prolactin and total testosterone within normal range. It had carried out a comprehensive, phased treatment, which included treatment of diabetic neuropathy and hypothyroidism with carrying out non-specific stimulation (Yohimbin Hydrochlorid and L-arginin) as well as the therapy by PDE-5 inhibitor. Above-mentioned treatment led positive results because the treatment of ED was initiated in a timely manner. In our clinical case DM and DN was diagnosed at the same time. It is interesting that the patient underwent to thyroidectomy and soon after he attended our Clinic. The question is: does thyroidectomy and high level of TSH could be the reason of early manifestation of ED?
Conclusion
The early diagnosis of ED is important for successful treatment especially among man who had ED and multiple serious endocrine disorders. So it is important to reveal it in the early stage. The easiest way not to miss ED in diabetic patients is the questionnaires, which we use successfully in our clinic.

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EP799

Epileptic seizures in patients with large and giant prolactinomas

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Objective
To study epileptic seizures in patients with large and giant prolactinomas.
Patients and methods
The study group included 45 patients with large prolactinoma (more 36 mm in diameter) and 23 patients with giant prolactinoma (more than 60 mm in diameter). 55 men and 13 women aged 16–67 years (mean 39). Patients were followed by hormone measurements, magnetic resonance imaging (MRI), electroencephalogram (EEG) and endocrinological, psychopathological, neurologic examinations.
Results
Mean serum prolactin level ranged between 12 990 and 1 038 000 mU/l (mean 198 000 mU/l). Epileptic syndrome was revealed in 14 patients (21%): partial seizures with secondary generalization (64%), complex (28%) and simple (14%) seizures or their combinations. Seizures differed in structure depending on growth of the tumor. Partial seizures with secondary generalization were mostly revealed in patients with growth of adenoma to temporal region on left (50%) and right (14%). Complex partial seizures were revealed in patients with growth of the adenoma to temporal region on left (21%) and into the III ventricle (7%). Simple partial (psychosensory) seizures were in patients with growth of adenoma into diencephalic region (14%). Diagnosis of epileptic seizures was based on the detection of typical pathological patterns in EEG.
Conclusion
21% patients with large and giant prolactinomas have epileptic syndrome. Structure of epileptic seizures depends on extension of the adenoma and intrusion in different regions of the brain.

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Neuroendocrinology

EP798

Dissecting the androgen excess phenotype of women with idiopathic intracranial hypertension

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Abstract
Idiopathic intracranial hypertension (IIH) is a devastating neurological condition, with elevated intracranial pressure of unknown aetiology. IIH is largely a disease of obese females of reproductive age. The clinical phenotype of IIH overlaps with polycystic ovary syndrome (PCOS), with prevalent obesity, hyperandrogenism and anovulation. In this study, we aimed to delineate the androgen excess phenotype of IIH women compared to those with PCOS and simple obesity. Women with IIH ($n=70$), alongside age- and BMI-matched cohorts with PCOS ($n=60$) and simple obesity ($n=40$), were recruited to an *in vivo* study. Serum classic and 11-oxygenated androgens were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and urinary steroid excretion by gas chromatography-mass spectrometry. Cerebrospinal fluid (CSF) androgens were quantified by LC-MS/MS in IIH women ($n=49$) and a female cohort with non-IIH neurological disease ($n=30$). PCOS patients had increased insulin resistance, as measured by HOMA-IR ($P<0.05$), while HOMA-IR in IIH and controls did not differ. Serum testosterone was higher in IIH compared to both PCOS and control women ($P<0.001$ for both); conversely, serum androstenedione was higher in PCOS women than in IIH ($P<0.001$) and controls ($P<0.01$). Serum levels of the 11-oxygenated androgen precursors 11β-hydroxyandrostenedione and 11-ketoandrostenedione were increased in PCOS ($P<0.0001$), while levels in IIH patients did not differ from controls. Systemic 5α-reductase activity, as measured by the ratio of 5α-tetrahydrocortisol/tetrahydrocortisol, was higher in IIH women compared to both PCOS and controls ($P<0.05$ for both). IIH women had increased CSF androstenedione and testosterone compared to controls (all $P<0.0001$). Using mass spectrometry-based analysis, we show that women with IIH have a distinct androgen excess phenotype compared to PCOS and simple obesity, with higher active serum androgens, 5α-reductase activity and increased CSF androgens. Further studies are needed to understand the role of androgen excess in the pathogenesis of IIH.

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EP800

Prednisolone reinforces the food reward system by bilateral amygdala activation – an fMRI study

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Introduction
A well known side effect of glucocorticoid treatment is abdominally centred weight gain due to increased sensation of hunger but the underlying mechanism is still only incompletely clarified. To elucidate whether the brain reward system is involved in this regulation we studied here the effects of an acute prednisolone infusion on brain centres responding to food stimulation by fMRI in healthy males and correlated these findings to the 24 h food intake of the subjects.
Methods:
20 healthy normal-weight men were tested in a prospective randomized cross-over setting after an overnight fast respectively. They were either infused for 30 min with 250 mg prednisolone or placebo. fMRI scans were taken 4 h later while presenting food and object pictures. At the following morning participants had a supervised breakfast at a standardized buffet. All were restricted from eating during the four hours until fMRI and kept a food diary until the next morning.
Results
When presenting palatable food pictures in contrast to object pictures we obtained a significant activation in brain regions known to be part of the food reward system like the hippocampus, anterior cingulate cortex, bilateral amygdala and insula. Application of prednisolone significantly increased the activity in the bilateral amygdala and right insula in contrast to placebo. The buffet test did not reveal any significant difference in calorie intake or preferences of different macronutrients nor did the food diary.
Discussion
The present imaging results support a direct stimulatory, prednisolone specific effect on food reward centres in the bilateral amygdala and the right insula. This interaction may represent an increased anticipated reward value of high calorie food mediated by glucocorticoids, an effect which most likely needs to be present for a prolonged period of time to relate to a measurably increased food intake (supported by DFG).

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Nuclear Receptors and Signal Transduction

EP801

18β-glycyrrhetinic acid reduces VLDL secretion as a modulator for HNF4α

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Glycyrrhizin (GL) is a major bioactive triterpene glycoside of licorice root, a traditional Chinese herbal medicine. GL and primary metabolite 18β-glycyrrhetinic acid (GA) have been developed as anti-inflammatory and antiviral drugs for liver diseases in China and Japan. Hepatic VLDL secretory pathway is not only responsible for lipid homeostasis but also associated with viral particles assembly and secretion. Hepatocyte nuclear factor 4α (HNF4α) together with its downstream targets, namely, secreted phospholipase A2 G12B (PLA2G12B) and microsomal triglyceride transfer protein (MTP), regulate VLDL production and secretion. We hypothesized that GA may act through HNF4α to mediate some of its beneficial effects. We found that GA inhibits the transcriptional activity of HNF4α. Specifically, promoter reporter expression of PLA2G12B, MTP and ApoB activated by HNF4α are dose-dependently suppressed by GA. Through lipid droplet analysis *in vitro*, we further found that GA trended to elevate intracellular triglycerides levels in a dose dependent manner in Huh7 cells, indicating that VLDL production and secretion is suppressed. To investigate GA effects *in vivo*, we fed mice a high-fat diet for 19 weeks. These mice were then gavaged with GA 60 mg/kg (HFD-GA) or vehicle (HFD-ctrl) every day for 6 weeks. We found that VLDL secretion rate was lowered significantly by GA treatment in HFD mice compared to HFD-ctrl mice. Data from blood biochemistry analysis revealed that treatment with GA significantly reduced blood TG, TC, ALT, AST, and glucose. While hepatic TG and TC levels were increased by HFD feeding, GA blunted the amount elevated by HFD. Oil red O staining showed that the amount of fat droplets in HFD-GA hepatocytes were reduced noticeably compared to HFD-ctrl, indicating that GA treatment reduced neutral lipid accumulation in the liver. These evidence collectively suggested that GA acts as a modulator of HNF4α, not only alleviating hepatosteatosis but also reducing hepatic secretion of TG-rich VLDL implying an underlying mechanism for antiviral and hepatoprotective properties.

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EP802

5α-THB as a novel anti-inflammatory drug: The roles of the glucocorticoid and mineralocorticoid receptors

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Glucocorticoids (GC) are potent anti-inflammatory compounds, acting mainly through the glucocorticoid receptor (GR). GC therapy, however, has debilitating side-effects, necessitating safer new alternative therapies. The natural GC metabolite 5α-Tetrahydrocorticosterone (5αTHB) is anti-inflammatory *in vivo* in mice, but with fewer side-effects. Its mechanism of action is unknown, and here we test signalling via GR and the mineralocorticoid receptor (MR). 5αTHB displaced dexamethasone (Dex) from primary rat hepatocytes ($n=6$, Kd (nM): Dex 37 ± 8, corticosterone 153 ± 59, 5αTHB 268 ± 78) but only negligibly from isolated human GR ($n=3$, EC_{50} (μM): Dex 0.004, cortisol 0.019, 5αTHB 480). GR nuclear translocation was quantified by western blot after nuclear (N) and cytoplasmic (C) separation of steroid-treated A549 cells. Dex (100 nM) increased the N/C GR ratio, after 30 minutes (0.59 ± 0.26 to 2.97 ± 0.50, $P<0.0001$) and 24 h (0.47 ± 0.29 to 2.23 ± 0.72, $P<0.05$). In contrast, GR translocation was not observed with 5αTHB (1, 3 or 10 μM) at either time ($n=6$). Similarly, GR Ser211 phosphorylation was increased by (1 μM) corticosterone (B; 5.00 ± 1.05 fold vs vehicle, $P<0.0001$) but not by (10 μM) 5αTHB (2.74 ± 0.35 fold vs vehicle, not significant). MARCoNI (Pamgene) peptide array analysis ($n=3$) demonstrated that Dex altered the interaction of GR ligand binding domain (LBD) with 75 co-regulator peptides, whereas 5αTHB induced weak changes with only 3. Interestingly, interactions between the MR LBD and its co-regulator peptides were altered to a comparable extent by F and 5αTHB treatment (76 vs 41 interactions altered, respectively). In addition, both aldosterone (10 nM) and 5αTHB (5 μM) increased transcriptional activity of a luciferase tagged MR reporter construct in HEK293 cells (13.50 ± 1.09 fold and 11.20 ± 1.24 fold vs vehicle, respectively, both $P<0.0001$, $n=4$). Both effects were antagonised by spironolactone. In conclusion, the mechanisms underlying the action of 5αTHB differ from those of classical GCs, consistent with its reduced side-effect profile, and may involve MR as much as GR.

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EP803

Development of novel human stable reporter cell line for the assessment of PPARγ transcriptional activity

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Endocrine disrupting chemicals (EDCs) are exogenous compounds that affect the endocrine system, disrupt the hormonal balance and consequently cause the adverse health effects in humans. These compounds persist and accumulate in the environment and can easily gain entry to the food chain. Peroxisome proliferator-activated receptor gamma (PPARγ) and its heterodimeric partner retinoid X receptor alpha (RXRα) are very often targets of EDCs. PPARγ play crucial role in lipid and glucose metabolism and disturbing of PPARγ signaling leads to serious diseases such as obesity, diabetes, insulin resistance and cardiovascular diseases. Therefore, it is of topical interest to develop reliable, high throughput *in vitro* system allowing screening and identification of compounds affecting PPARγ activity. In the current work, we developed the unique stably transfected human reporter cell line T24/83-PPARgamma for the assessment of PPARγ transcriptional activity. Reporter cell line was prepared by transfecting the human bladder carcinoma cell line T24/83 with reporter plasmid pNL2.1[Nluc/Hygro] containing three copies of PPARγ response element, coupled with minimal promoter. Design of response element was based on the sequences of promoter region of human acyl-CoA-oxidase. In the cells treated with PPARγ ligand 15-deoxy-δ12,14-prostaglandin J2 and prostaglandin D2 for 24 h, luciferase activity ranged from 40-fold to 50-fold and from 70-fold to 80-fold, respectively (RLU 10^4–10^5). Application of PPARγ selective antagonist T0070907 resulted in inhibition of luciferase activity, indicating specific response of T24/83-PPARgamma cell line. The inducibility of luciferase activity remained unaffected after cryopreservation and even after prolonged cultivation for more than 2 months. Based on these results, the novel human reporter cell line T24/83-PPARgamma can be considered as a potential tool for screening of compounds affecting PPARγ activity, applicable in various toxicological and environmental studies.

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EP804

Functional characterization of inherited S127F substitution in V2 vasopressin receptor revealed a loss-of-function mutation leading to nephrogenic diabetes insipidus

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The V2 vasopressin receptor (V2-R) mediates the effect of vasopressin on the water reabsorption in the kidney and several mutations in the V2-R have been identified causing nephrogenic diabetes insipidus (NDI). In this study, we investigated a previously not characterized mutation of the. We obtained genomic DNA of a young male patient with NDI, the AVPR2 gene was amplified with PCR and a missense mutation (S127F) was identified. We monitored the cellular localization of the S127F mutant V2 receptor using

HA-tagged receptors in confocal microscopy experiments. The S127F V2 receptor was detected only in the endoplasmic reticulum but not in the plasma membrane. We also measured the cAMP signaling capability of the mutant receptor with BRET measurements. The S127F receptor was not able to increase the intracellular cAMP levels in response to vasopressin stimulation. Certain ER retention mutations can be rescued by pharmacological chaperones, which cause misfolded mutant receptors to present in the plasma membrane. We examined the effect of tolvaptan (V2R antagonist) on the S127F V2 receptor. HEK293 cells were transiently transfected with the plasmid of the mutant receptor and after one day the cells were incubated for 18 hours with tolvaptan. After the pretreatment, the cells were exposed to vasopressin, and we were able to detect cAMP signal generation of the mutant receptor. We checked whether the result after tolvaptan pretreatment was due to restored plasma membrane location of the receptor. We were able to demonstrate significant increase of the mutant receptors in the plasma membrane using flow cytometry. Since the tolvaptan is already used in the treatment of multiple diseases, we plan to carry out clinical studies to assess the potential therapeutic usage of this drug in the NDI patients with S127F V2R mutation. This work was supported by National Research, Development and Innovation Fund (NKFI K116954).

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EP805

Effects of human interleukins on transcriptional activity of vitamin D receptor in transgenic gene reporter cell lines IZ-VDRE and IZ-CYP24

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Vitamin D receptor (VDR) signalling can be affected with a variety of compounds, both endo- or exogenous. However, any disruption of VDR transcriptional activity can exert severe physiological or pathophysiological outcomes. It is therefore of a great importance to have a reliable *in vitro* screening technique that would provide a tool for efficient identification of agonists and activators of human VDR. In the current work, we described two novel human reporter cell lines IZ-CYP24 and IZ-VDRE, constructed for the purpose of VDR transcriptional activity detection. Parental human adenocarcinoma cell line LS 180 was stably transfected with a reporter construct CYP24_minP-pNL2.1[Nluc/Hygro] containing a sequence from the promoter region of human CYP24A1 gene (IZ-CYP24), or VDREI3_SV40-pNL2.1[Nluc/Hygro] containing three copies of VDREI from the promoter region of human CYP24A1 gene (IZ-VDRE), respectively. Both our cell lines remained fully functional in the cell culture for more than 2 months (corresponding to 30 passages) and even after cryopreservation. Luciferase inductions ranged from 10-fold to 25-fold (RLU 10^6–10^7) and from 30-fold to 80-fold (RLU 10^3–10^4) in IZ-VDRE and IZ-CYP24 cells, respectively. Time-course analyses revealed the possibility to detect VDR activators as soon as after 8 hours of incubation. Both our cell lines were highly selective towards VDR agonists, no cross-talk with retinoids, thyroids or steroid was observed. As a proof of concept, the effect of 13 human interleukins on VDR transcriptional activity was examined. Luciferase assays showed an inhibition of VDR transcriptional activity by interleukin-4 and interleukin-13, reaching approximately 60% of calcitriol-induced luciferase signal in concentrations about 1 ng/ml after 24 h of incubation in IZ-CYP24 cell line. Similar results were obtained from expression analyses of human CYP24A1 mRNA. Taken together, both of these cell lines provide a tool for reliable, high-throughput and selective identification of VDR ligands, with possible implications in toxicological and environmental studies.

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EP806

3-Iodothyronamine induces transient receptor potential melastatin 8 (TRPM8) channel activation in human corneal endothelial cells and human corneal keratocytes

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3-Iodothyronamine (3-T_1AM) is an endogenous metabolite of thyroid hormone (TH) for which was shown to have various effects. One of the effects is body temperature decline, which may be related with menthol receptor TRPM8. Normally, this ion channel is expressed in neuronal tissue, where it has a nociceptive role. Functional TRPM8 expression has also been shown in non-neuronal cells of the eye such as corneal and conjunctival epithelial cells, corneal endothelial cells as well as human corneal keratocytes. Furthermore, we could demonstrate in previous studies that 3-T_1AM acts as a cooling agent in human corneal epithelial and conjunctival epithelial cells and that it is suppressing TRPV1 channel (capsaicin receptor), which plays an important role in dry eye disease. Here, we determined in a human corneal endothelial cell line (HCEC-12) and a human corneal keratocyte cell line (HCK) if 3-T_1AM also acts as a cooling agent to directly affect TRPM8 at a constant temperature. Functional activity was evaluated by comparing the effects of 3-T_1AM with those of TRPM8 known agonists on intracellular Ca^{2+} currents and whole-cell currents using fluorescent Ca^{2+}-imaging and planar patch-clamping. Menthol (500 μM), a specific TRPM8 activator, evoked a Ca^{2+} influx as well as an increase of whole-cell currents. This effect could be blocked by BCTC (20 μM) and AMTB (20 μM), both selective TRPM8 antagonists. Notably, comparable effects were observed with 1 μM 3-T_1AM. Overall, this study completes our previous studies of human corneal and conjunctival epithelial cells. Interestingly, the effect of 3-T_1AM has a similar Ca^{2+} response pattern and similar whole-cell current pattern in all three layers of the cornea. Therefore, this might represent a general biological phenomenon. Further investigation of 3-T_1AM effects on the cornea should be performed in order to better characterize a potential benefit of 3-T_1AM on the treatment of dry eye disease.

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EP807

Cytotoxic activity of plant extracts from Brazilian biome in prostate cancer cell lines

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Introduction
Prostate cancer is a public health problem worldwide. The cure is unlikely and therapeutic alternatives are limited. The Brazilian biodiversity represents a huge source of potential discovery of new drugs derived from plants. We therefore aimed to conduct a biomonitoring chemical study of plant extracts from *Pouteria sp.* previously shown to be cytotoxic in androgen-sensitive (LNCaP) and androgen-resistant (PC3) human prostate cancer cell lines.
Methods
The crude ethanolic extract of *Pouteria caimito* leaves and hexanic extract of *Pouteria ramiflora* were tested in PC3 and LNCap human prostate adenocarcinoma cells. The crude extract of *P. ramiflora* branches and stem was then pre-fractionated through sintered funnel. The pre-fraction hexane: ethyl acetate 1:1 was fractionated by column chromatography into 649 fractions, grouped according to the profile in thin layer chromatography into 49 samples. Among those, four samples were selected for Nuclear Magnetic Resonance (NMR) spectroscopy, based on their abundance and cytotoxicity biomonitored by MTT.
Results
The ethanolic extract of *P.* caimito showed a dose-dependent cytotoxic effect in PC3 cells (>50%), with a statistically significant inhibitory effect on the cell cycle. The hexanic extract of *P. ramiflora* showed a dose-dependent cytotoxic effect in LNCaP, with a high selectivity index (5.5 after 48 h of treatment), as compared to a non-cancerous human cell line (HaCat). Among the 49 samples obtained from this extract, fraction "8" was purified and the compound epi-friedelanol was isolated, whose bioactivity is under evaluation in prostate cancer cell lines.
Conclusion
Our biomonitored analysis of *Pouteria sp.* extracts has provided the purification of a number of cytotoxic fractions. Among those, a triterpenic bioactive compound (epi-friedelanol) was identified by RMN spectroscopy, and deserve

further studies regarding its specific cytotoxicity. Triterpens have been shown to exert cytotoxic effects on different types of cancer at low activity towards normal cells, including prostate cancer.

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Obesity

EP808

Evolution of patients with amyotrophic lateral sclerosis followed in a nutrition and endocrinology specific unit during 3 years

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Introduction
A high percentage of patients diagnosed with Amyotrophic Lateral Sclerosis (ALS) have malnutrition. The nutritional treatment in ALS is essential, affecting muscle strength, quality of life and survival.
Objective
To describe the nutritional characteristics of patients evaluated in a specific nutritional Unit in patients with ALS during 3 years.
Material and methods
A descriptive study of all patients diagnosed with ALS and evaluated in this specific consultation since October 2013. The nutritional status is assessed by anamnesis, 24-h ingestión count, physical examination (BMI, % lost weight, Plicometry, dynamometry), evaluation of dysphagia by EAT-10 (if positive, volume viscosity test) and analytical tests.
Results
Data were obtained from 60 patients. Mean age at diagnosis: 57.5 years (26–79 years), 65% male. Bulbar: 28.6%, spinal: 61.2%. The mean time until the evaluation in nutrition Unit was 22.1 month (12.6 in bulbar vs 24.7 in spinal, $P<0.05$). The initial BMI: 26.4 (18.1 to 36.2), in 78.3% > 25. The nutritional status in the first consultation was (VSG): 23% of patients with moderate malnutrition, 17.1% of severe malnutrition (30.8% of bulbars vs 5.9% of spinal, $P<0.05$). The most frequent analytical alterations were vitamin D insufficiency/deficiency (58.3%) and hypercholesterolemia (50%). The most frequent analytical disorders were vitamin D deficiency/insufficiency (58.3%) and hypercholesterolemia (22.5%). Nutritional intervention at the first visit was only diet in 46% (7.1% bulbar vs 69% in spinal, $P<0.05$), thickening prescription in 34%, nutritional supplements in seven patients, gastrostomy in three patients (all of them bulbar). Of the patients who were offered gastrostomy during follow-up (56.8%), 68.4% accepted. The main reason for this was weight loss (83%). The FVC (Forced vital capacity) at this time was: 58% (23 to 97%) and 100% were endoscopic. As complications of gastrostomy: three patients had accidental withdrawal. The mean survival time after gastrostomy was 14 months (2–25 months).
Conclusions
- 40.1% of patients with ALS present moderate/severe malnutrition in the first assessment.
- BMI and analytical parameters are not early markers of malnutrition, being weight loss the best marker.
- Patients with bulbar ALS present malnutrition more frequently than spinal forms and require an earlier and more aggressive nutritional intervention.

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EP809

Obesity, gonadotropic axis and breast cancer – is ghrelin the connexion?

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Introduction
Obesity and insulin resistance have been identified as risk factors for breast cancer and are associated with late-stage diagnosis and poor prognosis. Ghrelin is a unique gut-derived peptide that has major impact in energy homeostasis and weight regulation, with new emerging implications in tumorigenesis process, especially in hormone-dependent cancers.
Aim
To evaluate the relationship between ghrelin, clinico-biological parameters of obesity and gonadotropic axis in breast cancer patients.
Patients and Methods
We assessed the relationship between fasting ghrelin and anthropometric measures, insulin-resistance, lipid and glucose metabolism parameters, hypothalamic-pituitary-gonadal axis (HPG): FSH, testosterone/estradiol-ratio, SHBG, and body composition (evaluated by dual-energy X-ray absorptiometry) in 64 breast cancer patients. Both acyl-ghrelin (AG) and des-acyl-ghrelin (DAG) were evaluated through ELISA; total ghrelin (TG) was calculated as the sum of the two.
Results
DAG, but not AG, negatively correlates with BMI ($r=-0.280$, $P=0.013$), waist circumference ($r=-0.335$, $P=0.006$) and waist/hip ratio ($r=-0.302$, $P=0.015$). Concerning body fat distribution, DAG negatively correlates with sub-total ($r=-0.326$, $P=0.005$) and truncal fat mass ($r=-0.273$, $P=0.02$). Even stronger association of these parameters was observed with TG. Also, DAG negatively correlates with insulin l ($r=-0.354$, $P=0.003$) and HOMA-IR ($r=-0.343$, $P=0.004$). Concerning HPG, AG, but especially AG/TG-ratio were positively correlated with FSH ($r=0.354$, $P=0.004$) and SHBG ($r=0.272$, $P=0.03$). Even though no direct correlations were found between ghrelin and HPG, we observed that insulin positively correlates with testosterone/estradiol-ratio ($r=0.247$, $P=0.039$), as with SHBG ($P=0.341$, $P=0.004$), and that the hip circumference was positively correlated with free-testosterone levels ($r=0.251$, $P=0.044$).
Conclusions
Ghrelin has definitely indirect effects in breast cancer through its roles in obesity and insulin-resistance. We described different connections between ghrelin-obesity-gonadotropic axis in these patients, underlying discreet metabolic and hormonal modifications. However, ghrelin may also play a direct role in breast cancer pathogenesis due to its recently discovered anti-aromatase effect in adipocytes.

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EP810

Differences in calcium and thyroid homeostasis and thyroid volume after bariatric surgery

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Introduction
Bariatric surgery would end up with great alterations in homeostatic measures such as glucose and lipid metabolism and hormonal regulation, which of all are interweaved with some number of ways to each other. The hormonal modulation extands along a wide span starting from the change in gastrointestinal peptides, to the effect in insulin and other nutrient metabolism regulatory hormones and even the hormones establishing thyroid and calcium homeostasis. Secondary hyperparathyroidism is a common finding associated with decreased nutrient, mineral and vitamin D absorption after gut lumenal loss due to bariatric surgery. Meanwhile when the adaptation of thyrotropin (TSH) and free t4 (fT4) level shows variance among studies, in fact TSH frequently was reported to decrease. Free t3 (fT3) was constantly shown to decrease, used to be correlated with dysfunction in deiodination. The thyroid volume would also be a candidate of other parameter that is expected to change over postsurgical period.
Materials and Methods
We recruited 67 morbidly obese patients planned to have bariatric surgery. All the subjects were recorded for their body weight, BMI, metformin, insulin and levothyroxine(LT4) usage and if used dosage of the drug before the operation. The patients were examined with hormonal [parathormon(PTH), 25-oh-vitamin d3(25vitD3), TSH, fT3, fT4 and biochemical tests [calcium(Ca), ionized Ca(iCa), phosphorus(P), 24 hour(h) urinary Ca]. Thyroid ultrasonography (USG) were performed by one same practitioner and the diameters of each lobe was given as axbxc(cm). The volume of each lobe was calculated with axbxcx0.524 (cm^3), and total thyroid volume with addition of right to left lobe volume. The number of nodules and the size of largest nodule were also recorded. The antropometric measures, drug consumption data, laboratory tests and thyroid USG were repeated after 12 month of surgery.

Results
The mean age of patients was 41.5±9.6 year. 58 (86.5%) subjects were female, while 9(13.5%) were male. After 12 month of surgical approach, mean body weight decreased from 120.3±4.1 kg to 85.4±3.3 kg (*P*:0.00), BMI from 47.8±1.4 kg/m^2 to 34.0±1.2 kg/m^2 (*P*:0.00), TSH from 2.3±0.2 to 1.1±0.2 μIU/ml (*P*:0.00), fT4 from 1.0±0.0 to 0.5±0.0 ng/dl (*P*:0.00), fT3 from 2.5±0.1 to 1.3±0.1 pg/ml (*P*:0.00), PTH from 48.6±4.7 to 24.4±4.4 pg/ml (*P*:0.00), Ca from 8.0±0.4 to 5.0±0.6 mg/dl (*P*:0.00), and thyroid volume from 9.6±2.2 to 4.0±0.8 cm^3 (*P*:0.022) significantly. Levothyroxine and insulin requirement decreased after operation nonsignificantly. 25vitD3 increased, 24 h urinary Ca decreased again nonsignificantly.

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Paediatric Endocrinology

EP811

Sebaceous hyperplasia and androgen levels-still controversial

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Sebaceous glands are very sensitive to androgens which can modify the size but not the number of sebaceous glands. Sebaceous hyperplasia is a common benign proliferation of the sebaceous glands seen during the first weeks of life, being reported in 89.4% of 1000 newborns enrolled in across-sectional prospective study in the period of November 2007 to May 2009 in India [1] or in 35% of 2938 neonates aged up to three days of life hospitalized in a Brazilian city [2]. Sebum secretion is high in neonates probably induced by maternal androgen: dehydroepiandrosterone transferred trans-placental. [3] It is also named "the miniature puberty of the newborn" along with vaginal bleeding in infant girls and neonatal acne. Reduced androgen levels in elderly could explain hyperplasia of sebaceous glands (slower cell turnover), especially in women while high androgen-dependent sebum secretion in neonates results in neonatal sebaceous hyperplasia. The association between sebaceous hyperplasia and androgens has been demonstrated in animal models [5], but no correlation was found between serum androgen levels and the appearance of sebaceous hyperplasia lesions in women [6].Controversial data exist and further clinical studies are required.

Table 1 Differences between neonatal and adult form of sebaceous hyperplasia [4].

	Neonatal sebaceous gland hyperplasia	Adult sebaceous gland hyperplasia
Age of onset	First weeks of life	Middle age-elderly persons
Gender: males/females	1.08/1	
Sites of skin lesions	nose	forehead,genitalia, areola, chest
Androgen levels	high	low/normal (hyper-receptivity)
Evolution	Spontaneously remission within weeks	progressive evolution without treatment

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EP812

Microduplication of 15q26.3 not including IGF1R as a novel genetic cause of infantile overgrowth

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Introduction
Recently, a microduplication of 15q26.3 not including IGF1R was reported in subjects of two families with overgrowth and variable intellectual disability (Leffler M. *et al*., *Eur J Med Gen*, 2016).

Aim
To report the clinical findings in a third case with overgrowth related to a small microduplication of 15q26.3 not including the IGF1R region.
Methods
Comparative genome hybridization was done using an Agilent 180k microarray platform.
Results
Accelerated linear growth was observed after the first 3 months with a normal weight increase in a female patient, born at 36 weeks of gestation by normal delivery. At birth weight was 3200 g (>97th centile), length 52 cm (>97th centile) and head circumference (HC) 35.5 cm (97th centile). Mother's and father's height was 182 cm. She had transient feeding problems, necessitating nasogastric feeding in the first week of life. She presented with delayed motor development. Teeth erupted prematurely. At the age of 2 years, her length was 96 cm (> 97th centile), weight 16 kg (97th centile), HC 51 cm (97th centile) and armspan 96 cm. She showed a high forehead, mild synophris, epicanthal folds, deep-set eyes, a flat nasal bridge, mid face flattening, a prominent chin, and tapering fingers. Ultrasound of the abdomen and heart were normal. Bone maturation and serum IGF-1 were normal. ArrayCGH analysis showed a de novo 1.6 Mb duplication of 15q26.3 (arr 15q26.3q26.3 (98386658 99753407)x3). Speech delay and mild coordination and motor problems were noted later on, whereas height and weight progressed normally but above the 97th percentile. At the age of 4 year, mitral valve insufficiency developed, necessitating a surgical repair.
Conclusions
The previous and this case report highlight the possible involvement of the distal region of 15q in infantile overgrowth, independent of IFGR1 duplication. Delayed speech development, tall stature and macrocephaly with a prominent chin appear constant findings, while cardiac manifestations may be variably present.

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EP813

A very rare case of 48, XXYY syndrome

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Introduction
48, XXYY is a rare sex chromosome aneuploidy, being estimated to occur in 1:18000–1:40000 male births. Phenotypically it was considered a variant of Klinefelter syndrome (47,XXY), but currently, due to mental deficiency and behavioural characteristics associated, it's considered to be a separated genetic condition.
Case report
We report a case of a 8-year-old boy, first child of a young non-consanguineous couple, born at term. Due to minor dysmorphic facial features, hypospadias and bilateral talus valgus, a genetic test was conducted and the karyotype identified was 48,XXYY. He was frequently hospitalized for upper respiratory infections, gastro-enteritis, recurrent otitis. He was diagnosed with viral induced asthma and IgA and IgG subclass deficiencies, developing food and medication allergies. Physical examination revealed normal height and weight, dysmorphic facial features (thick eyebrows, hypertelorism, mongoloid slant of the eyes, convergent strabismus, thin lips, dental problems), bifid scrotum, hypospadias, sacral sinus, clinodactyly of the fifth finger, bilateral talus valgus surgically corrected. Neuropsychiatric evaluation revealed borderline mental retardation, delayed speaking, aggressive behaviour, learning difficulties. The endocrinologic consult showed a normal thyroid axe, with a normal-low testosterone level (<0.025 ng/ml) associated with a FSH level of 0.98 mUI/ml (0.4–3.8) and LH level <0.1 mUI/ml (0–3,8). Thyroid ultrasound was normal, testicular ultrasound revealed hypoechoic testis, the X-ray of the hand revealed delayed bone age.
Conclusions
48,XXYY was described as a variant of 47,XXY syndrome. It is very important to distinguish the two syndromes regarding the associated medical conditions (as in our case – asthma, food allergies, dental problems, strabismus, recurrent otitis, frequent upper respiratory infections), cognitive and behavioural problems, learning difficulties which are more frequently correlated with 48,XXYY syndrome. Due to complexity and specific features of this particular syndrome,

it is recommended a thorough evaluation and a different therapeutic attitude for each case.

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EP814

Clinical case of early manifestation of autoimmune polyglandular syndrome type 3 A in children

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Autoimmune polyglandular syndrome (APS) type 3 – is a rare orphan disease, which is a combination of autoimmune thyroid disease and diabetes mellitus (DM) type 1 and/or pernicious anemia, vitiligo, alopecia. Due to the rare occurrence in pediatric patients we give our own observation of early manifestation of APS type 3 A in a girl 10 years. Complaints in the primary treatment: sweating, irritability, cardiopalmus, weight loss. Survey results: ultrasound examination of the thyroid gland: expressed diffuse changes, the increase in volume $-22.0\ cm^3$ (normal 2.74–6.76). Indicators: thyroid-stimulating hormone (TSH) 0.05 mkIE/ml (normal 0.27–4.2), free thyroxine (T4) >100.0 pmol/l (normal 12.0–22.0), free triiodothyronine (T3) 43.1 pmol/l (normal 3.1–6.8), TSH receptor antibodies 18.0 IU/l (normal 0–1.75). Ophthalmologist: ophthalmopathy low degree of both eyes. Primary diagnosis: Graves' disease (GD), goiter grade 2, thyrotoxicosis of medium gravity, decompensation. Autoimmune ophthalmopathy. Starting treatment: tiamazol 20 mg/day; metoprolol 25 mg/day. 6 months later the patient was hospitalized with complaints during the month of thirst, frequent urination, weight loss of 4.5 kg, weakness. Survey results: blood glucose level 34.1 mmol/l. Acid-base balance: metabolic acidosis. Indicators: C-peptide 155.6 pmol/l (normal 160–1100), antibody titer to glutamic acid decarboxylase 93.2 U/ml (normal 0–1.0), glycated hemoglobin 9.5%. The metabolic compensation of thyrotoxicosis was observed on maintenance therapy (tiamazol 5 mg/day): T4 17.16 pmol/l, TSH <0.05 mkIE/ml. There was a volume reduction 16.2 cm^3 on thyroid ultrasound. Final diagnosis: APS type 3 A: DM, type 1, decompensation. GD, medical euthyroidism. Autoimmune ophthalmopathy. Treatment: insulin therapy 22 U/day; tiamazol 5 mg/day. 2 months later a child was hospitalized due to worsening indicators of thyroid hormones and severe fluctuations in blood glucose on the treatment of human genetic engineering insulins. Survey results: thyroid ultrasound: negative dynamics – increase to 21.08 cm^3. Indicators: TSH 0.009 mkIE/ml, T4 24.8 pmol/l, T3 10.06 pmol/l. Correction of therapy: increasing the dose of tiamazol to 20 mg/day and using insulin analogs. The simultaneous presence of two or more autoimmune diseases of the endocrine glands (thyroid and DM) aggravates the symptoms of each of them, leads to the decompensation of patients.

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EP815

A novel p.H80Y mutation in the AVPR2 gene causing congenital nephrogenic diabetes insipidus

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X-linked nephrogenic diabetes insipidus (NDI) is a rare disease caused by a defect in the vasopressin V2 receptor in renal collecting duct cells which is encoded by the *AVPR2* gene (Xq28). More than 200 mutations have been found comprising missense, nonsense, small insertions and deletions, large deletions and complex rearrangements in *AVPR2* gene to date. In this study, a 6-year-old boy was referred to the Pediatric Nephrology Department of Kecioren Research and Training Hospital for abnormal fluid intake (5 l/day) and diuresis (4.3 l/day) which was noted to have started in the first few days of life. He had normal serum sodium concentration (142 mmol/l), high serum osmolality (311 mOsm/l), low urinary osmolality (129 mOsm/kg), and hyponatriuria (15 mmol/l) on admission. The water deprivation test was stopped due to weight loss higher than %3 at 3.5th hour of the test. The plasma vasopressin (16.75 pmol/l, range:0–13) drawn at the conclusion of the dehydration test was high, and the urine parameters showed little insignificant changes. The desmopressin challenge test did not affect the urine parameters, either. There was a continuous high urine output, low urine osmolality and impaired ability to increase urine osmolality to normal levels after ADH administration. The *AVPR2* gene of this patient was sequenced with ABI310 and revealed a novel hemizygous missense mutation causing a conversion of the histidine residue to tyrosine in the protein sequence, at the position 80th in exon 2. We suggest that bioinformatical analysis and functional characterization studies will enlight the function of the mutant AVPR2 protein. This research was funded by The Scientific and Technological Research Council of Turkey (SBAG Project Numbers: 112S513 and 115S499).

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EP816

Type 1-like diabetes mellitus in an oncological endocrinology unit

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Introduction
Asparaginase is a component of chemotherapy regimens used to treat paediatric acute lymphoblastic leukaemia (ALL). One of its well-known side effects is hyperglycaemia which is probably related to hypoinsulinemia. Its incidence rises significantly when associated with corticotherapy. We present two cases of diabetes related to asparaginase and corticoid administration.
Case 1
Eleven-year-old girl diagnosed with an ALL. Before treatment she had a normal body weight and was normoglycaemic. She started the DFCI-2011 protocol and on the day of the first peg-asparaginase administration she was found to have polydipsia, polyuria and a glycaemia of 700 mg/dl with no clinical evidence of pancreatitis. She started an intensive insulin scheme of therapy with an average dose of 0.6 U/kg/day. On the 16th day insulin dose started to be reduced. Despite the higher doses of corticosteroids in the following asparaginase infusions she needed lower doses of insulin to maintain euglycaemia.
Case 2
Six-year-old boy diagnosed with an ALL at the age of three. He was first treated with DFCI-2005 protocol without evidence of hyperglycaemia. A remission lasting 10 months was achieved with recurrence diagnosed at the age of six. He started the IntReALL-SR-2010 protocol and before this treatment his body weight was between P25-50 and he was normoglycaemic. Seven days after the first peg-asparaginase administration he was found to have a glycaemia of 519 mg/dl with ketonuria of 5 mg/dl, without clinical evidence of pancreatitis. He started an intensive insulin scheme with an average dose of 1.5 U/kg/day. Eleven days after the second peg-asparaginase administration insulin dose started to be reduced and at the end of induction course was stopped. Peg-asparaginase was administered one last time without hyperglycaemia.
Conclusion
Asparaginase-induced hyperglycaemia may cause diabetic ketoacidosis or hyperosmolar hyperglycaemic nonketotic syndrome which can be fatal. It is recommended a frequent assessment of glycaemia in these patients. Its occurrence usually does not lead to suspension of therapy. Hyperglycaemia frequently gets better despite continuous use of asparaginase.

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EP817

P3NP has high-normal values in GHD children and correlates negatively with IGF1

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Aim
Procollagen type III N-terminal peptide (P3NP) occurs during type III collagen synthesis. Previous studies about the GH misuse in athletes proved the P3NP as a growth hormone (GH) responsive biomarker. We evaluate the P3NP levels and correlate with IGF1 depending on GH status.
Subjects and Methods
We determined P3NP levels in 81 prepubertal children (35 girls) with a mean age of 6.2 y.o [3.37–9.95]. The group consists of 37 subjects with normal height, 18 subjects with growth hormone deficiency (GHD) and 26 subjects with non-GHD short stature. We measured P3NP with a commercially available (for research purpose) ELISA kit (catalog code: DL-PIIINP-Hu) with the detection range 62.5–4000 pg/ml.
Results
In 50 subjects with values of IGF1 below 0 SDS, we found a negative correlation of P3NP and IGF1 (rs = −0.292, $P = 0.039$). Even not statistically significant, P3NP correlate negatively with height-SDS (rs = −0.210, $P = 0.144$). 26 values of P3NP were out of the reference range for this biomarker. Five of these records belongs to GHD subjects with conditions that can explain high P3NP levels (hypothyroidism in the context of multiple pituitary deficiencies, trauma or inflammation). We analyzed 55 registrations with P3NP in the normal range available for the whole group, according to GH status. We found higher P3NP levels, expressed as median of SD in the GHD group compared to normal stature children ($M = 0.7$, $n = 9$ vs $M = -0.17$, $n = 28$) and this difference was statistically significant $U = 70.5$, $z = 1.96$, $P = 0.049$).
Conclusion
The lack of GH-IGF1 effect in GHD children could lead to normal -high levels of P3NP because this biomarker of collagen synthesis is not effectively incorporated into collagen supportive tissues.

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EP818

Turner Syndrome (TS): overview of surveillance in a tertiary care hospital

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Introduction
Turner syndrome is one of the most common human chromosomopathy and represents an important cause of short stature and ovarian insufficiency. It is caused by total or partial loss of X-chromosome and its prevalence is about 1 in 2000–2500 live female births.
Objectives
To review the patients with TS followed in a Paediatric Endocrinology Unit since 1999.
Methods
A retrospective study regarding diagnosis, course, treatment and current status of patients with TS was performed, based on medical records' review.
Results
Thirty-five female patients were included; 62.9% showed mosaic karyotype; 5 patients had a prenatal diagnosis and 3 during the neonatal period and in the others ($n = 27$) the mean age of diagnosis was 7.83 years (0.40–16.11). The main reason for investigation was short stature (46%); other less frequent and sometimes combined included failure to thrive ($n = 5$), primary amenorrhea ($n = 2$), foot oedema at birth ($n = 2$), dysmorphic features ($n = 6$), cardiomyopathy ($n = 1$) and hepatitis ($n = 1$). The main associated morbidities were: learning disabilities (31%), hearing and visual problems (40 and 29%, respectively), congenital heart defects (29%), renal malformations (26%), autoimmune thyroiditis (17%) and celiac disease in one patient. Sixty-nine percent ($n = 24$) were eligible for growth hormone (GH) treatment. Among these, 13 reached their final stature with a variation of the mean z-score from −2.78 (−4.38–−1.31) before to −2.16 (−3.85 to 0.00) after treatment. Among patients older than 12 years ($n = 21$), in 62% puberty was induced by transdermal oestrogens. One patient had two spontaneous pregnancies.
Conclusions
In our study treatment with GH showed improvement of the height z-score. Some girls were diagnosed very late and some of them after attended final height without GH treatment. It is essential to be alert to the main clinical manifestations of the syndrome and provide an earlier diagnosis to optimize the treatment.

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Pituitary – Basic

EP819

Non-functioning pituitary adenomas: association between clinical-pathological and molecular parameters

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Non-functioning pituitary-adenomas (NFPAs) represent the most common pituitary tumor-type. To date, there are not clinical, biochemical, anatomo-pathological, immuno-histochemical or molecular parameters useful to predict their remission. Therefore, the aim of this study was to evaluate the potential relationship between the clinical, biochemical and pathological characteristics of patients with NFPAs, the expression profile of these tumours and the clinical outcomes during their follow-up. An observational/retrospective-study of patients with NFPAs evaluated between January 2002-December 2015 was implemented at our hospital, by collecting a complete set of clinical/biochemical/radiological-data from patients ($n = 34$; 50% women; age: 56.2 ± 11.9 years-old), and anatomopathological and molecular (26 genes measured by qPCR) data from the tumours. Mean follow-up of patients: 5.2 ± 3.9 years. Symptomatology: 38.2% campimetric alterations, 35.3% headache and 11.8% symptoms derived from hormonal deficits. A predominant expression of Dopamine-receptor 2 (DRD2) followed by somatostatin-receptors (sst) 3 and 2 was found. Furthermore, a consistent increase in the expression of the majority of receptors analyzed between first and second surgery of the patients was observed. Interestingly, lower expression-levels of sst1 and sst3 were found in patients pre-treated with statins. Correlations between receptors and/or molecular markers (i.e. DRD2 with AVPR1b, sst5TMD5 with serum testosterone-levels or sst5TMD4 with p53-levels) were observed. Additionally, male sex, lower levels of pre-surgery cortisol and testosterone and low sst5, AVPR1b and PTTG1 expression were associated with a higher curation of patients. Although further studies with a larger cohort of well-characterized patients are needed, our molecular and clinical data suggest that a putative pharmacological treatment for this pathology might be somatostatin-analogues with affinity for sst3 or dopamine agonists (e.g. pasireotide or cabergoline), that statin-treatment might influence the expression levels of some sst-subtypes (e.g. sst3), and that some clinical/molecular markers (i.e. sex, pre-surgery cortisol and testosterone levels and sst5/AVPR1b/PTTG1-expression) could be associated with the curation of patients with NFPAs.

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Steroid Metabolism + Action

EP820

Reference values for the urinary steroid metabolome: the impact of sex and age on human adult steroidogenesis

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Background
Urinary steroid metabolomics by GC-MS is an established method in clinic and research to describe steroidogenic disorders, but normative data are scarce.
Methods
The 24-hour urinary excretion of 40 steroid metabolites was measured by GC-MS in 1128 adult participants of the Swiss Kidney Project on Genes in Hypertension (SKIPOGH), a multicenter, family-based, cross-sectional study. Sex- and age-specific reference ranges were created in the units µg/mol Creatinine and µg/24 hours.
Results
Most urinary steroids showed an age- and sex-specificity. An age- but no sex-specificity was found for etiocholanolone, 18-OH-11-dehydro-TH-corticosterone, TH-cortisol, α-cortol, and β-cortol in the unit µg/mol Creatinine. No sex- but an age-specificity was found for 20α-DH-cortisol in µg/24 hours and neither a sex- nor an age-specificity was found for TH-corticosterone and 18-OH-cortisol in µg/24 hours.
Conclusions
Sex- and age-specific reference ranges for 40 steroid metabolites measured by GC-MS were established in a thoroughly characterized general Caucasian population and can be used in routine clinical work.

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EP821

Does music effect the stress of daily life?

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Introduction
It's assumed that music has health beneficial effects by its potential stres-reducing life. There are some reports that chorists in choral soceity are influenced by music positively during their activities.
Research design and methods
37 healthy volunteers who perform Turkish art music in Bahcesehir Music Society with mean age 50.3 ± 10.3yrs, were included into this study. The state and trait anxiety status of chorists was evaluated by using a Likertscale at the time of beginning (19.00) and the end (21.00) of choir, on chorus working day. After each assesments, chorists were asked to collect saliva samples for cortisol levels to be measured later by using electrochemiluminescence immunoassay. Participants were requested to repeat the same procedure at similar times of any day in their normal lives. All data was evaluated with SPSS 20 version.
Findings
Although results were within normal limits in all subjects, differences were observed on normal and chorus activity days. While mean cortisol levels (ng/dL) were detected as 248.69 ± 140.50 and 286.11 ± 179.50, respectively, at hours 19.00 and 21.00 on the normal day of life (Group I); the levels were observed as 260.64 ± 114.81 and 211.44 ± 91.67, respectively, on chorus working day (Group II) at similar hours. Saliva cortisol levels showed a 33% decrease in Group II while an increase of 21% was detected in Group I ($P < 0.02$). Also a reduction 14% in stres scores was observed in Group II ($P < 0.04$); especially remarkable in women, individuals with non-alcoholic, but smokers, active employeers and people who have less time engaged in music.
Conclusion
We can say that individuals who perform a two-hour Turkish art music per week, are affected positively by music different from the day of their normal life. Particularly due to fact that mucic is very popular, cheap and easly applicable in daily life, it seems promising to use music in daily life as strategy for stress reduction.

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EP822

Inhibition of 11β-hydroxysteroid dehydrogenase 2 by the fungicides itraconazole and posaconazole

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Impaired 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2)-dependent cortisol inactivation can lead to electrolyte dysbalance, hypertension and cardiometabolic disease. Furthermore, placental 11β-HSD2 essentially protects the fetus from high maternal glucocorticoid levels, and its impaired function has been associated with altered fetal growth and a higher risk for cardio-metabolic diseases in later life. Despite its important role, 11β-HSD2 is not included in current off-target screening approaches. To identify potential 11β-HSD inhibitors amongst approved drugs, a pharmacophore model was used for virtual screening, followed by biological assessment of selected hits. This led to the identification of several azole fungicides as 11β-HSD inhibitors, showing a significant structure-activity relationship between azole scaffold size, 11β-HSD enzyme selectivity and inhibitory potency. A hydrophobic linker connecting the azole ring to the other, more polar end of the molecule was observed to be favourable for 11β-HSD2 inhibition and selectivity over 11β-HSD1. The most potent 11β-HSD2 inhibition, using cell lysates expressing recombinant human 11β-HSD2, was obtained for itraconazole (IC_{50} 139 ± 14 nM), its active metabolite hydroxyitraconazole (IC_{50} 223 ± 31 nM) and posaconazole (IC_{50} 460 ± 98 nM). Interestingly, experiments with mouse and rat kidney homogenates showed considerably lower inhibitory activity of these compounds toward 11β-HSD2, indicating important species-specific differences. Thus, 11β-HSD2 inhibition by these compounds are likely to be overlooked in preclinical rodent studies. Inhibition of placental 11β-HSD2 by these compounds, in addition to the known inhibition of cytochrome P450 enzymes and P-glycoprotein efflux transport, might contribute to elevated local cortisol levels, thereby affecting fetal programming.

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EP823

Cortisol levels and thyroid hormones in surgical patients with different sensitivity to pain

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Objective
To determine the intraoperative levels of cortisol and thyroid hormones in surgical patients with different sensitivity to pain.
Material and methods
We analyzed the individual sensitivity to pain in 94 people the day before surgery. Patients were ASA 1-2. Age 46 ± 10.2 years. We used a mechanical stimulus (1 × 5 mm wire with stop) and the visual analogue scale of 10 points (color, grayscale, 10 fields, from light to black). Incentives applied to the base of the thumb. Patients divided into 2 groups, first group - low sensitivity to pain (VAS 1-5). 2nd group - high sensitivity to pain (VAS 6-10). All patients underwent laparoscopic cholecystectomy under general anesthesia. Anesthesia consisted of premedication, induction, myoplegia, intubation, ventilation with a mixture of oxygen supply, nitrous oxide and sevoflurane, anodyne - fentanyl, paracetamol. We used

hemodynamic monitoring and ventilation system. Control thyroid hormones (T3, T4, TSH) and cortisol before operation, 3 times during surgery and after surgery. Statistical analysis was performed using the software package Statistica 7.0

Results

In all patients, the level of thyroid hormones remained normal throughout the study period. Not observed any changes of thyroid hormone levels in patients with both high and low sensitivity to pain. Plasma cortisol levels remained within the normal range in 92% of patients. In 8% of the patients (all patients in the second group, the high sensitivity to pain) noted the excess of normal levels of cortisol. After the start of operation of cortisol level was higher than baseline. Intraoperatively, in patients with high sensitivity to pain of the plasma cortisol level was higher than in patients with low sensitivity to pain.

Conclusion

Perioperative levels of thyroid hormones and cortisol most surgical patients remains within the normal range. Patients with high sensitivity to pain was higher cortisol levels after starting operation as compared to the level of cortisol in patients with low sensitivity to pain.

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EP824

Ritonavir induced Cushing's Syndrome in a patient under inhaled corticosteroids

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Introduction

Cushing's Syndrome secondary to inhaled or topic corticosteroids is very rare, although there are reports of a link to cytochrome inhibitors. Ritonavir, a protease inhibitor used for treatment in human immunodeficiency virus (HIV) infection, is a potent inhibitor of cytochrome P450 3A4.

The case

A 41 years old man - with personal history of asthma, HIV infection diagnosed in 2002 and hepatitis C infection since 1999 – was sent to an endocrinology consult in January/2015 for obesity investigation and orientation. The patient presents with a one-year history of truncal and facial obesity and global weakness of the lower limbs. Moreover, the patient presented with cushingoid facies, facial plethora, centripetal obesity and hypotrophic upper limbs. At that time, the patient was under therapy with ritonavir 100mg/day, salmeterol/fluticasone 50/250 µg two inhalations per day and a topic betamethasone lotion 0,5mg/g twice a week. Morning total plasma cortisol levels were low (0,6 µg/dl) and ACTH was suppressed (5 pg/ml). Cosyntropin stimulation test confirmed a suppressed pituitary-adrenal axis. Consequently, ritonavir was concluded and the clinical picture resolved progressively.

Conclusion

The present case underlines the importance of cytochrome inhibitors in the modification of corticosteroid metabolism and their extended effect – as in Cushing's Syndrome.

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Thyroid (non-cancer)

EP825

Thyroid hormone T3 protects skeletal muscle metabolism during fasting in mice

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Background

Skeletal muscle is known to be a target of THs, regulating oxygen consumption, fiber composition, calcium mobilization and glucose uptake. However, a possible role for THs in muscle homeostasis and cellular metabolism under pathological has never been investigated. Food deprivation induces skeletal muscle atrophy, causing metabolic changes, and forcing the tissue to utilize fatty acid as the main oxidation substrate. Aim of this project was to understand whether T3 influence skeletal muscle metabolism during fasting.

Methods

Adult male BALB/C mice were food deprived for 48h (STV), and daily treated with intraperitoneal injections of T3 (100 µg/Kg BW) (STVT3) or vehicle as controls. At the end of the experiments, Tibilias anteriors were collected and firstly laminin stained sections were analyzed for myofiber sizes by IF microscopy. Secondly, the number of glycolytic, intermediate or oxidative fibers per cross section area on NADH stained histological sections was analyzed. Mitochondria content, indicative of a more oxidative metabolism, was then analyzed by qRT Syber Green PCR for PGC-1a mRNA.

Results

As expected, laminin staining evidenced a reduction in Cross Sectional Area of the myofibers induced by fasting (STV), as a sign of atrophy. The cited reduction was significantly hampered by the presence of T3 in the STVT3 group. Secondly, T3 was able to significantly reduce the shift in the metabolism towards a more oxidative state ($P<0.05$) and a less glycolytic one ($P<0.01$) induced by fasting. Coherently, T3 reduced the increase in PGC-1a mRNA level induced by fasting in the STV group ($P<0.05$).

Conclusions

The decrease of the amount in oxidative muscle fibers during T3 treatment in STV agrees with a less expression of PGC-1a, a molecular marker of mitochondriogenesis and fatty acid oxidation. Therefore, T3 treatment during fasting seems to exert a protective role on the metabolism of muscle fibers.

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EP826

False memory in elderly patients with thyroid disease

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Introduction

The phenomenon of false memory is quite prevalent among people with cognitive impairment. Cognitive dysfunction and its relationship with the thyroid gland has been described. In contrast, little is known about the phenomenon of false memory in patients with thyroid diseases. That is why we want to introduce our preliminary observation.

Method

Patients aged 64 to 90 years (average 77) with endocrine disorders were subjected to tests for typical geriatric assessment and tests investigating the so-called. false memory, that is. "remembering" the words that were not spoken, according to the method Roediger and McDermott's

Results

We investigated 31 patients, of which 17 had thyroid disease. All patients with thyroid diseases, "remembered the" unspoken words. The best result was only 6% of the words false "recalled", the worst result was 75%, on average, about 35%. This result did not differ significantly on the outcome of patients with other endocrine disorders, but among them were two people without the presence of false memory. We found a negative correlation between the results of the test of false memory and mini mental status ($P<0,01$). We did not find significant correlations between the results of the tests and TSH.

Conclusion

False memory may prove to be an important problem among older people with thyroid disease. Although its clinical significance needs further study.

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EP827

Orbital disease primer for Endocrinologists-not always thyroid associated orbitopathy (TAO): a case vignette

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Background
TAO is a rare disease, seriously involving 5% of patients with autoimmune thyroid disease. The clinical presentation may be difficult to distinguish from other orbital conditions.
Case 1
A 63-year-old woman was admitted to the Neurology Service for worsening diplopia over the previous six months, with a working diagnosis of myasthenia gravis or multiple sclerosis. The Endocrine Service was consulted because of a long history of Hashimoto's thyroiditis. The patient was euthyroid on thyroxine replacement. Clinical activity score was 0, but there was restriction in elevation of the right eye. Orbital MRI demonstrated thickening of the right inferior rectus. The diagnosis of TAO was made and the patient received intravenous methylprednisolone with symptomatic improvement.
Case 2
A 48-year-old man with a history of Crohn's disease, was referred for presumed TAO, with severe diplopia, right retrobulbar pain and exophthalmos. He was euthyroid, with negative thyroid antibodies. Orbital MRI demonstrated thickening of all extraocular muscles of the right eye. A diagnosis of orbital myositis was made. The patient received 1.5g intravenous methylprednisolone with marked improvement, but a month later presented with a red left eye and diplopia. Orbital CT demonstrated thickening of the superior oblique and the medial rectus. The patient again received intravenous methylprednisolone with complete remission and remains asymptomatic from his orbital and bowel disease one year later.
Case 3
A 45-year-old woman was referred to the Endocrine Service with right sided ptosis, for presumed TAO. She was euthyroid, with negative thyroid antibodies. Eye exam was normal except for right-sided ptosis. Orbital MRI was normal. On further questioning, the patient admitted having had botulinum toxin injections on the forehead and right brow a week before.
Conclusion
The differential diagnosis and management of orbitopathy often relies on the Endocrinologist and spans the spectrum of divergent medical specialties.

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EP828

Management of very severe Graves' orbitopathy with low dose rituximab: report of two cases

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Introduction
Although Graves' orbitopathy (GO) is common in the course of Graves' disease, dysthyroid optic neuropathy and corneal breakdown are rare. We describe two cases of severe GO treated successfully with rituximab.
Case 1
A 50-year-old female smoker with Graves'disease, presented with disfiguring eyelid edema, exophthalmos and diplopia, preserved visual acuity and clinical activity score (CAS) $\geq$ 5. She received pulsed medroxyprednisolone to a total of 6 gr and standard orbital radiotherapy 3 months later with minor improvement. Thyroid status stabilized on methimazole combined with lithium and an uncomplicated thyroidectomy followed. However, visual acuity declined to "hand motion", necessitating two cycles of rituximab at 375 mg/m^2 each, two weeks apart. Lymphocyte depletion was immediate and sustained and visual acuity improved to 4/10 bilaterally. Three years later CAS = 0 and the patient maintains a visual acuity of 2/10.
Case 2
A 78-year-old male non-smoker presented with hyperthyroidism initially thought to be due to toxic multinodular goiter and had thyroidectomy four months later. An incidental papillary thyroid carcinoma measuring 1.05 cm, insular type, was found at histology in the right lobe. He was referred for management of GO one month postoperatively, characterized by retrobulbar pain, chemosis and diplopia, CAS $\geq$ 7, loss of color vision and visual acuity of 1/10 bilaterally. He received pulsed methylprednisolone to a cumulative dose of 8 g and orbital radiotherapy, resulting in mild improvement in inflammation, but worsening of the acuity to light perception on the right only, with relative afferent pupillary defect on the left and fixed globes. The patient then received two infusions of rituximab of 500 mg two weeks apart. He recovered vision to 2.5/10 in the right eye, which allowed his return to independent living. He subsequently received 100mCi ^{131}I without GO relapse.
Conclusion
Rituximab therapy can benefit vision and quality of life in refractory, severe GO.

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EP829

Evaluation of clinical performance of a new immunoassay in the determination of thyroid stimulating immunoglobulins (TSI)

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Introduction
Anti-TSH receptors (TRAb) are an important marker in the differential diagnosis of the etiologies of hyperthyroidism. They detect serum TSH receptor immunoglobulins that interact with the TSH receptor without the functional discrimination of stimulating from blocking antibodies. A new assay has recently been released, that utilizes recombinant human TSH receptors (hTSHR) for the specific detection and quantification of thyroid stimulating autoantibodies (TSI).
Objective
To evaluate the agreement of a new TSI test by method comparison with a TRAb RIA, in the assessment of Graves disease (GD) in clinically well defined patients.
Material and methods
We studied 162 patients regularly assisted at CHLC, Lisbon: 104 clinically documented GD, 29 with other thyroid diseases and 29 with non-thyroid autoimmune disease. The serum samples were analyzed by a RiaRSR TRAb CT, traceable to WHO standard 90/672, and a new automatic chemiluminescent immunoassay, Immulite 2000 TSI (Siemens), traceable to WHO 2nd IS, NIBSC 08/204.
Results
At manufacturer TSI cut-off (0.55 IU/l), the clinical sensivity and specificity were: 97.1 and 91.4% and at TRAb cut-off (1.5 IU/l), 80.7 and 94.8% respectively. The agreement of the results in the range of 0–1.5 IU/l revealed the occurrence of 17 positive results in TSI that were negative or gray in RIA.
Conclusions
TSI may prove to be a useful method in clinical practice, by automating and discriminating the functional activity of the TRAb.The high sensitivity of TSI may be of great value in the diagnosis and follow up of GD and a good alternative to the RIA assay.

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Eposter Presentations: Pituitary and Neuroendocrinology

Adrenal Cortex (to include Cushing's)

EP830

The metabolic impact of ACTH-dependent versus ACTH-independent Cushing's syndrome: a retrospective study of 99 patients

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Introduction
Although the metabolic impact of Cushing's syndrome and hypercortisolemia are well known, the metabolic impact of ACTH is less established.
Objective
To identify differences in the glucidic, lipid and bone metabolism in ACTH-dependent versus ACTH-independent Cushing's syndrome.
Methods
Retrospective, cross-sectional study of 99 patients with Cushing's syndrome (54 with ACTH-dependent Cushing's syndrome and 45 with ACTH-independent Cushing's syndrome) admitted to 'C.I.Parhon' National Institute of Endocrinology during 1998–2016. Clinical and paraclinical data were analyzed.
Results
Type 2 diabetes was found in 39% and prediabetes was found in 31% of the patients in the ACTH-dependent group; in the ACTH-independent group 31% of the patients had diabetes and 27% had prediabetes. Regarding lipid metabolism, 15% of the patients in the ACTH-dependent group were already on lipid-lowering drugs compared with 29% in the ACTH-independent group; of the remaining patients, who were not on lipid-lowering drugs, 63% had hypercholesterolemia and 46% had hypertriglyceridemia in the ACTH-dependent group, compared with 75% having hypercholesterolemia and 50% having hypertriglyceridemia in the ACTH-independent group. Osteoporosis was found in 31% of the tested patients in the ACTH-dependent group and in 60% of the tested patients in the ACTH-independent group.
Conclusions
Lipid and bone metabolism were more affected in the ACTH-independent group, while glucidic metabolism was more affected in the ACTH-dependent group.

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EP831

ACTH-independent subclinical Cushing's syndrome in patient with acromegaly and adrenal incidentaloma

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Introduction
It is well established that acromegaly is associated with increased risk of cancer. However, it is currently unclear whether patients with acromegaly are at increased risk of developing adrenal tumors and little is known about the association between acromegaly and adrenal adenomas. The simultaneous occurrence of preclinical Cushing's syndrome in patients with acromegaly and adrenal adenoma is extremely rare, and to our knowledge, so far only 5 such cases have been reported in literature.
Case report
73-year-old female with typical acromegalic appearance and acromegaly suspected 34 years ago and recognized 16 years ago. She underwent non complete transsphenoidal resection of somatotroph macroadenoma 15 years ago. Since neurosurgery she is chronically treated with long-acting somatostatin analogue, currently with lanreotide autogel 120 mg every 28 days. The current GH level is 2.59 ng/ml [n:0.126–9.88] and IGF-1 252.2 ng/ml [n:29–204]. Approximately 3 years ago, a focal lesion 22×17 mm was detected in left adrenal gland, with a basal density (−)12HU (tumor density in the adrenal protocol: (+)18HU, (+)10HU, (−)1HU respectively), suggesting adenoma. The patient had long-term arterial hypertension with no cushingoid features. An examination of pituitary-adrenal axis showed lowered ACTH level=4,76 pg/ml [n:7.2–63.6], a tendency to lose a circadian rhythm of cortisol [19.6–10.3 μg/dl] and the lack of cortisol secretion inhibition by 1 and 2 mg of dexamethasone [8.5 and 5.3 μg/ml, respectively]. Daily excretion of urine cortisol was normal [172.5 and 123.6 μg; n:55.5–286.0].
Conclusion
In order to determine the incidence and the relationship between the adrenal tumors and acromegaly, standard evaluating of the adrenal glands is indicated in patients with acromegaly.

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Clinical Case Reports – Pituitary/Adrenal

EP832

Coexistence of TSH-secreting pituitary adenoma, primary hyperparathyroidism and vitamin D deficiency

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Introduction
The simultaneous occurrence of central hyperthyroidism and primary hyperparathyroidism is extremely rare. Few cases of TSH pituitary adenoma in the setting of multiple endocrine neoplasia type 1-associated syndrome were reported in literature. Herein, we report a new case of TSH secreting pituitary adenoma particular by the coexisting of primary hyperparathyroidism and vitamin D deficiency.
Observation
A 76-year-old woman was referred to our Department with thyrotoxicosis and elevated TSH levels. She presented with an important weight loss, intolerance to heat, restlessness, flapping tremor, diarrhea and vomiting. On examination, she had a body mass index of 19 kg/m^2, a clinical signs of dehydration, a blood pressure of 120/60 mmHg and an irregular pulse of 120 beats/min. Thyroid gland was asymmetrically enlarged. No proptosis was observed. Electrocardiogram showed an arythmic tachycardia (120/min). Echocardiography revealed moderate, asymmetric hypertrophy of the left ventricle. Systolic and diastolic functions were preserved. Laboratory tests revealed central hyperthyroidism and primary hyperparathyroidism. The 25 OH vitamin D was 4.6 μg/l (nr: 30–100 μg/l). Serum creatinine was 131 μmol/l and creatinine clearance was 59 ml/min. Pituitary hormone explorations revealed hypogonadotropic hypogonadism with normal lactotropin and corticotropin functions. Pituitary MRI scan showed an invasive pituitary adenoma measuring 21×15×17 mm and causing right cavernous sinus invasion. Sestamibi parathyroid scintigraphy, cervical and thoracic magnetic resonance imaging were normal. Bone densitometry revealed osteopenia. The patient was symptomatically treated with intravenous fluid replacement therapy, antithyroid drugs and beta blockers. Due to the patient's poor general condition, surgical approach of the TSH-oma was contraindicated and pituitary radiotherapy was considered.
Conclusion
Although vitamin D deficiency and primary hyperparathyroidism are common disorders in the elderly population, their association to TSH pituitary adenoma is a rare condition.

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EP833

Central diabetes insipidus in children: about eight cases

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Introduction
Central diabetes insipidus (CDI) is a rare but potentially dangerous dysregulation of the water balance secondary to an arginine vasopressin (AVP) deficiency. Diabetes insipidus may have different manifestations in children compared to adults. CDI is more common in children than nephrogenic diabetes insipidus.
Methods
A retrospective study of eight patients collected in the pediatric department of Mahdia.
Results
The average age of patients was 2.8 years. The reason for hospitalization was a prolonged fever in three patients, weight stagnation in three patients, severe dehydration in one patient and headache and decreased visual acuity in one patient. A history of polyuropolydypsic syndrome was found in five patients only. Diuresis was quantified at 9 ml/kg per hour on average. In biology, the plasma osmolarity was 296.8 mosmol/Kg and the urinary osmolarity was 95.8 mosmol/kg with a urinary density at 1001 on average.Water deprivation test was carried out in four patients only confirming the diagnosis of CDI while the four remaining patients had underwent directly a Desmopressin stimulation test. The etiological assessment revealed a cerebral malformation in 4 patients, a Langerhans cell histiocytosis in three patients and a craniopharyngioma in one patient. Hormonal assessment revealed adrenal insufficiency in one patient and thyrotropic insufficiency in two patients. Treatment with intranasal Desmopressin was started at the mean dose of 0.125 ml/day in combination with the etiological treatment. The evolution was favorable in most of our patients.
Conclusion
The discovery of a CDI in children leads to an etiological investigation with an urgent need to identify tumor pathologies (craniopharyngioma, dysgerminoma). Infiltrative pathologies may be already known or reveal the disease (histiocytosis,

and more rarely sarcoidosis). The objective of the management is to ensure a normal water balance by normalizing the diuresis by the administration of Desmopressin, to prevent any water retention and therefore any hyponatremia. It is associated with the treatment of the etiology of the CDI and the hormone replacement therapy of the associated anterior pituitary insufficiency.

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EP834

A hpothyroid case with pituitary hyperplasia mimicking TSHoma

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A 36-year-old female patient was referred to endocrinology outpatient clinic due to increased TSH levels. Two years ago, she had been diagnosed and treated as Graves' disease with propylthiouracil. Total thyroidectomy was performed in another center due to ineffective medical treatment and oral levothyroxine sodium (LT4) was started. During the follow-up her TSH levels were normal. Thirteen months after the last normal TSH value, she consulted the endocrinology outpatient clinic due to high levels of TSH (23 uIU/ml). She was questioned about the proper usage of medication and the LT4 dose was increased. Despite the higher dose of LT4 (400 μg/day), her TSH level was still increased at >100 uIU/ml. Although pituitary function test were normal, pituitary MRI showed a macroadenoma with suprasellar extension. TSH α-subunit was 4.25 ng/ml (0–0.90 ng/ml). She was hospitalized for operation of TSHoma by brain surgery department. After endocrinological evaluation request, we advised medical treatment because of more likely pituitary hyperplasia. She re-checked up for ruling out possible malabsorption due to Celiac disease, but symptoms of malabsorption and Anti- Gliadin antibody (IgA) was negative. Also 200 μg oral LT4 treatment was given and 2 hours later plasma free T4 level was measured due to incompliance the medical treatment was not successful and it was found increased levels of free T4. Intramuscular (i.m) LT4 200 μg/day treatment was started. Ten days later her TSH level had decreased to 27 uIU/ml. After another 10 days of i.m LT4 treatment every other day, her TSH level decreased to 0.35 uIU/ml, while her fT4 and fT3 rose to slightly above the upper limit. A control pituitary MRI showed significant regression of hyperplasia. During the i.m LT4 treatment period the patient was consulted by a psychiatrist to explore possible underlying psychiatric causes that could account for the previously unsuccessful oral treatment and she was convinced to take oral LT4 properly.

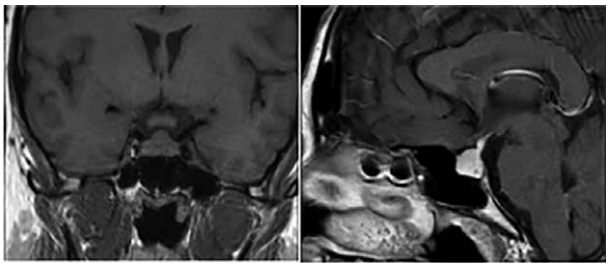

Figure 1 Pretreatment pituitary MRI image.

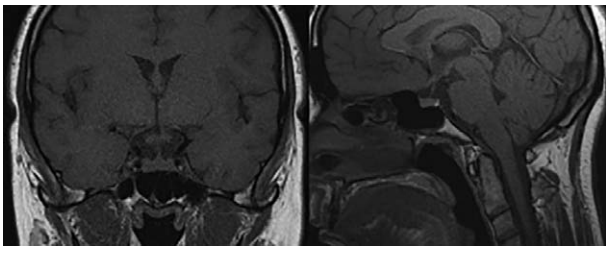

Figure 2 Pituitary MRI image after 3 weeks i.m LT4 treatment.

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EP835

Pachydermoperiostitis associated with non secrettory pituitary macroadenoma in patient with toxic multinodular goitre

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Pseudoacromegaly is associated with acromegalic phenotype but normal insulin like growth factor-1 (IGF-1) levels and suppressed growth hormone levels. The reasons of this condition may be pachydermoperiostitis insulin resistance, drug intake such as minoxidil and hypothyroidism (4). We describe pachydermoperiostitis in a patient with hyperthyroidism and non-secretory pituitary macroadenomas.

Clinical case

A 62 year old man presented with palpitation, sweating and weight loss. Physical examination revealed that's multi nodular goitre, acral enlargement, gigantism, fall in the left eye lid and thickening of the skin (heel-pad thickness was 27 mm on right foot and 28 mm on left foot) Laboraory results revealed that serum st4 37.7 pmol/l ($12.8<n<20,4$), TSH <0.006 μIU/ml ($0.47<n<4.2$), IGF-1 91.8 ng/ml (75(n(212). We re-evaluated GH-IGF-1 levels after treatment of hyperthyroidism. After being euthyroid, GH level 0.379 ng/ml ($1<n<9$), IGF-1 88 ng/ml ($75<n<212$). GH level was suppressed after 100 gr oral glucose load. Pituitary magnetic resonance imaging revealed 10.5 mm macroadenoma. All pituitary hormone levels of patient was normal. Advanced investigation for hyperinsulinemia, hypothyroidism and drug use revealed nothing. In contrast patient has hyperthyroidism. Two sons of the patients physical exam revealed acral enlargement, gigantism and thickening of the skin as a patient. GH levels, IGF-1 levels and pituitary MRI of the sons of patient was normal. We considered patient and two sons have autosomal dominant inheritance pachydermoperiostitis.

Conclusion

This is a very rare case of pseudacromegaly due to pachydermoperiostitis with nonfunctioning pituitary adenoma in patient with toxic multinodular goitre.

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EP836

Successful management of macroprolactinoma with aromatase inhibitor in a patient with hypogonadotropic hypogonadism

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Introduction

Hypogonadism persisting in man with macroprolactinoma requires exogenous testosterone replacement therapy (TRT). But TRT may cause secondary elevations of prolactin. We report here a case of macroprolactinoma and hypogonadotropic hypogonadism with persistently high prolactin level after initiating TRT.

Case report

A 28 year-old male was admitted to outpatient clinic with complaints of headache, low libido and blurred vision on left eye for three years. Magnetic resonance imaging (MRI) revealed a pituitary mass ($3.6\times3.5\times2.3$ cm) occupying entire sella, extending to sphenoid sinus, internal carotid arteries (ICA), encasing right ICA and deviating stalk to left. Tumor compressed optic chiasm causing bitemporal hemianopsia. Laboratory tests: prolactin: 133 ng/ml (1/100 diluted prolactin: 77 ng/ml), cortisol:6.75 μg/dl (unresponsive to low dose ACTH stimulation test), TSH:2.31 uIU/ml, fT4:0.47 ng/dl, fT3:1.06 pg/ml, FSH:0.43 mIU/ml, LH:0.29 mIU/ml, t.testosteron <20 ng/dl, GH <0.05 ng/ml, IGF-1:86.9 ng/ml (*n*:117–329). Nonfunctional adenoma and panhypopituitarism was the diagnosis. Transnasal transsphenoidal adenomectomy was performed after hormone replacement. Pathology revealed prolactin-secreting pituitary adenoma with Ki67:1–2%. Cabergoline therapy (1 mg/week) was started on postoperative 15th-day as prolactin was 323 ng/ml. Prolactin decreased to 80 ng/ml on the 2nd-month of therapy but t.testosteron was still low. TRT was started intramuscularly per 3 weeks for complainment of low libido. After then, prolactin level increased abruptly to 470 ng/ml. Despite gradual increament of dosage to 4 mg/week, prolactin remained elevated (451 ng/ml). No enlargement of residual mass was noted on new MRI. When TRT was quitted for 3 months, prolactin decreased to 93 ng/ml. Then TRT was started with selective aromatase-inhibitor anastrozole 1 mg/day. With cabergoline dosage decreased gradually to 3 mg/week, prolactin decreased to 18.8 ng/ml and t.testosterone was normal (300 ng/dl).

Conclusion
Aromatisation of exogenous testosterone to estradiol and subsequent estrogen-stimulated prolactin release may complicate the control of hyperprolactinemia. Aromatase-inhibitor added to therapy may facilitate successful TRT for patients with macroprolactinoma.

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EP837

Multifocal multisystem langerhans cell histiocytosis – a rare cause of panhypopituitarism and diabetes insipidus – a case report

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Introduction
Langerhans cell histiocytosis (LCH) is a very rare disease in adults and as well a very rare cause of sellar expansion. The clinical presentation can be heterogeneous, from a single bone lesion to potentially fatal, widespread disease. We describe the difficulties with the evaluation and the treatment of LCH.
Case
39 years old woman has had amenorrhea for 2 years and higher intake of fluids (5–7 l/day) for 6 years. Non-functioning pituitary expansion with pituicytoma appearance was found on MRI. She was followed up for almost 3 years. Panhypopituitarism developed during the follow-up and replacement therapy with adiuretin, thyroxin and hydrocortisone was initiated. Finally, she underwent biopsy for slow progression of sellar expansion – Langerhans cell histiocytosis was confirmed histologically, with S100 a CD1a protein immunohistochemical positivity. Staging of the disease revealed suprasellar expansion, skeletal and retrobulbar infiltration, lymphadenopathy along the right internal carotid artery and retroperitoneal and mediastinal lymphadenopathy with FDG avidity on 18-FDG-PET/CT. She received five cycles of cladribine monotherapy with subsequent PET/CT restaging.
Discussion
Hypothalamus-pituitary-adrenal axis infiltration is present in up to 50% of LCH; the most common disorder is diabetes insipidus (DI). The frequency of DI is 30–40% and 94% if other pituitary hormone deficiencies exist. The diagnosis can be tricky. The primary treatment modalities for LCH include local excision of the lesion, corticotherapy, chemotherapy, radiotherapy, and imunnotherapy with anti-CD1a monoclonal antibodies. The data regarding the treatment of the central nervous system involvement with LCH are very limited. Cladribine (2-CdA) is a promising agent in this setting as previously reported. Cladribine has good bioavailability in the CNS. A total of six cycles of cladribine monotherapy can be administered with respect to the good profile of toxicity in this indication. However, prolonged neutropenia and respiratory infections led to premature termination of the treatment in our case.

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EP838

A rare association of autoimmune diabetes insipidus and hypophysitis with partial pituitary insufficiency

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We present the case of a 40 year old man presenting at first consultation an 'idiopathic' fast-onset and severe polyuro-polydipsic syndrome (diuresis of 10 l/24 hours, with urine osmolality of less than 50 mOsm/kg and urine gravity lower than 1001). Clinical examination showed pallor and decreased pilosity at an asthenic patient with limited lesions of vitiligo and loss of libido. Water deprivation test showed the persistence of excretion of highly diluted amounts of urine, confirming the diagnosis of diabetes insipidus. The patient responded spectacularly to therapy with sublingual desmopressin, with a decrease of diuresis to under 2500 ml/24 hours and an increase of urine gravity to 1010 under a dose of 60 μg×3/day, supporting the diagnosis of central diabetes insipidus. Serum testosterone was of 1.01 ng/ml (normal range – between 2.6 and 10 ng/ml) and low-normal LH and FSH (LH = 1.5 mU/l and FSH = 2 mU/l) suggesting the presence of central hypogonadism. Serum fT4 was of 0.545 ng/ml (normal range – between 0.9 and 1.9 ng/ml) with 'normal' TSH (1.6 mIU/l) suggestive for central hypothyroidism. Corticotroph axis was undamaged (morning plasma cortisol of 15.5 μg/dl and ACTH of 38.9 pg/ml). Osteodensitometry revealed osteopenia. MRI investigation of the hypothalamo-pituitary region showed a small pituitary gland (7/3/6 mm) accompanied by partial empty sella without images of pituitary adenomas and absence of the native hypersignal of the neurohypophysis. The pituitary stalk was deformed, taking a nodular shape with dimensions of 4/5/6 mm. This image was highly suggestive for neuroinfundibular hypophysitis, most probably of autoimmune origin. Injections with testosterone undecanoate every three months and daily oral supplementation of thyroid hormones added to desmopressin therapy significantly improved patient's quality of life. Autoimmune associations of the anterior and posterior pituitary are very rare and may raise difficulties of diagnosis and therapeutic decisions.

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EP839

Pituitary apoplexy while treating recurrence of Cushing's disease with Pasireotide

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Introduction
ACTH producing macroadenoma and pituitary apoplexy are rare in Cushing's disease. Somatostatin receptor agonist Pasireotide is indicated for the treatment of patients with Cushing's disease for whom surgery is not an option or has failed. We present a case of pituitary apoplexy in patient with recurrence of Cushing's disease treated with Pasireotide.
Case
38 years old female presented with quick weight gain, weakness, irregular menstruation, hirsutism, hypertension, newly diagnosed diabetes mellitus. High levels of blood cortisol and ACTH were observed. Cortisol was not suppressed after 1 mg overnight dexamethasone suppression test (DST) and after low-dose DST. High-dose DST suppressed cortisol secretion. Pituitary macroadenoma with diameter of 12×9 mm was diagnosed on MRI. Patient underwent transsphenoidal surgery in January, 2012. In 2014 recurrence of Cushing's disease was diagnosed and second transsphenoidal surgery was performed in January, 2015. In November, 2015 recurrent pituitary adenoma with diameter of 15×11 mm was identified on MRI and hormonal tests confirmed hypercortisolemia with elevated ACTH again. Therapy with Pasireotide was started in January, 2016. After 9 months of successful use of this medication patient was emergently hospitalized to the Department of Endocrinology with an episode of an acute headache, nausea, vomiting. Ptosis of a right eyelid and blurred vision occurred. Head MRI demonstrated pituitary apoplexy and tumor spreading around right optical nerve and optic chiasm. Pituitary apoplexy led to hypocortisolemia and need of hydrocortisone for several days. Two weeks later normal cortisol levels were observed, hydrocortisone discontinued. Further treatment with Pasireotide 0.6 mg b.i.d. was continued. 4 months after pituitary apoplexy and further treatment with Pasireotide, ptosis and blurred vision regressed, eucortisolemia was achieved.
Conclusion
To our knowledge we report the first case of pituitary apoplexy in patient with Cushing's disease treated with Pasireotide. This complication might be related to Pasireotide effect on tumorogenesis mechanisms.

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EP840

Hemodialysis patient with metastatic renal cell carcinoma to the pituitary stalk presenting as hypopituitarism: an autopsy case

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Introduction
Pituitary metastases occur in 1% to 4% of cancer patients in autopsy studies. The most frequent primary tumors are breast and lung tumors. Renal cell carcinoma (RCC) is a rare cause of pituitary metastases, with only 25 previously reported cases.
Case report
A 77-year-old-man was admitted to our hospital because of acute progression of chronic renal failure presenting with appetite and weight loss in August 2014. He underwent hemodialysis. His fasting blood glucose was low without any symptoms. In 1998, he had undergone left nephrectomy and adrenalectomy, and was diagnosed with a clear cell RCC. In 2001, lung metastasis was diagnosed and he was treated with interferon therapy, which led to remission. In 2009, lung metastasis was observed again, but he declined treatment. He had hyperprolactinemia and hypopituitarism; levels of PRL: 292.8 ng/ml, free T4: 0.56 ng/ml, TSH: 0.953 μIU/ml, cortisol: 2.0 μg/ml, ACTH: 5.4 pg/ml, IGF1: 42 ng/ml. Magnetic resonance imaging revealed a $7\times8\times9$ mm mass with a pituitary stalk that compressed the optic chiasm without visual disturbance. Dynamic tests showed hyporesponses of cortisol, LH, FSH, TSH, and GH. We considered panhypopituitarism due to pituitary stalk metastasis from RCC but could not diagnose it histologically. Diabetes insipidus was not recognized, probably owing to renal failure. Hormone replacement was started with hydrocortisone and L-thyroxine; his hypoglycemia and anorexia improved. In September 2015, he died of pneumonia. The autopsy showed that the clear cell RCC had spread to the thyroid gland, right lung, and pancreas in addition to the pituitary stalk.
Conclusion
We reported a case of a hemodialysis patient presenting with a symptomatic pituitary metastasis from RCC. It is difficult to distinguish symptoms of hypopituitarism from nonspecific symptoms in a hemodialysis patient. In this case, we diagnosed an extremely rare pituitary stalk metastasis by autopsy.

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EP841

Effect of the addition of lanreotide autogel to the treatment of an aggressive prolactinoma – a case report

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Case report
A giant prolactinoma (size = $5.2\times4.1\times3.2$ cm; PRL = 6 400 ng/mL) was diagnosed in an amenorrheic 19-year old girl who presented to the emergency room complaining of headaches and bilateral decrease in visual acuity for 10 days. The patient was started on cabergoline (CAB) in progressive doses up to 3 mg/week. PRL levels decreased from 6 400 to 4 600 ng/dl within 60 days, with improvement of visual complaints and visual fields defects. The dose was subsequently increased up to 6 mg/week over the next 6 months but PRL did not normalize (1 840 ng/dl) and amenorrhea persisted. A new pituitary MRI was performed revealed a ~50% tumor reduction. Six months later, worsening of visual fields and a 20% increase in tumor volume were detected, whereas PRL levels increased to 2 270 ng/ml. A transsphenoidal surgery (TSS) was therefore undertaken (Ki-67 expression = 8%), which led to a ~30% reduction of tumor volume whereas PRL levels decreased from 2 270 to 1 210 ng/dl within 4 months. CAB was restarted but PRL did not normalize (520 ng/dl), despite the use of doses up to 4 mg/week (maximal tolerated dose) for 6 months, and amenorrhea persisted. Lanreotide autogel (120 mg every 28 days) was added to CAB (4 mg/week). The combined treatment was well tolerated and lead to decrease of PRL levels to 91 ng/ml (NR: 2.8–29.2) within 8 months, as well as to resumption of a regular menstrual cycle.Moreover, the combination of CAB + lanreotide autogel enabled further tumor shrinkage but invasion of both cavernous sinuses persisted. CAB dose could be subsequently reduced to 3 mg/week.

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EP842

A hypopituitarism case diagnosed after sphenoid sinus mucocele operation

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Introduction
Mucoceles-mucus containing benign cysts of paranasal sinuses- are common with an incidence of 1% but involvement of sphenoid sinus is much less common. In this case report, we reported a patient presented with hypopituitarism after sphenoid mucocele drainage operation.
Case report
A 59- year-old woman was admitted to our endocrinology out-patient clinics with a complaint of fatigue over the past 2 months. One month prior to admission, she had been internalized for about 10 days in our hospital's infectious diseases clinics for fever of unknown origin. After extensive medical investigation, a sphenoid sinus mucocele and pansinusitis had been diagnosed. An operation for drainage of the mucocele with endonasal surgical approach had been performed and she had been externalized for follow-up with an attention card indicating that her nasal cavity was in direct contiguity with the optic nerve. Three weeks after the operation, she admitted to our clinics. The physical examination revealed that her arterial blood pressure was 90/50 mmHg, heart rate was 108 bpm, respiratory, abdominal, cardiac examinations were normal. Her skin was pale and minimal pitting edema was detected. In her repeated laboratory examination, serum cortisol levels were found to be less than 1 μg/dl. Coexisting secondary hypothyroidism and GH deficiency were detected. The magnetic resonance imaging of the pituitary region was revealed no tissue corresponding to the adenohypophysis. Following adequate replacement therapy with methyl-prednisolone and levo-thyroxine, her fatigue relieved. GH replacement therapy was refused by the patient for its administration difficulty.
Conclusion
For mucoceles involving sphenoid sinus, pre-operative and post-operative endocrinological evaluation is essential.

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EP843

Coexistence of acromegaly and rheumatoid arthritis: presentation of three cases

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Introduction
Musculoskeletal system is widely affected in acromegalic patients which might cause difficulties in the diagnosis and treatment of inflammatory rheumatological diseases. Here, we report coexistent rheumatoid arthritis (RA) in three acromegalic patients presenting with continuing joint and back pain although acromegalic state was in remission.
Case 1
A 64 years old female patient with acromegaly and macroadenoma had undergone transsphenoidal surgery 11 years ago and radiosurgery 7 years ago because of clinical and laboratory evidence of disease. The patient got into remission 3 years after radiosurgery. Because she had morning stiffness and symmetrical pain and swelling in interphalangeal joints, she was consultated with rheumatology and diagnosed as seronegative RA. Her complaints improved dramatically at the second month of methotrexate, prednisolone and indomethacin treatment.
Case 2
A 62 years old female had undergone transsphenoidal surgery for acromegaly 12 years ago. She had been treated with conventional radiotherapy and radiosurgery 4 and 10 years after diagnosis, respectively because remission could not be achieved by medical treatment which had been stopped about a year after

radiosurgery. She had symmetrical pain, swelling and deformities in interphalangeal and metacarpal joints. Seronegative RA was diagnosed and methotrexate and prednisolone were started.
Case 3
Acromegaly had been detected 13 years ago in a 57 years old female. Because she had refused surgery, she had been treated with conventional radiotherapy and cure had been achieved in a year. She complained morning stiffness, back pain and pain and swelling in hand joints. She was diagnosed to have seropositive RA and treated with methotrexate, sulfosalazine and indomethasine.
Conclusion
Symptoms related with RA might be confused with musculoskeletal symptoms seen in acromegaly. Detailed rheumatological physical examination and immunological evaluation might be helpful to display concomitant rheumatological disease in acromegalic patients with ongoing musculoskeletal complaints despite achievement of treatment targets.

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EP844

Case of TSH secreating pituitary adenoma (TSHOMA) where course was modified by coexistant autoimmune hypothyroidism

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Introduction
TSHOMAs are rare pituitary tumors with prevalence of 1–2 cases per million. We present a case of of TSHoma where the course was complicated by the coexistence of autoimmune hypothyroidism.
Case
41 year old male presented with fatigue, lethargy and palpitations. On screening was found to have raised t3 – 216.30 ng/dl (N-70-204 ng/dl), t4 – 12.10 μg/dl(N-4.2-11.6 μg/dl) and TSH – 27.55 uIU/ml (0.2–5.7 uIU/ml). Further evaluation revealed raised free t3 (FT3), free t4 (FT4) and TSH (column 1, Table 1), raised anti thyroid peroxidase antibodies and negative TSH receptor antibody, normal cortisol – 10.8 μg/dl (N-5-25), testosterone – 769.73 ng/dl (N-275-900), prolactin – 18.89 ng/ml (5–25), IGF1 – 124 ng/ml (64–210) levels. Thyroid function of first degree relations was normal. SHBG – 78.20 nmol/l (N-11.2-78.1) and alpha subunit levels – 3.8 ng/ml (0.1–0.5) were raised. TSH concentration significantly reduced 5 hours after single octride dose as well as after three doses of 100 μg octride over 24 h. MRI confirmed presence of pituitary macroadenoma 2.4 × 1.2 × 1.2 cm abutting the chiasma (visual fields normal). Patient was subjected to transsphenoidal surgery. The adenoma immunostained positive for TSH, was also positive for p53 with MIB index 3–5%. Patient FT3, FT4 and TSH was low 2 weeks post surgery and 25 μg thyroxine was started. Follow up report at 6 weeks showed low FT3, FT4 and raised TSH levels after which thyroxine was stepped up. Patient did not need any other hormone replacement.

Table 1 Serial free t3 free t4 and TSH levels.

	Baseline	After 5 h of octride	After 3 doses of 100 μg octride	Post surgery 2 weeks	Post surgery 6 weeks	Post surgery 12 weeks
Free t3 (1.7–3.7 pg/ml)	4.86			1.19	1.1	2.7
Free t4 (0.7–1.8 ng/ml)	1.83			0.53	0.62	1.12
TSH (0.2–5.7 uIU/ml)	25.5	13.8	7.6	0.1	54	3.82

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EP845

Cyclic Cushing's syndrome: a diagnostic challenge

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Introduction
Cyclic Cushing's syndrome is a rare disorder, characterized by repeated episodes of cortisol excess interspersed by periods of normal cortisol secretion ranging from days to years. It remains a difficult diagnostic challenge in endocrinology, we report a case.
A case report
The patient was 41 years old woman, she presented in 2012 a period of symptomatic hypercortisolism. Urinary free cortisol was elevated to 113 μg/24, Low-dose dexamethasone testing was negative, ACTH was elevated to 20.2 pmol/l, the high-dose dexamethasone suppression test was positive, a pituitary MRI and a thoraco pancreatic scanner were normal; These finding led us to an ACTH-dependent Cushing's syndrome. The patient was revaluated 5 months later and she was clinically and biochemically better. Six months later she presented relapsed symptoms and a biochemical recurrence of hypercortisilosm (high urinary cortisol: 125.7 μg/24 and negative Low-dose dexamethasone testing). In 2015 the patient presented a sudden tumor syndrome, pituitary MRI revealed an intrasellar arachnoidocele that was in favour of the apoplexy of an adrenocorticotropic pytuitary adenoma. The patient was revaluated 9 months later and she was clinically better, The Urinary free cortisol was normal (20 mg/24).
Discussion
Cyclic Cushing's syndrome is characterized by rhythmic fluctuations in glucocorticoid production, both clinical and biochemical spontaneous remissions may occur in patients with this disorder. Our patient presented two periods of normal glucocorticoid production and two periods of hypercortisolism. Causes of cyclic Cushing's syndrome are multiple dominated by pituitary adenoma. The biological and radiological investigations in this case and therfore the subsequent evolution enabled a diagnosis of a Cushing's syndrome spontaneously regressive by the apoplexy of pytiutary adrenocorticotropic adenoma. Clinicians should be aware that hypercortisolism may occur periodically and the duration of the periods of normal and abnormal cortisol secretion can vary significantly, so the correct diagnosis can be a challenge in clinical practice.

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EP846

Breast cancer and newly discovered non-secretor pituitary mass- as risk of metastases?

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Introduction
Even if breast cancer is rare cause of pituitary metastases, the diagnosis of a pituitary adenoma, shortly after surgery for breast cancer, raises suspicion of a possible secondary determinations.
Material and method
This is a case report revealing the medical history and endocrine profile of a female with breast cancer and pituitary macroadenoma.
Case data
A 64-year old non-smoking female (with menopause at age of 52), who had undergone treatment for breast cancer (diagnosed at the age of 60), with left radical mastectomy pT2N0M0 L0 V0 Pn0 R0, followed by adjuvant radiation treatment and aromatase inhibitor hormonal treatment, was admitted for headache, dizziness, diplopia, and narrowed visual field. Pituitary MRI performed pointed a 40/26/36 mm-sized mass of oval shape, with intra and extra-sellar expansion. Endocrine evaluation indicated low levels of serum gonadotropins (FSH of 10.5 U/l, normal: 30–150 U/L and LH of 1.6 U/l, normal of 8.2–41 U/l), low FT4 levels (free thyroxine of 0.61 ng/dl, normal: 0.89–1.76 ng/dl), normal levels of morning plasma cortisol (of 19.8 μg/dl, normal: 5–25 μg/dl), and moderate increase of prolactin (24.4 ng/ml, normal:1.3–20 ng/mL). Thyroxine substitution therapy was initiated and followed by transsphenoidal adenomectomy. Histopathology revealed a mixed pituitary adenoma. Assessement performed three month after surgery highlighted persistent hyperprolactinemia (of 22.9 ng/ml), central hypogonadism (FSH of 10.1 U/l, LH of 2.6 U/l), normal FT4 levels (of 0.95 ng/dl), and persistent pituitary mass (of 36/21/30 mm) on MRI. The patient will be further followed-up by a multidisciplinary team regarding endocrine and oncologic profile.

Conclusions
This case emphasizes that diagnosis of pituitary macroadenoma can be difficult when occurs in the context of a pre-existing breast cancer. Intensive follow-up is necessary for specific treatment.

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EP847

Meningoencephalitis as the first clinical sign of a pituitary macro adenoma: a case report

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Introduction
The classical revealing manifestations of a pituitary adenoma are represented by the combination of a tumor syndrome and endocrine syndrome. The occurrence of meningoencephalitis as a mode of revelation of a macroadenoma is exceptional.
Case
Mr. M.O, 36 years old, with no significant medical history, brutally presented severe headaches, vomiting, behavioral disorder with fever and bilateral decreased visual acuity. On examination, the patient was conscious, febrile to 39.8 with nuchal rigidity. At presentation: leukocytosis at 18 000/m3, a C-reactive protein at 69 mg/l. The head CT scan showed bilateral areas of hypo density with Intra-and suprasellar invasive lesional process. The magnetic resonance imaging showed a pituitary macroadenoma 30×32 mm invading the sphenoid sinus, the right cavernous sinus and elevating the optic chiasm. The cerebrospinal fluid analysis showed a lymphocytic liquid with elevated protein and normal glucose level. Culture was negative as well as herpes simplex virus PCR. The biological analysis of endocrine hormones balance objectived a pan hypopanpituitarisme insufficiency. The patient received ceftriaxone, acyclovir, replacement therapy and was scheduled for surgery.
Discussion
Meningoencephalitis is a rare presentation as first manifestation of macro-adenoma. In literature, only three cases of Meningoencephalitis were reported as revealing macroadenomas. We illustrate this observation through an unusual and serious form of revelation of a macroadenoma.

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EP848

A rare case with acromegaly: increased hypophyseal FDG uptake in PET/CT performed for lung cancer staging

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Acromegaly affects 4–6 people in a million and hypophyseal GH releasing adenoma is the most common cause of the disease. It shows its effects on GH and IGF1. Since they grow rapidly, they are usually diagnosed at the stage of macroadenomas. Heart failure, arthritis, OSAS and DM may develop during course of the disease. Although the most common accompanying malignancy is colon cancer, the incidence of malign melanoma, breast, thyroid, gastric and lung cancers is also increased. Increased hypophyseal Fluorine-18 fluorodeoxyglucose uptake is rare on positron emission tomography and computed tomography (FDG-PET/CT). Since hypophyseal adenomas may give false positive results on PET/CT, verification should be made by MRI. In this study, we aimed to present a case with increased FDG uptake in hypophysis and lung on PET/CT. 64-year male patient was presented with dyspnea and weight loss. Physical examination revealed prognatia, acral enlargement in hands and feet, dermal thickening and decreased breath sounds on apikal part of left lung. Chest X-ray and thoracic CT imagings demonstrated 2 cm sized nodular opacity in the upper lobe of the left lung. On FDG-PET/CT examination, increased FDG uptake was observed in this 2 cm sized nodular lesion in the lung and in 3 cm sized hypophyseal region. Hypophyseal MRI was performed and macroadenoma was detected. Ocular examination revealed hemianopsia. Laboratory examination findings were as follows: hemoglobin: 12.3 g/dl (13.7–17.5), sodiuum:140 mmol/l (normal: 135–145), potassium: 4.4 mmol/l, creatinin: 0.73 mg/dl, ACTH: 5 pg/ml (normal: 0–46), basal cortisol: 3.4 μg/dl (n:5–29), growth hormone: 2.25 ng/ml and IGF1: 440 ng/ml (n:70–212). Hypophyseal-thyroid and hypophyseal-gonadal axis were normal. GH levels measured 30-60-90 and 120 min after oral 75 g glucose tolerance test were 2.16, 1.65, 1.5 and 1.8, respectively. The patient was diagnosed with acromegaly and intramuscular octreotide 20 mg/month, prednisolone 5 mg in the morning and 2.5 mg in the evening were initiated before hypophyseal surgery. Left upper lobectomy of the left lung was performed and pathologic examination of surgical material revealed squamous cell carcinoma. Vinorelbine + cisplatin chemotherapy was initiated and the patient was scheduled for hypophyseal surgery.

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EP849

Abstract withdrawn.

EP850

Temozolomide alone or in combination with bevacizumab and capecitabine in the treatment of atypical pituitary adenomas – own experience

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Introduction
Atypical pituitary adenomas are tumors refractory to conventional therapy and characterized by a tendency to rapid progression and high recurrence rate. The aim of the study was to summarize our experience in treatment of atypical pituitary adenomas with temozolomide (TMZ).
Material
5 patients (3F;2M) aged 44–58 (mean 52.4 ± 5.4) years treated in 2013–2016. We analyzed the results, tolerance and side effects of TMZ.
Results
In three patients (1F;2M) atypical corticotroph adenomas were diagnosed (two Nelson's syndromes, one Crooke's cells adenoma), in 1F-prolactinoma resistant to dopamine agonists and in 1F-type 3 silent adenoma (GH+, PRL+). The disease duration ranged 3–23 years (mean 12.4 ± 7.2). Before TMZ implementation, patients underwent a total of 11 transsphenoidal adenomectomies (1–4), four craniotomies, two patients – stereotactic X-ray-therapy, 1 – tomotherapy and 2 – bilateral adrenalectomy. All patients started with TMZ monotherapy 150 mg/m^2 for five consecutive days with 23-days intervals. The number of courses ranged from 2 to 13. The total remission, lasting from 45 months was obtained in a patient with Crooke's adenoma, partial remission in one patient with Nelson's syndrome, transient stable disease (2–4 months) in two patients (with Nelson's syndrome and somatotropinoma). The prolactinoma was refractory to TMZ. The only side effect was vomiting. In two patients with relapse of Nelson's syndrome TMZ was used in combination with bevacizumab (six courses) in 1F and in 1M with capecitabine (CAPTEM – five courses), but in both cases it caused short-term disease stabilization.
Conclusion
TMZ is the most effective in treatment of atypical corticotroph adenomas as a single agent and in the first line of treatment, however it is less effective in recurrent form of the disease.

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EP851

Pachydermaperiostosis: a rare syndrome presented with acromegaloid changes

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Introduction
Pachydermoperiostosis (PDP) is a rare hereditary syndrome with familial and idiopathic forms that is characterized by subperiosteal new bone formation with pain, polyarthritis, cutis vertices grata, seborrhea, hyperhidrosis and digital clubbing. Periostosis and cutaneous thickening along with the absence of any signs of cardiovascular, pulmonary, hepatic, intestinal and mediastinal diseases causing secondary hypertrophic osteoarthropathy suggest PDP. The incidence of the disease is unknown. It is manifested mainly by dermatological and rheumatological symptoms. Rheumatoid arthritis, acromegaly, neurofibromatosis, hypothyroidism must be considered at differential diagnosis.
Case report
A 21-year-old male presented to the internal medicine department with polyarthritis and acromegaloid facial features. The patient had clubbing, swelling without an inflammation signs at knee joints and wrist; and thickening and folding of the facial skin (cutis verticis gyrata). The patient had hyperhidrosis but didn't have enlargement of hand, feet or lingua. Laboratory examination including growth hormone assay, thyroid profile, romatoid factor, anti nükleer anticor, anti CCP, tests for syphilisis, ESR were normal. He did not have family history and genetic transmission is ruled out by HPGD gene analysis. There were symmetric subperiostal bone formation at the radiographs of forearms and legs. The scintigraphy showed a osteoblastic hyperactivation in the distal radius, metacarpal bones and tibia. Based on clinical and radiological findings PDP was diagnosed. We consulted the patient to rheumatology department for arthritis and steroid theraphy was started.

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EP852

Temozolomide Treatment in Aggressive Pituitary Adenoma

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Background
Aggressive pituitary adenomas (APAs) take place phenotypically between benign pituitary adenomas and pituitary carcinomas with systemic metastasis. Frequent recurrence and resistance to conventional treatments are characteristic features of APAs in their clinical course. Temozolomide is an alkylating agent that has been used in the treatment of pituitary carcinomas and APAs since 2006. Herein, we report a patient who received temozolomide treatment due to APA.
Case presentation
A 57-year-old male patient with complaints of headache and visual impairment had been admitted to state hospital in 1991. Laboratory and imaging studies had revealed nonfunctioning invasive pituitary macroadenoma, and he had underwent transcranial operation. The patient had developed pituitary insufficiency after operation; therefore replacement therapy had been started. Thirty radiotherapy (RT) sessions had been performed due to the lack of complete resection of the mass. Then, he was referred to our department. He was reoperated in 2006 and 2009. In magnetic resonance imaging (MRI) after surgeries, a macroadenoma ($37\times35\times30$ mm in size) was observed and follow-up was planned because of its size to remain stable. In 2012, MRI revealed that the mass grown in size ($50\times40\times38$ mm). It filled suprasellar cistern and sphenoidal sinus, and infiltrated cavernous sinuses. After six cycles of temozolomide were given with 30 conventional RT sessions, minimal reduction in mass size was observed. Six more cycles of temozolomide was given. After treatment, the mass was measured as $40\times38\times28$ mm. The patient's monitoring still continues with stable disease.
Discussion
In our case, minimal shrinkage and stabilization of the mass size were achieved after temozolomide treatment. According to the case reports published in the literature, the effectiveness of temozolomide in APAs is about 55%, although interpretation of efficacy criteria differs in various publications. However, large-scale studies are needed to determine the indications, proper doses and duration of temozolomide treatment.

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EP853

Ocult Cushing syndrome: (adicional) difficulties in hypercortisolism approach

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Introduction
Cushing syndrome (CS) result from inappropriate exposure to increased non regulated glucocorticoid levels. It remains challenging regarding diagnosis and management. Pituitary ACTH-secreting adenomas account for most of the cases if exogenous and paraneoplasic forms are excluded.
Case report
A 45-year-old women was referred to the endocrine outpatient department because of obesity, muscular weakness, high blood pressure (HBP), diabetes *mellitus* (DM) and hypercholesterolemia beginning 3 years before. Analytic evaluation evidenced ACTH- dependent hypercortisolism, with no cortisol suppression after dexametasone 1mg overnight. Low-dose dexametasone (0.5 mg quid for 48 h) excluded pseudocushing; high dose dexamethasone (2 mg quid for 48 h) suggested pituitary CS. However no lesion was identified in pituitary RMN and inferior petrous sinus catheterization with simultaneous CRH dynamic testing was inconclusive. Treatment with metyrapone 1500 mg/daily normalized 24-h urinary cortisol excretion and morning cortisol levels, but clinical manifestations persisted with progressive weight gain, worsened diabetes control, increased blood pressure levels and pathologic rib fractures, despite additional drugs. The patient was submitted to bilateral adrenalectomy, which immediately controlled the disease with no further need for antidiabetic or blood pressure drugs and significant weight loss.
Discussion
Even when imaging and functional evaluation are diagnostic, CS treatment may be challenging. Bilateral adrenalectomy is not the first line therapeutic option, but as in this case correction of hypercortisolism more than apparent normalization of cortisol levels may require it. Life-long morbidity is expected regarding glico- and mineralocorticoid reposition, however this is easier to obtain and may be associated with less co-morbidities than sustained hypercortisolism.

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EP854

A case of cystic prolactinoma responsed to medical treatment

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Introduction
Cystic prolactinomas are considered resistant to volume depletion by dopamine agonists (DAs). Because of the effectiveness and tolerability, dopamine agonists (DAs) are the first line therapies in prolactinoma and reduce tumor mass as well as prolactin levels in most of all patients. Rathke's cleft cysts, craniopharyngiomas and arachnoid cysts are differential diagnoses to keep in mind. DAs resistance or intolerance, psychiatric disorders associated with dopamine agonist use and patient preference can be indications for surgical intervention. Large, predominantly cystic prolactinomas are usually treated surgically and are presumed to be resistant to volume reduction by DAs. Although optimal management of cystic prolactinomas are not defined yet, several individual case reports and case series have suggested that DAs may reduce these lesions. Here we present a patient with cystic prolactinoma responsed to medical treatment.
Case report
A 20-year-old women presented with secondary amenorrhea and spontaneous galactorrhea for three months. She has not taken any prolactin-increasing medications and was not pregnant. Her biochemical, hematological laboratory tests and hypophysis function tests were normal except prolactin. Her prolactin level was 133 ng/ml (normal value is 2.7–19.6) and macroprolactin was negative. Pituitary MR scan revealed a 9×7 mm cystic adenoma at the left side of adenohypophysis. Infundibulum, suprasellar cistern and optic chiasm were intact. Hence her clinical picture was consistent with prolactinoma, we administered cabergolin 0.25 mg twice a week. After three months of cabergolin therapy her prolactin level decreased to 6.5 ng/ml. She had regular menses and no galactorrhea. After eight months, hypopsis mr scan demonstrated a remarkable reduction in the tumor size, measured as 6×3.5 mm.

Discussion
In conclusion, it is appropriate to consider dopamine agonist therapy in patients with cystic prolactinomas before considering surgery.

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EP855

A case of pituitary apoplexy in a patient with Cushing's disease due to corticotroph macroadenoma

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Corticotroph macroadenomas are exceptionally found in Cushing's disease. Pituitary apoplexy is a rare endocrine emergency condition caused by either hemorrhage or infarction of the pituitary gland. We report a case of a 56-year-old female diagnosed with type 2 diabetes in 2008. One year after, at the periodical follow up, she presented with uncontrolled diabetes (HbA1c = 12.26%) and clinical manifestations suggestive for hypercortisolism, therefore insulin therapy was initiated; hormonal profile revealed baseline cortisol = 26.4 ng/ml, cortisol level after low-dose dexamethasone suppression test = 21.7 ng/ml, ACTH = 122 ng/ml, and a 2.4/1.8/2.9 cm pituitary macroadenoma was found. While waiting for surgery appointment, in January 2010 the patient experienced severe headache, nausea, vomiting and diplopia. She was admitted to ICU, diagnosed with pituitary apoplexy and transferred to neurosurgery department where surgery was performed. Clinical improvement of Cushing's symptoms, diplopia, hypertension and diabetes (HbA1c = 6.5% without insulin therapy) was noted. The postoperative pituitary MRI revealed a rest tumor (7/8 mm); slightly increased ACTH levels (70.1 pg/ml) and abnormal 1 mg DXM overnight suppression test (5.33 ng/ml). She received medical treatment with ketoconazole (not tolerated) and cabergoline (2 mg/week); the clinical manifestation of hypercotisolism reappeared and diabetes was poorly controlled. Despite medication, ACTH and cortisol secretion remained elevated and pituitary MRI scan showed tumor progression. Considering the development of the tumor in close proximity of the optic chiasm she was refused for surgery and gamma knife radiation therapy, being lost to follow-up for 2 years. In 2016 she was admitted with severe hepatic cytolysis (ALT = 766 U/l, AST = 484 U/l), mild cholestatic syndrome, hypercortisolism and uncontrolled diabetes HbA1c = 9.6%. The presence of hepatic cytolysis caused postponement of bilateral adrenalectomy. Our patient presented pituitary apoplexy in a corticotroph macroadenoma, with persistence of Cushing's disease after surgery and no therapy of hypercortisolism at the moment. Bilateral adrenalectomy is probably the best option, after the control of hepatic function.

Keywords: pituitary apoplexy, corticotroph macroadenoma

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EP856

Ectopic ACTH syndrome presenting with partial loss of conciousness and nonconvulsive status epilepticus in a patient with no signs of Cushing syndrome

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Introduction
Ectopic adrenocorticotrophic hormone (ACTH) syndrome is associated with variable tumor groups most commonly originating from neuroendocrine cells. Here, we reported a patient considered to have nonconvulsive status epilepticus initially due to neurological symptoms and diagnosed as neuroendocrine tumor with ectopic ACTH syndrome.

Case
A 85 years old woman with regulated hypertension admitted with partial loss of conciousness. She had cachectia and body mass index was 16.7 kg/m^2. There was no acute pathology in cranial imaging. Because electroencephalography revealed findings compatible with nonconvulsive status epilepticus, levatiresatam was started. In laboratory examination, she had hypokalemia (2.5 mg/dl) resistant to i.v. replacement. Her serum cortisol was 126 µg /ml (5–20 µg/ml) and ACTH was 331.7 pg/ml (0–60 pg/ml). Hypophysial MRI showed a 6×3 mm lesion in right hypopysis. She did not any physical signs of Cushing syndrome. In thoracal CT, a 16 mm solid irregular lesion extending to the parencyma and costal pleura in right lung was observed. Abdominal CT revealed a 125 mm heterogenous mass and satellite lesions in the liver and hypertrophic adrenal glands. A tru-cut biopsy from the lesion was reported as metastasis of neuroendocrine tumor. The lesion was diffusely positive for TTF-1, cytokeratin 7, synaptophysin and chromagranin. Ki67 proliferation index was 10–15% and primary tumor was suggested to be atypical carcinoid tumor of lung according to the immunohistopathological findings. The patient died at the 20th day of intensive care unit due to sepsis.
Conclusion
Ectopic ACTH syndrome is a rare cause of ACTH dependent Cushing syndrome. It can be easily included in the differential diagnosis in a patient with classical signs of Cushing syndrome and without adenoma in hypophysis. However, like ours, well-known physical appearance and signs of Cushing syndrome might not be seen in all patients, and the only clinical presentation might be neurocognitive dysfunctions.

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EP857

Cushing's disease management through time- a case report

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Cushing's disease (CD) is a rare disorder caused by an increased secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary gland, usually as a result of pituitary adenoma. Transsphenoidal tumour resection is the best first line therapy option for these patients but 10–30% of them fail to achieve remission and need further treatment modalities to eliminate hypercortisolemia. Long-term outcomes and possible impacts on quality of life in these patients are still not well examined. We report a case of a 73-year-old patient who presented in 1982, as 38-year-old women with generalized malaise, facial fullness, increased skin pigmentation, hirsutism, hypertension, hyperglycemia and depression. Laboratory evaluation showed elevated serum levels of ACTH and cortisol with loss of diurnal variation and no suppression after overnight low-dose dexamethasone test. Computerized tomography (CT) scan revealed hypodense zone in posterior pituitary and no lesions in adrenal glands. The patient underwent transsphenoidal surgery which confirmed 5 mm pituitary tumour in posterior lobe with anterior spreading into normal tissue that inhibited the complete resection. Histological finding was ACTH – secreting microadenoma. During the postoperative course, patient developed diabetes insipidus; depression and high blood pressure were still present. Serum cortisol level was 832 nmol/l, ACTH 26.3 pmol/l (reference range:1.2–10.2 pmol/l). The patient consented to bilateral total adrenalectomy in November 1984. which showed adrenal hyperplasia. After second surgery, the symptoms of CD were diminished and steroid replacement therapy was started as following treatment. During time, patient developed hypothyroidism, electrolyte concentrations are kept in balance. ACTH levels were up to 194 pmol/l (with marked hyperpigmentation localized predominantly in face area), cortisolemia up to 579 nmol/l according to which the Hydrocortisone dose adjustments were made. Recent pituitary magnetic resonance imaging (MRI) demonstrated no signs for tumour recurrence. After 33 years of therapy, the evaluated quality of life in our patient is not significantly impaired.

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EP858

A case of extrapontine myelinolysis after surgery for a pituitary tumor

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Introduction
Rapid correction of hyponatremia is known to cause central pontine myelinolysis. It may concurrently involve other areas of brain as well, referred as extra-pontine

myelinolysis (EPM). Isolated EPM however is a very rare occurrence. We present a case of EPM where the hyponatremia was secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH) after surgery for a pituitary macroadenoma.
Case report
A 36-year-old man underwent transsphenoidal surgery for a non-functional 2.4×2.6×1.8 cm pituitary macroadenoma causing chiasmatic compression. During the immediate postoperative period, the patient developed polyuria and received desmopressin. Six days after surgery, he left the hospital asymptomatic receiving hydrocortisone. Diuresis volume was normal and desmopressin was not necessary anymore. On the 8th postoperative day, his level of consciousness decreased and suffered from seizure requiring intubation. Blood examination revealed severe hyponatremia (serum sodium level of 108 mEq/l) and 1 day later serum sodium increased rapidly to 135 mEq/l. On the 16th postoperative day, orotracheal intubation was discontinued but the patient was unable to communicate. Physical examination revealed global hyperreflexia, clonus, dysarthria and gait disturbance. Head MRI on the 18th postoperative day demonstrated intense high-signal bilateral lesions in corpus striatum on FLAIR and DWI, and extrapontine myelinolysis was diagnosed. The patient's symptoms improved gradually after rehabilitation and antispasticity treatment. It was suggested that the changes in serum sodium levels after pituitary surgery were due to SIADH due to degeneration of nerve terminals in the posterior pituitary.
Conclusions
Incidence of hyponatraemia following pituitary surgery is reported between 3 and 25%. The delay in onset of SIADH can lead to practical problems for neurosurgical units where there is very early discharge following pituitary surgery. As pituitary surgery may trigger changes in serum sodium leading to myelinolysis, this possibility should always be borne in mind when treating such patients.

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EP859

Hypopituitarism caused by an intrasellar meningioma: case report

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Meningioma is a common, usually benign, tumor of the brain and the spinal cord that originates from any dura surface. Such lesion accounts for 10 to 15% of nonadenomatous sellar masses. Purely intrasellar meningiomas are relatively rare and can mimic a nonfunctioning adenoma. A 33-year-old man with a history of 1.5 year fatigue, anemia and erectile dysfunction referred to our department. The laboratory data revealed low levels of ACTH, Cortisol, FSH, LH and Testosterone, while TSH, FT_4, IGF-1, PRL, K^+ and Na^+ levels were normal. Pituitary MRI demonstrated the presence of an intrasellar mass measuring 2.4×2.4×1.7 cm in diameter. The suprasellar extension was causing displacement of the optic nerves and the chiasm. There were foci of low signal intensity consistent with areas of calcification or hemorrhage. Formal visual field testing resulted normal. The patient received replacement therapy with hydrocortisone and testosterone and referred to a Neurosurgeon. Few days before surgery the patient complained of polyuria and polydipsia and desmopressin was prescribed. The mass couldn't be totally resected through transsphenoidal approach due to its hard fibrous tissue. The histological report showed Grade I psammomatous meningioma. The postoperative MRI revealed residual tumor measuring 1.8×1.8×1.6 cm in diameter. A debulking surgery followed and the postoperative blood tests demonstrated panhypopituitarism with low levels of ACTH, Cortisol, FSH, LH, Testosterone, TSH, FT_4, PRL and IGF-1. Thyroxine replacement therapy was added. Meningiomas of the pituitary fossa represent approximately 5 to 10% of intracranial meningiomas. They commonly cause visual dysfunction and infrequently hormonal insufficiency. In our case the patient presented with hypopituitarism caused by the meningioma, but no visual disturbances. To our knowledge this is the first case that an intrasellar psammomatous meningioma causes pituitary insufficiency of both the anterior and posterior lobe with normal visual fields.

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EP860

A case of tuberous sclerosis complex associated with non-functioning pituitary incidentaloma and moderate hyperprolactinaemia

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Tuberous sclerosis complex is characterised by non-malignant tumours in the skin, brain, kidneys, heart, eyes, lung, but sometimes angiomyolipomas may develop in the adrenals, ovaries, thyroid, and rarely neuroendocrine tumours in the pancreas, pituitary gland, parathyroids. The case of a 46-years-old female patient suffering of tuberous sclerosis and endocrine disturbances is presented. She is known with temporal lobe epilepsy since early childhood, and anxious depressive disorder with obsessive elements since young adulthood, currently receiving carbamazepine, sulpiride and fluvoxamine. At 41 years of age she was diagnosed with bilateral scleroatrophic kidneys, stage 2 chronic renal disease, hypocalcemia, and endocrine investigations were recommended. The diagnosis of tuberous sclerosis was based on four major (facial angiofibroma, periungual fibroma, Shagreen patches, cardiac rhabdomyoma) and one minor criteria (confetti skin lesions). Endocrine investigations and follow-up started from 2012. Low serum calcium level (total Ca: 8.32 mmol/l, normal: 9–11, ionic Ca: 0.92 mmol/l, normal: 1.1–1.6) with high intact parathyroid hormone value (iPTH: 133 pg/ml, normal: 15–67) showed a secondary hypoparathyroidism. Alfacalcidol and calcium therapy have normalized iPTH (47.8 pg/ml) and calcium levels (2.34 mmol/l, normal: 2.1–2.56). In 2015, at 44-years of age amenorrhoea-galactorrhoea syndrome developed due to hyperprolactinaemia (139.9 ng/ml, normal: 5–26). Polyethylene glycol treatment showed the presence of macroprolactin and a moderate genuine hyperprolactinaemia, which was explained by the use of antidopaminergic therapy. 5 mg/day bromocriptine normalized menstrual disturbancies, but psychiatric symptoms worsened, therefore we reduced the dose to 2.5 mg/day (PRL: 40.75 ng/ml). In 2015 cranial and abdominal MRI were performed. None of the typical lesions of tuberous sclerosis were observed, but a 4 mm pituitary microadenoma was detected, which was interpreted as a non-functioning pituitary incidentaloma. In the literature a few cases of GH, ACTH- or PRL-secreting pituitary adenomas, and one non-functioning adenoma were reported.

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EP861

Patient with empty sella and clinical features of acromegaly

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Introduction
Acromegaly is a systematic disease with charecteristic clinical features, which is due to GH hypersecretion mainly from pituitary adenomas and in rare cases it can be due to ectopic GHRH and GH hypersecretion. Sometimes localizing the source of hypersecretion is difficult. Here we present a case of a woman with acromegalic phenotype and empty sella.
Presentation
A 47 years old woman referred to our department after recent onset of high blood pressure, headache and dizziness and a head MRI which revealed an empty sella. Clinically she had acromegalic features and acromegaly was confirmed biochemically (IGF-1 941.1 ng/ml and basic GH 5.41 μg/l and after OGTT 3.36 μg/l). A pituitary MRI confirmed the empty sella with no obvious pituitary tissue present. In order to localize the source of the GH hypersecretion further biochemical and imaging tests were performed (plasma chromogranin and calcitonin, 24 hour urine metanephrines and nonmetanephrines, head and neck CT, abdomen CT, ^{111} In-Octreotide scanning) and all were negative. Determination of IR-GHRH though was indicative of pituitary hypersecretion. Octreotide LAR 40 mg failed to result in biochemical control of the disease and Pegvisomant (10 mg/day) was added. Eleven months later biochemical control was achieved (normal for her age IGF-1 and GH $<$ 1 μg/l), but a pituitary MRI at that time revealed an 9×4.4×6 mm adenoma.
Conclusions
Pegvisomant, a GH antagonist, used as monotherapy or in combination for treating acromegaly is very effective in controling the disease, but growth of the pituitary adenomas is being described in rare cases. Although when combined with somatostatin analog this risk is lower, in our case revealed the adenoma.

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EP862

Esthesioneuroblastoma causing ectopic ACTH Syndrome

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Introduction
Esthesioneuroblastoma is an uncommon malignant neoplasm with an average 5-year survival rate of about 45%. Ectopic ACTH syndrome due to esthesioneuroblastoma is extremely rare and there have been very few cases reported.
Case report
A 54-year-old woman was admitted to our hospital with symptoms of leg edema and general fatigue of one month's duration. Physical examination showed moon facies and edema on her lower extremities bilaterally but no other cushingoid features. Laboratory examination revealed a severe hypokalaemia (1, 99 mmol/l) and endocrine tests revealed a marked elevation of plasma ACTH (1123 pg/ml) and cortisol levels (cortisol in serum 110, 1 mcg/dl and 24-hour urinary cortisol 296, 7 mcg). Dexametasone suppression tests both with 1 and 8 mg were non-suppressible. These physical and endocrine findings were consistent with the diagnosis of ACTH-dependent Cushing's syndrome: ectopic Vs secondary to pituitary macroadenoma. Computed tomography (CT) scans of the chest, abdomen and pelvis were normal except for hyperplastic adrenal glands. A pituitary magnetic resonance image (MRI) showed a normal pituitary; however, there was a large and aggressive mass centred in both nostrils. The mass extended into the frontal sinus and ethmoidal cells. Otolaryngology department was consulted and a biopsy of the lesion was performed. The pathologic study of the biopsy confirmed the diagnosis of esthesioneuroblastoma. Therapy with ketoconazole 1000 mg daily was initiated preoperatively. Three weeks later the patient underwent a combined frontal craniotomy and endoscopic transnasal approach. Adjuvant postoperative radiation treatment was performed without complications. The patient's symptoms completely resolved and the ACTH and cortisol levels returned to normal values.
Conclusions
Cushing's syndrome due to olfactory neuroblastoma may have satisfactory prognostic and control of symptoms with combined therapy consisting of surgery and radiation. We herein present a patient with a 3 year disease free survival after successful treatment.

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EP863

Lymphocytic hypophysitis which underwent surgery despite the absence of compression of nearby structures. A case report

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Introduction
Lymphocytic hypophysitis is a strange cause of hypopituitarism which can represent a difficult diagnostic and therapeutic challenge.
Objectives and methods
Describe the diagnosis, evolution and treatment of a case of lymphocytic hypophysitis in a patient who began with hypopituitarism and a year after the diagnosis had local symptoms. We reviewed the medical history of the patient from the moment the patient contacted with us to the months after the patient went surgery. It has been collected clinical, laboratory and radiological data during this period.
Results
This 51-year-old man presented with low TSH (0,122), low ft_4 values (0.45) and hypogonadotropic hypogonadism without any other pituitary alterations. His visual examination was normal. The MRI demonstrated a $15.5 \times 10 \times 8.5$ sellar lesion, thickening in the pituitary stalk (6 mm), loss of differentiation (hyperintensity) of the neurohypophysis and heterogeneous parenchyma of the adenohypophysis. Because of the absence of symptoms in the patient, we corrected the deficits and we followed up. At 3 months after diagnosis the patient developed adrenal insufficiency so we corrected this new deficit. At 1 year after diagnosis the patient presented with severe headache and Tolosa-Hunt syndrome, so we began treatment with high dose of dexamethasone. The patient had initial improvement but relapsed after decreasing dexamethasone, so the patient was treated with trans-sphenoidal surgery with a total removal of the lesion. The patient remains asymptomatic on pituitary replacement therapy.
Conclusions
Lymphocytic hypophysitis is an uncommon cause of hypopituitarism which can present symptoms long time after the diagnosis. Due to the inflammatory changes, the patient could present headache and other local symptoms despite the absence of compression of nearby structures. In this case, if the patient does not respond to high doses of steroids, surgery is mandatory.

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EP864

Title: IgG4 related hypophysitis

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Introduction
IgG4 Related Hypophysitis (IgG4-RH) is a newly recognized form of hypophysitis. It usually appears as part of IgG4-Related Disease (IgG4-RD), an immune mediated disease, with manifestations in many organs. Isolated hypophysitis without other IgG4-RD manifestations is rare.
Presentation
A 64 years old female referred to our department for further investigation of a 9 month history of fatigue, muscle weakness, recurrent episodes of right temporal headaches, anorexia and weight loss and a month's history of diplopia and right eyelid ptosis. Past medical history was unremarkable. On clinical examination there was marked proximal muscle weakness, right eyelid ptosis, diplopia, but visual fields were normal. Laboratory evaluation revealed hypopituitarism of the anterior pituitary lobe. Magnetic resonance imaging (MRI) showed a thickened pituitary stalk and an enlarged heterogenous pituitary gland with expansion to the right cavernous sinus. IgG4 levels were elevated (192 mg/dl, normal values: 8–140 mg/dl). Based on these findings the diagnosis of IgG4-RH was made. The patient was commenced on prednisolone 40 mg/day and thyroxine. A remarkable clinical improvement was observed within the first forthnight. Three months later she had no diplopia, no muscle weakness and repeated MRI of her pituitary gland showed great improvement of the previous picture. IgG4 levels were reevaluated and were found to be reduced.
Conclusion
Isolated IgG4-RH is a rare entity. IgG4 levels should be obtained in cases suggestive of hypophysitis. Corticosteroid treatment greatly improves the clinical picture.

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EP865

Pituitary apoplexy as the first manifestation of silent somatotropinoma

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Introduction
Pituitary apoplexy is a rare endocrine disorder which can occur due to haemorrhage into pituitary gland. It is often associated with the presence of pituitary adenoma, uncommonly being the first clinical manifestation of an underlying tumour. It can cause hypopituitarism and diabetes insipidus. Pituitary adenomas are classified by their secretion properties as functional and clinically non-functioning, the latter, however, can exhibit positive immunostaining for pituitary cell types in histologic examination and are thus classified as 'silent adenomas'.
Case study
A 37-year-old male patient was admitted to the Department of Neurosurgery with complaints of strong persistent headache with accompanying temporal visual fields narrowing. Pituitary tumour apoplexy was diagnosed after the imaging revealed a pituitary tumor 25 mm in diameter with features of haemorrhage. Preoperative assessment revealed gonadotropin deficiency with low concentrations of prolactin. After undergoing transsphenoidal resection of pituitary

macroadenoma, hormonal evaluation unveiled additional deficiencies in the form of secondary adrenal and thyroid insufficiency with accompanying diabetes insipidus. At that point, the patient was transferred to the Department of Endocrinology of Medical University of Lublin for further evaluation. The replacement therapy with hydrocortisone, levothyroxine, testosterone and desmopressin was introduced, stabilizing and improving the patient's condition. During the follow-up no restoration of pituitary secretion function in any axis was observed. Histologic examination of the tumour sample displayed a larger size than previously assumed (50 mm in the largest diameter), positive immunostaining for GH (diffuse) and PRL (sparse) allowing to classify the tumour as silent subtype 3 adenoma. Clinical and laboratory evaluation did not reveal any acromegalic features; decreased prolactin levels persisted.

Conclusions

Pituitary apoplexy and/or hypogonadrotropic hypogonadism can be the first symptom of pituitary macroadenoma. Clinically non-functioning adenomas may immunostain positively for more than one pituitary hormone determining their classification as silent subtype 3 adenomas.

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EP866

Unprogrammed pregnancy in women with active Acromegaly: a case report

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Introduction

Reports of pregnancy occurring in acromegalic patients are uncommon. Nevertheless, it appears that women are usually able to carry their pregnancy to full term

Case

39 year old woman referred to endocrinology for secondary amenorrhea and hyperprolactinemia (PRL 55.54 mg/dl). As she mentioned typical symptoms of Acromegaly, we extended the study, finding high levels of IGF1 and a pituitary macroadenoma (25×16 mm) in MRI. Presurgical treatment with Octreotide was started (120 mg/28 days) and complete transsphenoidal surgical resection of GH/PRL secreting pituitary adenoma was performed. 6 months later, as IGF1 levels and GH during oGTT remained high, and no biochemical remission was achieved, treatment with octreotide and cabergoline was restarted. 13 months later, she got unexpectedly pregnant and pharmacological treatment was withdrawn as soon as pregnancy was diagnosed (7–9 weeks). Patient was clinically and biochemically evaluated throughout pregnancy with at least one visit per trimester. In spite of medical treatment withdrawal, IGF significantly decreased compared to preconceptional values. Normal fetal growth and development was observed, with no maternal complications (gestational diabetes or gravid hypertension) and no congenital malformations in the newborn. After delivery IGF1 increased to pregestational levels. During the postpartum period, there was no problem for breastfeeding until medical treatment was restarted.

Discussion

Several reports conclude that GH-supressive treatment can be safely withdrawn after conception in most women with acromegaly. In this case, withdrawal of octreotide and cabergoline was safe for obstetrical and fetal outcomes with an uneventful course of pregnancy and delivery, with a helthy newborn.

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EP867

Acromegaly and pregnancy: case report

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Introduction

Pregnancy in patients with acromegaly is a rare and challenging medical situation. Here in, we report a patient with acromegaly who presented to us in the 3rd trimester of pregnancy after endoscopic transnasaltranssphenoidal radical excision of the tumor.

Observation

A 36-year-old lady (Gravida 3 Parity 2 Live Birth 2), presented to our outpatient clinic on May 2007 forsuspicion of acromegaly. Clinical examination revealed acromegalic features. Hormonal profile revealed elevated human growth hormone (HGH) 47.3 μUI/l and insulin-like growth factor 1 (IGF-1) 576 ng/ml (normal 109–358 ng/ml), her serum prolactin PRL was also mildly elevated 76.7 ng/ml Follicle-stimulating hormone (FSH), luteinizing hormone (LH), Thyroid stimulating hormone (TSH) and Free Thyroxine (FT_4) were within normal range. Cortisol level during hypoglycaemia insulin test was 73 and 107 μg/l. Magnetic resonance imaging of the pituitary gland revealed: Left postero-lateral intra-pituitary expansive lesion measuring 17×11 mm with extension to the sphenoid sinus. Final diagnosis was: Pituitary macro-adenoma on GH, with Hyperprolactinemia and Secondary adrenal insufficiency. She underwent endoscopic transnasaltranssphenoidal radical excision of the tumor on Mars 2009. Magnetic resonance imaging of the pituitary gland after surgery revealed: Absence of evidence of adenomatous residue. On June 2010, patient present in 3rd trimester of the pregnancy. Ophthalmological examination, hormonal profile and Oral glucose tolerance test (OGTT) of 75 gr glucose were without anomaly. She then went on to deliver a full-term baby girl by caesarean section in August 2010.

Discussion

Pregnancy in a patient with acromegaly is very unusual, as the enlarging pituitary adenoma suppresses gonadotropin secretion rendering the patient amenorrheic and infertile. Up to 30% of HGH-secreting pituitary adenomas also secrete prolactin and this adds to the problem.Although pregnancy is unusual in acromegaly, it is by no means rare.

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EP868

Clinical case report: MEN-1 syndrome with coincident AIP gen mutation and MEN-1 gen deletion

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We present the clinical case of a family with an initial diagnosis of AIP syndrome with AIP mutation and a secondary diagnosis of MEN syndrome associated because of a large MEN-1 gen deletion. A male patient 16 years old was evaluated because of delayed growth and pubertal development. He had headaches, nausea and vomits since seven years old. MRI showed: Large pituitary mass of 47.6×22×47.2 mm that erode the floor of the sella, extending into the left prepontine cistern and surrounding the carotid. After some months with high dosis of cabergoline there were not response so surgical treatment was decided. Four months after surgery MRI showed again a mass of 30×20×30 mm, remained hipopituitarism and hyperprolactinemia. Family history: The mother consulted with gynecologist in 2004 because of menstrual disturbances and bilateral galactorrhea. Pituitary macroadenoma without invasion of surrounding structures was diagnosed. During the follow up the mass had the same volume and Pituitary axis were normal. Results of the Genetic study of AIP geneheterozygous mutation in exon 6: 974G > A (p.Arg325Gln.The mother and the brother, had the same mutation while the rest of the family does not carry it. An MRI and hormonal analysis were performed in the brother and initially were normal, but last MRI showed a pituitary microadenoma. Two years ago hypercalcemia appeared in a routine analysis of the mother. We confirmed hyperparathyroidism and an image suggestive of adenoma was confirmed in the imaging tests. A parathyroidectomy was performed. In both sons calcium and iPTH are rising slightly in progressive analytics. After this, we requested abdominal CT and gastrointestinal and pancreatic hormones to rule out a possible association of neuroendocrine tumor. The results were normal in the two children, but in the mother we discovered a pancreatic polypeptide elevation and a 8 cm mass in pancreatic body and tail. The genetic study of MEN gen with MLPA (multiplex ligation dependent probe amplification) revealed the following result: heterozygous deletion corresponding to exon 1- 11(chr11 positions:64571868-64578482).To our knowledge, this is the first case of a family with the two genetics disorders (AIP and MEN-1) matching and resulting in MEN-1 syndrome.

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EP869

Coexistence of thyrotropinoma and chronic autoimmune thyroiditis, a diagnostic challenge

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Introduction
TSHomas are rare TSH producing tumors, whereas chronic autoimmune thyroiditis is a frequent condition. Patients with TSHoma are characterized by increased circulating levels of peripheral thyroid hormones, but when a chronic autoimmune thyroiditis is associated, they may be normal or low, making the diagnosis challenging.
Case report
A 55 year-old woman, with previous medical history of obesity and impaired fasting glucose, was diagnosed of primary autoimmune subclinical hypothyroidism, with fT4 1.01 ng/dl (0.85–1.75), TSH 9.45 mUI/l (0.3–4.2) and positive antithyroid peroxidase antibodies. Levothyroxine treatment was started, but despite increasing doses with fT4 values over the normal range, normalization of TSH could not be achieved, therefore, she was sent to the Endocrinologist. She was under levothyroxine 150 μg/day, with fT4 1.87 ng/dl, fT3 4.2 pg/ml (2.0–4.4), TSH 54.56 mUI/l. She complained of asthenia and nervousness, with no other relevant symptoms. On suspicion of resistance to thyroid hormones and the asthenia, levothyroxine dose was increased to 175 μg/day, with subsequent blood test: fT4 1.93 ng/dl, fT3 4.3 pg/ml, TSH 40.90 mUI/l, free-α-subunit 370.8 mUI/mL (< 1.3). Pituitary magnetic resonance imaging showed a big infiltrating tumor mass at the pituitary region. The rest of pituitary function was normal. She presented worsening visual impairment. Levothyroxine treatment was withdrawn, with fT4 0.92 ng/dl, fT3 3 pg/ml and TSH 413 mUI/l. Surgery was performed with a partial exeresis. Diagnosis of pituitary adenoma was confirmed, visual impairment improved, and TSH and free-α-subunit concentrations fell down to 49.2 mUI/l and 220.8 mUI/ml. Treatment with somatostatin analogues has been started.
Conclusions
TSHomas can be misdiagnosed if they coexist with chronic autoimmune thyroiditis. Normal peripheral thyroid hormones may cause us to not think of TSHoma as a cause, therefore, if increasing doses of thyroid hormone therapy do not achieve to normalize TSH, we always have to exclude a thyrotropinoma.

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EP870

Central diabetes insipidus and cerebral salt wasting syndrome: a challenging coexistence

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Introduction
Combined central diabetes insipidus (DI) and cerebral salt wasting syndrome (CSW) is a rare clinical finding. However, when this happens, mortality is high due to delayed diagnosis and/or inadequate treatment.
Case report
42-year-old man referred to neurosurgery due to a non functional pituitary macroadenoma with bitemporal hemianopsia. He underwent partial ressection of the tumour on July 2nd 2015. On the following day of surgery he presented poliuria with sodium (Na) 149 mEq/l, plasma osmolality (pOsm) 301 mOsm/kg and urine osmolality (uOsm) 293 mOsm/kg. He started nasal desmopressin 0.05 mg/day with good response. He was already on dexamethasone 4mg and levothyroxine 75 μg due to hypopituitarism. On july 9th he became confused. Cerebral CT was performed with no significant changes. His natremia dropped to 128 mEq/l, with development of poliuria despite maintenance of desmopressin doses. Hemoglobin and hematocrit rose from 9.1 g/l to 11.6 g/l and 27.5–32.5, respectively. Thyroid function was normal and the patient was on hydrocortisone 30 mg/day. At 1200 h he initiated 150 mg/hydrocortisone infusion, but Na did not increased. Plasma and urine osmolality were 264 mOsm/kg and 679 mOsm/kg, respectively. At 1600 h hydrocortisone was increased and hypertonic saline replacements started. At 1800 h he was dehydrated with poliuria and vomiting and natremia of 124 mEq/l. Hyponatraemia was very resistant to treatment despite hypertonic saline replacements, hence desmopressin was suspended. On next day urine spot analysis showed that natriuresis was 63 mEq/l with serum sodium 132 mEq/l. This was interpreted as CSW and control was achieved with aggressive hypertonic saline replacements and fludrocortisone 0.1 mg/tid. Two days after, Na levels were normalized and desmopressin was restarted. Hypertonic saline dose was gradually decreased and switched to sodium chloride tablets. He was discharged on fludrocortisone 0.1 mg/bid, oral sodium chloride 16 g/day, oral desmopressin 0.1 mg/bid, hydrocortisone 20 mg/day, levothyroxine 100 μg/id. Two months later he was only on hydrocortisone, desmopressin and levothyroxine.
Conclusion
We presented a rare case of a patient with DI and CSWS successfully treated. Hyponatremia in a DI patient may erroneously be interpreted as inadequate DI control leading to therapeutic errors. Thus, all clinical and analytical data should be evaluated together for an early and proper diagnosis.

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EP871

Adipsic diabetes insipidus – a diagnostic and therapeutic challenge

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Introduction
In diabetes insipidus (DI) the serum sodium is often in the high normal range, required to provide the ongoing stimulation of thirst to replace the urinary losses. Marked hypernatremia can occur if a central lesion impairs both ADH release and thirst.
Case report
A 57-year-old woman presented with dysuria, polyuria and fever. She was medicated with ciprofloxacin, however, she maintained symptoms, accompanied in the next day by nausea, vomiting and notion of decreased urine output. Analytical study revealed a normal blood count, urea 116 mg/dl and Cr increased from 0.87 to 3.85 mg/dl, hypernatremia 155 mEq/l and CRP 41.8 mg/dl. Urinalysis was normal. Renal ultrasound and abdominal CT did not show alterations. Her past medical history was significant for diabetes mellitus treated with metformin 850 mg/bid, arterial hypertension under losartan 25 mg/id and spironolactone 25 mg/id and dyslipidemia under pravastatin + fenofibrate 40 + 160 mg/id. She had a history of hypernatremia known for 1-year that resulted in two hospital admissions. We found records of a plasma osmolality (POsm) of 348 mOsm/kg and a urine osmolality (UOsm) of 947 mOsm/kg. When questioned, she reported polyuria and nocturia, without polydipsia. In the present admission, POsm and UOsm were 320 and 118 mOsm/kg, respectively. As there was a record of UOsm incompatible with the diagnosis of DI, the patient performed a brief dehydration test, during which UOsm was stable below 350 mOsm/kg and there was no urine output following desmopressin administration. She performed a therapeutical trial with desmopressin that resulted in increased UOsm > 9% and corresponding reduction of POsm. Basal pituitary function was normal. Pituitary MRI showed a reduced pituitary gland and thinning of pituitary stalk lower half suggesting the existence of an arachnoid cyst.
Conclusion
In patients with free access to water, hypernatremia should be exceptional since intact thirst mechanism is a powerful defense against hyperosmolality. We report a case of severe hypernatremia caused by partial DI with hypodipsia.

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Endosalpingiosis – re-thinking risk tumours in acromegaly

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Introduction
There is circumstantial evidence supporting a role of growth hormone and insulin-like growth factor 1 in the development and progression of tumors. Endosalpingiosis is characterized by the presence of non-neoplastic fallopion tube-like epithelium in ectopic anatomical locations.
Case report
A 45-year-old woman presented with a constant moderate to intense perianal pain limiting basic daily life activities. She also complained about pain at right posterior superior iliac spine area that worsened with body movements. There was no history of trauma and inspection of the area and rectal examination were normal. Her past medical history was significant for acromegaly diagnosed 4-year earlier and confirmed by anatomopathological analysis of a pituitary macro-adenoma removed by transsphenoidal surgery. She had history of hyperplastic polyposis of the rectum but further investigation with colonoscopy showed no apparent mucosal lesions. Pelvic CT revealed a poorly delimitated nodular soft tissues densification in the right ischiorectal fossa of indeterminate nature. Pelvic MRI showed a spiculated soft tissue mass involving the lateral planes of the levator ani muscle and the internal obturator muscle, conditioning obliteration of the fat planes around the sciatic nerve. Given the surgical risks inherent to resection of the lesion, CT-guided biopsy was performed and the histological examination was compatible with endosalpingiosis. Since the benign nature of the lesion, medical treatment with an oral contraceptive was chosen.
Conclusions
Acromegaly appears to be associated with an increased risk of benign and malignant tumors. This case reports an unusual association between acromegaly and endosalpingiosis. Surveillance of signs and symptoms in acromegalic patients as well as adequate screening for possible comorbidities is crucial to allow timely diagnosis, clinical differential diagnosis and appropriate treatment of future lesions.

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Developmental Endocrinology

EP873

Can dehydroepiandrosterone-sulphate be a new diagnostic parameter in male patients with idiopathic hypogonadotropic hypogonadism?

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DHEA and its sulphate derivative DHEA-sulphate (DHEA-s) are major androgen hormones of adrenal origin. The purpose of this study was to investigate DHEA-s levels in male patients with idiopathic hypogonadotropic hypogonadism (IHH) and to determine whether DHEA-s levels are a useful marker in the diagnosis of hypogonadotropic hypogonadism. 91 subjects, 31 male patients diagnosed with IHH (mean age 19.7 ± 2.6 years) and 60 healthy males (mean age 20.7 ± 2.6 years) as a control group, were included in the study. The patients in the IHH group were selected from subjects who had not yet started treatment for hypogonadism and who had no additional disease, while the healthy control group consisted entirely of individuals presenting to the clinic for routine check-ups. Both groups' FSH, LH, total and free testosterone, ACTH, cortisol and DHEA-s levels were investigated. Mean DHEA-s levels were 133.4 ± 56.5 μg/dl in the IHH group and 433.3 ± 160.3 μg/dl in the control group. The difference was statistically significant ($P = 0.000$). Total testosterone levels in the patient and control groups were 28.0 ± 26.3 nmol/l and 568.1 ± 288.0 nmol/l, respectively ($P = 0.000$), free testosterone levels were 9.7 ± 14.3 pg/ml and 18.0 ± 9.0 pg/ml ($P = 0.006$). The differences were statistically significant. Low DHEA-s levels in patients with IHH were determined to be independent of age, cortisol and ACTH at multivariate logistic regression analysis. ROC analysis showed that DHEA-s ≤ 38.2 μg/dl supports a diagnosis of IHH with 100% specificity and 100% sensitivity. DHEA-s is as useful and predictive marker as total testosterone, which is used in the diagnosis of patients with IHH. DHEA-s levels were significantly lower in patients diagnosed with IHH compared to the control group, and we conclude that DHEA-s may be a predictive marker capable of use in the diagnosis of IHH.

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Endocrine Tumours and Neoplasia

EP874

Insulinoma in MEN type 1 mistaken as temporal lobe epilepsy

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Multiple endocrine neoplasia type 1 (MEN 1) is a rare autosomal dominant disease characterized by pancreatic, parathyroid, and anterior pituitary tumours. Hypercalcaemia due to parathyroid tumours is usually the first manifestation. Pancreatic islet tumours occur less frequently, among them gastrinomas and insulinomas are the most prevalent. Insulinomas can be difficult to diagnose. It was not uncommon for patients to have been misdiagnosed with psychiatric illnesses or seizure disorders before insulinoma was recognized. We presented a patient who was diagnosed to have temporal epilepsy, which later turned out to be an insulinoma in MEN-1. A 23-yr-old male presented with an auditory hallucination of a voice asking him to kill his mother. He has had seizure for a year, and was being treated as temporal lobe epilepsy (TLE) with two antiepileptics. Asymptomatic hypoglycaemia was noted during his follow up for TLE; but did not trigger further investigation. He has been having recurrent hypoglycaemia during admission and remains asymptomatic even though his blood glucose went down as low as 1.8 mmol/l. Fasting C-peptide level taken during hypoglycaemia was inappropriately normal i.e. 947 pmol/l (298–1324 pmol/l). MRI pancreas revealed a mass at the head and uncinate of pancreas; measuring $2.86 \times 3.2 \times 2.9$ cm. H e was also diagnosed to have hypercalcaemia secondary to primary hyperparathyroidism. Neck US showed the presence of a probable right inferior parathyroid adenoma. He has bilateral renal calculi; with left proximal ureteric calculus causing moderate hydronephrosis and hydroureter requiring stenting. A final diagnosis of MEN-1 with Insulinoma and primary hyperparathyroidism was made. He underwent Whipple's procedure instead of enucleation of the insulinoma as the tumor is adjacent to the pancreatic duct and major vessels. A total parathyroidectomy and implantatation of the left parathyroid was also performed, together with prophylactic thymectomy. He remains euglycaemic following the surgery. Insulinoma can pose a diagnostic challenge even to an experience clinician. Misdiagnosis of insulinoma as psychiatric illness and seizure is common; and might lead to disastrous consequences. This is unfortunate as insulinoma is curable after surgery. This case highlights the importance of considering insulinoma in patients presenting with seizures or psychosis.

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Pregnancy in multiple endocrine neoplasia type 1: a case report

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Multiple endocrine neoplasia type 1 (MEN1) is a rare inherited endocrinopathy characterized by tumours of the parathyroid glands, adenohypophyseal and pancreatic tumours. We present a case of a young, 24 years old female patient with a positive familial background for MEN1 (on the fathers' side of the family). She is one of two sisters with determined heterozigocity of the MEN 1 gene (Exon 2, codon 111). At the age of 12, insulinoma of the head of the pancreas was diagnosed in our patient, with dimensions 2×2.5 cm. She underwent two operations in order to remove the insulinoma, with consecutive pancreatojejunostomia and duodenojejunostomia. In the same period, adenohypophyseal prolactinoma measuring 8 mm was diagnosed and Cabregoline therapy was initiated. One year before she got pregnant, primary hyperparathyroidism was diagnosed and hypoparathyroidectomy was counselled, but the patient did not decide to do the operation. The possible maternal and foetal complications of hyperparathyroidism were pointed out to the patient, but she decided to keep the pregnancy. The PTH values are above 100 pg/ml (ref. values 15–65 pg/ml) with increased values of total and iodised calcium (1.5–1.65 mmol/l). The patient is currently in the seventh lunar month of the pregnancy, with reported normal foetal development by the gynaecologist, and delivery is planned for the 36th week of pregnancy.

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EP876

The giant who could not stop growing

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Introduction
The presentation of a patient with Gigantism, gynaecomastia and increasing height suggests underlying Hypogonadotrophic Hypogonadism. Aetiologies such as a pituitary hamartoma is unlikely.
Case study
A 39 year old male presents with a 20 year history of increasing height, shoe size, headaches, sweatiness and gynaecomastia for the past 10 years. He was 2.08 m tall with features in keeping with Acromegaly. He had normal secondary sexual characteristics and Tanner stage 3 gynaecomastia. Acromegaly was confirmed. His bone age was 17 years. He had hypogonadotrophic hypogonadism. Pituitary MRI showed an enlarged, partially empty sella turcica and a hypothalamic hamartoma. He received testosterone cypionate, oestrafem and a somatostatin analogue. He improved clinically but his gynaecomastia had worsened. He was referred for a mastectomy.
Discussion
Acromegaly/Gigantism are uncommon disorders. tumors ususally arise de-novo and secrete GH. Occasionally, there is a family history and an Aryl hydrocarbon mutation (FIPA) or Multiple Endocrine Neoplasia should be considered. Hypothalamic Hamartomas are rare causes of GNRH secretion, but usually present in childhood. This patient's presentation suggests that the onset of Acromegaly was in late teenage years, and therefore unlikely to be due to the Hypothalamic Hamartoma. The enlarged, partially empty sella turcica, suggests possible auto-infarction of a prior macroadenoma.

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EP877

Intrasellar malignant haemangiopericytoma: a rare case

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We report a case of malignant hemangiopericytoma in sellar region in a 73-year-old lady who initially presented with symptomatic hyponatraemia. She was found to have hypocortisolism on short synacthen test. She was treated with hydrocortisone and was found to have secondary hypothyroidism. Her gonadotropin levels were commensurate with menopause, prolactin levels were normal and there was no suggestion of diabetes insipidus. Initial pituitary magnetic resonance imaging (MRI) was normal. Ten months after the initial presentation, she developed bi-temporal visual field deficits, and repeat imaging revealed a large sellar mass compressing the optic chiasm. She underwent emergency endoscopic endonasal resection. Histopathology was consistent with malignancy haemangiopericytoma (WHO Grade III). She had residual tumour on repeat imaging and underwent intensity modulation radiotherapy allowing high precision delivery of radiation to the tumour avoiding nearby structures. Her repeat MRI seven months after surgery suggests stable appearances, and she is on thyroxine, hydrocortisone and desmopressin replacement. Haemangiopericytomas are rare mesenchymal tumours arising from pericytes of the capillaries and can happen anywhere in the body. Sellar and parasellar malignant haemangiopericytomas are exceedingly rare with only a few cases reported worldwide. They can present with mass effects like headache or visual symptoms or symptoms of hypopituitarism. They often mimic pituitary adenomas on imaging. There are no guidelines available for the optimal management of these tumours as they are rare. They are very aggressive tumours that tend to recur and metastasize, even after complete resection, therefore postoperative radiotherapy is essential.

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Growth Hormone IGF Axis - Basic

EP878

Initial response to octreotide LAR in Mexican patients with acromegaly

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Introduction
In Mexico there is scant literature about medical management and its response in patients with acromegaly. Octreotide LAR at a dosage of 20 mg weekly is considered as first line treatment in patients who failed to surgery or who are not candidates to surgical treatment. The goal of this initial dosage is to reach GH levels below 1.0 ng/ml and insuline like factor type 1 (IGF1) levels within range for age and gender. The objective of this study is to determine the percentage of patients that attain goals for GH and IGF1 after 3–6 doses of Octreoride LAR.
Methods
We included patients with acromegaly diagnosis within our centre, between the years 1995 and 2015 that received a minimum of three applications of Octreotide LAR before obtaining new levels of GH and IGF1 to determine response to treatment. We included patients that received surgical treatment before institution of Octreotide and those who had contraindications to surgery and had to initiate Octreotide as part of initial treatment.
Results
A total of 34 patients were included, with an average of five applications of Octreotide LAR before evaluation, 67% had surgical treatment, 68% were male, with an age average of 47 years, 20% had diabetes, and 38% had systemic hypertension. Initial GH levels were 8.19 ng/ml in average and with an average tumour diameter of 15 mm. In all patients a decrease in GH and IGF1 levels was observed (3.65 ng/ml in average), but only 15% attained GH and IGF1 levels goals, 50% continued with active disease and the rest had a discordant pattern. Among patients that received surgical treatment prior to Octreotide LAR only 8% attained goals, 52% remained active. Of the patients who did not receive surgery 27% attained goals and 46% remained active.
Conclusion
Despite a decrease in GH and IGF1 levels in all patients after Octreotide LAR treatment only 15% attained goals. Patients who did not received surgery had better results than patients who received it. This initial mode of treatment is not enough to control disease so over 70% of patients will need higher doses of Octreotide LAR and perhaps association with other drugs.

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Pasireotide: an effective treatment for resistant acromegaly

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The granulation pattern of somatotroph adenoma is well known to be associated with differing clinical and biochemical characteristics and it has been shown that sparsely granulated tumors respond poorly to commonly used somatostatin analogs. We report a challenging case of acromegaly with a sparsely granulated tumor, resistant to multiple modalities of treatment given over several years and ultimately achieving biochemical control with pasireotide. A 26-year-old lady presented with classical features of acromegaly. She had no family history of pituitary tumors or hypercalcaemia. An OGTT confirmed acromegaly, IGF-1 was 1710 μg/l and mean growth hormone (GH) was >600 mU/l, indicating high disease burden. In addition, there was secondary hypogonadism, marginally elevated prolactin and hypothyroidism. MRI scan showed a 4 cm pituitary macroadenoma with suprasellar extension and right side cavernous sinus invasion. She underwent trans-sphenoidal pituitary surgery. Histology displayed moderate amounts of sparsely granular eosinophilic cytoplasm, staining only for GH. Postoperative investigations showed uncontrolled disease (IGF1-1474 μg/L, mean GH-228 mU/l) and residual tumor in the cavernous sinus. She received external beam fractionated radiation. Over the years she received octreotide LAR (up to 30 mg), lanreotide (up to 120 mg) 2 weekly, cabergoline, pegvisomant and stereotactic radiosurgery to no avail. Only pegvisomant resulted in some disease control; however this had to be stopped due to abnormal liver functions. Fifteen years after the diagnosis, she was started on pasireotide 40 mg monthly. Within a month, her IGF-1 dropped and has remained within the normal range for age (103–310 μg/l). Pasireotide was well tolerated and the patient's symptoms improved significantly. Somatostatin receptor subtyping revealed a positivity score of two for both SST5 and SST2a subtypes.
Conclusion
Tumours that poorly respond to first generation SST, especially sparsely granulated somatotroph adenomas, can respond to pasireotide and treatment should be considered early in the management of resistant tumours.

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EP880

The disorder of secretion of somatotropic hormone in women with the polycystic ovaries syndrome (PCOS) by comparison to patients with the non-functional pituitary adenomas (NFPA)

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Material and methods

Under our supervision in the department of neuroendocrinology of the Center of Endocrinology of PH Ministry of RUz ambulatory in a period from September 2015 for December, to 2016, 15 adult patients of fertil age were observed with PCOS and 15 – with NFPA. Middle age of patients to make 25.5 and 28.9 accordingly. The remoteness of disease hesitated in limits from 7 months to 9 years.

Results

It was set that in both groups there were neuroendocrine violations peculiar to each of pathologies. So, in a 1 group of patients with PCOS such violations, as obesity, met most often, strium, acanthosis, acne, hyperandrogenemiya. hyperpolymenorheya, and in the second is secondary amenorrheya, hyperprolactinemiya, pahhypopituitarism. In both groups there was anovulation, and also decline of secretion of STH, IGF-1. In addition, in the group of patients with NFPA the most for certain mionectic basale levels of trope hormones of hypophysis were educed – STH, LH, FSH on a background hyperprolactinemiya and normal values of IGF-1, while for patients with PCOS the decline of STH, LH, FSH, was marked on a background hyperandrogenemiya and declines of IGF-1.Thus, it is set that in the group of patients with PCOS the most reliable decline of basale levels of IGF-1 was educed, while the deficit of STH met rarer.

Conclusions

The secretions of STH and IGF- 1 educed in our research of violation confirm these literatures that for patients with PCOS the decline of levels of STH and IGF-1 takes place on a background hyperinsulinemiya and hyperandrogenemiya that requires further research.

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EP881

The levels of decorin in patients with Cushing's disease and acromegaly

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Decorin is myokine expressed and released in response to muscle contractions. It induces growth and hypertrophy of skeletal muscles in different ways including myostatin inhibition. It is still not clear whether decorin takes part in development of muscle atrophy in endocrine pathologies.

Objective

To evaluate decorin levels in patients with endogenous hypercortisolism and GH oversecretion.

Materials and methods

Three groups were involved in our study: 1) patients with Cushing's disease ($n=29$), 2) patients with acromegaly ($n=25$) and 3) healthy controls ($n=20$). 24-h urine free cortisol (24-hUFC) (immunochemiluminescent assay, Vitros ECi) and evening salivary cortisol (electrochemiluminescent assay, Cobas e601) were measured in patients with Cushing's disease, and IGF-1 (immunochemiluminescent assay, Liaison) was evaluated in patients with acromegaly. Serum decorin levels were measured by enzyme immunoassay Human Decorin ELISA kit SK00641-01, serum myostatin values were also determined (Myostatin ELISA kit Immundiagnostik AG).

Results

One-way ANOVA was performed for all patients and controls. There were not found any differences among the groups in sex ($P=0.959$), age (The National Research Centre for Endocrinology, Moscow, Russia $=0.180$) and BMI (The National Research Centre for Endocrinology, Moscow, Russia $=0.270$). No differences were found in myostatin levels among the groups (The National Research Centre for Endocrinology, Moscow, Russia $=0.785$). The Duncan *post-hoc* test demonstrated significantly lower values of decorin in patients with acromegaly compared to patients with Cushing's disease and healthy controls: (1) 5015.38 pg/ml (95% CI 4855.71–5175.06), (2) 4469.89 pg/ml (95% CI 4285.85–4653.94), (3) 4841.29 pg/ml (95% CI 4633.86–5048.71) (The National Research Centre for Endocrinology, Moscow, Russia <0.001). This finding was confirmed by performance of Student's *t*-test in pairs for groups (1) and (2) (The National Research Centre for Endocrinology, Moscow, Russia <0.001) and groups (2) and (3) (The National Research Centre for Endocrinology, Moscow, Russia $=0.008$). Significant negative moderate correlation was demonstrated between decorin and IGF-1 values – $\rho=-0.413$ (The National Research Centre for Endocrinology, Moscow, Russia <0.001). There was also a weak negative correlation of very low significance between decorin and myostatin – $\rho=-0.111$ (The National Research Centre for Endocrinology, Moscow, Russia $=0.425$).

Conclusion

The serum decorin levels tend to be reduced in subjects with acromegaly. At the same time, the levels of myostatin don't depend significantly on decorin values.

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EP882

Could statin modify molecular phenotype of pituitary growth hormone-secreting tumors?

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Background

Acromegaly is the consequence of excessive growth hormone (GH) secretion, usually produced by a pituitary adenoma. In the last years, statins have been implicated in the response to treatment of patients with acromegaly. Although this fact is not very clear.

Objective

To analyze whether pretreatment with statins modifies the adenoma molecular phenotype of the acromegalic patients and how this changes could help to influence the response to treatment.

Material and methods

Observational study including patients with acromegaly, diagnosed at the Endocrinology and Nutrition Unit of the Hospital Reina Sofía from 2007 to 2012, in which surgery, radiology and molecular phenotyping of the adenoma was carried out.

Results

22 patients were included (38 ± 15 years old; 65% women). Three patients meet cure criteria. These who take statins have lower prolactin levels (9.33 ± 2.77 mg/dl) than those who do not (54.30 ± 52.31, P 0.005). There were no differences about molecular phenotype between two groups, it shown in Table 1. Patients meet cure criteria had taken more statins that those who had not (P 0.048).

Conclusion

Overall, our results indicate that there is a significant correlation between stantin pre-surgical treatment and the disease cure. However, there is not correlation between use of statin and molecular phenotype.

Table 1

	Statin		
	Yes	No	*P*
GH	91.56 ± 72.49	213.90 ± 515.02	>0.05
Prolactine	0.99 ± 1.31	44.18 ± 132.25	>0.05
Sst1	0.000042 ± 0.000046	0.00279 ± 0.0056	>0.05
Sst2	0.0055 ± 0.0067	3.3070 ± 13.1979	>0.05
Sst3	0.00067 ± 0.00048	0.0047 ± 0.01146	>0.05
Sst5	0.0099 ± 0.00789	0.07180 ± 0.2312	>0.05
DR1	0.0042 ± 0.0036	0.0296 ± 0.0561	>0.05
DR2T (2L)	0.0740 ± 0.1185 (0.018 ± 0.019)	0.179 ± 0.056 (0.119 ± 0.329)	>0.05

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A surprising and dramatic neuroendocrine-immune phenotype of mice deficient in Growth Hormone-Releasing Hormone (GHRH)

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In the framework of close interactions between the immune and neuroendocrine systems, Growth Hormone (GH) has been proposed to exert significant effects on the immune system, but there is not yet a consensus about GH immunomodulatory properties. These studies investigated the immune and anti-infectious response of dwarf *Ghrh*$^{-/-}$ mice presenting a severe deficiency of the GHRH/GH/IGF-1 axis. In basal conditions, thymic parameters and T-cell responses of *Ghrh*$^{-/-}$ mice were not severely affected but a constant B-cell lymphopaenia was observed. Thus, we investigated vaccine and anti-infectious responses of *Ghrh*$^{-/-}$ mice toward *Streptococcus pneumonia,* a B-dependent pathogen, *Ghrh*$^{-/-}$ mice were unable to trigger production of specific IgM and IgG against serotype 1 pneumococcal polysaccharide (PPS) after vaccination with either native PPS (Pnx23) or protein-PPS conjugate (Prev-13) vaccines. These vaccines both include the serotype 1 (our *S. pneumoniae* strain) and provide an effective protection in mice. A short GH supplementation to *Ghrh*$^{-/-}$ mice (1 daily injection of 1 mg/kg GH for 4 weeks) restored IgM and IgG response to Pnx23 vaccine but not to Prev-13. This suggests that GH could exert distinct impacts upon spenic areas. Furthermore, after intranasal instillation of a non-lethal dose (defined by the full clearance by WT C57BL/6 mice after 24 h) of serotype 1 *S. pneumoniae*, *Ghrh*$^{-/-}$ mice exhibited a dramatic susceptibility. This was proved by a marked time-dependent increase in pulmonary bacterial, a septicemia already 24 h after infection and a survival limit of 72 h. We also observed a dramatic decrease in lung B- and T-cell populations and an increase in proportion of inflammatory macrophages. By contrast, WT and heterozygote mice completely cleared *S. pneumoniae* infection after 24 h. In conclusion, our data show without ambiguity that the somatotrope GHRH/GH/IGF-1 axis plays an important and unsuspected role in defense against *S. pneumoniae*.

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Safety of growth hormone replacement therapy (GHRT) in adult patients with GH deficiency: data from kims

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Background
The efficacy of recombinant human growth hormone replacement therapy (GHRT) has been demonstrated, in part, through clinical trials conducted worldwide. KIMS (Pfizer International Metabolic Database), established in 1994 and active until 2012, includes treatment outcome data and real world safety from 15 809 patients from 31 countries.
Objective
The main objective of this analysis was to evaluate the long-term safety of patients with hypopituitarism or with Idiopathic GH deficiency receiving GHRT in adult life.
Study design
This open label, international, multi-center study enrolled adult and adolescents with hypopituitarism and GH deficiency. Patients were treated according to the standard of care of their physicians. A total of 15 809 patients (94.4% Caucasian, 50.5% males, 22.2% childhood-onset) were enrolled, with a mean age (S.D.) of 43.9 yr (15.3) at time of enrollment; the mean duration of follow-up was 5.3 yrs and 83 128 patient-years. Safety outcomes included all reported causality adverse events (AEs), treatment related (TR) and serious AEs (SAEs), including neoplasm incidence.
Results
8093 (51.2%) patients were reported to have 27118 AEs, of which 16.6% TR, and 3998 (25.3%) patients were reported to have 7154 SAEs. 12.2% were reported to have an AE that led to study medication discontinuation and 5.5% to a dose reduction. The most frequently reported all causality AEs were arthralgia (4.6%), headache (3.6%), influenza (2.8%) and depression (2.8%), whereas for TRAEs these were arthralgia (2.6%) and peripheral edema (1.8%). The most frequently reported SAE was pituitary tumor recurrence, all causality ($n=320$/15 809, 2.0%) and TR ($n=154$/15 809, 1%). The reported occurrence of death was highest for general disorders and neoplasms (benign, malignant and unspecified) in 148 and 146 patients, respectively.
Conclusion
The results of this large study of GHRT in adult/adolescent patients with GHD complement data from clinical trials and confirm the favorable safety profile of GHRT.

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EP885

Effect of GH treatment on coagulation and fibrinolysis parameters in prepubertal children with growth hormone deficiency

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Background
Increased fibrinogen levels have been reported in prepubertal children and adolescents with growth hormone deficiency (GHD), which were reduced after rhGH treatment. rhGH treatment has also been shown to exert a beneficial effect on the amount of aPAI-1 in children with GHD. Aim of the study was to evaluate whether prepubertal GH deficient (GHD) children showed any impairment in coagulation- and fibrinolysis-related parameters and the effect of GH therapy on these parameters.
Patients and methods
Fifteen prepubertal children (ten girls and five boys) of a mean (S.D.) age of 9.8 (0.4) yrs with GH deficiency were included in this hospital based prospective study. Serum levels of PT, APTT, fibrinogen, VII, VIII, AT, PC, D-dimers, Plg, and PAI-1 were measured before and after 6-12 months of GH treatment.
Results
At baseline all studied parameters were within normal ranges. A significant increase in PT values was noted after a mean (S.D.) interval of 9.3 (0.4) months of treatment: 12.46 (0.2)sec vs 12.1(0.15)sec, $P=0.045$. A significant decrease in PAI-1 levels (3.04 (0.1) U/ml vs 2.28 (0.3) U/ml, $P=0.018$) was noted at the same time. No significant changes in the rest of parameters were found during the study period.
Conclusion
GH replacement therapy for 6–12 months led to a significant increase in PT values, while fibrinogen levels did not change. Moreover, GH treatment reduced PAI-1 levels in GHD children, suggesting a beneficial effect of GH treatment on possible risk of future atherothrombosis. Further evaluation of the clinical significance of these changes is needed.

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EP886

Nodular thyroid disease in acromegaly: cohort of 69 patients at a single institution

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Materials and methods
The aims were to evaluate the frequency of nodular thyroid disease (NTD) in acromegalic patients and to correlate clinical and metabolic features with disease activity and other. We conducted a cross-sectional study including retrospectively 69 acromegalic patients attending to an University Hospital in Madrid, Spain between 1980 and 2016. Mean age was 63 (32–92) years, 63.8% of patients were

female. Mean age at diagnosis of acromegaly was 48 (11–78) years, time between initial symptoms and diagnosis was 24 (0–240) months, 50 patients (72.5%) had a macroadenoma and 23 (33.8%) were cured after transsphenoidal resection, among the other medical treatment or radiotherapy was necessary for attaining disease control. Thyroid function was normal in 42 patients (60.9%), 22 (31.9%) had hypothyroidism (15 primary, seven secondary) and 5 (7.2%) had hyperthyroidism. NTD were observed in 56 patients (81.2%) and 10 (14.5%) had diffuse goitre. Thyroid volume was 16.1 (4.7–272.7) ml. Fine-needle aspiration biopsy (FNAB) was performed in 17 patients. Suspicious or malignant cytology was detected in 23.5% of the FNABs specimens, all of them (11 patients, 15.9%) underwent thyroidectomy. Pathology revealed nodular goitre in six and thyroid carcinoma in five patients (7.2%). Other cancers detected were colorectal, breast, prostate and gastric in 4 (5.8%), 2 (2.9%), 2 (2.9%) and 1 (1.4%) patients, respectively. Patients with NTD ($n=56$) showed similar age, duration of disease, thyroid volume, concentrations of GH/IGF-1 at diagnosis and IGF-1 at last follow-up compared with the group of patients without NTD ($n=13$). Considering only patients with NTD, thyroid volume was not correlated with age, estimated acromegaly duration, time between the first symptoms to diagnosis, fT_4, TSH, GH/IGF-1 at diagnosis or IGF-1 at last follow-up. Thyroid volume was not different whether acromegaly was active or not (17.5 vs 14.3 mm).
Conclusions
Thyroid structural abnormalities are frequent in patients with acromegaly, therefore routine physical examination and thyroid ultrasound are recommended in all of them. Thyroid cancer was the most common neoplasia in our study, which is similar to other reports.

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EP887

Somatropin treatment Supported by NHS: characterization of submitted patients – 2006 to 2016

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Introduction
In our country somatropin treatment is supported by the National Health Service. A National Committee (CNNHC) rules and analysis the submission papers of patients with: isolated/multiple somatotropin deficiency (STD), short stature in: renal chronic disease (DRC), small for gestational age (SGA), Turner syndrome (TS) and Prader Willi syndrome (PWS). In adults only isolated somatropin deficiency diagnosed in childhood.
Aims
To analyze the characteristics of patients submitted to the CNNHC from 2006 to 2016.
Methods
Retrospective study of cases submitted to CNNHC for somatotropin (2006–2016). Data collected: demographic, submission date, diagnosis and committee's decision. Statistic analysis by SPSS21 ($P<0.05$).
Results
Total submissions $n=1968$ corresponding to 1909 children/six adults; Males (59.5%) and Females (40.5%). Mainly coming from Pediatric centres ($n=1573/80.3\%$). Submissions increased along time, with a minimum of 87 in 2007 and a maximum of 252 in 2011. Were approved a total of $n=1412$ (72%) cases: at first submission $n=1243$ (63.4%) and after reevaluation $n=169$ (8.6%). Not approved $n=535$ (27.2%). Diagnostic prevalence: somatotropin deficiency $n=1233$ (62.9%): isolated $n=1067(54.4\%)$ and multiple $n=166(8.5\%)$; SGA $n=324(16.5\%)$, TS $n=177(9\%)$; RCD $n=122(6.2\%)$ and PWS $n=53(2.7\%)$. Somatotropin deficiency remained the most frequent diagnosis along the years. Age at submission: DRC were submitted earlier (6.4 ± 4.2y), followed by SGA (7.9 ± 3.0y), TS (8.5 ± 3.6y), PWS (9.4 ± 4.0y), multiple STD (9.7 ± 5.1y) and isolated STD (10.3 ± 3.5y). Except from TS, male gender was more frequent at all diagnosis. Were associated with oncologic disease $n=182/1968(9.2\%)$: $n=97/182(53\%)$ had primary tumours of CNS and $n=66/182(36\%)$ due to hemato-oncologic disease (leukemia/lymphoma).
Conclusions
Somatotropin supported treatment in our country has evolved along time, with new approved indications after 2010. The most frequent diagnosis remains isolated somatropin deficiency with a high age at submission witch probably compromises the final stature. We must have more support for deficient somatropin adult patients.

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Male Reproduction

EP888

Delayed puberty revealing an uncommon genetic disease: about one case

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Contexte
Kallmann syndrome is a rare genetic disease which can affect both men and women. It combines hypogonadotropic hypogonadism which characterised by a failure to start or to fully complete puberty naturally; olfactory disorders such hyposmia or anosmia, impaired color vision, deafness, unilateral or bilateral renal aplasia and midline anomalies.
Objective
We report a case of this rare syndrome, responsible of delayed puberty view of infertility.
Patient – intervention
A patient of 23 years, from a non consanguineous marriage, consultant for delayed puberty with a Tanner stage to P2G2, without cryptorchidism or hyposmia.
Intervention
We realized a hormonal exploration, with a morphological exploration of hypothalamic-pituitary region.
Main outcome measure
We have suspected this diagnosis through severe hypogonadism (absence of developpement of secondary sex characteristics). The definitive diagnosis relies on the detection of the genetic anomaly, not available to our level, hormonal explorations, olfactometry, abnormalities on MRI Kallmann syndrome.
Result
Hormonal exploration showed hypogonadotropic hypogonadism. MRI is in favor of a predominant Hypoplastic right olfactory tract and the olfactory grooves, with a normal rod.
Conclusion
Kallmann syndrome is a rare disease, responsible of severe hypogonadism, the diagnosis is based on characteristic abnormalities of the olfactory bulbs on MRI. With the correct diagnosis and treatment, fertility can be achieved in many cases and the risk of osteoporosis reduced.

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Neuroendocrinology

EP889

Empagliflozin increases urinary volume output in healthy volunteers with artificial SIADH – a placebo-controlled double blind crossover study

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Introduction
The Syndrome of inappropriate antidiuresis (SIADH) is the predominant cause of hyponatremia and its therapy options are unsatisfying. SGLT2-inhibitors have

become a valuable treatment option for type 2 diabetes by increasing glucose excretion in the urine with concomitant osmotic diuresis. We therefore hypothesized that SGLT2-inhibitors could be a novel treatment option for SIADH.
Material and methods
We included 14 healthy volunteers in this prospective placebo controlled crossover study. To induce SIADH, participants were concomitantly administered desmopressin i.v. and hydrated. After the initial oral volume load and administration of desmopressin, a single dose of the study drug empagliflozin 25 mg or placebo was given in random order. The main outcomes were total urinary volume excretion, glucosuria and the area under the curve (AUC) of the serum sodium concentration. The outcome measures were obtained 2–8 hours after administration of the study drug.
Results
Fourteen participants (64% males), BMI 23.1 kg/m^2 ($\pm$2.4), age 28.6 years ($\pm$9), with similar serum sodium levels on both study days (empagliflozin 140 mmol/l ($\pm$1.5) vs placebo 140 mmol/l ($\pm$1.3)) completed the study. Empagliflozin lead to significantly increased urinary volume excretion (579.3 ml $\pm$194.8 vs 367.3 ml $\pm$158.8; $P=0.001$) due to glucosuria (74.18 mmol $\pm$22.3 vs 0.12 mmol $\pm$0.04; $P<0.001$). There was no difference in the AUC of the serum sodium concentration under Empagliflozin compared to Placebo (Difference of AUC 0.2, CI -7.38; 6.98, $P=0.96$).
Conclusion
In healthy volunteers with artificially induced SIADH, empagliflozin increased volume excretion due to osmotic diuresis. Most probably due to the short treatment duration serum sodium levels remained unchanged. Additional studies in real live setting are needed to further examine the possible role of empagliflozin as a new treatment option for SIADH.

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EP890

Metformin increases pressure pain threshold in lean PCOS women

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Background
Despite the strong preclinical rationale, there are only very few data considered the utility of metformin, as a potential pain therapeutic in humans. The aim of this study was to determine, the association between metformin therapy and pressure pain threshold (PPT) in lean polycystic ovary syndrome (PCOS) women. We hypothesized that metformin therapy in lean PCOS women increases pressure pain threshold.
Materials and methods
Twenty-seven lean PCOS women with free androgen index (FAI) phenotype $>$ 5 and 18 lean healthy controls were enrolled to the study. Fifteen of PCOS women were randomly assigned to be treated with metformin 1500 mg daily for 6 months. PPT and plasma β-endorphins levels were measured in all women at the beginning of the study and after 6 months observation.
Results
We observed increase in pressure pain threshold values measured on deltoid and trapezius muscle in PCOS with metformin group after 6 months metformin administration, (4.81 ± 0.88 kg/cm^2, $P<0.001$ on deltoid muscle and 5.71 ± 1.16 kg/cm^2 on trapezius muscle). We did not observe any significant changes in PPT values in PCOS without treatment group and controls. We did not observe any significant changes in serum β- endorphin levels in any studied groups during 6 months observation.
Conclusion
We conclude that metformin therapy increases pressure pain threshold in PCOS lean women, without affecting β- endorphin plasma concentration. Our results may suggest the potential role of metformin in pain therapy. We propose that larger, randomized studies, on metformin impact on pain perception should be performed.

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EP891

Clinical features and natural history of clinically non-functioning pituitary incidentalomas

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Objetive
To assess the clinical features of incidental clinically non-functioning pituitary adenoma (NFPA) and to analyze its natural history.
Methods
A multicenter retrospective study in patients with NFPA followed-up from 1992 to 2015 was performed.
Results
Fifty-seven patients were studied (29 women (50.9%); age 55.8 ± 16.7 years. 43.9% were older than 60 years, 40.3% belonged to the age group of 40–60 years and 15.8% were younger than 40 years. Most patients ($n=55$, 96.5%) were diagnosed by magnetic resonance imaging (MRI). 71.9% ($n=41$) were macroadenomas; 2 of them (3.5%) were giant adenomas ($\geqq$4 cm). Patients with macroadenomas were older than those with microadenomas (59.5 ± 16.7 vs 46.4 ± 18.1 years, $P=0.007$). Microadenomas were more common in women (41.3 vs 14.3%, $P=0.023$). About half of them ($n=28$; 49.1%) showed suprasellar extension; of these, 19 (33.3%) were accompanied by chiasmatic compression. Invasion of the cavernous sinuses was present in 28.1% ($n=16$). Hypopituitarism was present in 14 (24.6%) patients. Twenty-four patients (42.1%) underwent surgery. Twenty-six non-operated patients were evaluated after a median follow-up of 15.5 months (interquartile range, 5.7–32.7). No significant changes were found in the maximum tumor diameter at the end of follow-up (1.2 ± 0.6 vs 1.2 ± 0.7 cm; NS). The majority of NFPAs evaluated ($n=23$, 88.5%) did not show any changes in size. In two cases (7.7%) tumor size decreased and in one patient (3.8%) increased.
Conclusion
Incidental NFPA is diagnosed by MRI preferably from the 5th decade of life without sex predilection. Most of them are macroadenomas, more commonly diagnosed in men and at an older age, compared to microadenomas. The suprasellar extension with chiasmatic compression and hypopituitarism are frequent at diagnosis. Most of the non-operated NFPAs remain with stable tumor size over time, being growth an unusual event.

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EP892

Pituitary stalk lesions - experience of single center

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Introduction
Lesions of the pituitary stalk (PSL) are a challenging diagnostic problem for clinicians. Because of the critical location and role of the pituitary stalk, mass lesions in this area are not often biopsied, and the diagnosis may be based on clinical evaluation and imaging. Due to biopsy risk, about 40% PSL diagnosis are 'probable' or 'unknown'.The main clinical symptoms of PSL are visual field defect, DI and hypopituitarism.
Aim
To evaluate etiology, clinical manifestations and MRI in patients (pts) with PSL who were seen at our department over 10 years.
Patients
We selected 20 pts (11 females) with abnormal pituitary stalk visualized on MRI. The mean age at diagnosis was 38.3 years $\pm$10.2 (range, 8–67 years).
Results
Neoplastic lesions were diagnosed in 7 pts (35%): germinoma, pituicytoma, craniopharyngeoma, non-Langerhans hystiocytosis, pituitary adenoma, Rathke cyst and simple cyst one each. Distant metastatic tumors in pituitary stalk were confirmed in 3 pts (15%). Inflammatory lesion were noticed in 4 pts (20%): 2 lymphocytic infundibuloneurohypophysitis and 2 tuberculosis. Congenital anomalies were noticed in 2 pts (10%). Four patients (20%) with PSL were of unclear etiology. Tissue biopsy samples from the pituitary stalk itself were

obtained in eight patients. Six pts have suffered from diabetes insipidus. Growth hormone deficiency was the most common hormone deficiency (15 pts, 75%), followed by secondary hypogonadism in 12 pts (60%) and ACTH and TSH deficiency in 8 pts (40%) each. Complete hypopituitarism was noticed in 8 pts (40%). Nine pts had visual field defect.
Conclusion
The risks associated with obtaining histological samples from the pituitary stalk, even in the group presented, the diagnosis was frequently based on other clinical findings and serial MR imaging. For the most challenging pituitary stalk lesions, an individualized approach, guided by clinical expertise, remains the best strategy.

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EP893

First pediatric case of successfully treated Cushing's disease in Armenia

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Introduction
Cushing's disease (CD) is the most common albeit rare in paediatric and adolescent population form of ACTH-dependent Cushing's syndrome, with potentially serious morbidity. Thus, it presents diagnostic and therapeutic challenges for the clinician. Early diagnosis and treatment of Cushing's disease is vital for long-term outcome. Paediatric pituitary-dependent Cushing's disease, caused by an ACTH-secreting corticotroph adenoma, accounts for 75–80% of Cushing's syndrome and is almost always caused by a pituitary microadenoma.
Case report
14 yo girl presented to endocrine clinic with severe headaches, increased blood pressure (BP) up to 140/100 mmHg, wide reddish-purple abdominal striae, amenorrhea and weight gain up to 20 kg during last year. She was unsuccessfully managed by a gynecologist with oral contraceptives for 8 months. In endocrine clinic patient was examined according to Endocrine Society guidelines with subsequent diagnosis of Cushing's disease due to ACTH-secreting pituitary microadenoma (corticotropinoma). Patient underwent surgical removal of adenoma with gamma knife (GKS) resulting in reversal of symptoms.
Conclusions and follow up
Endocrine parameter normalization after GKS included normal 24-hour urinary free cortisol (UFC) concentration and normal levels of pituitary and peripheric hormones 4 months. However, posttreatment secondary hypothyroidism was diagnosed with TSH of 2.2 IU/ml (0.5–4.0) and FT_4 of 12.1 pmol/l (12.0–22.0). BP was stable at 110/70 mmHg. Regular menstrual function resumed 6 months after the surgery, and weight loss of 10 kg was documented 10 months after the surgery. Adenoma size decreased from 0.6 to 0.2 cm in 7 months by MRI. Current medications comprised of Levothyroxin 75 mcg only. This is the first case of successful treatment of paediatric Cushing's disease in Armenia. Although transsphenoidal neurosurgery is the gold standard therapy of pituitary Cushing's disease, GKS seems to be safe and effective way of treatment, however, long-term follow-up is necessary.

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EP894

SCTR/AT1aR heteromer related osmoregulation in hypothalamus

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Emerging studies suggest that GPCR oligomerization could confer functional advantages to receptors and even constitute clinical applications. Recent study found that angiotensin II 1a receptors (AT1aR) and secretin receptors (SCTR) can form heteromer and participate in osmoregulation. Studying GPCR dimerization faces many technical challenges, including selectivity and specificity. Since transmembrane (TM) peptides can act as competitors against the interacting surfaces between two receptors and therefore, it is utilized in this study as a unique tool to illustrate the specific functions performed by SCTR/AT1aR heteromer. STM-II and ATM-4 are discovered as the interacting surfaces of SCTR/AT1aR heteromer, in which STM-II can only disrupt heteromer formation, while ATM-4 can inhibit both receptor homomer formation. Previous study shows that hyperosmolality-induced water drinking behaviour in mice is greatly suppressed after intracerebroventricular (i.c.v.) injection of STM-II and ATM-4 upon hyperosmotic shock, suggesting that this heteromer has an essential role in mediating water drinking behaviour on hyperosmotic stress. However, *in vivo* role of SCTR/AT1aR in central osmoregulatory centre is yet to be elucidated. Vasopressin (Vp) is one of the key components to access osmoregulation because of the physiological link between Vp release and drinking behaviour, meanwhile, ANGII and SCT are potent in stimulating Vp release, hence it is a spate of interest to understand whether SCTR/AT1aR heteromer regulate osmoregulation via Vp release pathway. In this study, we demonstrated that SCTR/AT1aR heteromer is involved in the regulation of Vp release and expression, as well as the central neural involvement in PVN. Upon SCT/ANGII-stimulation, plasma Vp release was largely reduced (47.64% decrease) and Vp expression in PVN is significantly dropped (64.08% decrease) 15 mins after i.c.v injection of STM-II or ATM-4. This finding supports the hypothesis of SCTR/AT1aR in mediating water balance, and also provides concrete basis in demonstrating the *in vivo* role of a GPCR heteromer.

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EP895

The hyponatremia in neurosurgical patients

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Background
Hyponatremia is a relatively frequent and serious complication developed in patients with different neurosurgical pathology. The aim of the study was to identify the frequency of occurrence of hyponatremia in neurosurgical patients.
Materials and methods
A retrospective analysis included 39479 patients operated in the Institute of Neurosurgery from January 2008 to December 2014.
Results
785 patients (2% of all operated patients): 554 adults and 231 children had hyponatremia with Na level less than 130 mmol/l. In 63% of cases (497 patients) we observed a moderate decrease of Na (125 to 130 mmol/l), in 11% of cases (88 patients) the level of Na was less than 120 mmol/l. The mortality rate in patients with hyponatremia was 14.3%, what is 10 times faster than that of the rest of patients without hyponatremia operated during these years. In adults most often hyponatremia developed either after surgical removal of craniopharyngiomas (11%) or as a result of an acute stroke (22%). In children - after surgery of craniopharyngiomas (10%), astrocytomas (7%), ependymomas (24%) and germ cell tumors (10.5%).

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EP896

Bilateral inferior petrosal sinus sampling and the outcome of transsphenoidal surgery in patients with Cushing's disease: experience of a Tertiary Portuguese Hospital

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Introduction
Bilateral inferior petrosal sinus sampling (BIPSS) is the gold-standard for the differential diagnosis of ACTH-dependent Cushing Syndrome when the pituitary adenoma on MRI is doubtful or absent. This study aimed to analyze whether BIPSS can influence the outcome in patients with Cushing disease (CD).
Methods
Retrospective, descriptive study. Forty-two patients with CD submitted to transsphenoidal surgery (TS) between 2005 and 2016 were divided into two groups based on the performance of BIPSS. Different variables were analyzed: year of diagnosis, preoperative laboratory tests and pituitary MRI, immediate postoperative laboratory tests, histological findings, postoperative hypopituitarism, presence of permanent diabetes insipidus, follow-up duration and final outcome.

Results
Ten out of forty-two patients with CD were submitted to BIPSS.

	BIPSS	No BIPSS	*p*-value
Diagnosis Year (%): 1995–2000 / 2001–2010 / >2010	0/70/30	9/47/44	0.355
Preoperative sellar MRI (%): Microadenoma / Macroadenoma / Indeterminate Lesion / No Image	20/0/30/50	66/16/0/6	<0.01
Preoperative Laboratory Tests (%): Classical / Non-Classical	100/0	59/13	0.159
Immediate Postoperative Laboratory Tests (%): Criteria for Cure / No Criteria for Cure	40/40	41/41	1
Histology (%): Adenoma / Corticotroph Hyperplasia / Normal tissue	60/10/30	78/3/9	0.462
Postoperative anterior pituitary deficiency (%): Isolated / Multiple / None	20/20/20	28/25/44	0.713
Permanent Diabetes Insipidus (%): Yes / No	0/100	6/94	0.418
Mean Follow-Up (years)	5.7±3.8 (0–11)	6.8±5.1 (1–21)	0.544
Final Outcome (%): Remission / Active Disease	70/30	47/50	0.386

Note: In some parameters the sum of the partial percentages is not 100% because some patients didn't have that information.

Discussion
Groups were different in terms of the preoperative imaging. For the other variables, no differences were observed. The final outcome, despite the higher number of macroadenomas in the group without BIPSS was not statistically different. Results await further confirmation.

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EP897

The prevalence of colorectal cancer and colon polyps in acromegaly: thirty years' experience of a tertiary referral center

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Introduction
Several studies suggest a higher risk of colorectal cancer (CRC) and colon polyps (CP) in acromegaly, however there is still controversy regarding associated factors (AF) able to contribute for its development. Data on the prevalence of CRC and CP in Portuguese patients with acromegaly are limited.
Objectives
To assess the prevalence of CRC and CP in acromegalic patients and compare to the normal Portuguese population. To determine the relevance of a number of AF (growth hormone, insulin-like growth factor-1, body mass index and age at diagnosis, gender, diagnostic delay and disease duration) for its development.
Methods
Retrospective study of 101 acromegalic patients assisted in a tertiary center from 1985 to 2016, who underwent at least one colonoscopy. Comparative analysis with data from screening studies conducted in the normal Portuguese population. Statistical analysis was performed with SPSS software, version 20. Statistical significance: $P < 0.05$.
Results
Of the 101 patients (female: 62.4%; mean age at diagnosis: 49.5±12.8 years), 47.5% presented abnormal colonoscopy with CP, which were more frequent in the left colon. Histological analysis identified hyperplastic polyps (HP) in 29.7% of the patients, adenomas in 16.8% and CRC in 5%. In total, 27 adenomas and 69 HP were detected. The prevalence of CRC, CP and adenoma found in this study compared to normal population was: 5 vs 1% ($P=0.001$); 47.5 vs 32.6% ($P=0.003$) and 16.8 vs 38% ($P=0.001$), respectively. Concerning AF, there was no differences between patients with abnormal and normal colonoscopy.
Conclusions
The prevalence of CRC and CP was significantly higher in patients with acromegaly. On the contrary, adenoma was significantly less prevalent. No association between any of the factors studied and the phenotype CRC/CP was observed. To our knowledge, this is one of the largest Portuguese series, nevertheless results have yet to be validated.

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EP898

Acromegaly and malignant neoplasms

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Introduction
Acromegaly is a rare disease resulting from pathological oversecretion of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). The clinical spectrum includes cardiovascular and respiratory diseases but also increased risk of benign and malignant neoplasms.
Objectives
Evaluate the prevalence of cancer and seek for associated factors in acromegaly.
Methods
Retrospective study of 94 patients with acromegaly treated in a single tertiary center from 1985 to 2016. The group with malignant neoplasms was compared with the group without malignancy. Statistical analysis was performed with SPSS software, version 20. Statistical significance: $P < 0.05$.
Results
63.8% of the patients were female and the mean age at diagnosis was 48.7±12.9 years. Median GH and mean IGF-1 at diagnosis was 9.8 ng/ml (range: 0.61–228) and 857.4±412.7 ng/ml, respectively. Median diagnostic delay of acromegaly was 7 years (range: 1–36). Cancer was present in 13 (13.8%) of the 94 patients. Colon cancer was diagnosed in five patients (5.3%), breast cancer and renal cell carcinoma each in 3 (3.2%), follicular thyroid cancer, melanoma and endometrial carcinoma each in 1 (1.1%). In three cases, cancer was found before acromegaly (breast cancer in 2 and colon cancer in 1). One patient had two malignancies (thyroid and renal cell carcinoma). The diagnostic delay of acromegaly was higher in the group with malignant neoplasm ($P=0.004$). There was no statistically significant difference between the two groups relative to GH, IGF-1, age and body mass index at diagnosis and gender.
Conclusions
Colon cancer was the most prevalent, followed by breast and renal carcinoma. In the group with malignant neoplasms, diagnostic delay was significantly higher, suggesting that prolonged exposure to high GH and IGF-1 levels can be related to cancer development. Search for cancer should be a major task in the follow-up of these patients.

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EP899

Endogenous Cushing's syndrome (clinical and biochemical features in a large cohort of patients

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Patients and methods
We retrospectively analysed the clinical and biochemical characteristics of a cohort of 150 patients with endogenous Cushing's syndrome (CS). Cushing's

disease (CD) accounted for 61.3% of cases ($n=92$), ectopic ACTH secretion (EAS) 7.3% ($n=11$), and adrenal diseases 31.3% ($n=47$). Among CD cases, there were 19 macroadenomas (20.6%), a female predominance (60.5%) and a median age of 33 years old (range 14–55). Bronchial carcinoid was the most frequent cause of EAS ($n=7$). When biochemical and clinical features were compared in cases of CD and EAS, the only significant difference was the higher frequency of hypocalemia in EAS (80% vs. 15%; $P<0.001$). Concerning screening tests, the sensitivities of overnight 1 mg-DST (cut-off, 1.8 μg/dl (50 mmol/l)), UFC and late night salivary cortisol (LNSC) were 94%, 90% and 96%, respectively. The combination of two of these tests yielded a sensitivity of 98% ACTH levels were normal (42%) or elevated (58%) among patients with CD; they were above the normal range in all EAS cases and <10 pg/ml in all patients with adrenal disorders. Regarding dynamic tests, HDDST had a mean sensitivity and specificity of 79/55 and 70/100%, respectively, using the supression cut-offs of >50% and >80%, respectively. The diagnostic accuracy of CRH test and desmopressin test did not significantly differ ($P=0.28$) in the distinction between CD and EAS. The combination of HDDST and CRH or desmopressin tests was more accurate than each test alone. The overall diagnostic accuracy of BIPPS was 94%. Pituitary MRI depicted all macroadenomas and 64% of microadenomas. CT scan and/or MRI detected 90% of bronchial carcinoid, as well as all thymic carcinoid.

Conclusion

CD and EAS cannot be accurately be distinguished based only on clinical and biochemical features. LNSC was the most sensitive screening test for CS.

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EP900

Hyponatremia predating the diagnosis of malignancy in oncological/hematological patients with SIADH

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Introduction

Euvolemic hyponatremia (HN) caused by the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) can predate a diagnosis of malignancy. It is thus essential to accurately diagnose the etiology of HN/SIADH when detected.

Methods

Retrospective, descriptive study of all 52 oncological/hematological malignancy patients diagnosed with SIADH in our Department between January 2011 and December 2016. HN was detected via computerized Primary-care/hospital case histories, and the computerized laboratory data base. Hyponatremia was considered to predate detection of malignancy/initiation of diagnostic study when a serum sodium (SNa) <135 mmol/l was detected 6 months before definitive oncological/hematological diagnosis (PTD). A patient was considered probably euvolemic (PE) when SNa descent was accompanied by a predominant pattern of lowering serum urea, creatinine and Uric acid levels, probably hypovolemic (PH) if urea, creatinine and Uric acid levels rose while not hypervolemic. SNa in mmol/l.

Results

Males: 32/52(61.5%), mean age:63.4 (s.d.:11)years. Etiology of SIADH: lung cancer: 18/52(34.6%), gastrointestinal: 6/52 (23.1%), genitourinary: 11/52 (21%), hematological: 5/52 (9.6%). 11/52 (21%) patients presented HN$>$ 6 months PTD: median 40 (24–60), median age: 67 (63–76) years, initial SNa: 133 (130–134). Three patients were PH. Eight were PE, one receiving enalapril, another carbamazepine, another thiazide. In 5/8 (62%) PE patients, case histories revealed no initial cause for HN. HN was present a median of 25 (19–40.5) months PTD, range: 14–41. Initial SNa: 133 (129.5–133). None presented a low Urine Density. Hyponatremia was persistent, present in 42/50 (84%) tests, with a continuum up to ectopic-SIADH diagnosis, suggesting that SIADH induced their sustained hyponatremia. Etiology: lung (epidermoid), endometrial, breast, gastric, prostate. In only 1/11 (9%) patients was hyponatremia studied PTD, with SIADH workup responsible for prostate tumor diagnosis.

Conclusion

Mild hyponatremia can predate the diagnosis of a malignancy. However, in our series of 11/52 patients, in only one was hyponatremia studied. The lack of importance given to the finding of frank hyponatremia, albeit mild, could delay tumor diagnosis.

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EP901

Hyperprolactinemia as a manifestation of hormonally inactive pituitary adenoma

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Aim

The work was initiated to study prolactin levels in hormonally inactive pituitary adenoma by the size of the tumor.

Material and methods

We examined 85 patients with hormonally inactive pituitary adenomas, 45 women and 40 men among them aged from 18 to 50 years (mean age 44.5 ± 3.85 years). The disease duration from the onset to diagnosis based on the medical history and MRI ranged from 1 to 15 years.

Results and discussion

Guided by the aim of study we divided the patients into three groups. 26 patients with the tumor size up to 10 mm were included into the first group. Thirty-three patients with the tumor size up to 20 mm comprised the second group. Twenty-six patients with the tumor size 30 and more mm were included into the third group. Analysis of hormonal parameters demonstrated correlation between prolactin level and the tumor size. Hyperprolactinemia was registered in 2, 45 and 100% of patients in the first group, second and third groups, respectively. In patients with macroadenomas hyperprolactinemia was clinically presented in combination with hypopituitarism. Among patients of the third group, chiasmal and cephalgic syndromes, the latter with the oculomotor nerve damage, were the main symptoms; lactorrhea-amenorrhea syndrome came the third.

Conclusions

Quite frequent sign of hormonally inactive adenoma, hyperprolactinemia upon formations in chiasmal-sellar area not always can be an outcome of prolactin-secreting adenomas; the fact is to be taken into account in choosing the treatment tactics.

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EP902

Abstract withdrawn.

EP903

Abstract withdrawn.

EP904

Study of CHD7 gene in KAL 1-negative patients previously diagnosed with congenital hypogonadotropic hypogonadism that develop new pituitary deficiencies

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Introduction
Recent studies suggest that some patients initially diagnosed with congenital hypogonadotropic hypogonadism (CHH), may evolve towards a combined pituitary hormonal deficiency (CPHD). Heterozygous pathogenic CHD7 variants impair neural cell crest guidance causing CHARGE syndrome and have been associated with abnormal pituitary development/function/structure and isolated CHARGE features, including HH. We aimed to genotype CHD7 and phenotype thoroughly those adult patients previously diagnosed with CHH that developed new pituitary deficiencies during the follow-up.
Patients
From 20 unrelated KAL 1-negative patients with a past CHH diagnosis followed in our adult endocrinology clinic during an average of 21.2 years (13–37), we selected those with new pituitary deficiencies – 7/20, all males, mean age 37.2 years (29–53) – and studied CHD7 using a targeted NGS panel (HYPOPIT.V1). Markedly low IGF-1 levels were detected in 6/7 (85%) and of TSH in 4/7 (57.4%).
Results
2/7 patients (28.6%) harboured heterozygous CHD7 rare variants. The variant of unknown significance NM_017780:exon31:c.G6255T:p.L2085F that suggests pathogenicity but lacks functional sudy, was found in a 53-year-old male, that has a left temporal arachnoid cyst, a pars intermedia cyst, low IGF-1 levels, a pigmentary glaucoma treated with iridotomy, aortic elongation and a "Sertoli-cell-only syndrome" diagnosis based on testicular biopsy performed at 38 years. Another 37-year-old-male, that was hormonally and surgically treated for bilateral cryptorchidism during childhood, and currently shows a partial empty sella, absence of neurohypophysis and low TSH and IGF-1 levels, had the rare pathogenic heterozygous variant NM_017780.3:c.8416C>G:p.Leu2806Val, involved in CHARGE, isolated HH, and in a few CPHD cases with atypical CHARGE features. Curiously both fathers of these two patients died before 65 years of age due to lung diseases (the first being cancer).
Conclusions
Our results suggest that CHD7 should be included in the genetic study of CHH patients, especially in those that develop new pituitary deficiencies over time.

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EP905

MR-characteristics as predictors of pituitary adenomas hormonal and proliferal activity

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Introduction
Previous studies demonstrated a relationship between T1- and T2-weighted signal intensity and tumor growth pattern in pituitary somatotropinomas. The goal of this retrospective study was to analyze the MRI characteristics of pituitary macroadenomas with different hormonal activity in newly diagnosed patients.
Material and methods
Pre-treatment T1- and T2-weighted MR-images (Intera Achieva, PHILIPS, 3.0T) of patients with 42 non-functional adenomas (NFA), 18 macroprolactinomas, 55 somatotropinomas were analyzed, taking into account the intensity of the signals produced by the tumors, as well as their dimensions and growth direction. The results were expressed as M? (25%; 75%).
Results
In NFA group, majority of patients (30/42, 71%) had isointensive T1-signal in the most common combinations with hyperintensive or isointensive T2 (18/42, 42.9 and 9/42, 21.4%, accordingly). NFA's volumes did not differ between these subgroups. In prolactinoma group 15/18 (83.3%) patients showed hyperintense T2 in the most common combination with isointensive T1 (7/18, 38.9%) and hypointensive T1 (6/18, 33.3%). IsoT1/hyperT2 prolactinomas had bigger volume compared to hypoT1/hyperT2 ones. In somatotropinoma group 43/55 (78.2%) patients had hypointensive T1 in combinations with hypo-, iso- or hyperintensive T2 (22/55, 40%; 12/55, 21.8%; 9/55, 16.4%, respectively). HypoT1/hypoT2 tumors had the smallest volume.
Conclusion
In all type of pituitary tumors hypointensive MR-signal (either T1 or T2) was associated with infrasellar tumor expansion and smaller tumor volume. In contrast, hyperintesive T2 was associated with suprasellar tumor expansion and bigger tumor volume. IsoT1/isoT2 tumors were found only in NFA group; hypoT1/hypoT2 tumors were observed only in somatotropinomas so further investigations should be carried on to prove the diagnostic value of these results. Accurate determination of T1/T2 signal intensity can be used as additional predictors of hormonal and proliferative activity of pituitary tumors.

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EP906

Cholinergic modulation of the hypothalamic-pituitary-adrenal activity and somatotroph function in smokers and non-smokers

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Introduction and objectives
The inhalation of tobacco smoke leads to an acute increase in cortisol, ACTH and GH concentration, both in chronic smokers as in non-smokers. However, most studies have failed to demonstrate differences between both groups in basal levels of these hormones in plasma or urine. Additionally, cholinergic pathways have been shown to play an inhibitory role in ACTH secretion in non-smokers. UFC and circulating levels of cortisol, ACTH and GH were evaluated basally and after pyridostigmine in smokers and non-smokers.
Subjects and methods
We studied UFC (urinary free cortisol) on 24 h urine samples and the effects of administration of placebo and pyridostigmine on ACTH, cortisol and GH secretion in 10 young males: five smokers and five non-smokers. In each test, placebo or pyridostigmine (120 mg) were given orally in random order on different days at 0830. Blood samples were drawn at 0830, 0900 and then every 15 min until 1130. Area under the curve was calculated. Data are expressed as mean ± SEM.
Results
Basal levels of UFC, plasma ACTH, and serum GH were not different between smokers and non-smokers. In contrast, basal serum cortisol was higher in smokers at 1015 (15.42 ± 1.38 vs 10.29 ± 1.40 mcg/dl) and 1045 (12.96 ± 1.14 vs 8.89 ± 1.19 mcg/dl). PD raised GH secretion within each group, while it decreased cortisol at 1015 (15.42 ± 1.38 vs 13.20 ± 1.50 mcg/dl) in smokers and ACTH at 1115 (16.87 ± 1.54 vs 12.49 ± 1.65 pg/ml) in non-smokers.
Conclusions
Chronic smoking is associated with increased basal serum cortisol and normal UFC, while it is related to a decrease in serum cortisol after pyridostigmine. Besides, an inhibitory effect of cholinergic stimulation on ACTH is confirmed in non-smokers.

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EP907

Diagnosis, treatment and follow-up of non-functioning pituitary adenomas

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Introduction
Non-functioning pituitary adenomas (NFPAs) represent the most common pituitary tumour. They usually appear in the middle age of life, without differences between genders. Mass growth produces the first symptoms so the diagnosis is usually late. Surgery is the first-line treatment with variable success

(19-83%). The objective of this study is to evaluate the symptoms, diagnosis, treatment and final state of patients with NFPAs.
Methods
Observational retrospective study of patients with NFPAs evaluated between January 2002 and December 2015 at "Hospital Universitario Reina Sofía" in Córdoba. Results were analysed with SPSS 18.0.
Results
34 patients, 50% women. Mean age: 56.2 ± 11.9 years old. Mean follow-up: 5.2 ± 3.9 years (range: 1-14 years). Symptomatology: 38.2% campimetric alterations, 35.3% headache and 11.8% symptoms derived from hormonal deficits. 29.4% incidental diagnosis in magnetic resonance imaging. Mean diameter of tumour: 30.2 ± 11.4 mm. 64.7% extrasellar growth, 55.9% chiasmal compression, 23.5% grade I of Knosp classification. Initial treatment: 91.2% transsphenoidal surgery (8.8% cabergoline). 64.7% post-surgery complications. Anatomopathological diagnosis: pituitary adenoma, except 1 patient with tissue necrosis; 11.8% patients had p53 positive; mean Ki-67: 2 ± 2.4%. Only 5 patients were cured after the first surgery (2 patients had recurrence) and 29 had radiological persistence of disease. Adjuvant treatment: cabergoline (10 patients), radiotherapy (11 patients), radiosurgery (2 patients), second surgery (10 patients) and third surgery (2 patients). Finally, 26.5% of patients are cured and 73.5% have persistent disease. Hormonal deficits: 44.1% pre-surgery and 79.4% post-surgery. Campimetry improved in all patients.
Conclusions
i) There are not differences in the prevalence of NFPAs by gender in our series. ii) The diagnosis was motivated by the symptomatology (predominantly visual); less frequent incidental diagnosis. iii) Most patients underwent transsphenoidal surgery, being the success of this first surgery in our series less than the published rates.

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EP908

Decreased prolactin levels in plasma and cerebrospinal fluid in naïve to treatment patients with multiple sclerosis

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Background
Data from the literature has documented a remarkable immune-modulating role of prolactin. Previous evaluations of prolactin levels in patients with multiple sclerosis (MS), disease of autoimmune origin, showed conflicting results. Thus, to clarify the impact of prolactin on MS pathology we decided to assess prolactin levels in plasma and cerebrospinal fluid in naïve to treatment subjects with newly diagnosed MS.
Material and methods
A total number of 83 individuals were included: 41 patients with MS (30 females/11 males) and 42 age-matched controls (36 females/6 males). All MS subjects were newly diagnosed and they were without any treatment at the time of taking the samples of blood and cerebrospinal fluid. Prolactin was determined both in plasma and cerebrospinal fluid, and cytokines (TNF-alpha, IL-6, IL-10) were evaluated in plasma in all subjects.
Results
Prolactin levels in plasma were found to be markedly lower in MS patient when compared to those of the controls (7.64 ± 5.99 ng/ml vs 10.12 ± 6.76 ng/ml; $P < 0.05$). These results correspond with concentration of prolactin measured in cerebrospinal fluid as in MS individuals prolactin was significantly decreased (2.84 ± 0.35 ng/ml vs 3.42 ± 0.89 ng/ml; $P < 0.05$). The comparison of cytokines levels revealed no differences between the examined groups. A positive correlation between prolactin concentration in plasma and TNF-alpha levels was found in MS subjects.
Conclusion
Decreased levels of prolactin may reflect disturbed pituitary activity as well as disrupt immunological system regulation at the early stage of multiple sclerosis.
Acknowledgment
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EP909

Cholinergic modulation of the hypothalamic–pituitary–adrenal activity and somatotroph function in DM-1

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Introductions
Alterations of the somatotrophic and hypothalamic–pituitary–adrenal (HPA) axes occur frequently in patients with poorly controlled DM-1. These disorders could be related to abnormalities in the cholinergic tone regulating both hormonal axes.
Subjects and Methods
UFC (urinary free cortisol) on 24 h urine samples and the effects of placebo and pyridostigmine on ACTH, cortisol, GH and glucose circulating levels were studied in 16 young males: 10 normal controls and 6 patients with poorly controlled DM-1 (HbA1c 9.2%) without retinopathy or nephropathy. Placebo or pyridostigmine (120 mg) were given orally on different days at 0830. Blood samples were drawn at 0830, 0900 and then every 15 min until 1130. Area under the curve (AUC) was calculated for the full sampling period and for 1 hour intervals. Data are expressed as mean ± SEM.
Results
UFC (47.21 ± 7.29 vs 33.70 ± 2.63 mcg/24 h, $P < 0.05$), and GH and glucose levels were higher in diabetics than in controls, whereas ACTH and cortisol levels were not different. Pyridostigmine did not alter ACTH nor cortisol levels, while it raised GH secretion within each group, with the greatest increase in diabetics (AUC 0–60 min: 149.46 ± 82.34 vs 23.68 ± 12.01 ng/ml/60 min, $P < 0.05$). UFC was negatively correlated with HbA1c. Basally, GH did not correlate with ACTH nor cortisol levels.
Conclusions
The higher UFC figures in diabetics suggest some degree of hypercortisolism in poorly controlled DM-1. Cholinergic activation in diabetics elicits GH hyperresponse, but does not modify cortisol nor ACTH levels, either in diabetics or controls. This fact speaks against an altered common mechanism in the cholinergic system regulating somatotrophic and HPA axes in DM-1, suggesting that cholinergic tone is not involved in the raised UFC excretion seen in these patients.

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EP910

Increased GH response to GHRH plus pyridostigmine unrelated to augmented glomerular filtration rate in DM-1

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Introduction and Objectives
In patients with poorly controlled DM-1, the frequently observed alterations of somatotrophic axis seem to be related to abnormalities in the hypothalamic cholinergic tone regulating this axis. The effects of cholinergic stimulation on GH responses to GHRH were evaluated in patients with poorly controlled DM-1 and the relationship of these responses to metabolic control and kidney function tests.
Subjects and Methods
Microalbuminuria and creatinine clearance (GFR) on 24 h urine samples, and the effects of GHRH plus placebo and plus pyridostigmine on GH and glucose circulating levels were studied in 16 young males: 10 normal controls and 6 patients with poorly controlled DM-1 (HbA1c 9.2%) without retinopathy or nephropathy. On different days, placebo or pyridostigmine (120 mg) were given orally at 0830 and GHRH 50 mcg IV at 0930. Blood samples were drawn at 0830, 0900 and then every 15 min until 1130. Response parameters were calculated. Data are expressed as mean ± SEM.
Results
GHRH raised GH levels within each group. However, while GH responses were not different between diabetics and controls after GHRH plus placebo, they were actually higher after GHRH plus pyridostigmine in diabetics (AUC of response of GH: 4085.83 ± 1227.86 vs 1914.46 ± 385.06 ng/ml/120 min, $P < 0.05$). GFR was greater in diabetics, although not significant (134.85 ± 20.62 vs 110.12 ± 8.13 ml/min). GH was not correlated with glucose in any of the tests. Furthermore, HbA1c, microalbuminuria and GFR showed no correlation with GH in diabetics.

Conclusions
In this study, the higher GH responses to GHRH plus pyridostigmine in diabetics suggest that there is an augmented cholinergic tone in poorly controlled DM-1 patients. Furthermore, these findings are not related with the higher GFR observed in diabetics.

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EP911

Increased morbidity associated with the treatment of craniopharyngioma

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Background
Craniopharyngioma is a rare epithelial tumor of the central nervous system, affecting both children and adults and associated with significant morbidity.
Objective
To study the posttreatment evolution of craniopharyngioma in children and adults in a large mixed cohort.
Material and Methods
We performed a retrospective review of craniopharyngioma patients evaluated in the National Institute of Endocrinology in Bucharest between 1990 and 2016.
Results
A total of 82 patients (59 adults, 39.27 ± 15.5 years old; 23 children, 12.96 ± 4.2 years old) with a mean follow-up of 6.85 years were included. All underwent surgery (57 cases, 69.5% transcranial, 25 cases, 30.48% transsphenoidal approach,), 34 being operated on more than once. 13 patients (15.85%) were irradiated (1 before surgery, the others after). The surgical excision was complete in 26 cases (31.7%). Surgery led to anosmia (in 7 cases), CSF leak (3 cases), subdural hematoma (2 cases). After surgery 21 cases (25.6%) had cognitive impairment, 5 (6.09%) had hypothalamic syndrome (diurnal sleepiness, appetite and memory dysfunction). The endocrine dysfunction was aggravated after treatment in 64 cases (78%), improved in 5 (6%) and stable in 14 cases (17%). The evolution of the tumor revealed stable remnant in 29 cases (35.3%), progressively increasing remnant in 23 (28%), recurrence in 2 (3.4%) and cure in 28 cases (34.14%) during follow-up. There was no significant difference in the complications rate between children and adults.
Conclusions
Craniopharyngioma is a tumor frequently necessitating repeated treatments, associated with very significant morbidity. The results and complications of treatment are similar in adults and children.

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EP912

The PATRO adults study of Omnitrope for the treatment of adult patients with growth hormone deficiency: latest results

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Introduction
The ongoing, international, open, longitudinal, non-interventional study, PATRO Adults, aims to determine the long-term safety and efficacy of Omnitrope® (Sandoz), a recombinant human growth hormone (rhGH). Safety data from an interim analysis are presented here.
Methods
Eligible patients are male or female adults who are receiving treatment with Omnitrope® and who have provided informed consent. Patients treated with another rhGH before starting Omnitrope® therapy are eligible for inclusion. The primary objective of the study is to assess the safety and efficacy of Omnitrope® in adults treated in routine clinical practice, with particular emphasis placed on the risk of glucose intolerance or diabetes and normalisation of IGF-I levels.
Results
As of December 2016, 1121 patients had been enrolled on the study, of whom 586 (52.3%) were pre-treated with another rhGH. Mean (standard deviation [SD]) patient age is 49.7 (15.3) years, and mean (SD) BMI is 29.4 (6.3) kg/m^2. In total 2455 adverse events (AEs) in 665 (59.3%) patients have been reported, with 444 (in 247 [22%] patients) of these regarded as serious. One hundred and thirty-nine AEs in 80 (7.1%) patients were suspected to be drug-related; these included general disorders/administration site conditions in 19 patients, nervous system disorders in 23 patients and musculoskeletal/connective tissue disorders in 24 patients. A total of 26 serious AEs in 17 (1.5%) patients were suspected to be related to Omnitrope® treatment, including one incidence of diabetes. Of the 188 patients who discontinued treatment, 47 (25%) did so due to an AE.
Conclusions
Based on this interim analysis, Omnitrope® treatment in adults with GHD is well tolerated in a real-life clinical practice setting, both in previously treated and rhGH-naïve patients. The ongoing PATRO Adults study will provide further data on the diabetogenic potential and overall safety of long-term GH treatment in this population.

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EP913

Clinical case description of family with hereditary pituitary adenoma

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Introduction
In recent years, more attention is driven to the cause of hereditary forms of pituitary adenomas. Although for most cases causal genes are not discovered yet, *AIP* mutations are the most prevalent.
Materials and Methods
Case descriptions, high-parallel sequencing using a gene panel (*MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHS, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2*).
Case description
Index case – a 59-year-old man with clinical features of acromegaly (the size of adenomas at baseline 3.9 × 3.2 × 3.9 cm, growth 165 cm), secondary diabetes mellitus, multinodular goiter, obesity I grade, arterial hypertension. First clinical symptoms were noted since the age of 30 years. At the age of 51 he underwent transcranial adenomectomy, then at the age of 58 years – transnasal adenomectomy. Because of persistent disease activity he was initiated medical therapy with sandostatin analogs (40 mg of octreotide depo) without hormonal control of acromegaly – IGF 497.5 ng/ml (15–250) and GH 80 ng/ml (0–1.2). MRI after surgery pituitary adenoma with supra-, infra- and parasellar extension. The patient's 28-year-old son also has acromegaly (intrasellar pituitary macroadenoma at MRI (the size of adenomas 0.7 × 1.2 × 0.6 cm), first clinical symptoms were noted since the age of 27 years, growth 167 cm, without complication); he was operated transnasally at the age of 28 years without postoperative remission: GH at OGTT 2.67-2.52-1.95-2.05-2.37 ng/ml, IGF 567.2 ng/ml (60–280). Genetic investigation revealed a mutation in exon 6 of the *AIP* gene pR271W (not previously described, possible pathological).
Conclusion
AIP mutation in our family with hereditary pituitary adenoma is associated with high aggressiveness and resistance to medical therapy with somatostatin analogs.

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EP914

Molecular and genetic basis of the disease in families with pituitary adenomas

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Introduction
Most of the work on the analysis of molecular genetic defects in pituitary adenomas devoted to the study of 1–2 candidate genes. The high-performance parallel sequencing is more promising.

Materials and Methods
There were a total of 26 families (58 patients, 36 (62.1%) men and 22 (37.9%) women) with pituitary adenomas secretion of various types. The number of families with homogenous type was 17 (somatotropinomas 13, prolactinomas 2, corticotropinomas 1, inactive pituitary adenomas 1), with a heterogeneous type – 9 (7 of theses families had somatotropinomas/inactive pituitary adenomas, 2 families had prolactinomas/inactive pituitary adenomas. The number of family members with hypertension ranged from 2 to 7.The high-performance parallel sequencing was implemented with the gene panel (*MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2*).
Genetic investigation
According to a study in four patients with somatotropinomasidentified mutations were *AIP* p.R271W and p.A411GfsX47, one patient was identified with polymorphisms with unproven value in pathological gene *SDHA* p.V589V, and one patient with the phenotype of McCune-Albright syndrome had heterozygous p.S163P replacement in *SDHB* gene.
Conclusion
The genetic changes using a multi-gene panel were identified in only 20% of tested families. New gene candidates are highly needed for familial pituitary adenomas.

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EP915

Pituitary adenoma with gigantism and TSH-induced hyperthyroidism: a case report

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Abstract
A 14-yr-old male patient with acromegaly and TSH-induced hyperthyroidism is reported. He was referred for hormonal study due to clinical suspicion of acromegaly. Physical examination showed acromegalic/gigantism features (high stature: 194.5 cm ($P > 90$), such as: abnormal growth of the hands and feet, furrowed forehead and pronounced brow ridge). No goiter was found. GH levels were high and were not suppressed after oral glucose (GH: 12.50 ng/ml, GH after glucose: 6.19 ng/ml; IGF-1: 1391 ng/ml); Serum thyroid hormones levels were high, although TSH levels were not suppressed (TSH: 0.96 mU/ml, T4: 3.57 ng/dl T3: 11.06 pg/ml). Antithyroglobin, antimicrosomal autoantibody, and TSH receptor antibody were negative. Gonadotropines, prolactine and ACTH leves were normal (Prolactina: 12.79 ng/dl, LH: 9.37, FSH: 4.56, Testosterona: 760.9 ng/dl, Cortisol: 5.9 mcgr/dl, ACTH: 15.1 pg/ml). A pituitary magnetic resonance imaging of the pituitary revealed a 7-mm adenoma. He was diagnosed of acromegaly and hyperthyroidism. Pre-operative treatmen with octreotide was iniciated and transsphenoidal surgery was performed to remove the pituitary adenoma. Post-operative serum thyroid hormone and GH levels returned to normal, and IGF-1 levels were still elevated (786 ng/ml). Immunohistochemical staining of the operative specimen showed positive reactions to both TSH and GH. Pituitary gigantism is a rare condition caused by growth hormone secreting pituitary tumor. Choromophobe adenoma producing either acromegaly and hyperthyroidism have been described in a limited number of cases none of them on an infant.

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EP916

Secretin protects from apoptosis by activation of ERK1/2 and CREB

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Abstract
There are a growing number of studies identifying secretin as a neuroprotective factor. Consistently, our previous data showed that neuronal apoptosis considerably increased in the developing cerebellum from secretin knockout (Sct-/-) mice. However, the underlying mechanisms remained poorly understood. Extracellular signal-regulated protein kinase (ERK) and AKT signalling pathways are known for the regulation of apoptosis. Additionally, these two pathways could activate cAMP-response-element-binding protein (CREB), which has been shown to promote cell survival. Therefore, their phosphorylation levels in the cerebellum were compared between Sct-/- and WT mice. The basal levels of phosphor-ERK1/2 (pERK1/2) and phosphor-CREB (pCREB) showed a significant decrease in Sct-/- mice, but not phosphor-AKT (pAKT). The cerebellar slices obtained from Sct-/- displayed a dose-dependent increase of pERK1/2 and pCREB, but not pAKT, in response to graded concentrations of secretin peptide and the impaired phosphorylation of ERK1/2 and CREB in Sct-/- cerebellar slices was able to be recovered by the treatment of secretin compared with WT, suggesting the involvement of ERK1/2 and CREB. Specific inhibitors were applied for further confirmation. Secretin failed to reduce the level of activated Caspase-3 when either ERK1/2 or CREB was inhibited, revealing that ERK1/2 and CREB was required for secretin's neuroprotective function. Our results clearly provide evidence that ERK1/2 and CREB play a role in mediating the anti-apoptotic function of secretin.

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EP917

Predictors of remission after transsphenoidal adenomectomy in patients with Cushing's disease

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Abstract
Cushing's disease (CD) is the heavy disease of the hypothalamic–pituitary–adrenal axis. The cause of the disease is pituitary adenoma (corticotropinoma). Hypersecretion of ACTH by a pituitary adenoma leads to increased secretion of cortisol by the adrenal cortex and the development of total endogenous hypercortisolism. The gold standard treatment for this disease is surgical removal of corticotropinoma. However, adenomectomy is not effective in all cases and approximately 20% of cases after the radical treatment fails to achieve remission of the disease and then comes the relapse. The aim of our work was to evaluate the factors influencing the result of adenomectomy in patients with the Cushing's disease and identification of recurrence predictors. Materials and methods: retrospective assessment of clinical and hormonal factors in 84 patients with CD, influencing early and long-term results of adenomectomy.

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EP918

Copeptin after arginine infusion for the differential diagnosis of the polyuria–polydipsia syndrome "The CARGO-Study"

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Background
The spectrum of polyuria-polydipsia syndrome (PPS) includes diabetes insipidus (central or nephrogenic) and primary polydipsia. In clinical practice the differential diagnosis particularly of central diabetes insipidus (cDI) and primary polydipsia (PP) is often difficult. The current gold standard – the water deprivation test (WDT) with or without vasopressin (AVP) measurements – lacks reliable diagnostic accuracy. Arginine infusion is known to stimulate various hormones secreted by the anterior pituitary gland such as growth hormone and prolactin. Based on own preliminary data we hypothesized that arginine also stimulates AVP mirrored by copeptin, the C-terminal part of the precursor peptide. The aim of this study was to evaluate the diagnostic utility of copeptin measurements after arginine infusion in patients with PPS.
Methods
Between 2013 and 2017 patients with polyuria-polydipsia syndrome were included in this prospective study. Patients underwent first a standard water deprivation test for diagnosis of PP or cDI and second an arginine infusion (L-Arginine Hydrochloride 0.5 g/kg body weight i.v. over 30 min). Blood was withdrawn at different time points (e.g. 30, 45, 60 min) after arginine infusion for copeptin measurements. Additionally, 20 healthy controls underwent arginine infusion without prior WDT.

Results
A total of 51 patients (63% female) were enrolled. 28 (55%) patients were diagnosed with PP, 11 (22%) with complete DI and 12 (23%) with partial DI. The study was terminated in January 2017. Final results of copeptin levels will be measured in batch analysis in February 2017 and compared between patients with complete cDI, partial cDI and PP as well as 20 healthy volunteers. We would be delighted to present the final results of this study at the 19th European Congress of Endocrinology.
Significance
If our hypothesis is true, copeptin measurements after arginine infusion are a promising new tool in the differential diagnosis of polyuria–polydipsia syndrome with the advantage of short and safe test protocol.

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EP919

Diabetes mellitus in Cushing' syndrome: a systematic review

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Introduction
Diabetes mellitus (DM) is an expected condition in Cushing syndrome (CS) but there are few data about prevalence and factors associated to occurrence of DM in these patients.
Objective
To determine the main aspects of DM in CS through a systematic review (SR) of the literature.
Methods
MEDLINE and LILACS were searched for studies published until March, 2016. Search strategy comprised the terms "Diabetes Mellitus", "Glucose Intolerance", "Hyperglycemia", "Cushing Syndrome", "Pituitary ACTH hypersecretion", "diabete melito", "Cushing". Observational/interventional studies in patients with endogenous CS with characterization of DM were included. We excluded case reports, animal models, and studies about exogenous hypercortisolism or subclinical CS.
Results
The initial search yielded 726 titles, 58 were full-text reviewed. Of these, 12 were included in RS. Seven studies (all cross-sectional) accessed DM prevalence. Most patients were women (93.5%) aged 40–50 years, with disease duration between 29 and 180 months. Pituitary, adrenal and ectopic-ACTH were origin of CS in 325 (70.65%), 134 (29%) and 2 (0.5%) patients, respectively. DM prevalence ranged from 17 to 47%. Four studies evaluated the role of body mass index (BMI) on DM occurrence, but none of them found a statistically significant difference. Two studies demonstrated a higher risk of DM in older ages at CS diagnosis. The correlation of DM and severity of hypercortisolism was analysed in four articles and two of them presented a positive result. The effect of CS remission on DM cure was accessed by two studies, with discordant results. DM was associated with higher mortality. Three studies (open-label trials) analysed effect of CS drug therapy on glycaemic control. Mifepristone demonstrated a diabetes improvement after 6 months, as rosiglitazone after 30–120 days.
Conclusion
DM is a frequent CS comorbidity and its occurrence seems to depend on age at diagnosis and disease duration. If CS remission leads to DM remission is still uncertain.

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EP920

Thyroiditis and hypophysitis caused by nivolumab

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Introduction
Nivolumab is an anti-programmed cell death-1 monoclonal antibody approved for the treatment of metastatic malignant melanoma. Several endocrine disorders have been reported as immune-related adverse effects. However, nivolumab-induced hypophysitis has a lower incidence than ipililumab.
Case report
A 69-years old man with metastatic melanoma started to receive nivolumab. Ten weeks after the first cycle of nivolumab he presented hyperthyroidism in blood test. As it was suspected Hashimoto's thyroiditis none antithyroid drug was started. The thyroid scintigraphy and the presence of anti-thyroid peroxidase antibodies confirmed the diagnosis and the thyroid function was monitoring. Forty days later, the laboratory findings showed hypothyroidism and levothyroxine was provided. Nivolumab treatment continued to be administered. Three months later, the patient was admitted because of general weakness and mild confusional state. Blood test showed severe hyponatremia (110 mEq/l) with a decreased plasma osmolarity (250 mOsm/kg). Adrenal insufficiency was suspected so a new blood sample was taken in order to determine cortisol (2.68 μg/dl) and ACTH ($<$ 5 pg/ml) and hydrocortisone treatment was beginning promptly. The assessment of hypothalamic-pituitary-gonadal axis showed a slight decrease in testosterone (1.24 ng/ml) with LH and FSH normal levels. Insulinlike growth factor-1 (IGF-1) was normal, as well as prolactin. Thyroid function was abnormal because of discontinuation of treatment with levothyroxine: TSH 25.47 μUI/ml, FT4 0.39 ng/dl. Magnetic resonance imaging scan was performed and it was reported as mild enlargement of the pituitary gland and the stalk. Hydrocortisone treatment was continued after the patient was discharged from hospital. Two weeks later, normal sodium levels were showed in biochemical test.
Discussion
Monoclonal antibodies used in malignant melanoma as ipililumab or nivolumab could cause several endocrine auntoimmune disorders. Despite hypothyroidism is a common adverse effect, hypophysitis is a rare finding associated to nivolumab in contrast to ipililumab. Clinicians should suspect this pathology in order to achieve a promptly diagnosis.

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EP921

Kallmann syndrome: about eleven clinical cases

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Idiopathic congenital hypogonadotropic hypogonadism (CHH) is a rare reproductive disorder that is primarily caused by a gonadotrophin-realising hormone (GnRH) deficiency. When CHH is associated with hyposmia or anosmia is designated by Kallmann Syndrome (KS). This syndrome is a genetic disorder with significant genetic heterogeneity that may present as a sporadic or familial case, following autosomal dominant, autosomal recessive, or X – linked recessive modes of inheritance. This work aim is to review all KS cases followed in the Endocrinology service. A total of 11 cases were evaluated, 10 men and 1 woman. Patients were mainly diagnosed in late adolescence, between 17 and 18 years old, when sought a doctor for delayed puberty. All cases presented hypogonadotropic hypogonadism and hyposmia or anosmia with MRI olfactory bulb atrophy criteria. No other changes in the neuroendocrine axis were found. The patients were followed between 2 and 33 years (mean time 12 years). All had gonadal steroid hormones treatment (testosterone or estrogens) and had a good secondary development of the sexual characteristics, Tanner stage IV/V. Three patients had fertility therapy with gonadotropin and until now only the girl had clinical improvements. Four cases made a genetic study: two mutations in KAL1 gene, one in FGFR1, and one in PROK2 were found. The two patients with KAL1 mutation presented cryptorchidism and one the two also had unilateral renal agenesis. The patient with FGFR1 mutation also had an history of cryptorchidism. The one with recessive mutation for PROK2 only presented anosmia and hypogonadotropic hypogonadism.
Conclusion
The presence of a delayed pubertal development is suspicious of CHH/KS occurrence. In our study, patients with KS presented good clinical results with the use of gonadal steroid hormones attaining stages IV/V of Tanner. Women appear to have better fertility responses to therapy than men, although this findings demand further investigation.

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Paediatric endocrinology

EP922

Endocrine manifestations of multisystem Langerhans cell histiocytosis

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Introduction
Multisystem Langerhans cell histiocytosis (LCH) is a rare heterogeneous disorder caused by accumulation in multiple organs of dendritic cells phenotypically similar to cutaneous Langerhans cells. Pituitary involvement is present in about 25% of cases, and central diabetes insipidus is the most common deficit in that setting. Panhypopituitarism is rare, but hypothalamic-pituitary dysfunction is amongst the most frequent long-term complications of the disease.
Case report
We describe the case of a child with normal health status until the age of 7. He developed polyuria and polydipsia, was hospitalised and submitted to a water deprivation test, considered indicative of psychogenic polydipsia. At 14-years-old, elevated liver enzymes were attributed to EBV infection. Liver ultrasound showed hepatomegaly and heterogeneous echotexture. At 16-years-old, he presented with hypernatremia, delayed puberty and short stature, as well as slowly progressive dyspnea. Investigation revealed multiple pituitary deficits (hypogonadotrophic hypogonadism, secondary hypothyroidism, secondary adrenal insufficiency, growth hormone deficit) and central diabetes insipidus. Brain magnetic resonance imaging showed a hypothalamic mass (17 mm). He was started on hormonal replacement therapy (urofollitropin, human chorionic gonadotropin, levothyroxine, cortisone, desmopressin). LCH was suspected, and chest computed tomography revealed multiple cystic pulmonary lesions suggestive of the diagnosis, later confirmed by pulmonary biopsy. He started standard treatment with vinblastine and prednisone, with intermediate response after 6 weeks. He developed glucocorticoid-induced diabetes and needed multiple daily injections of insulin.
Conclusions
This case report illustrates the importance of investigating multiple signs and symptoms that arise in a multisystem and complex disorder. In this case, the endocrine consequences of LCH assume a central role. As was the case here, central diabetes insipidus can be the first manifestation of the disease, but its diagnosis is not always straightforward. Early diagnosis can prevent or delay permanent complications associated with multisystem disease; pituitary deficits, once established, are mostly permanent.

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EP923

Growth hormone deficiency – the experience of one pediatric endocrinology unit of a Portuguese hospital in the last 5 years

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Introduction
Hypopituitarism is a clinical syndrome of deficiency in growth hormone (GHD) production, which can occur isolated or associated with others pituitary defects. GHD has an incidence of 1:4000 to 1:10 000. It may be idiopathic, congenital or acquired.
Purpose
Characterize the paediatric population with GHD followed at the Paediatric Endocrinology Unit of our centre and compare the clinical presentation and treatment response of the patients with an idiopathic form with the ones with isolated and multiple hormonal deficiencies.
Methods
Retrospective observational study with analysis of clinical records of children and adolescents with GHD under treatment with GH in the period from 2012 to 2016. Statistical analyses were performed using SPSS 24.0 for Windows.
Results
The final sample consisted in 49 patients, 61.2% were male. Mean age at the beginning of therapy was 9.7 ± 4 years (0.13–16.92). Mean height z-score at time of diagnosis was -3.16 ± 0.94, corresponding the mean z-score of the target height to -1.24 ± 0.77. The mean delay in bone age was 2.22 ± 1.50 years (0–6.5 years). Two growth hormone stimulation tests (clonidine and L-Dopa) were performed in 69.4% of the cases. Brain MRI showed changes in 42.9% of the cases. Of the 49 patients, 55.1% had an idiopathic GHD, 30.6% isolated deficiency and 14.3% had multiple deficiencies. Mean age at the time of diagnosis was 11.16, 8.84 and 6.57 years in the three groups respectively. Mean treatment duration was 3.92 years (in 14.2% less than 1 year). The z-score variation in the group of idiopathic GHD was 0.99, 1.50 and 2.53 in the group of isolated and multiple deficiencies respectively.
Discussion
As previously described, GHD is more prevalent in males. Comparing the three groups, patients with multiple deficiency are diagnosed earlier and have better results with the treatment (higher z-score variation).

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Pituitary – Basic

EP924

SSTR2 inhibits GH-secreting pituitary tumoral cells migration and invasion by increasing cofilin phosphorylation

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Although generally benign, pituitary tumors frequently present local invasiveness that strongly reduces neurosurgery success. We recently demonstrated a role for the actin binding protein cofilin in promoting non functioning pituitary tumors invasiveness and an inhibitory effect of dopamine receptor type 2. Somatostatin (SS) receptor type 2 (SSTR2) is the main target of pharmacological therapy of GH-secreting pituitary tumors, reducing both GH secretion and cell proliferation, but its effects on cell invasion have never been investigated. Aims of this study were: i) to evaluate the effects of SSTR2 agonist on migration and invasion of rat somatomammotroph GH3 cells and human GH-secreting pituitary tumoral cells, and ii) to investigate the molecular mechanisms focusing on the role of cofilin and the cytoskeleton protein FLNA, that directly interacts with SSTR2. Our data demonstrated that SSTR2 agonist BIM23120 incubation significantly reduced migration ($31.3\% \pm 12.2\%$, $P<0.01$) and invasion on collagen IV ($22\% \pm 3.6\%$, $P<0.001$) of GH3, these data being replicated in human GH-secreting tumoral cells ($14 \pm 2.9\%$ and $41.7 \pm 11.3\%$ reduction of cell migration and invasion, respectively, $P<0.05$). Moreover, BIM23120 induced a marked increase of phosphorylated (inactive) cofilin in both GH3 and primary tumoral pituitary cells (about 2.7 and 2.1-fold over basal, respectively). This effect was completely abolished by specific ROCK inhibitor Y27632 but not by pertussis toxin, suggesting an involvement of Rho/ROCK/LIMK pathway and excluding a role for inhibitory hetero-trimeric G proteins. Co-immunoprecipitation experiments revealed an association of SSTR2 with FLNA, cofilin and LIMK1, suggesting a role for FLNA as scaffold protein mediating SS effects on cofilin pathway. In conclusion, our data revealed an inhibitory effect of SSTR2 on GH-secreting pituitary tumor cells migration and invasion involving ROCK-dependent phosphorylation of cofilin.

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EP925

Anti-proliferative effect of sodium metaarsenite (KML001) on ACTH-secreting pituitary adenoma cells

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KML001 is an orally bioavailable and water soluble trivalent arsenic compound having anti-cancer activity via controlling the numerous signaling pathways including phosphoinositide 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase (ERK) signaling pathways. PI3K/Akt and ERK signaling pathways are overactivated in adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. In this study, we evaluated the effects of KML001 on cell viability, cell cycle, apoptosis, and ACTH secretion in mouse ACTH-secreting pituitary adenoma cells, AtT-20 cells. KML001 inhibited the cell viability in time-dependent and concentration-dependent manners and significantly decreased the ACTH secretion in a concentration-dependent manner. As the treatment time or treatment concentration increased, KML001 significantly increased the percentage of AtT-20 cells in apoptosis. As the treatment time or treatment concentration increased, KML001 significantly increased the percentage of AtT-20 cells in the G0/G1 phase and significantly decreased the percentage of AtT-20 cells in the S and G2/M phases. The effect of KML001 on numerous signaling pathways was determined by western blots. The phosphorylated form of Akt and mammalian target of rapamycin (mTOR) proteins were decreased in KML001-treated AtT-20 cells. The phosphorylated form of ERK protein was also decreased in KML001-treated AtT-20 cells. However, the phosphorylated form of p38 and JNK protein were increased in KML001-treated AtT-20 cells. Consequently, KML001 inhibited cell proliferation in ACTH-secreting pituitary adenoma cells via inhibition of cell cycle by inhibition of PI3K/Akt and ERK signaling pathways and induction of apoptosis by activation of p38-MAPK and JNK pathways and might reduce ACTH secretion. These results suggest that KML001 could be a candidate for the treatment of persistent or recurrent Cushing's disease.

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EP926

Angiogenesis-related proteins in pituitary adenomas

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Pituitary adenomas are frequent intracranial tumors that often associate with the hypersecretion of pituitary hormones or may be non-secreting (nonfunctioning pituitary adenomas, NFPA). Tumors resembling human NFPAs develop with complete penetrance in rats affected by the multiple endocrine neoplasia syndrome, MENX. This syndrome is caused by a germline loss of function mutation in $p27^{Kip1}$. Gene expression array analysis performed in our group identified a considerable number of genes deregulated in rat pituitary tumors compared to normal pituitary tissues. Some of the deregulated transcripts are associated with angiogenesis, including vascular endothelial growth factor (Vegf), angiopoietin-1 (Ang-1) and -2 (Ang-2). VEGF and ANG-2 were found to promote angiogenesis in several tumor types, while ANG-1 inhibits this process and stabilizes mature vessels. We analyzed mRNA and protein expression changes of these 3 genes in the pituitary adenomas of MENX-affected rats and compared the results with similar analyses conducted on the corresponding human tumors. We could show that Ang-1 was down regulated in rat and human NFPAs whereas Ang-2 mRNA was highly expressed in almost all of the rat pituitary adenomas and was enhanced in less than the half of the human NFPAs. Vegf mRNA was up-regulated in MENX-rats but not in NFPAs. At the protein level, we have so far set up the immunohistochemical staining for Ang1 and -2 on both rat and human tumors. We could show that rat pituitary adenomas and human NFPAs show reduced cytoplasmic Ang-1 staining compared to adjacent non tumor cells while Ang-2 was more strongly expressed in tumor areas.

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EP927

Ketoconazole induces inhibition of cell viability and apoptosis in an ACTH-secreting tumour cell line model

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Chronic cortisol excess as a consequence of ACTH overproduction from a pituitary tumour is responsible for the development of Cushing's disease (CD). The first-line treatment for CD is pituitary surgery, but medical treatment is an alternative second-line approach to control cortisol excess. Among pharmacological agents, the adrenal-blocking drug ketoconazole (KT), is able to control cortisol excess in the majority of patients with CD. During KT treatment, the adrenal block of cortisol production is expected to induce increase in ACTH levels, but conflicting data demonstrated ACTH to be increased, unchanged or decreased, suggesting a possible direct KT effect on the pituitary tumour. The aim of the current study was to evaluate the effects of KT on cell viability and apoptosis in mouse corticotroph tumour cell line (AtT20-D16). MTT assay was assessed to evaluate cell viability and to evaluate the induction of cell apoptosis the study of mitochondrial membrane potential by JC-1 assay and of PARP cleavage by western blot were performed. KT induced a dose- (from 10–12 M to 6×10–5 M, concentrations covering KT therapeutic range of 200–1200 mg/daily) and time – (from 24 h to 144 h) dependent inhibition of cell viability (82.4%, $P<0.0001$ at 6×10–5M, 84.4% $P<0.0001$ at 4×10–5 M, 81.1% $P<0.0001$ at 2×10–5 M and 34% $P<0.01$ at 10–5 M after 144 h). KT treatment at 24 and 48 h induced depolarization of mitochondrial membrane potential (108%, $P<0.027$ at IC50 2.5×10–5 M) followed by PARP cleavage, confirming the activation of apoptosis. In conclusion, these preliminary data suggest that KT has a direct effect on pituitary tumour significantly reducing cell viability and inducing apoptosis on a corticotroph tumour cell model, shedding new light on the possible mechanisms by which KT may control cortisol excess in CD.

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EP928

GPR101 orphan receptor: a novel cause of growth hormone deregulation

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GPR101 is an orphan G-protein coupled receptor with unknown ligand. In 2014, an international study clearly pointed to a strong association between this receptor and the X-linked acrogigantism (X-LAG) syndrome, which begins in childhood and causes the "tallest giants". The children (carriers of the GPR101 duplication on the X chromosome) grow abnormally even before they are one year old, secrete phenomenal quantities of growth hormone, and develop pituitary adenomas that do not respond to current therapies. The mechanism by which GPR101 contributes to increased growth hormone secretion is currently not known. Nevertheless, the lack of mechanistic insight into the function of GPR101 precludes its validation as a drug target. This lack of knowledge on GPR101 is the consequence of the paucity of specific pharmacological/research tools currently available. Therefore, we propose to study GPR101 functions and its role in growth hormone regulation. First, we determined the receptor precise cellular localization and trafficking. We also deciphered its constitutive signalling pathways by detecting high cAMP levels as well as arrestin recruitment to GPR101. We completed our study with an examination of receptor coupling to other pathways and G proteins. In parallel, we screened small molecule libraries in order to identify GPR101 specific ligands, to establish the link

between GPR101 and X-LAG with a pharmacological approach. Furthermore, we applied targeted mutagenesis to modulate the receptor constitutive activity in order to understand the receptor function at a molecular level. These GPR101 mutants will help us to understand the role of this receptor in GH regulation and/or to treat people suffering from pituitary dysfunction. This information is an absolute prerequisite to link molecular pharmacology of GPR101 with physiological functions.

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EP929

Potential role of biguanides and statins in the treatment of pituitary adenomas

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Pituitary adenomas (PA) comprise a commonly underestimated pathology in terms of incidence and associated morbimortality. To date, somatostatin and dopamine analogs represent the main medical treatment, but an appreciable subset of patients are resistant or poorly responsive to these drugs. Therefore, the search for new approaches to control tumor growth and/or hormone secretion is crucial. Biguanides such as metformin (MF; commonly used to treat type-2 diabetes), phenformin (PF) and buformin (BF) have been shown to exert antitumor actions in different tumor types. Likewise, statins (such as atorvastatin or simvastatin) treatment have been also related to antineoplastic effects in several tumor types. Accordingly, the aim of this study was to elucidate the direct effect of biguanides and statins, alone or in combination, on key functional parameters (i.e. cell viability, hormone secretion, etc.) in human PA cell-cultures [non-functioning pituitary adenomas (NFPAs; $n=8$), corticotropinomas (ACTHomas; $n=7$) and somatotropinomas (GHomas; $n=4$)] and/or rodent pituitary cell-lines (AtT-20 and GH3). The results showed that biguanides and statins clearly inhibited cell viability in pituitary cell-lines (being PF and simvastatin the most effective compounds, respectively), and a similar effect was also observed with biguanides in all PA-subtypes. Additionally, the co-administration of biguanides and statins did not alter the initial inhibitory actions of these compounds separately in cell lines, which might suggest that biguanides and statins exert their effects through common signaling pathways. In addition, biguanides were able to significantly reduce GH and ACTH secretion in GH3 and AtT-20 cell lines, respectively. Taken together, our results reveal a clear inhibitory effect of biguanides and statins on PA cell viability and, given their demonstrated clinical safety, suggest a potential therapeutic role of these compounds for the treatment of patients with PA.

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EP930

Abstract withdrawn.

EP931

Whole exome sequencing of two non-secreting pituitary adenoma tumors from the same patient

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Pituitary adenomas (PA) are benign tumors that develop in pituitary gland. Hormone secreting PA can cause overproduction of pituitary hormones leading to different systemic endocrine disorders (acromegaly, Cushing's disease and others). Non-secreting PA can promote headaches (stretching of the dural sheath) and visual field defects (chiasma compression). We managed to obtain resected tumor samples from the patient having non-secreting PA, first tumor was resected in 2010, after operation patient had rapid regrowth and second resection was performed in 2012. Patient had two AIP gene variants rs641081 and rs4930199 in genomic DNA. Whole exome sequencing of both tumors and genomic DNA from white blood cells was carried out using single end sequencing in 3 batches on IonProton semiconductor sequencing system with average coverage 10x. Data analysis was performed using Galaxy main server (http://usegalaxy.org/). Variants were annotated using Annovar tool and obtained variants filtered. SNVs were filtered according to following parameters: sequencing depth >10, base Q at SNV position >13, non-synonymous SNV or stop-gain or stop-loss SNV, variation represented on both strands. Remaining SNV were manually inspected for irregularities using IGV. 9 non-synonymous SNVs were found in both tumors and not in genomic DNA, further 24 additional nonsynonymous SNVs were found in the second tumor that were not present in the first. The detected alterations include ALKBH8, ASB12, CST1, CLMN, PRSS41, ENPP1, E2F6 and SNVs in other genes, that are described to influence various cell functions, like regulation, signalling and cell cycle. All SNVs still to be validated by Sanger sequencing. Our findings indicate that second tumor had increased number of variations compared to first tumor, that could be caused by regrowth of second tumor from specific cell subpopulation from initial PA. Exome sequencing helps to discover genetic spectrum of known PA gene alterations and reveals new potential PA causative factors.

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EP932

Ubiquitin specific peptidase 8 (USP8) in human corticotroph pituitary tumors- possible targets and mode of action

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Recently, somatic, heterozygous mutations in the gene encoding the deubiquitinase USP8 have been identified in 30–60% of corticotroph tumors. These mutations were found to hinder binding of 14-3-3 proteins, increasing its deubiquitinating activity. One substrate is Epidermal Growth Factor Receptor (EGFR), USP8 triggering EGFR recycling and increased EGFR signaling. However, tumors harboring mutations in USP8 are smaller than WT tumors, raising the debate if EGFR, as a potent growth factor, is the only substrate of USP8 in these tumors. We aimed to identify other putative USP8 targets that might explain the tumorigenesis and increased ACTH secretion of these cells. A literature search revealed several proteins with deregulated expression associated with corticotroph tumors that might be the result of increased USP8 deubiquitination (such as the transcription factors TR4 and CREB). Candidates were analyzed by IHC for their expression levels on FFPE tissue (corticotrophs ($n=54$), functionally inactive ($n=19$), somatotrophs ($n=12$) adenoma and normal pituitary glands ($n=5$)). We further metabolically labeled, transiently

transfected the murine corticotroph cell line AtT-20 with USP8 WT or mutant plasmids and performed Tandem-Ubiquitin-Binding-Entity (TUBE)-assays, followed by nanoLC-MS/MS analysis to identify changes in poly-ubiquitinated protein abundance. Of the 10 analyzed proteins by IHC, 4 had an altered expression pattern between USP8 WT and mutated tumors, namely $p27^{kip1}$ (mean expression: 1 ± 0.8 vs 0.4 ± 0.6 ($P = 0.01$), HSP90 (mean expression: 1.8 ± 0.8 vs 0.7 ± 0.8 ($P = 0.03$), CRHR (mean expression: 0.4 ± 0.5 vs 0.6 ± 0.7 ($P = 0.2$) and PRKACA (mean expression: 0.6 ± 0.8 vs 1.1 ± 0.6 ($P = 0.1$). TUBE assays revealed an increased de-ubiquitination of Small Ubiquitin-Like Modifier 3 (SUMO3) in $USP8^{mut}$ transfected cells, suggesting co-occurrence of another post-translational protein modification. In conclusion, these results suggest a much more complicated mechanism of action of the identified mutations in USP8, with sumoylation adding another dimension to the regulation of a USP8 mediated equilibrium between degradation and recycling.

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EP933

Acquired temozolomide resistance in ACTH-secreting pituitary tumour cells

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Introduction
Temozolomide (TMZ) treatment has been used for aggressive pituitary tumours with positive results, but has proven ineffective in controlling tumour regrowth in cases of disease recurrence. TMZ resistance has been linked to the expression of O6-methyl-guanine-DNA-methyltransferase (MGMT) protein and mismatch repair components (MMR). In the present study, we describe the development of an *in vitro* model of acquired resistance to TMZ and the mechanisms involved in such resistance.
Methods
Mouse AtT20 corticotroph pituitary adenoma cells were used. The TMZ resistance protocol consisted of three challenges of TMZ using a previously determined EC_{50} (50% of the maximal effect) dose. AtT20 cells treated with challenges of the vehicle dimethyl sulfoxide were used as control.
Results
The first TMZ challenge already induced a significant increase in EC_{50} (decreased sensitivity) in TMZ-challenged cells (17 μM vs control 3 μM, $P < 0.001$). After 9 weeks following the third TMZ challenge, TMZ-challenged cells remained resistant (18 μM vs control 2 μM, $P < 0.001$). In control cells, TMZ treatment caused an accumulation of cells in G2/M phase ($P < 0.001$), while in TMZ-challenged cells no accumulation was observed ($P = 0.91$). In control cells, 50 μM of TMZ induced maximum 11-fold stimulation of apoptosis ($1132 \pm 241\%$ vs $100 \pm 5\%$, $P = 0.0008$), whereas in TMZ-challenged cells a significantly lower (2.4-fold) increase in apoptosis was observed ($244 \pm 55\%$ vs $100 \pm 26\%$, $P = 0.003$). The mRNA expression of MGMT was higher and of MMR components (MSH6, MSH2 and PMS2) was lower in TMZ-challenged cells compared to control cells ($P < 0.001$).
Conclusion
The present study describes an acquired temozolomide resistant cell corticotroph pituitary adenoma model. The TMZ resistance is demonstrated by a sustained increase in TMZ EC_{50}, a lack of cell cycle changes and lower TMZ-induced increase in apoptosis. Acquired TMZ resistance is associated with strongly increased MGMT expression and lowered expression of components of the MMR system.

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EP934

PP4C restrains dopamine D2 receptor expression in rat pituitary MMQ cells

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Objective
Decline in the number of D2 receptor (D2R) is considered as the reason of resistance to dopamine agonists (DA). PP4R2 gene was observed up-regulated in prolactinoma patients according to our previous genechip study. In this study, we demonstrated that PP4C was crucial for D2R expression and PRL secretion in rat pituitary MMQ cells.
Methods
In this study, we used rat pituitary MMQ cells which could secrete abundant prolactin and express functional dopamine receptors. RNA interference on PP4C gene was carried out in rat pituitary MMQ cells. The pCDH vector was used as a PP4C overexpression system to assess the functional consequences of PP4C overexpression. Total RNA and proteins were extracted from rat pituitary MMQ cells after PP4C silencing or overexpression. Q-PCR method was used to detect the changes in D2R mRNA levels. And western blotting was used to detect the changes in D2R protein levels. Enzyme-linked immunosorbent assay (ELISA) was carried using ELISA kit for rat PRL.
Results
PP4C silencing increased D2R expression and decreased PRL secretion in rat pituitary MMQ cells. PP4C overexpression reduced D2R expression and enhanced PRL secretion in rat pituitary MMQ cells.
Conclusion
Our study indicates that PP4C restrains D2R expression and increases PRL secretion in rat MMQ cells. These findings suggest the potential role of PP4C in the pathogenesis of prolactinoma.

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EP935

HER2, EGFR and PDGF family members as potential prognostic markers and their therapeutic implications

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Background
The role of EGFR, HER2, PDGF-A and the axis PDGF-B/ PDGFR-β in the pathogenesis of pituitary adenomas and their correlation with the tumoral immunoprofile are poorly understood.
Materials and methods
The study included 92 cases. We used morphological stains, immunohistochemistry and molecular methods to characterize the tumors.
Results
33.33% of adenomas showed a positive immunohistochemical reaction for HER2- with a membranous and cytoplasmatic pattern- the first one prevailing. The restriction of HER-2 expression to the membrane was noticed in the basophilic cells of basophilic or mixed adenomas. For the acidophilic cells: the expression of HER2 was mostly cytoplasmatic with a granular pattern. In pure adenomas, the only significant correlation with the expression of HER-2 was shown for prolactinomas. For bihormonal adenomas we obtained a significant correlation of HER-2 with the coexpression of GH-PRL, PRL-LH, TSH-FSH, TSH-LH. The gene amplification pattern confirmed the expression of HER-2 in 33,3% of adenomas positive for HER-2. For adenomas positive for EGFR, we obtained a significant correlation with the coexpression of GH-PRL, PRL-TSH (partial correlation), PRL-ACTH (total correlation). We analyzed the effects of PDGF-A and PDGF-B on adenoma cells, depending on their immunoprofile. For each of these 2 factors, 60–80% of tumor cells were immunohistochemically positive. We obtained data contradictory to the published one: a positive correlation between PDGF-A and prolactin expression. We confirmed the known association between PDGF-B and somatotropinomas.
Discussions and conclusions
We identified a positive correlation between PDGF-B and PDGFR-β expression, implying a role for this axis in the pathogenesis of pituitary adenomas. The FSH-LH association induces the overexpression of HER-2 in pituitary adenomas, specifying a unique subtype of adenomas. We noticed the expression of EGFR in peritumoral macrophages and folliculo-stellate cells, leaving new opportunities for studying the role of folliculo-stelate cells and the pathogenic role of EGFR in these tumors.

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EP936

Carbohydrate metabolism disturbances at different types of acromegaly treatment

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Purpose
To investigate the carbohydrate metabolism in depend on acromegaly treatment.
Material and methods
23 patients with newly diagnosed acromegaly (NA) were observed. Carbohydrate metabolism were investigated after somatostatine analogues treatment (SSA) (14 patients) or after surgery (TSA) (9 patients). Groups were comparable on age, BMI, acromegaly duration. Were researched HbA1c, fasting plasma glucose level (FPG), indexes of insulin resistance (the HOMA-IR, a Matsuda-index), areas under the curve of insulin within the first 30 minutes (AUCins30) and from 30 to 120 minute (AUC ins30-120) of the oral glucose tolerance test initially and after the treatment.
Results
At NA patients FPG, HbA1c authentically ($P<0.05$) worsened within 3–6 months of SSA treatment and considerably ($P<0.08$) improved after TSA. In 3 months of SSA therapy extent of depression of an AUCins30 considerably exceeded extent of depression of an AUCins30-120 (in 11 and 2.3 times respectively ($P<0.05$)). Whereas in 3 months after TSA extent of depression of an AUCins30 was comparable to extent of depression of an AUCins30-120 (2.4 times and 3.2 times respectively).
Conclusions
The decreasing of hepatic IR and peripheric insulin sensitivity in condition of higher level of insulin in compare with patients receiving SSA at most of these patients leads to normalization of carbohydrate metabolism. The greatest changes of parameters of carbohydrate metabolism (Matsuda-index augmentation, depression of the NOMA-IR index, insulin secretion depression) are noted in 3 months of SSA therapy, and further remain at the previous level or change slightly. It is recommended to carry out control of a condition of carbohydrate metabolism at patients with an acromegaly, first of all, in 3 months both after the carried-out surgical treatment, and after the beginning of SSA therapy.
Keywords: acromegaly; insulin resistance; secretion; insulin; somatostatine analogues; carbohydrate metabolism

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Pituitary – Clinical

EP937

Four decades without diagnosis: Sheehan's syndrome, a retrospective analysis

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Aim
Sheehan's syndrome (SS) remains a frequent cause of hypopituitarism in undeveloped and developing countries, but due to improvements in obstetric care, it is rare in developed countries. We aimed to share the results of a retrospective study analyzing the demographic, clinical, imaging, and hormonal characteristics of a large group of patients with SS, and also increase awareness of this syndrome especially in developed countries.
Methods
The medical records of 124 patients with SS patients who were followed up in the Endocrinology Department of Dicle University between 1995 and 2015 were assessed retrospectively.
Results
The mean period of diagnostic delay was 20.37 ± 8.34 years on average. 5.7% of patients with SS were literate; 62% of patients delivered at home. Anemia was identified in 64.5% of SS patients. Mean blood sodium levels were 129.8 ± 11.3 mEq/L. The mean urine densities were 1013 ± 6.5. Osteoporosis and osteopenia were found in 44 (35.4%) and 71 (57.2%) patients, respectively, According to pituitary magnetic resonance imaging (MRI) analyses, 92 (74.2%) patients with SS had completely empty sella, 29 (23.3%) had partially empty sella, and 1 patient had microadenoma, and 2 had normal pituitary MRI results.
Conclusions
Improved obstetric care and effective interventions for postpartum hemorrhage have limited the prevalence of SS in developed countries. However, in developing countries like Turkey, SS due to postpartum bleeding remains common. Thus, physician's awareness of the symptoms of SS is urgently required to avoid the associated morbidity and mortality.
Keywords: Hypothalamic amenorrhea, osteoporosis, pituitary gland

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EP938

Prevalence of discordant acromegaly after surgical treatment and its clinical implications in a third LEVEL hospital in Latinamerica

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Background
Acromegaly results from excess growth hormone (GH) secretion by a pituitary adenoma in 95% of the cases. Discordant acromegaly is defined by the elevation of GH with normal levels of insulin-like growth factor type 1 (IGF-1) or normal levels of GH associated with an elevation of IGF-1. Its an important situation in the follow-up period of patients with acromegaly because there is little information about patient treatment, comorbidities and follow-up. The objective of this study was to describe the prevalence of discordant acromegaly after pituitary surgery, follow changes in GH and IGF-1 patterns over time and explore possible correlations with blood pressure and HbA1C.
Methods
We retrospectively analyzed the prevalence and characteristics of patients who had an elevated IGF-1 but normal GH or an elevation of GH with normal IGF-1, in consecutive post-surgical acromegaly cases from the year 2000 to 2015 at our institution. To define discordant acromegaly in our study hormonal evaluation was obtained at the 3 months post surgically (GH, and IGF-1). Discordant patients were categorized into two groups according to the postoperative GH and IGF-1: high IGF-1 group (normal GH and high IGF-1), high GH group (high GH and normal IGF-1). We followed discordant patients at 6 and 12 months with GH, IGF-1, magnetic resonance (only at 6 months), blood pressure and HbA1c.
Results
The prevalence of discordant acromegaly was 11.7% (9/77). Of this patient population 77.7% (7/9) changed their biochemical pattern after 12 months of follow-up. Of these, 11.3% (1/9) in the high GH group became inactive, 66.6% (6/9) became active (high IGF-1 group), and 22.2% (2/9) remained discordant (both in the high GH group) and had normal suppression of GH to glucose. Positive correlations were found between the level of IGF-1 at 6 months with systolic blood pressure ($R=0.89$, $P=0.001$) and diastolic blood pressure ($R=0.891$; $P=0.002$). No correlation was found between GH, IGF-1 and HbA1c or tumor size.
Conclusions
Discordant acromegaly in the postsurgical state is a rare entity, with variation in hormonal patterns at 12-month follow up and a positive correlation with blood pressure levels. We suggest that this patients need to be carefully followed due to the high likelihood of recurrence, particularly if the elevation is of IGF-1 and with the presence of residual tumor.
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EP939

A case of IgG4-related hypophysitis with long-term cyclic evolution

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Introduction
IgG4-related disease is a newly recognized entity associated with autoimmune conditions involving almost every organ system, characterized by elevated serum

IgG4 as well as mass like tissue infiltration by IgG4-positive plasma cells. Pituitary gland can be involved and can presented as hypophysitis.
Case description
We report a case of a 56-year-old man, who has been suffering for the nine last years of episodes of fatigue and headaches with spontaneous remission was admitted to our hospital for headaches, fatigue, myalgia, diplopia and visual disturbances. The endocrine assessment revealed a complete ante-hypopituitarism. Dynamic LHRH and CRH tests revealed a delayed but robust response of gonadotrophins and corticotrophin. MRI scan showed nodular thickening of the pituitary and pituitary stalk with minimal compression of the optic chiasm. Other pathology than sarcoidosis was suspected and further investigation showed high levels of blood IgG4. All these findings were highly suggestive for a diagnosis of IgG4-related hypophysitis. Steroids were administered and within 24 hours, the patient became completely asymptomatic. A month later, thyroid and gonadal function normalized. Cranial MRI scan showed a net decrease in the size of the pituitary gland compared to the previous examination.
Conclusions
We report a case of IgG4-related hypophysitis who responded completely and rapidly to steroids. Intriguingly, according to his pas medical history, he might have presented a cyclical evolution of his disease with periods of spontaneous remission. It's a rare condition but increasingly recognized and should be sought in face of an acute swelling of the pituitary gland and/or its stalk, since its favorable response to steroid therapy should help to avoid unnecessary surgery.
Keywords: Hypophysitis, IgG4-disease, panhypopituitarism

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EP940

Duhok/IRAQ acromegaly; one year of experience

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Background
Acromegaly is a rare hormonal disorder; the prevalence is ~60 cases/million population1, Incidence: 3.3 new cases/million/year1 Mortality rate 2–4 times that of general population2. It is usually the result of a somatotrope adenoma in more than 95% of cases.
Aim
By June 2016, we were celebrating one year of experience in acromegaly. It was first time to open acromegaly service in Duhok city/Kurdistan region/IRAQ. This review will include all registered patients during this year. Aim of this revision to give a brief about our patients' characteristics and how we can plan for future?
Methods
This is retrospective study involving ten patients, all patients diagnosed by high IGF1 level followed by GH suppression test and MRI of pituitary gland. Those patients underwent transphenoidal resection, diagnosis confirmed by histopathology too.
Results
Our patients characteristics are shown. The median age of presentation was 44.9. Headache and acral enlargement was the most common presentation.
Discussion
Most patients with acromegaly are diagnosed with a macroadenoma. This review include ten patients, eight of them were from Duhok including Zaxo and Akre, two of them they moved to live in this city, one from the capital Baghdad and another patient from syrian refugee. The prevalence of acromegaly in Duhok city was 8.2 persons/million/year 4, while the incidence was of new cases was 5.3/million/year. This high number of patients reflects the new input for patients to this service as this was not present before June 2015. Eight patients were operable they prepared by somatostatin analogue followed by surgery.
Conclusion and recommendations
The two dilemmas we are facing here in Duhok/IRAQ are: First; delayed diagnosis as reflected by the fact all of our patients are macroadenoma at presentation, that is why we need to increase awareness about this disease. Secondly; low compliance for medical treatment: to improve this we need to provide free measurement of both GH and IGF1 levels for all patients receiving somatostatin analogue treatment.

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EP941

Presurgical medical treatment in Cushing's disease

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Introduction
The duration of hypercortisolism in Cushing's disease (CD) appears to be inversely related to the reversibility of complications, which in turn increase mortality. This makes it necessary to identify medical therapies capable of normalizing cortisol overproduction before transsphenoidal surgery. The aim of this study was to determine if the clinical data of patients with CD before surgery allow predicting the presence and/or abundance of somatostatin (ssts) and dopamine (DRs) receptors at the corticotrophic adenoma, in order to start a more effective and personalized presurgical medical treatment.
Patients and methods
Retrospective study performed through review of clinical histories and molecular profile analysis of corticotrophic tumors. We included all patients diagnosed with CD (2005–2014) treated with transsphenoidal surgery, and whose tumor sample was analyzed in the Department of Cell Biology, Physiology and Immunology of the University From Córdoba. The correlation study was performed using Spearman's ρ.
Results
Nine women with CD and molecular profile analysis of corticotrophic tumor. Age 47.33 ± 12 years. A positive correlation was observed between tumor size at diagnosis and levels of receptor expression sst2 [$\rho = 0.731$ ($P = 0.04$)], sst3 [$\rho = 0.735$ ($P = 0.038$)], DR2 [$\rho = 0.821$ ($P = 0.023$)], DR4 [$\rho = 0.946$ ($P = 0.000$)] y DR5 [$\rho = 0.900$ ($P = 0{,}037$)]. In addition, there was a marked inverse correlation between ACTH levels at diagnosis and the sst5 receptor [$\rho = -0.767$ ($P = 0.016$)].
Conclusions
Tumor size at the diagnosis of CD seems to show a direct correlation with the levels of expression of sst2 and DR2 receptors, suggesting that in patients with CD with macroadenoma in the initial study, preoperative treatment with somatostatin analogs and/or dopamine may be helpful. In addition, the inverse correlation between ACTH levels at diagnosis and sst5 expression questions whether the specific analogues of this receptor would be useful in the preoperative treatment of CD.

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EP942

Characteristics and 1-year follow-up of patients with profound hyponatremia due to primary polydipsia – a multicentre prospective observational study

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Introduction
Hyponatremia due to excessive fluid intake (i.e. primary polydipsia (PP)) is common. It may culminate in profound hyponatremia – carrying considerable risk of morbidity. However, data on patients with PP leading to hyponatremia is largely lacking. Herein, we describe the characteristics of polydipsic patients hospitalised with profound hyponatremia, and assess one-year outcomes.
Method
In this prospective observational study, we included 23 patients with an episode of profound hyponatremia (≤ 125 mmol/l) due to PP. Patients were classified into subgroups: psychogenic polydipsia (PsyP), dipsogenic polydipsia (DiP), and beer potomania (BP). Symptoms, laboratory findings, and factors contributing to hyponatremia (co-morbidities, medication, and liquid intake) were assessed. A

1-year follow-up was performed to evaluate recurrence of hyponatremia, re-admission rate, and mortality.
Results
Of the 23 patients (median age 56 years [IQR 50–65], 74% female) 7 had PsyP, 8 DiP, and 8 BP. Median serum sodium of all patients was 121 mmol/l (IQR 114–123), median urine osmolality 167 mmol/l (IQR 105–184), and median copeptin 3.6 mmol/l (IQR 1.9–5.5). Psychiatric diagnosis, particularly dependency disorder (43%) and depression (35%), were highly prevalent. Factors provoking hyponatremia were found in all patients (e.g. acute water load, medication, stress). During the follow-up period, 67% of patients were readmitted, 52% of these with re-hyponatremia, and three patients (38%) with BP died.
Conclusion
Patients with PP have a high prevalence of addictive and affective disorders. Given the high recurrence, re-hospitalisation, and mortality rate, careful monitoring and long-term follow-up including controls of serum sodium, education and behavioural therapy is needed.

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EP943

Success rates of pituitary surgery in acromegaly – a tertiary centre experience in Romania

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Background
Pituitary surgery is the first treatment option for acromegaly. The reported success of pituitary surgery varies between 75 and 95% for microadenomas and 45 and 68% for macroadenomas. The aim of this study was to report our experience regarding the remission rate after pituitary surgery in acromegaly patients.
Methods
This retrospective study included 70 patients diagnosed with acromegaly in our clinic between 2009 and 2016. The criteria used to define remission were random GH <1 ng/ml and normalization of IGF1 levels for gender and age.
Results
11 patients were lost of follow-up after the first diagnostic visit. We analysed 59 acromegaly patients (33 women and 26 men) with a mean age at diagnosis of 44.93 ± 13.57 years. Microadenoms were found in 15 (25.4%) and macro-adenomas in 44 (74.6%) patients. 6 (10.2%) patients associated both GH and prolactin hypersecretion. Pituitary surgery was performed in 41 patients of which 9 (21.4%) were cured. Aditional 7 (21.2%) patients were cured after second surgery and radiotherapy. Radiotherapy was the first treatment in 11 patients of which 3 (27.2%) were cured. Persistent disease after sugery and/or radiotherapy was treated with somatostatin analogs (26), dopamin agonists (18) and GH receptor bloacker (6) in mono or combination therapy.
Conclusions
The rate of surgical success in our patients was found to be low (40% for microadenomas, 6.8% for macroadenomas). This could be explained by the fact that most patients presented late at the macroadenoma stage.

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EP944

Acromegaly and cardiovascular risk

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Background
Acromegaly (ACRO) is associated with increased cardiovascular morbidity and mortality, however, there is no evidence of an increase in ischemic heart disease in these patients. We hypothesized that non-classical cardiovascular risk factors such as epicardial fat (EF), interventricular septum thickness (IST), carotid intima-media thickness (CIMT), may be increased in ACRO and contribute to this higher cardiovascular morbidity.
Objective
To evaluate EF, IST, and CIMT in patients with ACRO compared to controls and identify possible predictors in this non-classical cardiovascular risk factors.
Material and methods
We studied CIMT, IST, EF in 30 patients with ACRO (16 males, 5 with active disease) and 30 matched controls (by age, sex and body mass index (BMI)).
Results
Both cohorts were identical regarding the presence of cardiovascular risk factors (CVRF. The ACRO cohort presented higher EF and IST compared to the control group (0.65 ± 0.16 vs 0.43 ± 0.14 cm, $P=0.001$ and 11.31 ± 1.17 vs 10.64 ± 1.47 mm, $P=0.035$, respectively). The presence of ACRO (ß 0.545, $P<0.001$; R2 297) was the unique positive predictor of EF, while BMI and hypertension were positive predictors of IST (ß 0.379, $P=0.006$ and ß 0.344, $P=0.013$, respectively, R2 0.298) in a multiple linear regression model.
Conclusions
Patients with ACRO have higher EF and higher IST (influenced by hypertension and BMI), compared with matched controls despite a similar prevalence of CVRF. Increased EF and IST could partially contribute to this increased cardiovascular morbidity and mortality observed in acromegaly.

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EP945

Pituitary insufficiency – etiopathogeny and diagnostic aspects

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The study group was represented by 155 cases of pituitary insufficiency (age: 37.21 ± 16.05; F/M = 116/39) hospitalized in the Clinic of Endocrinology Timişoara during the period 2006–2014. The cases were classified into ethiopatogenic groups, as follows: iatrogenic pituitary insufficiency (23.87%), tumor compression (21.29%), ischemia (14.84%), idiopathic hypogonadotropic hypogonadism (3.87%), congenital pituitary insufficiency (6.45%), empty sella (6.45%), functional pituitary insufficiency (23.23%). In majority, the studied cases presented hypogonadism (95.48%), while hypothyroidism was found in 65.16% patients and 50.32% of the cases presented adrenal insufficiency. Neurological signs caused by the tumoral mass were found in 42.58% cases. The ischemic and congenital forms of the pituitary insufficiency associated mostly panhypopituitarism (100%, respectively 50%), while the iatrogenic form and those caused by tumor compression presented in high percentages partial pituitary insufficiency. The comparison of the hormonal parameters (ethiopatogenic groups) revealed: significant inferior serum levels of testosterone in the congenital form and empty sella vs tumor compression ($P < 0.05$); significant inferior levels of the serum estradiol ($P < 0.01$) in congenital panhypopituitarism vs functional secondary hypogonadism; significant inferior levels of the serum TSH ($P < 0.05$) in patients with pituitary insufficiency caused ischemia vs tumor compression; significant inferior levels of FT4 ($P < 0.05$) in empty sella and ischemic form vs iatrogenic pituitary insufficiency. The applied therapy targeted the cause of the hypopituitarism and the hormonal substitution.

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EP946

Abstract unavailable.

EP947

Long-term outcomes of medical therapy in patients with acromegaly: a retrospective analysis

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Background
Acromegaly is a rare severe disease which, untreated, leads to increased cardiovascular and respiratory morbidity and mortality. Pituitary surgery is the first-line therapy, and medical treatment (somatostatin receptor ligands SRLs, dopamine agonists DA, and GH receptor antagonists GHRAs) is indicated for persistent disease. While selected patients are treated with DA and GHRAs, SRLs remain the mainstay of acromegaly therapy.
Objective
The aim of this study is to report our results regarding medical therapy in patients with persistent acromegaly after surgery and/ or radiotherapy.
Patients and methods
We retrospectively reviewed 59 patients (33 women and 26 men), diagnosed with acromegaly, mean age at diagnosis 44.93 ± 13.57 years, managed between 2009 and 2016 in our department. Controlled disease was defined as normal IGF-1 for age and sex and random GH < 1 ng/ml.
Results
19 patients, cured after surgery or radiotherapy were excluded. 31 patients received medical therapy and 9 were lost during follow up. 26 were treated with SRLs alone or in combination therapy, 3 received DA alone, one DA and GHRAs and one GHRAs alone. SRLs were used as monotherapy in 13 (50%), tritherapy in 3 (11.5%), in combination with DA in 9 patients (34.6%) and with GHRAs in one (3.8%). IGF-1 normalization was achieved in 10 patients (32%), 7 receiving SRLs (five in monotherapy, one with DA and one in tritherapy), two DA alone and 1 with GHRAs alone. Random GH < 1 ng/ml was achieved in six patients (19.3%) (three in monotherapy SRLs, two in association with DA and one on DA alone). Controlled disease was found in five patients (16.1%) (three receiving monotherapy with SRLs, one with tritherapy and one with GHRAs).
Conclusion
In long-term follow-up, almost 40% patients got full control of acromegaly, but only 20% of them on medical treatment. Medical approach in acromegaly should be individualized, combination therapy could provide additional biochemical control, but new therapies should be implemented.

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EP948

Resistant prolactinomas: Retrospective study of ten cases

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About 10–15% of prolactinomas (P) are resistant to Dopamine agonists (DA). We analyzed retrospectively ten resistant prolactinomas (RP) treated at our center between 1995 and 2014, to identify useful variables to predict DA resistance and its different patterns (biochemical resistance (BR), morphological resistance (MR) or both). BR is defined as the failure to normalize prolactin (PRL) levels with ≥ 2 mg/week of cabergoline (C) for at least 3 months. MR is considered when at that dose the tumor size is not reduced by at least 50%. The median age was 30.6 years and 5 subjects were male. All patients had secondary hypogonadism and 1 had TSH and GH deficiency. The median PRL levels were 548 (127–1000) ng/ml. There were eight macroprolactinomas (MP) and two microprolactinomas (mP), with an average size of 1.78 (0.4–3.5) cm. Seven had suprasellar extension and three invasion of cavernous sinuses. The median dose of C used was 3.4 (2–7) mg/week. The median follow-up was 93.2 (26–348) months. Five patients had MR, 1 BR and 4 patients both. Seven patients (2 mP and 5 MP) underwent transsphenoidal surgery. The indication was BR and MR in 4, BR in 1 and MR in the other 2 patients. The surgical remission was achieved in 3 patients. The remaining 4 patients were treated with DA and one of them also received radiotherapy. All of them achieved remission. In the 3 non-operated patients an adequate hormonal control was achieved, but with tumor persistence. In conclusion, prevalence of male sex, a size larger than 1 cm and suprasellar extension were higher in our resistant patients than that reported in non-resistant prolactinomas; thus, these features could predict DA resistence. The morphological response without biochemical response is uncommon, whereas MR without BR is relatively frequent, even more than the coexistence of both.

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EP949

Ocular findings in adult subjects with congenital, lifetime, isolated, untreated growth hormone deficiency

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Ocular function is fundamental for environmental adaptation and survival capacity. Growth factors are thought to be necessary to reach a mature eyeball and consequent adequate vision. However, the consequences of the deficiency of circulating growth hormone (GH) and its effector insulin-like growth factor I (IGF-I) on the physical aspects of the human eye are still debated. A model of untreated isolated GH deficiency (IGHD) may clarify this issue. The aim of this study was to assess the physical aspects of the eyeball of adult IGHD individuals who have never received GH therapy. A cross sectional study was carried out at the University Hospital, Federal University of Sergipe, Brazil, including 25 adult IGHD subjects homozygous for a null mutation (c.57 + 1G > A) in the GHRH receptor gene, and 28 matched controls. All underwent endocrine and ophthalmological assessment. The main outcome measures were visual acuity, intraocular pressure, refractive error, ocular axial length (AL), anterior chamber depth, and central corneal thickness (CCT). Despite unmeasurable serum IGF-I, there was no difference between the groups in visual acuity, intraocular pressure, and refractive error. IGHD subjects exhibited lower absolute values of AL (22.5 ± 0.6 vs 23.5 ± 1.0 mm, $P < 0.0001$), anterior chamber depth (2.98 ± 0.3 vs 3.26 ± 0.3 mm, $P = 0.001$) and CCT (539 ± 28 vs 546 ± 28 mμ, $P = 0.04$) than controls. All values were within their normal ranges. While mean stature in IGHD group was 78% of the controls, mean IGHD axial AL was 96%. These observations suggest no relevant consequences of congenital lack of pituitary GH and of circulating IGF-I on physical ocular findings. Autocrine or paracrine growth factors may be more relevant to ocular growth.

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EP950

Evaluation of estrogen effects on the anterior pituitary hormones by using combined pituitary stimulation test (CPFT) in the Korean postmenopausal women

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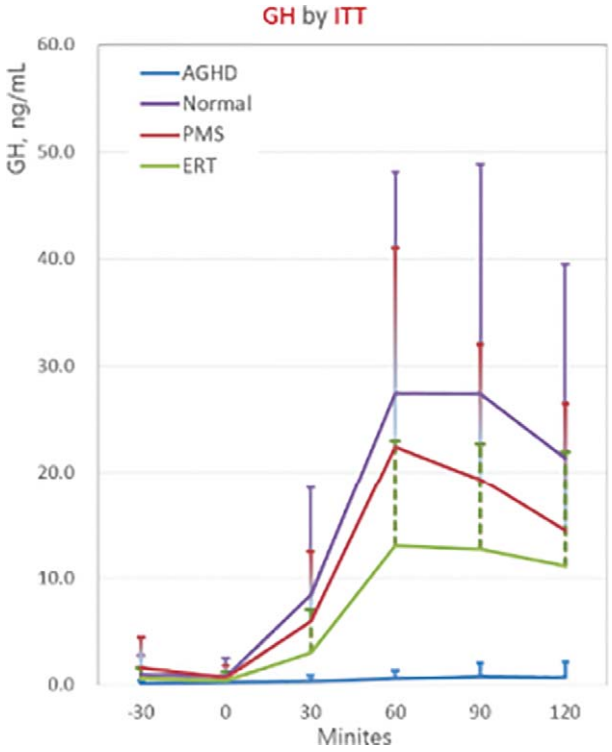
Pituitary hormonal status was important for the evaluation of various diseased state of hypothalamo-pituitary target organ axis as well as tumorous condition. Measurement of growth hormone (GH), adrenocorticotrophic hormone (ACTH) and cortisol during insulin-induced hypoglycaemia were commonly used to assess pituitary condition on hypoglycaemia stress. Sexual axis was evaluated with target organ hormones, i.e. estradiol or testosterone and LHRH stimulated luteinizing hormone (LH) and follicle stimulating hormone (FSH). TRH stimulated prolactin (PRL) and thyroid stimulating hormone(TSH), and simultaneously evaluated with thyroid hormones (free T4 and T3). All these separated axes were evaluated once with combined pituitary stimulation test (CPST) by combined use of regular insulin (0.1 unit/kg body weight), 100 to 500 μg of TRH (TSH releasing hormone) and 100 μg of LHRH respectively. We checked out pituitary hormonal status with CPST in normal Korean postmenopausal women for physiological situation of pituitary function after naturally shut down of oestrogen. We enrolled total 230 women, who were 30 adult GHD (growth hormone deficiency), 116 postmenopausal (PMS), 17 PMS on ERT (oestrogen replacement therapy) and 48 regularly menstrual women (normal). We did find GH response to hypoglycaemia (indirect) was much higher than that of GHRH (direct) stimulation. These findings were meant that GHRH-GH axis was more responded to life threatening stress, then mobilized glucose and stabilized human energy system. Peak GH levels after



hypoglycaemia stimulation were mild suppressed with ERT than that of PMS without oestrogen replacement. We will investigate all pituitary hormonal status with future full data processing in Korean postmenopausal women by CFST.

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EP951

Acute presentation of cushing disease: severe hyperglycemia and refractory hypokalemia

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Introduction
Cushing's syndrome (CS) is a rare disease resulting from prolonged exposure to supraphysiological levels of glucocorticoids. Cushing's Disease is the most frequent cause of endogenous CS. This disease has a broad spectrum of clinical manifestations and is associated with an increased morbi-mortality. Diabetes Mellitus (DM) and hypokalemic alkalosis affects up to 50 and 10% of CS patients respectively. Disease onset and severity reflects the magnitude of cortisol excess, being ectopic ACTH production is the most frequent cause of acute, severe CS. Cushing disease tends to have a slower onset with gradual appearance of the typical phenotype and associated metabolic consequences.
Case report
A 62 year old male with a known medical history of obesity and hypertension was admitted to the emergency department with altered mental status, hyperglycemia and hypokalemia. Physical examination was remarkable for obesity, moon face, facial plethora and proximal muscle weakness. At admission: plasma glucose was 452 mg/dl serum potassium 2.7 mmol/l and arterial pH 7.6. Excessive iv fluids led to congestive heart failure that was treated with standard doses of furosemide. Diuretics were soon stopped due to severe refractory hypokalemia (1.7 mmol/l) that after correction required maintenance iv potassium chloride doses of 120 mEq/day. Further laboratory (dexamethasone suppression tests 1 and 8 mg and inferior petrosal sinus sampling) and imaging (pituitary macroadenoma) investigations confirmed Cushing's Disease. Endoscopic transphenoidal tumor excision led to disease remission. Currently, 15 months postoperatively, the patient has no complaints, is normokalemic (without potassium supplements) and normoglycemic on metformin monotherapy.
Conclusion
The case is noteworthy for the atypical clinical presentation, severity of the hypokalemia and excellent treatment outcome. The authors emphasize the importance of high clinical suspicion for secondary causes of DM when investigating patients with new onset diabetes, as diagnosing and treating the underlying cause may render the diabetes and its complications potentially curable and preventable respectively.

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EP952

Uncomplicated pregnancy in a patient with McCune Albright syndrome (MAS) and active acromegaly

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Introduction
The association of acromegaly and polyostotic fibrous dysplasia is a rare entity that presents more difficulties in achieving an effective treatment than classical acromegaly. Pregnancy is infrequent and carries a high risk when acromegaly is active.
Clínical case
A 27 year old woman surgically treated for facial asymmetry, without café-au-lait spots or precocious puberty, was evaluated in 1992 after a normal pregnancy. In the biochemical tests the following was observed: PRL 95 ng/ml (1.2–40), GH 20.9 ng/ml not suppressed during oral glucose overload, IGF-I 943 ng/ml (101–333), T4 and T3 elevated with suppressed TSH. The rest of the data including basal hormones did not show significant alterations. Imaging tests showed diffuse hyperplasia/adenomatosis of the pituitary gland (14 x 20 x 6 mm) with increased left lining and cavernous sinus invasion and findings compatible with fibrous dysplasia affecting numerous bones of the base of the skull and the cranial vault. In the thyroid scan, a multinodular goiter with calcifications was found. Therapy with bromocriptine (BC) 2,5 mg/day and methimazole was initiated, but acromegaly remained active because the patient refused treatment with subcutaneous octreotide. In 1996 she had an uncomplicated second pregnancy and in January 2000 intramuscular Sandostatin LAR 30 mg/month could be included in the treatment. Magnetic resonance performed after pregnancy showed a small 5-mm focal image compatible with a microadenoma and a pituitary gland close to normal. In 2007 Sandostatin was replaced by GH receptor antagonist Pegvisomant, 20 mg/day subcutaneous because the control objective for IGF-I was not achieved. With this therapy the patient, who also received cabergoline 0.5 mg/wk and metimazol 5 mg/d, was asymptomatic and IGF-I, PRL, thyroid function, cardiac tests, fundus and campimetry were normal.
Discussion
This patient with MAS presented primary hyperthyroidism, hyperprolactinemia and acromegaly with partial response to Sandostatin LAR but complete response to pegvisomant. This drug can be especially useful in the management of MAS-acromegaly for the risks involved in surgery and radiotherapy. Although uncontrolled acromegaly can complicate pregnancy, especially by increasing the risk of gestational diabetes and hypertension, in this case, pregnancy evolved without incident.

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EP953

Impact of etiology, age and gender on onset and severity of hyponatremia in patients with hypopituitarism

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Hyponatremia can unmask hypopituitarism and secondary adrenal insufficiency due to potent non-osmotic stimulation of vasopressin release under stressful conditions. Patients and methods: In a retrospective study 25 patients (13f/12m, age 58.9±18.6 years) with hyponatremia (119.7±10.5 mmol/l) were identified

among 260 in-patients treated for hypopituitarism in our department over a decade. Results: Hyponatremia was recorded in 9.6% of our patients. In 84% it was the key to diagnosis of hypopituitarism. Patients with hyponatremia and non-functioning pituitary macro adenomas (group 1. NFPA $n=15$) were significantly older (71.47 ± 4.8 years), compared to patients with hyponatremia from other rare causes of hypopituitarism (group 2. $n=10$; age 40.2 ± 15.3 years, $P<0.01$): congenital ($n=2$), Sheehan's syndrome ($n=2$), intracranial aneurysm ($n=2$), lymphocytic hypophysitis ($n=1$), traumatic brain injury ($n=1$), surgery and radiotherapy for astrocytoma ($n=1$), pituitary metastasis from bronchial carcinoma ($n=1$). Male preponderance in patients with NFPA (10/15 i.e. 66.7%) was in contrast to female predominance in patients with other causes of hypopituitarism (8/10 i.e. 80%). Hyponatremia was more severe in group 2 compared to group 1 (113.5 ± 10.9 mmol/l vs. 124.3 ± 8.1 mmol/l, $P<0.01$). Conclusion: Hyponatremia is not uncommon in patients with hypopituitarism, especially at presentation. In older patients, NFPA is the most common pathology, usually leading to gradual onset of hypopituitarisim and non-specific symptoms, while acute hyponatremia can occur with pituitary apoplexy. In younger patients severe acute hyponatremia is more common leading to diagnosis of unrecognized secondary adrenal insufficiency and hypopituitarism from various causes.

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EP954

Changes in pituitary tumour biology and behaviour in FIPA patient with GH secreting aggressive pituitary macro adenoma

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40-year-old female patient presented with acromegaly in 2008 (GH 61 (g/L, IGF-1 774 ng/ml PRL 1500 mU/L). Macro-adenoma invading the right cavernous sinus was found on MRI and she underwent two pituitary surgeries revealing sparsely granulated GH adenoma with scattered PRL cells, low Ki 67 and negative p53 immuno-staining. Her second cousin was treated for macro prolactinoma. Both patients tested negative for germline mutations in the AIP and menin genes. Treatment with somatostatin analogue and dopamine agonist was initiated. She was well controlled (GH 1.1 (g/L and IGF-1 291 ng/ml) until 2011 (IGF-1 576...608 ng/ml, GH 4.1 (g/L) when she received 20 Gy gamma knife radio surgery, to the right para-sellar rest and clivus with good response (2012 IGF-1 235-306 ng/ml). In 2014 she became symptomatic with headache, VI cranial nerve palsy and biochemical deterioration (GH 5.3 (g/L and IGF 1 549 ng/ml). In November 2015 she developed VII & VIII cranial nerve palsy and biochemically deteriorated (GH 13 (g/L and IGF-1 857 ng/ml). MRI disclosed tumour progression from the right para-sellar to the infra-sellar region infiltrating clivus, sphenoid and temporal bone and posterior cranial fossa with progressive rise in GH 16(g/L and IGF-1 909 ng/ml levels despite treatment with somatostatin analogue and dopamine agonist. Avid tracer uptake was noted in the pituitary tumour and neck lymph node on the left side on FDG PET CT and SST2 scintigraphy. Third surgery using the posterior cranial fossa approach was performed. Tumour biology revealed sparsely granulated GH adenoma with high proliferative activity Ki 67 17.2%, positive p53 and 2/10 mitoses. Revised immunohistochemistry revealed recurrent sparsely granulated GH adenoma expressing SSTR2 and Pit1 with low proliferation (Ki 67: 0, mitoses: 0) positive p53 (1%) grade 2a. This case illustrates our AIP negative FIPA patient with sparsely granulated GH adenoma and aggressive behaviour refractory to multimodality treatment during long term follow up.

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EP955

Gambling and cabergoline

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Introduction
A link between Dopamine agonists and development of impulse control disorders is well recognized in the field of neurology. A similar finding in endocrine patients is emerging.
Case report
We report the case of a 38-year-old man with pathological addiction to gambling associated with low dose cabergoline treatment for a *mixed* growth hormone (GH) and *prolactin (PRL)*-secreting *pituitary adenoma*. At the age of 29 he was diagnosed with mixed (GH and PRL) functioning invasive pituitary adenoma. After surgery and radiotherapy he was given medical therapy with somatostatin analogues and cabergoline. During follow-up somatostatin analogues were withdrawn but he continued cabergoline treatment to control hypersecretion and the residual tumour. During follow-up the patient reported pathological gambling habits. He had spent a large sum of money and, although he had tried to stop gambling many times he was unable to quit. He did not stop his gambling behaviour despite a marital crisis and divorce. He had even been to a centre for addictive disorders without success. We decided to withdraw cabergoline. His impulse-control disorder (ICD) resolved within months after cabergoline discontinuation. After 6 months, somatomedin C level was in normal range, PRL level was mildly high with no sexual dysfunction and the tumour had not grown.
Conclusions
The gambling episodes diminished after the discontinuation of cabergoline, providing evidence for a causal relationship. Cabergoline-induced pathological gambling and another ICDs are probably underreported, and physicians should consider screening for these in patients treated with dopamine agonists. Screening for ICDs should be undertaken in all patients with DA-treated prolactinomas.

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EP956

Rare causes of hypopituitarism in adults in a tertiary care institution

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Objective
Hypopituitarism is a rare disease,a pituitary adenoma and is treatment being the most common cause of it. In recent years there is increased reporting of rare causes of hypopituitarism acquired in adulthood, such as other sellar and parasellar masses, brain damage caused by radiation and traumatic brain injury (TBI), vascular lesions, infiltrative/immunological/inflammatory diseases and infectious diseases. Aim of our study was to increase the awareness to these rare causes of hypopituitarism.
Patiens and methods
We performed a cross-sectional database study in our population investigating the etiology of hypopituitarism in 558 patients in a tertiary care institution recorded for the last 11 years. We excluded the patients with pituitary adenomas and congenital hypopituitarism. Sixty-eight patients (32 male, 36 female) were included in the study (mean age 37.3 ± 2.0 years, range 16–72 years).
Results
According to the causes of hypopituitarism the patients were divided in several groups: nonpituitary sellar and parasellar masses in 10 patients (pituicytoma $n=1$, chordoma $n=2$, metastasis $n=3$, intravascular lymphoma $n=1$, Langerhans cell histiocytosis $n=3$), brain damage in 27 patients (TBI in 9 patients and cranial irradiation in 18 patients), vascular causes in 17 patients (aneurysm $n=1$, apoplexy $n=3$, Sheehan's syndrome $n=6$, subarachnoid hemorrhage $n=6$, glomangioma $n=1$), immunological/infiltrative/inflammatory disease in 7 patients (primary hypophysitis $n=6$, secondary hypophysitis $n=1$) and pituitary infections in 7 patients (viral hypophysitis-hemorrhagic fever with renal syndrome, tuberculosis). Growth hormone and ACTH deficiencies were the most common hormonal deficits (57/68, 84%), followed by FSH/LH deficiency (52/68, 76%), TSH deficiency (49/68, 72%) and ADH deficiency (8/68, 12%). Ten patients (14.7%) had isolated pituitary hormone deficiency, 13 patients (19.2%) had 2–3 pituitary hormone deficiencies and 4 pituitary hormone deficiencies were present in 45 patients (66.1%).

Conclusion
A high index of suspicion is required for diagnosing rare causes of hypopituitarism. The symptoms and signs of hypopituitarism are usually nonspecific and the recognition of these patients remains the challenge.

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EP957

Recombinant Human Growth Hormone Treatment in liver transplant patient. Case report

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Background
Linear growth is often impaired after successful liver transplantation. Factors that negatively impacted growth are age, graft function and corticosteroid immunosuppression. Short-statured prepubertal liver transplant recipients who do not show sufficient compensatory growth after transplantation benefit from treatment with recombinant human growth hormone (rhGH).
Cas report
We communicate the results after the first year of rhGH treatment in a child of 12 years old, identified with growth failure after a liver transplantation. Liver transplant (live donor- the mother) to 9 years for secondary cirrhosis (biliary atresia), malabsorption syndrome, secondary osteoporosis with multiple femoral fractures on pathological bone. Height =108 cm (− 5, 92 SDS), and the weight was =20 kg (−2, 5 SDS). Bone age =7 years. Bone mineral density (BMD-DXA)-whole body=0.718 g/cm^2 (low bone mass acquisition). Blood samples for baseline growth hormone (GH) secretion, serum insulin-like growth factor (IGF-I) concentrations serum alkaline phosphatase, alanine aminotransferase, y-glutamyl transferase, and total bilirubin concentration, serum free T, and TSH levels were determined every 6 months. He was treated with subcutaneous injections of rhGH at 0.35 mg/kg/ wk. for one year. Treatment was begun after 3 years of x liver transplantation. He was treated for that with tacrolimus and prednisolone. After the first year, rhGH treatment was continued.
Results
After 12 months of treatment, median serum levels IGF-I increased from 86 to 231 ng/ml. Height velocity increased from 2 cm/yr. to 10,2 cm/yr. and BMD-DXA whole body from 0.718 g/cm^2 to 0.997 g/cm^2 (+38%); lean+BMC from 15735.6 g to 19510.5 g (+24%); fat decreased from 4378 g to 2990.7 (−32%); and total weight increased with 12%. There were no rejection episodes.
Conclusion
In our case rhGH treatment was effective in short, non-GH deficient, liver-transplanted child receiving long term glucocorticoid treatment.

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EP958

Immune checkpoint inhibitors: an emerging cause of hypophysitis

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Aim
To describe 2 cases of immune-mediated hypophysitis due to the therapeutic use of Ipilimumab, a cytotoxic T-lymphocyte antigen-4 (CTLA4)-blocking antibody.
Case 1
A 62 year-old male with history of metastatic melanoma was started on Ipilimumab. After finishing the 4th at 2 months he complained of weakness, fatigue, and fever, prescribed ciprofloxacin and prednisone 20 mg daily, and felt better. 2 days later he was hospitalized with weakness, BP 86/65 mmHg and temperature 101.7F. TSH was 0.050 uIU/ml, free T4 0.48 ng/dl, and free T3 1.20 pg/ml FSH 1.2 mIU/ml, LH 0.8 mIU/ml, and prolactin 0.3 n/ml (all low). A Cosyntropin Stimulation Test showed the following cortisol levels (in ug/dl): baseline 2.60, 30 min post-injection 6.30, and 60 min post-injection 7.90. Pituitary MRI was normal. The clinical picture was consistent with severe, recent-onset panhypopituitarism. The patient was treated with IV fluids, stress-dose dexamethasone, and levothyroxine, and discharged on hormonal replacement. He continues to do well on multi-hormonal endocrine replacement therapy.
Discussion
Ipilimumab (Yervoy*) is a monoclonal CTLA4 antibody and immune checkpoint protein-modulator approved for treatment of melanoma, and being studied in lung, prostate, and bladder cancer. Mechanisms of overcoming tumor-induced immune tolerance trigger 'Immune-related adverse events' (IRAEs) as side effects from autoimmunity and disruption of self-tolerance. They include colitis/diarrhea, dermatitis, hepatitis, and endocrinopathies (hypophysitis (0–17%), thyroid dysfunction (0–4%) and primary adrenal insufficiency (0.3–1.5%). Ipilimumab-associated hypophysitis is a new form of autoimmune pituitary disease with an average time of 11 weeks after starting therapy, suggesting a cumulative effect. Patients may present with weakness, headache, nausea, anorexia, confusion, memory loss, behavior change, hallucinations, visual impairment, loss of libido, temperature dysregulation, fever, and chills. Hormone levels show varying degrees of hypopituitarism, and MRI may be normal or reveal pituitary gland enlargement and thickening of the stalk. Symptoms resolve after withdrawal of the drug and starting hormone replacement; however, pituitary function may be impaired for considerably longer or even lifelong.
Conclusion
The increasing use of immune checkpoint inhibitors such as ipilimumab is an emerging cause of hypophysitis that generalists, ER physicians, oncologists, and endocrinologists need to be aware of.

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EP959

A case of hypopituitarism caused by hemorrhagic fever with renal syndrome

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Hemorrhagic fever with renal syndrome (HFRS) is a severe systemic infection caused by hantaviruses that included Hantaan, Seoul, Dobrava, Saaremaa, and Puumala. In Korea, the most common virus is Hantaan. The classical symptoms of HFRS are fever, hemorrhage, hypotension, and renal failure, but the clinical course can be very diverse. Among them, endocrinologic complications, such as hypopituitarism were developed rarely by HFRS. A 49 years-old man admitted our hospital with fever, myalgia and thrombocytopenia. He was diagnosed as HFRS caused by Hantaan and clinical manifestations. In oliguric phase of renal failure, abnormalities of thyroid function, fT4 0.35 ng/dl (0.89–1.78), T3 24.43 ng/dl (60–180) and TSH 0.358 uIU/ml (0.55–4.78), were found and other hormone tests were performed for differential diagnosis. The level of basal hormones were prolactin 13.77 ng/ml (2.1–17.7), GH 2.10 ng/ml (0–1), IGF1 112.87 μg/l (124–310), ACTH 27.8 pg/ml (10.0–60.0), cortisol 13.82 μg/dl (5.27–22.45), LH 3.94 mIU/ml (1.5–9.3), FSH 2.75 mIU/ml (1.4–18.1) and testosterone 104.99 ng/dl (241–827). These results indicated secondary hypogonadism and hypothyroidism and no evidence/was seen hypothalamic or other pituitary disease by sella MRI. According to this result, partial hypopituitarism by HFRS was suspected in the patient. After conservative treatment, manifestations and laboratory investigation were improved. He was discharged and tested the basal hormones again at the outpatient clinic. The results were fT4 1.16 ng/dL, T3 110.43 ng/dl, TSH 1.490 uIU/ml, prolactin 8.27 ng/ml, GH 0.41 ng/ml, IGF1 254.24 μg/l, ACTH 30.9 pg/ml, cortisol 10.36 μg/dl, LH 2.83 mIU/ml, FSH 6.54 mIU/ml and testosterone 214.05 ng/dl. The thyroid function was recovered to normal level spontaneously and the gonadal hormones were still low level. Compared with initial hormone level, the pituitary function is recovering sequentially. Our experience suggests the important to investigate the endocrinologic complications of HFRS and to determine whether treatment of hormone replacement is needed.

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EP960

Prevalence and Incidence of pituitary tumors: a nation-wide Population-based study using Korean National Health Insurance claims data

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Purpose
We conducted this study to determine the prevalence and incidence of pituitary tumors in South Korea.
Methods
This is a nationwide population- based retrospective study. We analysed two national databases, the Korean National Health Insurance (NHI) claims database and Rare Intractable Disease (RID) registration database, which include information on every patients with pituitary tumor diagnosed through uniform criteria from 2009 to 2013. Pituitary tumor was defined into three types based on

the ICD-code; i) D35.2 (benign pituitary neoplasm), ii) D35.2+E 22.0 (acromegaly) +E24.0 (Cushing disease), or iii) D35.2+E22.0+E24.0+E22.1 (Hyperprolactinemia) &co-entered D35.2.
Results
The prevalence and incidence of pituitary tumors were described based on the three definitions. By definition i), 25 135 patients had pituitary tumors and included in the prevalence estimates. The prevalence was 40.8, 31.4 and 50.1 per 10^5 populations in total, men and women, respectively. During 2011–2013, total 8 234 incident cases were identified and the incidence was 17.3, 13.7 and 21.0 per 10^5 in total, men and women, respectively. By definition ii), total 25 135 patients had pituitary tumors and prevalence was 52.4, 37.5 and 67.1 per 10^5 populations in total, men and women, respectively. For the incidence estimate, 10 359 patients were identified and the incidence was 21.6, 15.8 and 27.3 per 10^5 in total, men and women, respectively. By definition iii), total 30 175 patients had pituitary tumors and prevalence was 62.9, 38.7 and 86.8 per 10^5 populations in total, men and women, respectively. For the incidence estimate, total 12 544 patients were identified and the incidence was 26.1, 16.3 and 35.9 per 10^5 in total, men and women, respectively.
Conclusions
This study provides reliable information of the epidemiology of pituitary tumors in Asian population, and may help to manage this disease accordingly within our healthcare system.

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EP961

Prevalence of acromegaly in eight counties of North-East Romania

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Introduction
The prevalence of acromegaly is estimated to be 6-28/100000 but several studies suggest that acromegaly is underdiagnosed and its prevalence is underestimated.
Aim
To measure the prevalence of clinically relevant acromegaly in a well-defined population using data from 01.04.2004 to 01.11.2016.
Method
Cross-sectional study performed in 8 counties from the North-East Romania. Data of patients with acromegaly were collected using the INFOWORLD programme and acromegaly diagnosis code E22.0. The number of inhabitants for each county was in accord with 2011 Census and 2007 Statistical Directory. We identified all acromegalic patients who were born and resided for each of the eight counties diagnosed in the Department of Endocrinology from the University Hospital 'St Spiridon' Iasi, Romania.
Results
238 (164 females and 74 males) patients with acromegaly were identified in a total population of 4.2 million inhabitants. The prevalence for Iasi County was 9,94/100000, Suceava County 5.49/100000, Bacau County 4,13, Galati County 1,50, Neamt County 3,94, Botosani County 7,17, Vaslui County 7,37/100000 and Vrancea County 3,53/100000.
Conclusions
The highest prevalence was identified in 3 counties (Iasi, Vaslui and Botosani). The explanation of this results may be the more frequent use of diagnostic procedures like CT or IRM, the concern of local endocrinologists to identify this type of pathology. The sex distribution of the selected population was in favour of female patients (2F:1M) and was not consistent with 1:1 sex distribution of previous studies.

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EP962

A male patient with acromegaly and metastatic renal cell carcinoma: lung, gluteal and scapular metastasis

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Acromegaly is a chronic condition associated with an increased risk of cancer.
Case presentation
A 41-year-old man admitted to our hospital with gluteal and scapular mass. He had a clinical history of acromegaly which had been diagnosed two years ago, and was treated with trans-sphenoidal surgery. After surgery, although remission was not achieved, he had no doctor visit and control. On physical examination he had typical acromegalic features and there was palpable mass on right gluteal and scapular region, which was noticed by the patient within the last two months. Laboratory examination revealed high levels of GH (10.8 ng/ml), IGF1 (1072 ng/ml). Abdominopelvic CT revealed an 93×68 mm mass on right kidney, 100×65 mm on the right gluteal region and 200×80 mm on the right scapular region. Thorax CT revealed metastatic nodüler lesions on the right lung. The diagnosis of metastatic renal clear cell cancer (RCC) was verified with gluteal and scapular biopsies. Pituitary MRI revealed residual makroadenoma (2 cm). Therapy for acromegaly with octreotide LAR was initiated. The patient underwent radiation therapy for the tumors of right scapular, gluteal region. At the same time patient recieved interferon-alfa therapy for metastatic RCC. After three months of treatment, scapular, gluteal mass regressed but renal mass and lung metastasis progressed with diffuse plevral effusion on the right side. Sunitinib treatment was started for the follow up.
Discussion
Therefore we report a very rare case of acromegaly with RCC. In adition to the increased circulating GH/IGF-1 levels, local expression of GHR and IGF-1/IGF-IR in the tumor tisues may partly contribute to the growth of multiple tumors. Type 1/IGF1R has an influence on renal cells malignant transformation by induction of cell proliferation, dediferantiation and antiapoptotic effect. The risk of RCC progression would have been very high had the acromegaly been left untreated. control of acromegaly is mandatory in acromegalic patients with cancer.

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EP963

Infundibular lesion presenting with central diabetes insipidus and hypogonadism

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Introduction
Pituitary stalk lesions fall into three categories: congenital and developmental (rathke cleft cyst, ectopic neurohypophysis), inflammatory and infectious (hypophysitis, sarcoidosis, tuberculosis), and neoplastic (Langerhans cell histiocytosis, germinoma, metastatic tumors). Herein, we report a case with infundibular lesion presenting with central diabetes insipidus and hypogonadism.
Case report
A 27-years old woman was admitted to our clinic with the story of amenorrhea and polydipsia lasting for three years. She was on desmopressin for two years. Her physical examination was unremarkable. Hormonal profile was: TSH: 0.79 uIU/ml (0.4–4.67), freeT4: 15.49 pmol/l (11.5–22.7), FSH: 2.03 mIU/ml (1.2–15.4), LH: 1.02 mIU/ml (1.24–7.8), Estradiol: 28.7 pg/ml (30–119), Prolactin: 35.3 ng/ml (2.8–29.2), early morning cortisol: 15.2 µg/dl (4.3–22.4) and IGF1: 152 ng/ml (117–329). Pituitary MRI demonstrated a 7×5 mm infundibular mass with suprasellar extension. Diagnostic work-up for infundibular lesions was performed, including; chest X-ray, computed tomography (CT) of thorax, purified protein derivated (PPD) test and measurement of serum angiotensin converting enzyme (ACE) for ruling out granulomatous diseases. Neck ultrasound, bone scintigraphy, skeletal survey, brain CT and measurement of beta-HCG were performed for ruling out infiudibular neoplastic lesions, Serum anti-thyroid peroxidase, anti-thyroglobulin antibody were measured. All were negative. She exhibited no autoimmune background. Serum IgG4 was normal, as well. In addition to existing desmopression, estrogen-progesteron therapy was introduced and menses recovered in a few months. Due to rapid radiological progression at follow-up, methyl prednisolon 1 mg/kg per day was begun for a possible infundibulohypophysitis. Significant radiological regression was observed at the second month of glucocorticoid therapy.
Conclusions
Pituitary stalk lesions have diverse causes and hypophysitis is one of them. In our case, histopathological diagnosis was not possible due to critical location of the infundibular lesion. After detailed work-up, a diagnosis of possible infundibulohypophysitis was made and ampiric glucocorticoid therapy was introduced and resulted in radiological regression.

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EP964

Pregnancy in Cushing's disease after treatment with surgery and cyber-knife radiosurgery

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Women affected by Cushing's disease (CD) are often infertile due to abnormal follicular development or anovulation. In these patients, first line treatment is pituitary surgery, which is effective in more than 83% of cases with microadenomas, but only in about 35% of those with macroadenomas. When surgery do not normalize circulating ACTH and cortisol concentrations, such drugs, e.g. ketoconazole or metirapone, and radiotherapy are used as adjuvant treatment. Concerning radiotherapy, more precise and focused approaches of delivering larger amounts of radiation have been introduced recently in the management of pituitary tumors. Cyber-knife radiosurgery (CKR) is considered as a possible treatment for patients affected by unsuccessfully surgically treated pituitary adenoma or not suitable for surgery. The disadvantages of this technique seem to be the length of time to the onset of remission, which is known to be at least of 6 months, and the possible adverse effects. In patients treated with radiotherapy, however, mild hypercortisolism can persist for a long time and fertility could not be restored, even when menses have been normalized. We report here a case of a 37-yr-old female patient with Cushing's disease (CD) due to ACTH-secreting 5 mm adenoma on the left side of the pituitary. Because complete clinical remission was not obtained by a transsphenoidal surgery in 2010, CKR was performed for to achieve remission in January 2011. Thereafter, treatment with ketoconazole, at the dose of 400 mg daily, normalized serum cortisol and UFC levels, allowing the recovery of regular menses. Because of low FT4 and low TSH and undetectable AbTPO values, L-T4 replacement was started. 5 years after CKR, morning ACTH, cortisol concentrations, 24-h urinary free cortisol (UFC) and cortisol levels after 1-mg dexamethasone (1-mg dex) administration were normalized. MRI also showed partial shrinkage of the pituitary tumor. The patient, who had regular menses, became pregnant 60 months after CKR. During pregnancy, plasma ACTH, serum cortisol and UFC levels increased. Fasting glucose levels (FGL), HbA1c and blood pressure were normal all throughout pregnancy. Overall, patient's body weight increase was 13.6 kg. At the 38th week of an uneventful pregnancy, the patient delivered vaginally a healthy female newborn (length 48 cm, weight 2600 g). The baby and the mother did not show any biochemical signs or clinical symptoms of hypo- or hypercortisolism. In conclusion, pregnancy should be considered at risk in patients with CD, even the patient has normalized cortisol levels. Moreover, periodic evaluation of pituitary function is mandatory during gestation, due to the high risk of hypopituitarism.

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EP965

The clinic-hormonal description of patients with giant pituitary adenomas

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The aim
To study the results of researches 35 patients with different pituitary tumours of sellar area, from them men – 17 (48,6%%), women – 18 (51,4%%).
Materials and methods
Depending on sizes there are the adenomas of hypophysis, educed on CT/?RI, patients were up-diffused on two groups: the first group of patients is macroadenomas (from 20 to 30 mm) – 17 (48,6%%), and second group of patients – giant – (more than 30 mm) – 18 (51,4%%).
Results
It was educed, that in 2 groups of patients most often there was panhypopituitarism – at 8 from 18 patients (44,4%%), post-operating panhypopituitarism met – at 10 from 18 patients (55,5%%), while in the 1 group of panhypopituitarism not observed. A bytemporal hemianopsia also with greater frequency was observed for patients 2 groups – 11 supervisions (61,1%%). In addition, secondary amenorrhea met a bowl also for patients 2 groups – 6 (33,3%%). Such violations, as secondary ?steopeniya, endocrine encephalopathy, delay of physical and sexual development were educed only in 2 groups of patients. Thus, the most expressed neuroendocrine and ophthalmology violations met for patients 2 groups. For patients with the giant adenomas of hypophysis the decline of level of STH, FSH is first of all marked, LH (45%%).
Conclusions
From preliminary data of comparative description of sizes of tumour of sellar area and level of STH a tendency took place to that as far as growth size of tumour of the Turkish saddle the basale level of STH of plasma was below. For a receipt the further protracted supervision of data of patients is required of reliable results with an estimation in a dynamics MRI and STH of plasma with realization of loading tests, research of IGF1 and estimation of quality of life for questionnaire of adult growth hormone deficiency (AGDQoL).

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EP966

Gender differences in real-life GH dosing patterns in adults with GH deficiency (AGHD): experience from a Registry in France

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Introduction
Usually GHD women require higher GH doses than males, especially those with exogenous oestrogens (guidelines). This fact was assessed in real-life practice in France.
Methods
Data were from a Registry in 84 sites treating AGHD (Norditropin®) up to 5 years. Naïve patients did not receive GH 6 months before inclusion. Statistics were descriptive.
Results
328 patients (129 naïve) were included; mean age 49.2 years (± 14.3 S.D.). 180 were females (55%) with 72 (40%) naïve; data missing for 6. 147 (81.7%) women had a gonadotropic deficiency: 83 (79%) non-naive and 54 (75%) naive treated with oestrogen therapy. At inclusion the median IGF-1 SDS (Q1;Q3) in naive population was −2,20 (−3.20;−1.30) and in non-naïve was 0.00 (−1.30; +1.10). The median starting dose was similar for naive women and men: 0.20 mg/d. After the first year until the end of the follow up (FU) the median dose for naïve women was higher than for men. The median dose was higher for non-naive females (Table 1). At the end of the FU, the median IGF1 SDS (Q1; Q3) in naive population was +0.30 (−0.50;+0.80) and in non-naïve was +0.50 (−0.40;+1.20).

Table 1 Median GH dose (Q1;Q3) (mg/day)

Year	♀ naive	♂ naive	♀ non-naive	♂ non-naive
Inclusion	0.20 (0.20;0.30)	0.20 (0.20;0.30)	0.40 (0.20;0.60)	0.30 (0.20;0.40)
1	0.40 (0.30;0.50)	0.30 (0.20;0.40)	0.40 (0.30;0.70)	0.35 (0.20;0.50)
2	0.50 (0.30;0.60)	0.30 (0.20;0.40)	0.40 (0.30;0.60)	0.40 (0.20;0.50)
3	0.50 (0.30;0.70)	0.39 (0.20;0.50)	0.40 (0.30;0.60)	0.30 (0.20;0.50)
4	0.50 (0.40;0.70)	0.37 (0.20;0.50)	0.40 (0.30;0.65)	0.40 (0.20;0.52)
5	0.60 (0.45;0.80)	0.40 (0.30;0.50)	0.40 (0.30;0.70)	0.30 (0.20;0.52)

Conclusion
In real life, physicians consider the recommendation of higher GH dose for AGHD women at steady state, while the starting dose remains similar in both genders. Data from this Registry is consistent with the published data from other observational studies.

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EP967

Is there a role of immunohistochemical expression of pituitary hormones and proliferative marker ki-67 on long-term outcome in our acromegalic patients?

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Expression of hormones other than GH may affect the prognosis in acromegalic patients. Generally, Ki-67 is a well-known proliferative index used to predict remission in pituitary adenomas. We aimed to evaluate the relationship of immunohistochemical expression pituitary hormones, ki-67 and remission. Also we evaluated the role of pre, post-operative clinical and laboratory values, pathological characteristics on long-term remission. We included 64 acromegaly patients that were treated surgically and followed up in our Endocrinology and Metabolic Diseases Department. Demographic, clinical, laboratory and imaging data were collected. We also re-evaluated the immunohistochemistry of all pituitary hormones and ki-67 marker from paraffin blocks. We followed 64 patients (38 women, 26 Male; mean age 46.7 ± 11.8) for 61.8 (6–192) months. We did not found any relationship between remission and multihormonal expression in our patients. We also did not found a significant relationship between ki-67 expression or sex with remission. Early diagnosis age ($P=0.045$), greater adenoma diameter ($P=0.002$), low preoperative LH ($P=0.036$) and high postoperative IGF1 ($P<0.0001$) only factors that are significantly related with low rate remission. Preoperative cortisol levels are related to ki-67 index level ($P=0.004$). Low preoperative LH and high postoperative IGF1 levels and tumor diameter may be predictive for remission and low cortisol levels may be predictive for the high ki-67 index.

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EP968

Investigation of the pituitary functions long-term after the acute CNS infections

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Objectives
Acute bacterial or viral CNS infections have been shown to result in hypopituitarism during the acute phase, and 6–24 months after the event in a few studies. However, there are no data in the literature regarding the long term pituitary functions after acute CNS infections. This cross-sectional study was designed to evaluate the pituitary functions long-term after the acute bacterial or viral CNS infections.
Methods
19 patients with ages 18–65 (mean: 39.53 ± 17.089 years; 11 male patients, eight patients female) were included in the study. There were seven patients with acute bacterial meningitis, nine patients with acute viral encephalitis, and three cases of acute meningoencephalitis. Basal pituitary hormone levels were measured and glucagon stimulation test was performed 17–92 months (mean 48.47 ± 25.19 months) after the acute CNS infections. MRI was performed to evaluate the pituitary gland volume and to rule out any co-incidental pituitary mass.
Results
There were a total of 5 patients out of 19 (26.3%) with hypopituitarism; 3 (15.7%) with isolated GH deficiency, 1 (5.2%) with isolated FSH-LH deficiency and 1 (5.2%) with combined FSH-LH and GH deficiency in the study group. Mean pituitary volume was substantially lower in patients with hypopituitarism when compared to the patients without hypopituitarism. But the difference was not statistically significant.
Conclusion
This study clearly demonstrated that high frequency hypopituitarism, GH deficiency in particular, was still present long term after the acute bacterial or viral CNS infections. Therefore, the patients with acute meningitis, meningoencephalitis and/or encephalitis need to be screened at least 4–5 years after the acute event.

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EP969

A case with headache and pitosis: pituitary macroadenoma or ophtalmoplegic migraine?

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Case
A 28-year old man was admitted to our hospital with complaints of three days of severe headache, diplopia and ptosis of the right eye. He had pituitary macroadenoma and had been on cabergolin 0.25 mg/week for the last six months. At physical examination, he demonstrated ptosis and inability to move the right eye medially. Magnetic resonance imaging showed a 13×12 mm pituitary mass with suprasellar extension and hemorrhage. Visual field analysis was abnormal except the lateral movement of the right eye. Laboratory hormonal analysis showed mild cortisol deficiency only. According to clinical, radiological and laboratory results, he was diagnosed as non-functional pituitary adenoma with apoplexy and III.cranial nerve palsy due to increased intrapituitary pressure. Intravenous methyl-prednisolone was started and symptoms resolved. One month after discharge, although he was using methyl prednisolone 4 mg, he was again admitted with complaints of nausea, vomiting, hypotension and ptosis. He was immediately taken to pituitary surgery via transnasal-transsphenoidal approach. His complaints dissolved following the procedure and he was well at discharge. Histopathological analysis of the operation specimen exhibited a pituitary adenoma with necrosis and hemorrhage. On the fifth postoperative day, he was re-admitted with diplopia, photophobia, phonophobia, nausea and vomiting. Recurrent headache attacks lasting for about one week within the last 6 months reminded accompanying ophtalmoplegic migraine. Eighty mg eltriptan and parenteral pulse steroid (1000 mg methyl prednisolone/5 days) were started. The patient had no longer experienced an attack.
Conclusion
Pituitary apoplexy and ophtalmoplegic migraine are rare clinical entities. Ophthalmoplegic migraine has been recognized as a cranial neuralgia and characterized by repetitive III, IV and / or VI. cranial nerve palsies. If there is persistent headache and cranial nerve palsies following surgical decompression of an adenoma with pituitary apoplexy, accompanying ophtalmoplegic migraine should be kept in mind.

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EP970

Somatostatin analogues-induced diabetes mellitus in acromegalic patients reverts after drug withdrawal: a long-term study

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Context
Therapy with somatostatin analogues (SSAs) may have deleterious effects on glucose metabolism in patients with acromegaly, often leading to development of diabetes mellitus (DM).
Aim of the study
To evaluate whether DM, which developed during therapy with SSAs, may revert after drug withdrawal and cure of acromegaly with pituitary adenomectomy.
Design
Retrospective cohort study, in a tertiary referral center.
Patients
Eighteen acromegalic patients without DM at the diagnosis of acromegaly treated with SSAs as a primary therapy, and then cured by pituitary adenomectomy.
Methods
Endocrine status and glucose homeostasis were evaluated at diagnosis of acromegaly and at least every six months during SSAs therapy. At each control patients were classified in one of the following classes: normal glucose tolerance, prediabes, overt diabetes.
Results
Median follow-up after starting SSAs therapy was 60 months (IQR 53.2–96.2). During SSAs therapy, all patients had controlled acromegaly defined by normal serum IGF-1 concentrations for the age. Among the 13 euglycaemic patients at diagnosis three developed prediabetes and three diabetes, whereas, among the five

prediabetic patients at diagnosis two worsened to overt diabetes; three remained in the prediabetic range ($P=0.04$). After cure of acromegaly with pituitary adenomectomy and subsequent SSAs withdrawal, prediabetes reverted in five out of six patients, and diabetes in all five patients (in three reverted to euglycaemia, while in two reverted to prediabetes) ($P=0.01$).
Conclusions
In acromegalic patients with controlled disease changes of glycaemic status induced by SSAs are not permanent.

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EP971

Pituitary metastases of lung cancer presenting with hypopituatrism

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Pituitary tumors are the most frequent intracranial neoplasm, affecting 11 000 of the world wide population. However metastases in this location are rare and uncommon presentation of systemic malignancy. Although diabetes insipidus secondary to cancer metastasis to the pituitary gland is a common manifestation, anterior pituitary failure is rare. We present a −57-year-old man with hypopituitarism secondary to pituatry metastasis from lung cancer.
Case report
A 57-year-old patient active smoker presented with headache of 1 month. Cranial MRI revealed multiple subcortical lesions and hypophyseal noduler lesion 13.6 mm in diameter. The computary tomography scan of the Chest, Abdomen and Pelvis revealed a 23×22 mm rregularly margined mass in mass in the upper left lobe with mediastinal lymph nodes, liver and right adrenal metastases. Assessment of pituitary function revealed panhypopituitarism; Cortisol: 3.17 μg/dl, ACTH:11.5 pg/ml free T_4 0.64 ng/dl (normal range 0–97–1.65), thyroid stimulating hormone level of 0.005 mUI/ml (normal range 0.5–4 IU/ml), total testosterone level of 0.025 ng/ml (normal range 2.5–10 ng/ml), follicle stimulating hormone level of 0.5 IU/ml (normal range 1–8.4 IU/ml), luteinizing hormon level of 0.1I U/l (normal range 1–10.5 IU/l) and normal urine osmolarity. Complete blood count showed the following: hemoglobin 13.6 g/dl, white cell count 12.64 K/ul, and platelet count 322 K/ul Evaluation of serum chemistry revealed lactate dehydrogenase 245 IU/l, sodium 129 mmol/l potassium 4.3 mmol/l. A hormone replacement therapy was indicated urgently. Fiberoptic bronchoscopy did not show any endobronchial lesion. Histopathologic examination of brochoalveolar lavage revealed metastasis of lung adenocarcinoma.
Conclusion
Despite the fact that pituitary metastasis are rare, they must be evaluated in the presence of pituitary involvement. It may be difficult to differentiate symptoms due to panhypopituitarism from the constitutional symptoms caused by cancer progression. Considering that the life expectancy is limited for advanced lung cancer patients, detection and appropriate treatment of hormonal insufficiency are important to improve their quality of life.

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EP972

ACTH deficiency in patient with bilateral adrenal adenomas

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Introduction
ACTH deficiency is a rare disease with non-specific symptoms such as anorexia, fatigue and weight loss. Due to these silent symptoms the disease is easily overlooked and may escape detection for a long time, especially in elderly patient.
Case
67-year-old female patient applied with complaints of fatigue. Bilateral adrenal adenoma was detected during ultrasonographic evaluation and and patient was consulted to endocrinology clinic Her personal history included osteoporosis and multinodular goiter. On clinical examination; height 153 cm, weight: 67 kg, BMI:29 BP: 120/70 mm/Hg. The other physical examination findings were normal. Radiologic findings included: Abdominal MRI: in the right adrenal gland, 20×12 mm and 33×13 mm in left adrenal gland adenomas was detected. The laboratory findings were shown in Table 1. Basal Cortisol levels were detected as 6.6 μg/dl and insulin tolerans test and ACTH stimulation test were performed. (Table 2, Table 3).

Table 1 Results of basal endocrine and biochemical investigations of patient

Parameter (unit)	Value
Glucose (mg/dl)	87
Na (mmol/l)	137
K (mmol/l)	4.5
FT_4 (ng/dl)	2.69
TSH (μIU/ml)	4.70
Cortisol (μg/dl)	8.7
Vanillylmandelic acid (mg/24 s)	1.56
Metanephrine (μg/24 s)	168
Normetanephrine (μg/24s)	298

Table 2 Results during insulin tolerance test

Parameter	Value
Glucose (mg/dl)	45
Cortisol (ug/dl)	5
GH (ng/ml)	0.45
ACTH (pg/ml)	<0.5

Table 3 Results during ACTH stimulation test

Parameter			
Minute	0	30	60
Cortisol (μg/dl)	18.6	24	32

Conclusion
Acth deficiency is rare in elderly patients is a complex disease and many diseases that mimic. Sometimes patients are diagnosed by chance. When this case was examined for adrenal adenoma, ACTH deficiency was unexpectedly detected and replacement therapy was started. The clinic has the patient improved rapidly with replacement therapy.

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EP973

Clinical, histological, molecular features and outcomes of craniopharyngiomas: Single centre experience in Toledo, Spain

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Background
Craniopharyngiomas (CPs) are epithelial tumors that typically arise in the suprasellar region. They are associated with high levels of morbidity related to tumour location and/or treatment-related injuries. Recent discoveries have also led to a better understanding of CP development and potential treatments.
Objetive
To analyse the clinical, pathological, molecular features and outcomes of patients with CP.
Design
Retrospective observational study.

Methods
Clinical records review and re-evaluation of histologic samples from patients who underwent surgery of CP in our institution between 1999 and 2016.
Results
There were 26 patients (53.8% male), mean age at diagnosis 37 years (range 2–73). Mean follow-up was 86 months (range 3–288). The commonest presenting symptoms were: visual alterations 84% ($n=21$), headaches 53.8% ($n=14$), and behaviour disorders 11.4% ($n=3$). 92.3% (24/25) of tumours had suprasellar involvement, with cystic component in 80.8% (16/26). Median tumour size was 30.4 mm (12–50). Initial surgical approach was transcranial in 96.2% ($n=25$). Available histological and molecular results were: 72% ($n=18$) adamantinomatous CP and 28% ($n=7$) papillary CP (PCP). Three PCP harboured BRAF V600E mutation. In these cases, the average number of surgical interventions were higher (4 vs1.3) and time to recurrence was shorter (34 vs 99 months). Three patients (11.4%) undergone radiation therapy. Last neuroimaging assessment showed residual tumour in 50% of patients. At the end of follow-up, panhypopituitarism and diabetes insipidus were detected in 72% (18/25) and 75% (18/24) respectively. Symptoms related to hypothalamic dysfunction were found in 76% (19/25). The mortality was 11.5% ($n=3$). Causes of death were: initial surgery related complications (1), multiple recurrent PCP harboured mutation BRAF v600E (1) and cardiovascular disease (1).
Conclusions
In our study, treatment of craniopharyngiomas were associated with high rates of tumor persistence and substantial morbidity. Tumours harboured BRAF V600E mutation seemed to be associated with poor prognosis.

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EP974

Cushing's disease: is there a Continuum from corticotroph hyperplasia to adenoma?

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Introduction
Successful long-term management of patients with Cushing's disease (CD) remains a challenge. Few studies have analyzed the long-term recurrence rates of CD after transsphenoidal surgery (TS).
Objectives
1) to compare the outcome of patients with and without postoperative criteria for cure; 2) to compare the outcome of patients with and without a histological diagnosis of adenoma.
Methods
Retrospective, descriptive study. Forty-two patients with CD submitted to TS between 2005 and 2016 were included. Variables analyzed: postoperative criteria for cure, CD remission and recurrence rates, histological findings.
Results
Surgical remission was achieved in thirty-eight patients. The mean follow-up was 6.8 years. Sixteen patients recurred. The mean time to recurrence was 4.6 years. Immediate postoperative evaluation was performed in 34 cases; criteria for cure were observed in seventeen. Patients with clinical recurrence who presented postoperative criteria for cure had a mean disease free-time of 7.1 years, opposed to 2.2 years in those without biochemical criteria for cure (P-value 0.032). Six patients without biochemical criteria for cure after surgery are in remission. Histology documented an adenoma in thirty patients; from these, eleven recurred.
Discussion
In this study, 42.1% of the patients who achieved remission, after TS, recurred. This finding emphasizes the need for continued biochemical and clinical follow-up. On the other hand, some patients without postoperative criteria for cure were in remission, at last observation. Thus, suggesting that biochemical criteria for cure may be achieved at different timings from patient to patient. Evidence for recurrence in eleven patients with adenoma suggests that CD may be a *continuum*, in which there is a basal corticotroph hyperplasia likely to evolve to adenoma.

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EP975

The use of increasing doses of cabergoline in the management of cabergoline-resistant prolactinomas

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Introduction
Dopamine agonists (DA) are the ideal treatment for prolactinomas and cabergoline (CAB) is the drug of choice, for being much more effective and better tolerated than bromocriptine. However, 10-15% of patients with prolactinomas are considered to be resistant to CAB, as they dot not achieve prolactin (PRL) normalization, while in use of conventional doses of this drug.
Objective
To evaluate the effiaccy of increasing doses of CAB in prolactinomas refractory to CAB 3 mg/wk by in order to achieve prolactin (PRL) normalization.
Patients and methods
We prospectively evaluated the management of consecutive patients with prolactinomas refractory to CAB 3 mg/wk who were submitted to progressive increases in CAB dose, as needed and tolerated every 3 months, up to 9 mg/week. The patients were recruited over a 12-month period. Exclusion criteria were previous pituitary surgery or radiotherapy. Echocardiogram evaluation was performed in each patient every 6 months.
Results
Twenty five patients were included in this study, 20 with macroprolactinomas. Overall, normalization of PRL levels was achieved in 18 patients (72%): in 3 (12%) with a dose up to 4 mg/wk, in 9 (36%) with 5 mg/wk and in 6 (24%) with 6–7 mg/wk. No patients benefited from doses >7 mg/wk. No significant echocardio-graphic valve abnormalities were detected.
Conclusion
CAB doses up to 7 mg/wk were well tolerated and enabled PRL normalization in 18 (72%) patients with prolactinomas resistant to CAB 3 mg/wk. No patients benefited from doses >7 mg/wk.

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EP976

Long-term efficacy of octreotide LAR in acromegaly patients, a prospective single centre study with 7 years follow up

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Objective
The aim of this single centre prospective open trial was to evaluate the long-term efficacy of octreotide LAR in acromegaly patients.
Methods
In total of 19 patients with acromegaly diagnosed at Endocrinology Department of Clinical Centre of University in Sarajevo, somatostatin sensitive (ten females and eight males, age range 40–68 years, six patients with microadenoma and 12 patients with macroadenoma) were treated with octreotide. Follow-up period was 7 years (2009–2016). The concentration of human Growth Hormone (hGH) and insulin-like growth factor-1 (IGF-1) were evaluated every 6 months, while magnetic resonance imaging was taken every year during follow-up period.
Results
During the first year of treatment ten patients were included. In the second year, a further seven patients were involved. During the last 4 years, five patients were included. During the seventh year of follow-up, the treatment was successful discontinued at four patients, two patients was passed away due to co-morbidities and at two another patients' treatment was cancelled due to cancer; so currently we followed total of 11 patients. One of patient was treated by Gamma Knife radiosurgery and after that developed pituitary deficiency, but he is needed to continue with octreotide treatment because of high hGH and IGF-1 level. During octreotide treatment, significantly reduced GH (50.87 ± 10.56 vs $3{,}4\pm0.76$ ng/ml, $P<0{,}005$), IGF-1 (777.66 ± 118.40 vs 349 ± 97.54 ng/ml, $P<0.005$) and adenoma size (from 9.6 to 8 mm; $P<0.05$). GH decrease to less than 1 ng/ml was achieved in 66% of cases; tumour size decrease was achieved in 49%, while normalization of IGF-1 was achieved in 88% of the patients, respectively. At 1–4 years of follow-up, 20% of acromegaly patients had withdrawn treatment, without recurrence. Two patients on octreotide treatment have uncontrolled acromegaly.

Conclusion
Octreotide LAR treatment is effective in decrease of GH, IGF-1 and tumour size in well-selected acromegalic patients.

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EP977

Is there a gender difference in clinically nonfunctional pituitary adenomas?

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Introduction
Clinically nonfunctioning pituitary adenomas (NFPA) are the most common pituitary tumor type. They are usually recognized after they cause symptoms especially when tumor size increases and eventually invades adjacent structures. Nevertheless the discovery would also be accidental. In the literature some kind of gender difference is reported in NFA's behavioral results such as pituitary axis deficits or consequences of surgery however they resulted with controversial reports. In our study we investigated if there is male/female preponderance in terms of NFA's some number of features.
Materials and methods
We retrospectively examined 101 patients diagnosed as NFA biochemically and radiologically. All patients were questioned for each possible symptom of pituitary adenoma at diagnosis. Every patient was examined by laboratory pituitary hormonal tests. Pituitary adenomas were radiographically evaluated by MRI (dimensions(mm): d1$\times$d2$\times$d3). Microsurgical resection of adenoma was performed in patients with symptomatic or large and invasive tumors.
Results
101 patients (57 female (56.4%) and 44 male (43.6%)) were assessed in the study. The age at diagnosis was younger for women than men (40.0 yr vs 51.4 yr, *P*:0.000). Tumor size were larger for men (d1: 21.9$\pm$2.6 mm vs 9.4$\pm$1.4 mm, *P*:0.000). Among the rate of symptoms headache was the most frequent. Blurred vision was more common in men (45.5% vs 26.8%, *P*:0.06). The frequency of pituitary hormone deficiency was more common in men (37.0% vs 12.1%). 43 (42%) patients have been performed pituitary surgery. Postsurgical hypopituitarism was more commonly seen in female, whereas permanent DI was more abundant in male, with nonsignificance in both issues (38.5% in female vs. 27.5% in male, *P*:0.34; 7.7% in female vs. 13.3% in male, *P*:0.60; respectively).
Conclusion
Sex would be a prognostic parameter in NPA patients in terms of hypopituitarism, postoperative hypopituitarism and tumor mass. In our study, women were shown to be diagnosed earlier and men were defined to have larger tumors. Greatly would be explained with the mass effect, we determined hypopituitarism was more common in men. Selectively postsurgical hypopituitarism, however nonsignificant, was found more common in female group in our study.

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EP978

The value of early postoperative OGTT as a predictor of surgical outcome in patients with acromegaly after total transsphenoidal adenomectomy

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Introduction
Transsphenoidal surgery (TSS) is the treatment of choice for patients with acromegaly. However, even after radical surgery persistence of acromegaly may remain up to thirty percent by resent studies (Starnoni, 2016). Nadir growth hormone (GH) level less than 1.0 μg/l on an early postoperative oral glucose tolerance test (OGTT) have been suggested as early predictor of surgical remission (Kim 2012). However, the value of this approach remains to be defined.
Aim
The purpose of our study is to evaluate the utility of measurement of GH level during a 2-week postoperative OGTT as a predictor for surgical outcome in patients with acromegaly.
Materials and methods
Ten patients (five women and five men) with an average age of 47.4$\pm$14.8 years (range 27–71 years) who had underwent total transsphenoidal adenomectomy performed by one neurosurgeon were included in this study. All patients harbored macroadenomas, with average size of 18.9$\pm$5.2 mm (range 13–29 mm). Measurement of GH level during OGTT was performed 14 days after surgery. The outcome of TSS was evaluated 6 months after surgery by OGTT and measurement of insulin-like growth factor 1 (IGF-1). The biochemical remission of acromegaly according to the 2010 remission criteria were defined as nadir GH level on an OGTT $<$0.4 μg/l along with age and gender normalized values of IGF-1.
Results
Initial basal GH level was 23.7$\pm$24.9 μg/l, initial IGF-1 patient /IGF-1ULN ratio was 2.7$\pm$0.6. Six months after surgery the remission of acromegaly was achieved in five patients (50%) – mean IGF-1 patient/IGF-1ULN – 0.7$\pm$0.2, mean nadir GH level on an OGTT – 0.30+0.09 μg/l. Nadir GH level on an 2-week postoperative OGTT was less than 1.0 μg/l in all patients with remission of acromegaly. Whereas, all patients with persistence of the disease had nadir GH levels $>$1.0 μg/l on an early postoperative OGTT.
Conclusion
Our initial data suggest that nadir growth hormone level on an 2-week postoperative OGTT less than 1.0 μg/l associated with remission of acromegaly 6 months after surgery. Further researches are required to specify long-term outcomes.

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EP979

Giant macroprolactinoma in women still exist

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Background
Prolactinomas are the most common hormone-secreting pituitary tumors and are a common cause of anovulation and infertility. Giant prolactinomas (0.5–4.4% of all pituitary tumors) are rare tumors characterized by their large size ($>$4 cm), compressive symptoms and extremely high prolactin secretion ($>$1000 ng/ml). Men are most commonly affected, with a reported male to female ratio of 9:1.
Case report
We present the rare case of 53-years-old female, with a history of amenorrhea from age 35, who was never investigated or treated. In December 2015 she was admitted in the neurosurgery department for severe headaches and visual impairment. On clinical examination, left eye mydriasis and left lateral nystagmus were noted. A head CT showed a pituitary tumor of 55 mm diameter, invading the sphenoid sinus, both cavernous sinuses, the left orbit and compressing the third ventricle, with mass effect. The blood tests revealed a very high serum prolactin of 32625 ng/ml (4–23) and low sexual and gonadotrophic hormones. Given the clinical and CT aspects, decompressive transcranial surgery was performed, resulting in rapid improvement of the neurological signs and lowering of the PRL levels to 1980 ng/ml. Nasal fistula and transient diabetes insipidus occurred after surgery and were cured by sphenoid sinus filling and treatment with desmopressin. For the residual prolactin secretion, Cabergoline treatment was started (1.5–2 mg/week) which resulted in prolactin suppression and diminuation of the tumoral remaint. The restoration of the gonadotrophic secretion resulted in numerous painful ovarian cysts that were cured by bilateral oophorectomy.
Conclusions
We present this rare case in order to highlight the importance of the etiological investigation of secondary amenorrhea in women. The patient almost died because of the mass effect of a benign tumor, easily manageable by medical treatment and suffered multiple complications due to the neglect of her secondary amenorrhea.

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EP980

Associated neoplasia in Romanian acromegalic patients

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Introduction
Acromegaly has various complications that significantly alter patients' lives, one of which is developing neoplasia, a subject of high interest in the scientific community during the last years but without any firm conclusions.
Aim
The main objective of this paper was to verify if Romanian acromegalic patients are susceptible to developing neoplasia and what types of tumors are associated with acromegaly. Another purpose of the paper was to identify the risk factors involved in tumor predisposition.
Methods
This observational, retrospective study considered 336 acromegalic patients (217 of them females, 64.6%) followed from 2001 until 2015 in report to the evolution of acromegaly and the development of associated diseases, mainly neoplasia.
Results
Acromegalic patients had a higher risk of developing associated neoplasia (40% benign and 10% malignant). Activity of the disease was not an important factor (except for the thyroid – 54.84% of the patients had active acromegaly), whereas initial values of IGF-1 seemed to influence the developing of prostate neoplasia (mean corrected value 4.58, $P=0.025$). Sex has proved to be a factor too: women were more prone to developing neoplasia than men (57.14 vs 34.29%), and especially multiple types of tumors. The most frequently associated types of neoplasia in our patients were developed in: thyroid (47% women, 20.95% men), breast (11.93%) and uterus (5.99%)-for women, and colon (9.52%) and prostate (6.67%)-for men. The longer the duration of active acromegaly the higher was the risk of developing colonic neoplasia.
Conclusions
The results suggest that we need to perform a more meticulously screening of associated tumours in acromegalic patients, not only using ultrasound and colonoscopy for the thyroid gland and colon, but also mammography as well as PSA level determination. These evaluations should be taken into consideration periodically in all our acromegalic patients, regardless of the evolution of their main disease.

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EP981

Clinical and histopathologic characteristics of thyroid cancer in the patients with acromegaly

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Aim
There are some studies suggesting that the risk of developing cancers,especially thyroid cancer, is increased in the patients with acromegaly. The prevalence of thyroid cancer is 1.2-10.6% among the patients with acromegaly. In this study, we aimed to evaluate clinical and histopathologic characteristics of thyroid cancer among the patients with acromegaly.
Method
We retrospectively evaluated the patients with acromegaly who had been followed-up by our department between the years 2005 and 2016 and diagnosed with thyroid cancer.
Results
9 (81.8%) of 11 subjects were female and 2 (18.2%) patients were male. The mean age of the patients at the time of acromegaly diagnosis was 41 ± 11years. Among subjects who had been followed for 11.45 ± 9.37 years, all except one patient were not in remission and were receiving medical treatment. All subjects were diagnosed with thyroid cancer after the diagnosis of acromegaly and the mean time until the diagnosis of thyroid cancer was.27 ± 9.23 years. In terms of thyroid hormone status, nine subjects were euthyroid and two patients were found to have central hypothyroidism. Thyroid ultrasonographic examination revealed multinodular goiter in all patients. Thyroid fine needle aspiration biopsy was performed for nodules bigger than 1 cm or nodules with malignancy criteria. Thyroid fine needle aspiration biopsy demonstrated undetermined atypia in 27.3%, suspicious follicular neoplasia in 36.4%, follicular neoplasia in 9.1% and suspicious malignancy in 27.32% of the subjects. All patients underwent total thyroidectomy. Pathological examination of thyroid tissue revealed follicular variant papillary thyroid cancer in 5, classic and follicular variant papillary thyroid cancer in 3, diffuse sclerosing variant papillary thyroid cancer in 1, solid variant papillary thyroid cancer in 1 and follicular, classic and clear cell papillary thyroid cancer in one patient. 72.7% of the patients had multifocal disease and 63.7% of the subjects had unilateral disease. Lymphovascular invasion and extrathyroidal extension were present in 9.1 and 18.2% of the subjects, respectively. No distant or local metastasis was detected during mean follow-up period of 28.72 ± 16.18 months.
Conclusion
Patients with acromegaly should be considered for the presence of thyroid cancer.

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EP982

The triglyceride (TG)/HDL Cholesterol (TG/HDL-C) ratio as marker of adipose tissue dysfunction at patients with acromegaly

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Background and aims
The ratio of TG/ HDL-C can identify cardiometabolic risk and cardiovascular disease. The visceral adiposity index (VAI) is a sex-specific index, in which measurements of body mass index and waist circumference are combined with TG and HDL-C concentrations. T? study association between VAI and TG/HDL-C and the value of TG/HDL-C ratio as a marker of disfunction of visceral adiposity tissue at patients with acromegaly.
Subjects and methods
Eighty-eight patients (30 men and 58 women; aged 17–75 years) with acromegaly were under investigation. Disease activity was evaluated according to the Consensus Conference criteria (2000). Blood samples for GH, IGF-1, TG, HDL-C and total cholesterol were taken in fasting state. VAI score and normal values used by M. C. Amato et al., 2011. It was considered the normal VAI in an age-dependent group to 30 years <2.52, from 31 to 42 years – <2.23, from 43 to 52 years – <1.92, from 53 to 66 years – <1.93 and more than 67 years – <2.00 Taking into account a value VAI, all patients were divided on two groups: with normal VAI (55.7%) (group 1) and high VAI (44.3%) (group 2). The 10-years-old general cardiovasculary risk (CVD) was determined by a calculator «General CVD Risk Prediction».
Results
At nonlinear correlation, TG/HDL-C ratio was highly correlated with VAI in both men ($r_s=0.96$, $P=0.00001$) and women ($r_s=0.97$, $P=0.00001$), that TG/HDL-C can serve as more adequate criterion of estimation of disfunction of visceral adiposity tissue at patients with acromegaly. This supposition confirms exposed by us for patients in a general group positive correlation TG/HDL-C with the level of GH ($r_s=0.38$, $P=0.0001$). Before TG/HDL-C it was suggested to use for identification of cardiometabolic risk in general population (M. R. Salazar *et al*., 2014). In a group with high VAI 10-years-old CVD risk and MS risk in 1.6 and 1.4 times, according higher, than in a group with normal VAI (OR 1.56, OR 1.42).
Conclusion
By the equivalent of VAI for the estimation of expressed of disfunction of visceral adiposity tissue at patients with acromegaly can serve also TG/HDL-C ratio.

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EP983

Anti-proliferative effects of high doses cabergoline in patients with prolactinoma

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The aim of the study
To investigate the anti-proliferative effect of cabergoline (CAB) which was used in different regimes of suppressive therapy during 12 months in patients with prolactinoma (PROL).

Subjects and methods
It was examined and underwent a 12 month course of treatment by selective dopamine agonist CAB 61 patients with PROL: microadenoma 42, macro&giant PROL - 19. (52 women/9 men) aged 16–66 years. The total duration of the disease ranged from 1 to 60 months, average (12.3 ± 10.1) months. PROL was verified using MRI 1.5T. Pituitary volume was calculated by the Di Chiro-Nelson. Were estimated total and partial secretory activity (PSA) in PROL. PRL blood levels (ng/ml) were determined. Applied two modes of therapy: 1 – the mode of gradual increase of a CAB dose, since 0.5 mg/week with the subsequent control of the PRL blood level in each 4 weeks and titration CAB dose if necessary (increase in a week dose by 0.25–0.5 mg); 2 – the mode of high starting doses from calculation: the quantity of tablets CAB (0.5 mg) corresponded to frequency rate of increase of the PRL blood level in relation to the upper limit of age norm, but no more than 4 mg (8 tablets) a week. The statistical data analysis was carried out with SPSS version 9.0.
Results
At purpose of high starting doses of CAB after 1 mth of treatment PRL level in 58.1% of patients decreased to the reference values, including in patients with macroPROL after 1 month at 26.3% of patients had achieved target levels, after 3 months - at 84.2%, and by 6 months of treatment - at 100% patients. In all patients it was a statistically significant decreasing the pituitary volume after 12 months of treatment ($P < 0{,}001$), but only in patients who were treated high starting high dose CAB recorded decrease in the size of adenoma by 50% or more of the basal volume: at 9 microPROL and 4 macroPROL.
Conclusions
The most expressed anti-proliferative effect is noted at application of high starting doses of CAB. Optimum therapeutic average and cumulative doses of CAB for achievement of maximum therapeutic effect at patients with microPROL are doses of 0.8 mg/week and 33.8 mg/year, respectively; for patients with macro&giant PROL – 1.3 mg/week and 67.6 mg/year, respectively. At patients with microPROL the positive therapeutic effect is reached on a smaller cumulative CAB dose which is associated with a lower risk of complications in the long term period.

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EP984

Invasive macroprolactinomas and its response to treatment in male patients

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Introduction
Prolactin-producing pituitary adenomas are the most common pituitary tumors in clinical practice. In men they are more aggressive and their response to pharmacological treatment is unknown.
Objective
Describe the clinical characteristics and response according to the treatment of a group of male patients with invasive macroprolactinomas.
Materials and methods
A retrospective descriptive study, a series of cases, in 30 patients, attending two pituitary clinics (National Endocrinology Institute in Havana, Cuba and Imbanaco Cali Colombia Medical Center) between 2002 and 2012. Results Between the two types of treatment were compared and measures of central tendency and test of Student or Kruskal Wallis were used.
Results
The mean age was 44 ± 13.8 years; the disease duration was 5.2 ± 4.1 years; 96% of the patients presented headache, followed by hypopituitarism (80%). The median prolactin value at admission was 487 ng/ml. 53% required surgery plus dopaminergic agonists; in this group there was a decrease in prolactin levels of 86% at 6 months and 96% at 12 months; in the dopaminergic agonist group, there was a 71% decrease at 6 months and 95% at 12 months. Surgical patients had the mayor Tumor size reduction 11.4 mm compared with 8.3 mm, however a year there were no difference between the groups.
Conclusion
Surgical treatment plus dopaminergic agonist showed no differences with medical treatment in reducing prolactin values during the first year of treatment regardless of tumor size.

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EP985

Venous glucose levels, peak GH and peak cortisol during Insulin Tolerance Test using 0.15 UNITS/Kg and 0.1 UNITS/Kg body weight

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Insulin Tolerance Test (ITT) is a procedure commonly done by Endocrine Specialist Nurse in endocrine department. We look at over 120 ITT results done in 2 endocrine centres using Insulin Actrapid 0.15 UNITS/kg and 0.10 UNITS/kg dose plotting the glucose levels at 30, 45 and 60 min. We also look at peak GH and peak cortisol on each of these groups.
Aims
We wanted to know how many percentage of patients achieving hypoglycaemia below 0.5 mmol/l, 0.5–1.0 mmol/l, 1.1–1.5 mmol/l, 1.6–2.0 mmol/l and above 2.0 mmol/l. We also look at percentage of peak GH response achieving over 9 microgram/l, between 8–9 microgram/l and below 8 microgram/l. In the peak cortisol response, we looked at results over 550 nmol/l; 500–550 nmol/l; 450–500 nmol/l; 400–450 nmol/l and below 400 nmol/l. Within these data, we also look at a small groups of results for patients' using 0.15 UNITS/kg as repeat dose and repeat ITT using the lower dose to compare if these are difference in these markers.
Summary
We are unable to draw summary at the moment as well still got 30 data to go through.

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EP986

Long-term impact of primary medical and surgical therapy on bone density in men versus women with prolactinomas

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Purpose
The prevalence of pathological bone densities in men and women with prolactinomas treated either primary surgically or medically are infrequently reported across large cohorts. In the present study, we aimed at comparing the impact of either therapeutic approach on the bone density in men vs women with prolactinomas.
Methods
Retrospective case-note study including all consecutive patients with prolactinomas in whom osteodensitometry data was available at study entry and long-term follow-up (≧ 12 months). Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry. Clinical and biochemical characteristics, tumor size, and remission rates were recorded.
Results
Hundred patients (40 men, 60 women) met inclusion criteria. At baseline, men had a significantly higher prevalence of pathological BMD than women (28 vs 2%, $P < 0.001$). Primary medical therapy was considered in 47, first-line surgery in 53 patients. Median follow-up time was 79 months (range 12–408 months). Long-term PRL values significantly decreased in both cohorts, regardless of the primary treatment. There was a persisted need for dopamine (DA)-agonists in 75% men compared to 42% women ($P = 0.001$). The prevalence of pathological BMD in men remained significantly higher than in women (37 vs 7%, $P < 0.001$), independent of the primary treatment strategy.
Conclusions
The prevalence of pathological BMD in men remains significantly higher than in women, independent of the primary treatment strategy. While osteoporosis prevention and treatment is mainly focusing on women, awareness of the bone loss in men with prolactinomas should not be underestimated.

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EP987

Stenosis of the external auditory canal in an acromegalic patient: a novel complication

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Acromegaly is associated with a range of comorbidities, including cardiovascular disease, diabetes, hypertension and sleep apnea. Bony overgrowth and soft tissue thickening not only cause typical external features of acromegaly, but also debilitating musculoskeletal aches. Recently, a few papers reported auditory complications of acromegaly, but there has been no report on narrowing of the external auditory canal as a complication of acromegaly. A 58-year-old acromegalic patient complained of fullness of both ears. He had transsphenoidal surgery for GH-secreting pituitary adenoma 17 years ago. Somatostatin analogue therapy was discontinued 2 years earlier, because nadir GH after oral glucose loading and IGF-1 level were normal. On laboratory exam, random GH was 0.82 ng/ml, and IGF-1 264.74 ng/ml (reference range, 71–263). On otolaryngologic examination, both auricles were very hard and immobile, and orifices of external auditory canals (EAC) showed slit-like openings. In left ear, eardrum examination was impossible due to severe stenosis of EAC. On temporal bone CT, both ears showed thickening of tympanic membranes and evidence of chronic otitis media with severe soft tissue thickening of left EAC. Pure tone audiometry documented mild hearing loss in left ear. The patient declined any further evaluation and therapeutic intervention. Ear complications of acromegaly has not received much attention so far. We report a case of ECA stenosis developed in an acromegalic patient, as a novel complication of acromegaly.

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EP988

Is Pegvisomant correct choice for acromegaly patient with dilated cardiyomypathy?

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Objectives
Acromegaly may arise with several clinical presentations and cardiac involvement is the most important factor affecting the course of the disease.
Case
A 32-years old man admitted to hospital complaining with shortness of breath. After initial evaluation he was diagnosed as 'cardiac failure'. Cardiac evaluation revealed that he had 'dilated cardiomyopathy' with ejection fraction (EF) of 20%, global hypokinesia without valvular disease and coronary angiography was detected as normal. After immediate cardiac treatment he was consultated to endocrinology because of hyperglycemia. When the patient evaluated for hyperglycemia, physical examination findings consistant with acromegaly. He was diagnosed as acromegaly with high IGF-1 and GH level and 19 mm macroadenoma in pituitary MRI. Because of heart failure, surgery was delayed and medical therapy was initiated. After 6 months of therapy with high dose somatostatin analogue treatment, his cardiac status did not show any improvement and we decided transnasal transsphenoidal adenomectomy. After surgery he was not in remission and somatostatin analogues were initiated again. At the 6 months of additional therapy, IGF-1 and GH level were not in normal range. We decided to add pegvisomant to therapy. At the 2nd week of combination therapy, he developed severe cardiac failure with EF 10% and therapy was discontinued. After cessation of pegvisomant, his symptoms revealed minimally.
Conclusion
As we know cardiac problems are the first leading cause of death in acromegaly. Cardiac involvement may appear any of the followings; hypertension, valvular heart diseases, arrhythmias, hypertrophic cardiomyopathy and dilated cardiomyopathy. Most of the patients treated with pegvisomant show decreased cardiac muscle mass in hypertrophic cardiomyopathic patients. There is no data about pegvisomant use in acromegalic patients with dilated cardiomyopathy. Should we use it cautially in dilated cardiomyopathic patients?

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EP989

Preoperative HDDST in the prognosis of CD remission after transshenoidal endoscopic surgery

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Purpose
Transsphenoidal endoscopic surgery (TSS) is the first-line treatment for Cushing's disease (CD). Persistence and recurrence of hypercortisolism after TSS considered important problem. In this case search for CD remission predictors is actual.
Aim
To study the role of preoperative oral high-dose dexamethasone suppression test (HDDST) in the prognosis of CD remission after TSS.
Materials and methods
60 patients with Cushing's disease (nine men, 51 women, mean age 41 years (15–73) who had underwent TSS were included. HDDST was performed in all cases before the TSS. Postoperative examination was done one and two years after surgery. Remission criteria were: secondary adrenal insufficiency (the need for glucocorticoid replacement) or combination of normal midnight serum cortisol level, normal 24 h urine free cortisol (UFC) excretion and serum cortisol suppression less than 50 nmol/l in 1-mg dexamethasone test. The optimal threshold value of serum cortisol suppression in the HDDST for prediction of CD remission after TSS was calculated by ROC-analysis.
Results
One year after surgery CD remission was confirmed in 39 patients, whereas in 21 patients hypercortisolism persisted, after two years – in 36 and 24 patients, respectively. The optimal threshold value of serum cortisol suppression in the HDDST for prediction of CD remission in one year after TSS was 72%. Test's sensitivity and specificity were 82% and 84%, respectively. The probability of wrong prediction was 17% ($P=0.0001$).Two years after TS optimal threshold value of serum cortisol suppression remained 72%, with sensitivity and specificity 86% and 80%,the probability of wrong prediction was 16% ($P=0.001$).
Conclusion
According to our data serum cortisol suppression more than 72% in HDDST may be used as a prognostic criterion for CD remission after TSS.

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EP990

Somatostatin analogs in the treatment of acromegaly: single centre experience

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Introduction
The purpose of this study was to evaluate effectiveness of somatostatin analog (SSA) treatment in patients with acromegaly.
Methods
The study involved retrospective data collection from charts of 29 patients with acromegaly who received medical therapy at Vilnius University Hospital Santariskiu klinikos in 2016.
Results
Patient population consisted of 10 males (34.5%) and 19 females (65.5%), mean age 58 ± 26 years. Primary SSA therapy was administered in 13 (44.8%) patients who refused or had contraindications to surgical treatment. Secondary medical therapy was applied in 16 (55.2%) of patients with recurrent disease after transsphenoidal surgery. 28 patients received SSA treatment (6 of them in combination with a dopamine agonist (DA)), 18 patients recieved high-dose SSA treatment (Sandostatin LAR 40 mg or Somatuline Autogel 120 mg every 4 weeks). Based on GH and IGF-1 results, control and partial control was achieved in 16 (57.1%) and 8 (28.6%) patients receiving SSA treatment ($\pm$DA). 4 (14.3%) medically treated patients remained uncontrolled. High-dose SSA treatment failed to achieve disease control in 4 (22.2%) of patients. Disease control and partial control was attained in 5 (38.5%) and 5 (38.5%) of patients with primary SSA treatment and in 12 (75%) and 3 (18.8%) of patients with SSA treatment after transsphenoidal surgery. We found higher mean IGF-1 level in primary SSA

treatment group as compared to secondary SSA treatment patients (455 ± 56 μg/l vs 307 ± 40 μg/l, $P = 0.04$)
Conclusions
SSA treatment (±DA) results in disease control in 57.1% of patients with acromegaly. High-dose SSA treatment failed to achieve disease control in 22.2% of patients. SSAs are more effective when applied after transsphenoidal surgery as disease control is achieved in greater percentage of patients and mean IGF-1 level is lower when compared to patients who refused or had contraindications to surgical treatment.

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EP991

Biochemical normalization in acromegaly after 79 months' treatment with Pasireotide: case report

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Pasireotide, a multireceptor-targeted somatostatin analogue, was approved for the treatment of acromegaly, after being studied in two large, randomised, multicenter clinical trials. We reported the history of a 76 years old man affected by acromegaly, treated with Pasireotide long acting release (LAR) as first line therapy. Acromegaly was diagnosed in 2009, as the result of endocrinological investigation suggested by altered facial appearance and macroglossia. Hormonal assays demonstrated high levels of IGF1 (584 ng/ml) and GH (8.7 ng/ml), without any suppression of GH at oral glucose tolerance test. Patient consequently underwent brain magnetic resonance (MRI), with the finding of a 7 mm expansive formation of the right half adenohypophysis, suggestive for pituitary microadenoma. Patient, in November 2009, was enrolled in CSOM230C2305 study and was treated with Pasireotide LAR at blided dosage, with biochemical control of disease and progressive reduction of the pituitary adenoma volume. In May 2016, following the onset of dyspnea, dysphagia and dysphonia, patient was diagnosed with anti-MuSK-positive myasthenia gravis, treated with apheresis and steroid therapy, currently in good control. In this period, in according to the detection of very low level of IGF1 and in consideration of concomitant diagnosis of myasthenia gravis, therapy with Pasireotide LAR was discontinued and patient continued follow-up. The last brain MRI, performed in May 2016, documented the stability in size and morphology of the known pituitary microadenoma. Eight months later, in January 2017, patient is actually in remission, with IGF1 in the normal reference range for age and gender (196 ng/ml) and GH < 2.5 ng/ml (0.5 ng/ml). This clinical case shows the efficacy of Pasireotide in gaining biochemical control of acromegaly, factor that is primarily implicated in the reduction of disease morbidity and mortality.

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EP992

Abstract withdrawn.

EP993

Abstract withdrawn.

EP994

A eight successful pregnancies in six Algerian women with acromegaly: a monocenter study of Pierre and Marie Curie center.

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Introduction
Acromegaly usually results from GH hypersecretion elaborated by somatotrop adenoma. The occurrence of a pregnancy in an acromegaly is an infrequent event, but better described in recent years. It could be aggravate GH secretion and tumor volume.
Objective
Describe eight pregnancies including twin pregnancy in six acromegalics patients hospitalized in the endocrinology department of the Pierre and Marie Curie center in Algiers.
Materials and method
Materials: Eight pregnancies; their mean Age was 35.5 years.meanwhile of diagnosis: MRI revealed: macro adenoma ($n = 7$) and microadenoma ($n = 1$); The Visual Field was normal, Hypopituitarism was observed in 1 case and thyrotoxic insufficiency in er 1 case. No diabetes mellitus or hypertension were noted. Patients underwent surgery ($n = 5$), surgery and radiotherapy ($n = 1$). The pregnancies were spontaneous in all cases.
Method: Diagnosis of acromegaly: HGPO/GH; GH/IGF1,magnetic RM imaging pituitary and Visual Field were performed before conception and at T1, T2, T3 of the pregnancy and in the postpartum. We have searched Diabetes Mellitus, gravid hypertension, the Childbirth Incidents, and we examinated Newborns.
Results
Eight pregnancies resulted in nine healthy babies. Gestational diabetes occurred in Three cases and regresses in the postpartum in two cases; No Gravid hypertension. The IGF1 and GH concentrations did not change significantly during pregnancy and in the postpartum. Growth adenoma was noticed in two cases but without defect in any visual field. Fetal malformations were not observed, birth weight was normal.
Conclusion
Acromegaly remains a rare cause of infertility. Pregnancy in women with active acromegaly or uncontrolled acromegaly may be associated with an increases risk of gestational and gravid hypertension. Pregnancy is occasionally associated with an enlargement of adenoma.All these data must be confirmed by prospective studies.

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EP995

Abstract withdrawn.

EP996

Sheehan syndrome presenting 21 years later as severe heart failure

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Introduction
Sheehan syndrome (SS) is caused by postpartum necrosis of the pituitary gland, associated with significant haemorrhage during or after delivery. It is rare in developed countries, but still frequent in underdeveloped ones. We present a rare presentation of this syndrome.
Clinical case
A 48 years old black woman presented at the emergency department for long term fatigue and dyspnea that worsened a few days before. Her physical examination revealed muffled heart sounds, decreased breath sounds inferiorly and bilaterally, a puffy face and dry skin. Also, she had a slurred speech and hoarseness. No other significant findings. No relevant past medical history, except for a complication in her second pregnancy (at 17 years), with a significant internal haemorrhage at term and an emergency caesarean section (stillborn). No subsequent lactation. Amenorrhea since then. Blood tests: Hb 9.3 g/dl (microcytic, hypochromic anaemia); LDH 1778UI/; CK 6793UI/L; AST 401UI/L; ALT 168UI/L; AF 366UI/L; total cholesterol 366 mg/dl; LDL 293 mg/dl; triglycerides 218 mg/dl. Arterial blood gas analysis: hypoxemia and slight hypercapnia. Chest x-ray: bilateral pleural effusion and cardiomegaly. Abdominal ultrasound: cholelithiasis. EKG: low QRS voltage. Echocardiogram: severe bilateral ventricular systolic dysfunction raised filling pressures on the left, enlarged atriums and pericardial effusion. Heart coronarography: no evidence of coronary artery obstruction. Her thyroid function tests were suggestive of central hypothyroidism (TSH 0.70 mU/L; FT4 <0.24). Pituitary functions test reaveled panhypopituitarism (FSH 4.1 UI/L; LH 2.6 UI/L; Estrogen <10 pg/ml; Testosterone <10 ng/dl; prolactin 0.8 ng/ml, IGF1). ACTH was not reliable because the patient had been started on corticosteroids before L-thyroxine. Sellar MRI showed an empty sella. Given her medical history in this clinical setting we believe a SS, left undiagnosed for 21 years, caused the panhypopituitarism.
Conclusion
This case is illustrative of a rare presentation of SS, with severe heart failure and low prolactin levels (unusually found).

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EP997

Localization of the catheters during Bilateral sampling of the inferior petrosal sinuses can impact diagnostic power?

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Introduction
Bilateral sampling of the inferior petrosal sinuses (IPSS) is considerate actually the best diagnostic test for Cushing.
Patients and methods
We retrospectively reviewed our series of patients undergone IPSS for Cushing disease and we compared the difference between central and peripheral ACTH gradient in basal condition and after CRH stimulation in cases of localization of the tip of the catheters inside the inferior petrosal sinus or at the confluence of the inferior petrosal sinus into the internal jugular vein. All the pituitary contrasted Magnetic Resonance was blinded reviewed by two dedicated neuro-radiologist.
Results
A total of 10 patients achieved an IPSS with CRH stimulation suggestive for Cushing syndrome. Four patients had a MR visible pituitary adenomas. In any cases, infiltration of the para-sellar region was detected. At each time point of the CRH-test during IPSS (basal, +3, +5, +10, +15 min), central/peripheral ACTH gradient was higher in cases of localization of catheters inside the inferior petrol sinus (IPS) as compared to cases of localization of catheters outside (OIPS) the inferior petrosal sinus (respectively basal IPS: 9.3 pg/ml and OIPS: 3.8 pg/ml; +3 min: IPS: 68.9 pg/ml and OIPS: 27.8 pg/ml; +5 min: 35.5 pg/ml and OIPS: 19.9 pg/ml; +10 min: IPS: 123.9 pg/ml and OIPS: 10.9 pg/ml; +15 min: IPS: 16.2 pg/ml and OIPS: 12.2 pg/ml).
Conclusion
The localization of the catheters into the inferior petrosal sinus allow to achieve a higher diagnostic central/peripheral ACTH gradient as compared to other catheter localization.

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EP998

Ipilimumab-induced hypophysitis

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Hypophysitis are a heterogeneous group of inflammatory lesions affecting the hypophysis. Have been described hypophysitis secondary to administration of immunomodulatory drugs such as interferon and anti-cytotoxic T lymphocyte antigen-4 antibodies (CTLA-4). Ipilimumab is an anti-CTLA-4 human monoclonal antibody that blocks the union between CTLA-4 and B7 receptor on antigen-presenting cells causing an antitumoral effect and increasing the production of autoantibodies. Hypophysitis has been described in 17% of patients treated with this drug and usually appears before the fourth dose. Clinical presentation is similar to other causes of hypophysitis.
Case report
44 years old man. Medical history: ocular melanoma with hepatic metastases 12 years after surgery. After the 3rd cycle of treatment with intravenous Ipilimumab (3 mg/kg per 3 weeks), the patient began with intense headache. Cranial MRI showed an increased hypophysis so a morphofunctional study of hypophysis was performed. Laboratory evaluation: fasting blood glucose 76 mg/dl, creatinine 0.77 mg/dl, sodium 135 mg/dl, aspartate transaminase (AST) 80 UI/l, alanine transaminase (ALT) 311 UI/l, gamma-glutamyltransferase (GGT) 776 UI/l, TSH 0,04 μUI/ml, free T4 0.65 ng/dl, serum cortisol (0800 h) 14 μg/dl, ACTH 19 pg/dl, prolactin 8.83 ng/ml, FSH 11.97 mUI/ml, LH 3.23 mUI/ml, testosterone 1.2 ng/ml, GH 0.77 ng/ml, IGF-1 83.4 ng/ml (94–252). Pituitary MRI with contrast: glandular thickening with extension to cavernous sinus and irregular contrast enhancement. After the diagnosis of Ipilimumab-induced hypophysitis with gonadal and thyroid axis deficiency associated, Ipilimumab was stopped. The patient began levothyroxine replacement therapy and treatment with prednisone 60 mg/day, with a progressive dose decrease during a month until get the correct replacement dose.
Conclusion
The use of new immunomodulatory drugs makes necessary to identify and define this hypophysitis cause and set out protocols with the oncologists to avoid undue delay in its diagnosis and treatment.

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EP999

Somatostatin Analogue Treatment of a Persistant TSH-Secreting Adenoma: a report of case

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Introduction
Thyrotropinomas are usually considered when the TSH level is inappropriately elevated or normal in a hyperthyroid patient with increased serum T_4 levels, regardless of the presence of visible tumor on imaging. The prevalence of these adenomas, which account for 0.5–3% of all pituitary tumors has been estimated to

be around one case per million. Most thyrotroph adenomas are large and invasive at diagnosis, and present with signs and symptoms of an expanding mass, including temporal visual field defects. Here, we report a patient treated with somatostatin analogue with pituitary macroadenoma and hyperthyroidism.
Case reports
A 64-year-old female patient, who had undergone surgical procedure in 2014 for solitary fibrous tumor in the left parietal region, applied to be checked because of enlarged hypophysis gland documented via cranial MRI performed during follow-up visits. Laboratory findings revealed high levels of fT_3 (8.56 pg/ml) and fT_4 (2.1 ng/ml) with TSH (6.32 UI/ml) higher than its normal limit. On the MRI of the hypophysis, a $22\times18\times14$ mm lesion consistent with macroadenoma, which was heterogeneously contrasted after IV Gad injection, was detected in the mid-left half of the pituitary gland. The lesion exceeds the lateral inter-carotid line in the left aspect and surrounds the left ICA higher than 240 degree. Other hormones of the anterior hypophysis were within the normal range. SHBG was 153.9 (30–100 nmol/l) and alpha subunit was 3.9 (0–1.6 IU/l), which were high. There was no response to TRH stimulation test. Methimazole was commenced at a dose of 20 mg and transnasal transsphenoidal pituitary adenomectomy was performed. Somatostatin analogue (Octreotid LAR 10 mg/28 day) therapy was started for the patient, who had residual adenoma (20×15 mm) and in whom euthyroidism could not be achieved. Methimazole was interrupted in the 9th month of somatostatin analogue treatment and determining that the size of adenoma is $10\times9\times8$ mm.
Conclusion
Most thyrotrophs express variable number of somatostatin receptors (SSTR), particularly SSTR2 and SSTR5. Somatostatin analogues could be considered in the treatment of persistent disease following the surgical procedure performed for TSH-secreting adenomas.

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EP1000

Spindle cell oncocytoma of adenohypophysis: report of a rare pituitary tumor

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Introduction
Pituitary adenomas represent 95% of all sellar masses. Spindle cell oncocytoma (SCO), a rare histopathological entity (0.4% of all sellar tumours), clinically presents as a non-functional pituitary adenoma. According to WHO 2016 Classification of Tumours of the CNS it is a Grade l tumour, but prognosis remains uncertain since recurrence is frequently seen among the few cases reported.
Clinical case
A 59 year-old man presented with progressive fatigue, loss of libido and visual blurring for 5-years. He had pale and hairless skin and on visual field assessment a bitemporal hemianopsia was diagnosed. Hormonal evaluation confirmed low testosterone and gonadotrophins as well as central hypothyroidism and hypocortisolism. PRL and IGF1 levels were normal. MRI scan revealed a T1 and T2 isointense $29\times17\times17$ mm sellar mass with suprasselar extension causing optic chiasm compression. Transsphenoidal surgery removed a grossly bleeding tumour. Histopathological examination revealed a neoplasm composed of interlacing fascicles of spindle cells with eosinophilic and oncocytic cytoplasm. Tumour cells had moderate nuclear atypia and 2 mitotic figures per 10 HPF (Ki67/MIB-1 Proliferation Index 2–5%) were identified. The immunohistochemistry profile was Vimentin/S100/GFAP/EMA/Synaptophysin positive. The final diagnosis was SCO. Visual acuity and Goldmann perimetry improved significantly, but hypopituitarism persisted. MRI scan, 3 months after surgery, showed a contrast enhanced $9\times6\times11$ mm solid intrassellar mass – normal pituitary tissue or residual tumour? Reassessment is scheduled in the next 3 months.
Commentary
An apparent total resection of a SCO was obtained. However, prognosis is difficult to predict due to the short time of follow-up. Presence of cytological atypia and mitosis in this case and knowledge of frequent recurrence rates obeys to a stringent follow-up. The histogenesis of SCO remains unsolved. According to the latest genetic data, SCO and granular cell tumour of the sellar region (GCTSR) may be variants of another rare tumour, the pituicytoma.

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EP1001

A case of pituitary apoplexy. a acute medical emergency and restitutio ad integrum

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A 50-year-old woman with no history of interest who was admitted in hospital for progressive headache 2 weeks of evolution refractory to treatment that was accompanied by emetic syndrome and paresthesias in face and arms. A CT scan of the skull (urgency) was performed which was normal. Neurology improves with analgesia and steroids, presenting mild drowsiness and mild hyponatremia (121 mEq/l). A cerebral MRI was performed, showing a right subacute hemorrhagic adenoma of 1 cm that protrudes into the suprasellar cisterna without compressing the optic chiasm and extending slightly to the right cavernous sinus. Subsequently it begins with severe headache and vomiting, aiming hemiparesis of predominance crural initially improving with hydrocortisone until it presents convulsive crisis with prolonged decrease of consciousness and loss of control of sphincters, with difficult handling of ions. Urinary skull CT scan is performed with images compatible with mild diffuse cerebral edema, so that it enters the ICU with low level of consciousness and agitation with anisocoria and analytically it is objectively a plasma sodium of 108 mEq/l, remaining in this service five days. Campimetry was performed by the Ophthalmology Service that was normal and consulted the Neurosurgery Service together with Endocrinology was decided conservative management, ruling out endonasal transsphenoidal decompression. No precipitating factors have been identified. Once stabilized, the patient was switched to hydrocortisone 100 mg/8 h, Hypothesis Polyuria clinic and suspicion of partial DI progressing favorably after being discharged after 44 days of treatment with hydrocortisone and replacement desmopressin. Since then and after more than three years of the onset of the picture is followed by the Endocrinology Service, discarding other hormonal deficits. At present, five years later, there is no neuro-endocrine symptomatology, with adrenal axis recovery without substitute treatment and in treatment with desmopressin 100 mg with withdrawal approach, in joint follow-up with skull MRI study and hypophysis without alterations, normal. To conclude the interest of this case based on the literature and the entity we describe as a potentially serious acute pituitary stroke with vital risk and that is resolved satisfactorily with conservative treatment minimizing sequelae and restitution ad integrum, with autoimmune and differencial diagnois without evidence of underlying causes and satisfactory evolution with conservative management.

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EP1002

Resistant microprolactinoma with partial empty sella

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Introduction
Prolactinomas are the most common hormonally active pituitary tumors that account for 40–60% of all pituitary adenomas and are usually successfully treated with dopamine agonists. Surgery or radiotherapy is reserved for drug intolerance/resistance or in neuro-ophthalmological emergencies. We present a patient with refractory microprolactinoma with empty sella treated by transsphenoidal surgery.
Case
42-year-old female patient admitted with a 14 years history of prolactinoma being treated with dopamine agonists for ten years. At the end of the tenth year, the tumor was resistant to high dose cabergoline (4 mg/week). Magnetic resonance imaging (MRI) revealed a partial empty sella with 6.5×3.5 mm pituitary adenoma. She underwent transsphenoidal surgery. Histopathologically, a pituitary adenoma with rare mitotic figures, Ki-67 index of 2%, no expression of p53 and no other features of atypia was identified. Immunohistochemistry showed expression of prolactin by majority of the cells. Postoperative MRI demonstrated empty sella (height of the gland was 2 mm) and no residual mass. After operation, cabergoline was restarted because of high prolactin levels and amenorrhea. Despite a substantial increase in dosage there was no clinical improvement in amenorrhea and galactorrhea and there was not any biochemical

response. Her other anterior pituitary hormones were normal while serum prolactin was 255 ng/ml (4.79–25.3 ng/ml) in her last visit.
Conclusion
A minority of patients, ranging from 10–20% in different series does not achieve normoprolactinemia and/or tumor shrinkage despite treatment with high doses of dopamine agonists. Those tumors are usually macroadenomas with cavernous sinus invasion and rarely microadenomas. Resistance can be documented by demonstrating the absence or poor expression of D2 receptors on the membrane surface of tumor cells, or abnormalities at a postreceptor level. However, molecular biology studies cannot be routinely performed in our center. Exchange of cabergoline with bromocriptine was successful in few cases in the literature.

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EP1003

Acromegaly: clinical experience and determinants of remission

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Introduction
Acromegaly is a chronical and rare disease which is accompanied by excessive growth hormone (GH) secreting hypohysis tumor. In this study we presented acromegaly patients' datas who admitted to our center between the years 1998–2016. We discussed patients' charecteristics and we aimed to investigate the determinants which is effecting the remission rate of the patients'.
Method
70 acromegaly patients datas were analyzed retrospectively in our center. We evaluated patients' clinical, laboratory, imaging and treatment modalities informations. The parameters accepted as remission criteria are as follows: 1) Basal GH <2.5 µg/l, 2) Having GH <1 µg/l level after glucose-growth hormone supression test, 3) Having normal IGF-1 (insulin-like growth factor-1) level in accordance with age and gender.
Results
57.1% of the patients were female. Mean age was 44 ± 12. Mean age was 38 ± 12 when the diagnosis established. 97.1% of the patients had typical acromegaly symptoms. Other findings are: headache (77.1%), sweating (58.6%), vision defect (15.7%), galactorrhea (10%), impotence (10%). Preop GH and IGF-1 levels were 18.3 ± 15.8 µg/l, 954 ± 349 µg/l respectively. 87.1% of the patients had macroadenoma and % 61.4 of the patients had cavernous sinus invasion. Eight of the patients had drug therapy, 62 of them had surgery as first line therapy. 29% of the patients' pathology reports revealed that GH-Prolactin positive staining. Somatostatine analogues were administered to 64.5% of the patients after surgery. On the 3th month follow up remission rate was 53.5%, on the 12th month remisson rate was 65%, on the late period of the follow up remisson rate was 77.1%. There was statistically significant difference between preop GH levels, adenoma size, cavernous sinus invasion, ki67 proliferation index and remission rate ($P<0.05$).
Conclusion
We concluded that high preop GH levels, adenoma size, cavernous sinus invasion, high ki67 proliferation index were the determinants of the poor outcome. Besides surgeon experience should take into consideration for better outcome.

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EP1004

A rare case of macroprolactinoma presenting with SIADH

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Case
A 52-year-old gentleman was admitted with dizziness and collapse. Past medical history revealed dyslipidemia treated with statin. Physical examination was unremarkable. Initial investigations were consistent with SIADH (sodium: 109 mmol/l, serum osmolality: 243 mOsm/kg, urine Na: 59 mmol/l and urine osmolality: 191 mOsm/kg). Urea, creatinine and random glucose were normal. CT Head showed pituitary enlargement with sellar expansion. Pituitary profile showed high prolactin: 8305 mIU/ml, low IGF-1: 78.1 µg/l and low testosterone: 3.83 nmol/l with normal LH and FSH. Thyroid function was normal with intact pituitary–adrenal axis (normal Glucagon and ACTH stimulation tests). MRI pituitary confirmed macroadenoma with heterogeneous solid-cystic mass ($2.0\times1.9\times1.5$ cm) with deviation of pituitary stalk. He was treated with Cabergoline 0.5 mg per week and few days of fluid restriction with improvement of sodium level to 137 mmol/l and prolactin to 61 mIU/l after 2 weeks. Over 5 months follow up; he remained asymptomatic with normal sodium and prolactin on Cabergoline. Hypogonadisim has resolved and IGF-1 has normalized. Repeat MRI 4 months after discharge showed significant reduction in macroadenoma size to $1.4\times1.3\times0.7$ cm with pituitary stalk being in midline.
Discussion
Hyponataemia complicating pituitary macroadenomas is usually related to secondary hypoadrenalism. However, the presence of SIADH with intact pituitary–adrenal axis in such cases is very rare with only seven cases reported in literature (six non-functioning macroadenomas and one macroprolactinoma). The mechanism of AVP release in these cases is not fully understood, but is thought to be related to local mechanical stress on the AVP neurons axonal terminal and dislocation of pituitary stalk and neurohypophysis by pituitary tumor.
Conclusion
We hereby report the second case of SIADH secondary to macroprolactinoma with normal pituitary–adrenal axis. Pituitary macroadenomas should be considered in differential diagnosis of SIADH even in context of preserved pituitary-adrenal axis.

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EP1005

Clinical characterization and comparison of patients with hipophysary tumors and primary empty sella

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Introduction
Non-functioning pituitary tumors and primary empty sella are a common pathology within the differential diagnosis of pituitary masses. The manifestations will depend on the size of the tumor and the compression of adjacent structures being the most frequent neurological symptoms. Clinically the two entities are very similar and no clinical tools are known to be able to help the differential diagnosis.
Objective
Perform a clinical and comparative characterization between patients with non-functioning pituitary tumors and primary empty sella.
Materials and methods
A retrospective cohort study conducted in a highly complex center of the city of Cali, Colombia between January 2002 and December 2014.
Results
A total of 141 cases were found, 32% had a microadenoma, 30% had a macroadenoma and 38% had a primary empty sella. 61% of the patients with non-functioning pituitary tumors were women, as well as 51% of the cases of primary empty sella. The largest number of patients with pituitary tumors were between 20 and 40 years old while in primary empty sella was between 40 and 59 years. Headache was reported in 88% of cases, followed by visual disturbances in 59% and galactorrhea in 41% of cases. As expected, the non-functioning macroadenomas were those with the highest prolactin value with mean of 50 ng/ml. 97% of nonfunctioning microadenomas reported headache being more frequent than in cases of macroadenomas and primary empty sella, this suggests the presence of an additional tension component.
Conclusion
Nonfunctioning pituitary tumors and the primary empty sella are frequent entities within the pituitary masses. The clinical distinction of these entities is quite difficult and requires the accomplishment of an adequate clinical history, adequate interpretation of hormonal and imaging studies.

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EP1006

Prolactinomas in men: retrospective analysis

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Introdution
Prolactinomas in men are rare and the majority are macroadenomas. Some studies suggest that these tumors in men have higher proliferative activity and aggressiveness indicating gender-specific differences in biological behavior. Dopamine agonists (DA) are considered first-line therapy.
Material/methods
Retrospective analysis of male patients diagnosed with prolactinoma between 2005 and 2016. Age at presentation, clinical, hormonal and image data were collected. Mode and responses to therapy were analysed.
Results
Twenty two patients with median age at diagnosis of 50.8 years were observed. Sexual dysfunction was the main complaint (59.1%), followed by headaches (50%) and visual disturbances (36.4%). Imagiology revealed macroadenoma in 95% of the cases (19% giant). At the time of diagnosis mean value of prolactin (PRL) was 3.662 ng/ml (min 177 ng/ml, max 23.200 ng/ml). Hypogonadism was present in 54.5%. Fourteen patients (63.6%) were treated with DA as the only therapy and eight patients (36.4%) with DA and neurosurgery. From the latter three presented pituitary apoplexy, four were misdiagnosed as non-functioning adenoma and onepresented cerebrospinal fluid rhinorrhea. None of these patients were cured after surgery and all received medical therapy. At the last visit normalization of PRL level were observed in 59.1% of the patients (71.4% treated with AD as only therapy) and 77.8% of the remaining presented a PRL level less than 2X upper limit of normal. Reversal of hypogonadism occurred in 66.7%. Previous and after therapy MRI findings were available in 12 patients. A reduction $\geq$50% in tumor maximum diameter was achieved in 8 patients. The mean follow-up was 5.4 years.
Commments
Our data confirms that prolactinomas in men are usually symptomatic macroadenomas. Although DA were efficient in reducing tumor size and normalizing PRL, surgery was performed as first-line therapy in four patients due to misdiagnosis and possibly late referral to our department. The correct diagnosis is crucial for successful treatment and avoidance of unnecessary surgery.

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EP1007

Residual tumour diameter may influence reduced survival in females with nonfunctioning pituitary macroadenomas

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Objective
Patients with pituitary macroadenomas and concomitant hypopituitarism have a reduced life expectancy due to various comorbidities.
Aim
To investigate mortality in patients with non-functioning pituitary adenomas (NFAs) and independent prognostic factors influencing survival.
Design
Retrospective cohort study in a tertiary neuroendocrine university department.
Methods
A total of 364 patients (177F/187M) evaluated for a macroNFA between 2001 and 2016 were studied. PAMCOMP computation program was used to calculate standardized mortality ratio (SMR). Cox regression analysis revealed independent factors associated with mortality.
Results
During follow-up (median 7.5 years – 2135.94 person years), 47 patients died, versus 33 expected from general population, corresponding to a SMR of 1.39 (95% CI 1.02–1.84). Females had a doubled mortality ratio: SMR 2.13 (95%CI 1.30–3.29. 254 patients (69.8%) were operated and 87 patients (23.9%) were irradiated. After pituitary surgery and/or radiotherapy, pituitary tumour remnant diameter decreased with 35.62$\pm$37.35% (range 0–100%). Only 24 (6.6%) of patients were cured after radical therapy (no remnant). Cox-regression analysis demonstrated that age at diagnosis and pituitary tumour diameter at last evaluation remained independent predictor factors correlated to mortality (hazard ratio HR 1.07 (95%CI 1.046–1.101, $P<0.001$ and respectively HR 1.02 (95% CI 1.046–1.101, $P=0.018$)), whereas pituitary surgery or radiotherapy, pituitary failure had no impact.
Conclusions
In our patients with pituitary NFA mortality is still increased, especially in women, influenced independently by the age at diagnosis and residual pituitary tumour diameter. A greater extent of tumour removal may increase survival.

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EP1008

Autoimmune hypophysitis with isolated corticotroph cell destruction due to Pembrolizumab treatment in a female patient with metastatic melanoma

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Introduction
Pembrolizumab is a programmed death receptor-1(PD-1)-blocking antibody, used in a variety of advanced malignant tumors with promising results, although adverse events are not rare.
Case report
We present the case of an adult female, with negative personal and family history of autoimmune diseases, who developed malignant superficial melanoma of right wrist 6 years ago. She was initially treated with surgical resection (lesion and ipsilateral axillary lymphadenectomy) and high dose interferon treatment and re-operated due to multiple regional right in transit and left axillary lymph node metastases. Melanoma was positive for B-Raf mutation and the patient received Vemurafenib for 3.5 years and then Ipilimumab for four months (lung metastasis). During that period she developed subclinical hypothyroidism, treated with thyroxin. She finally received treatment with Pembrolizumab (multiple mediastinal and right axillary lymph node metastases) with gradual tumor recession within 4 months. She developed acute pancreatitis, without diabetes mellitus, treated conservatively. Two months after full melanoma recession she developed fatigue, anorexia and diplopia for a few days without significant findings in brain MRI. A 5-month period followed with exacerbations and remissions of somnolence, cognitive dysfunction, anorexia, and weight loss and finally developed hypotension and hypoglycemia. After a low morning cortisol (4 μg/dl) measurement, she received full hydrocortisone replacement therapy with complete symptoms remission. Thyroxin dose was increased and vitiligo was developed during that period. There were no significant findings in hypophysis MRI and melanoma restaging showed complete disease remission. Hormonal profile (2nd menstrual cycle day) showed: PRL 12 ng/ml (1.9–25), LH 1.2 mIU/ml (1.1–11.6), FSH 2.6 mIU/ml (0.7–11.1), E2 461 pg/ml (13–166), SHBG 103 nmol/l (18–114), GH 0.93 ng/ml (0.06–5), IGF-1 195 ng/ml (94–252), ACTH 1 pg/ml (7–50) while SST for cortisol was 1, 3 and 3 μg/dl at 0, 30, 60 min respectively.
Conclusion
Pembrolizumab completely controlled metastatic melanoma in our patient through immune stimulation. Hypophysitis with isolated corticotroph cell destruction was developed as an adverse event. If confirmed in other cases Pembrolizumab could be used in treatment of refractory Cushing's disease.

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EP1009

Aggressive pituitary tumors: a tertiary center experience

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Background
Pituitary adenomas (PA) are common intracranial tumors that are mainly considered benign. A small group of patients exhibit clinically aggressive behavior sometimes unrelated to the histopathological or radiological features.
Methods
Twelve patients were selected harboring a PA with clinical features of aggressiveness. All the patients underwent pre and postoperative endocrinologic/neuroradiologic evaluation.
Results
10/12 patients were male, mean age at diagnosis 38.1 years (range 12–58) and mean follow-up 14.3 years (range 5–28; died 3/12). In 9/12 cases, the first manifestation was visual impairment (visual field loss, reduction in visual acuity and/or cranial nerve palsies). All the patients had invasive pituitary macroadenomas with expansion into surrounding anatomical structures (11 cavernous sinus; 7 sphenoid sinus; 7 bone invasion). The 12 patients underwent a total of 52 surgical procedures (median 4; range 3–6). Apparently total removal was achieved in 8/12 patients at the first surgical procedure. Regarding histological subtype: 5 gonadotrophinomas; 2 null-cell adenomas; 2 corticotrophinomas; 1 thyrotrophinoma; 1 prolactinoma and 1 plurihormonal adenoma (GH/ACTH). Proliferation markers as ki67 $>3\%$ was identified in 4; >2mitoses/10 HPF in 3 and p53 IHC expression in 4/12 cases. Six patients underwent radiation therapy (RT) postoperatively (5 conventional external RT; 1 stereotactic radiosurgery). Medical therapy was tried in 4/12 patients: 3 with dopamine agonists; 1 with somatostatin analog (pasireotide); 2 with steroidogenesis inhibitors (ketoconazole and metyrapone). Possible metastatic pulmonary disease was identified only in one case; the patient died of tumor progression 10-years after the diagnosis.
Conclusion
Aggressive pituitary tumors constitute a challenging but not completely defined entity. We found an elevated number of surgical procedures by patient and smaller proportion of RT/medical treated patients compared with literature, however, with similar outcomes. Adverse results in treatment are possibly related to difficulty in early detection of this patients' subgroup that must be treated with a multimodal approach.

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EP1010

Hypertension, acromegaly and pegvisomant treatment: Experience from ACROSTUDY

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Introduction
Hypertension (HTN) is a major cardiovascular (CV) risk factor and independent predictor of the increased mortality in patients with acromegaly. Surgical cure of acromegaly is associated with improvement in blood pressure (BP) levels, however little is known on the effect of pegvisomant (PEGV) treatment on HTN.
Methods/design
ACROSTUDY is an open-label, international, prospective, non-interventional study monitoring the long-term safety of PEGV. After informed consent, study patients were enrolled on an ongoing basis. Data were analysed to identify the clinical characteristics and evolution of HTN in patients with acromegaly treated with PEGV.
Results
As of May 31, 2016, data from 2090 patients (15 countries) were available. At ACROSTUDY start, 1038 patients (49.7%, 51% male) had diagnosed HTN (96.4% were on anti-HTN medications). Most HTN patients were Caucasian (95%) and 75.8% was treated with PEGV before ACROSTUDY start. Modifiable CV risk factors that were reported besides HTN were BMI >25 (87.2%), diabetes (72.2%), dyslipidemia (10.2%), sleep apnoea (71.8%), and 17.7% had history of CVD. In the HTN group, the mean age at diagnosis of acromegaly was 48 years (s.d. 12.7) and the mean age at the start of PEGV (Baseline) was 56 years (s.d. 12.1) vs 36.3 years (s.d.11.7) and 43 years (s.d. 12.7) for non-HTN group. Time from diagnosis to PEGV treatment was 8.4 years (s.d. 8.5) vs 6.5(s.d. 7.2) in HTN and non-HTN group respectively. At baseline systolic BP(SBP) was 138.3 and diastolic BP(DBP) 85 mmHg. Follow up at year 5 showed SBP 134.5 and DBP 82.5 mmHg. Average IGF-1 level at baseline was 488.9 and 218 ng/ml at year 5.
Conclusions
HTN is a common comorbidity in acromegaly. Patients with HTN tend to be older at diagnosis and start of PEGV and have multiple CV risk factors. With PEGV treatment, blood pressure levels remain stable over time.

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EP1011

Assessment of macroprolactin through post-PEG monomeric prolactin measurement and comparison with gel fitration chromatography in hyperprolactinemic samples

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Macroprolactin interference is a common problem in the interpretation of immunoassays for prolactin. Identifying macroprolactinemia can prevent errors in diagnosis and subsequent delivery of treatment to patients. The search for macroprolactin through polyethylene glycol (PEG) precipitation followed by percentage recovery is the most common used method in clinical laboratories. This study aimed to evaluate the implementation of macroprolactin assessment in hyperprolactinemic samples, with the interpretation of the results based on validated post-PEG monomeric prolactin reference range. It also aimed to verify whether post-PEG monomeric prolactin measurements could match the results obtained through Gel filtration chromatography (GFC). Samples from 40 healthy subjects were utilized for the validation of the post-PEG monomeric prolactin reference range, according to predetermined data quality. The macroprolactin assessment by PEG precipitation was then performed on 112 hyperprolactinemic samples (96 women), and results obtained by percentage of post-PEG prolactin recovery were compared with post-PEG monomeric prolactin concentrations. Twenty-five out of the 112 hyperprolactinemic samples were randomly selected for evaluation through GFC for further comparisons. Assessment of post-PEG monomeric prolactin concentration with an appropriate validated reference range showed greater specificity than the conventional criterion of percentage of post-PEG prolactin recovery, as it identified samples with both excess macroprolactin and monomeric bioactive prolactin, and also reduced the rate of indeterminate results. Furthermore, most of the results obtained in samples analyzed by GFC were in agreement with results obtained by post-PEG monomeric prolactin measurement. The assessment of macroprolactin through a validated post-PEG monomeric prolactin reference range should be adopted as it outperformed the current utilized criterion.

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EP1012

Sheehan syndrome: Sequential hormone failure and late diagnosis

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Introduction
Postpartum infarction of the anterior pituitary, known as Sheehan's syndrome, is a rare cause of hypopituitarism. In many cases, the hormones deficiency is sequential which implies late diagnoses.

Case Report 1
A 51-year-old woman was observed because her mother had medullary thyroid carcinoma. She had no evidence of endocrine neoplasia. Nevertheless, she was experiencing fatigue, hair loss and dry skin for several months. Her history included a postpartum haemorrhage at 22 with blood transfusion requirement. She was unable to breastfeed and mentioned oligomenorrheic cycles after that and took two years to get pregnant again. Menopause was at 43. Physical examination was unrevealing. Baseline endocrine evaluation revealed low gonadotrophines, IGF-1 and fT4 with inappropriate normal tyrotrophin, PRL of 2.5 ng/ml and morning cortisol of 8.7 mcg/dl with ACTH of 15.3 pg/ml. A multiple pituitary stimulation test confirmed the deficiency of all anterior pituitary hormones except the pituitary-adrenal axis. Levothyroxine reposition was prescribed.
Case report 2
A 78-years-old woman was referred to the endocrinology outpatient department after hospital admission due to hypotension, hyponatremia (113 mmol/l) and rhabdomyolysis that improved with corticotherapy. She reported asthenia, weakness, myalgias and anorexia that worsened progressively 2 years before admission. Her third pregnancy occurred at the age of 28, with severe blood loss at delivery, inability to breastfeed, oligomenorrheic cycles after that and menopause at 36. Endocrine evaluation confirmed a panhypopituitarism and the CT scan showed an empty sella turcica. She became asymptomatic with hydrocortisone and levothyroxine reposition.
Conclusion
These cases represent two very late diagnosis of Sheehan's syndrome. Appropriate obstetric/gynaecologic history and clinical suspicion are required to avoid late manifestations of the disease, namely an adrenal crisis, because the pituitary-adrenal axis is usually the last one failing. Timely treatment may dramatically improve quality of life of these patients, who may experience hypopituitarism for long years before diagnosis.

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EP1013

Multimodal treatment in pituitary carcinoma arising from a ACTH-expressing pituitary macroadenoma with an unexpected long-term survival

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Pituitary carcinoma (PC) is defined by the presence of pituitary tumor that is either not contiguous with the primary sellar tumor and/or has metastasized to distant sites. It is very rare and associated with poor prognosis, with a median survival of 12 months when systemic metastases are present, and 30 months when metastases are confined to the central nervous system. A 20 years-old man was first diagnosed with a nonfunctioning pituitary macroadenoma in 1981 and submitted to transsphenoidal surgery (TSS). Histology showed ACTH positive tumor, p53 negative and Ki-67 1%. Three years later a recurrence was detected and a new TSS followed by conventional radiotherapy (Rxt) was performed. Hormone replacement therapy (HRT) was initiated for TSH, ACTH and FSH/LH deficiencies. In 2000, at age 39, he complained of prolonged nasal obstruction. Imaging showed a giant invasive sellar tumor with extension to suprasellar region, cavernous sinus, and nasopharynx; multiple extra-axial lesions in the posterior fossa suggesting meningeal secondary implants and a large mass in the cervical-thoraco-lumbar spine. Histology of the resected giant adenoma and the spinal lesion confirmed an ACTH-expressing PC with a high proliferative index. Fractionated stereotactic Rxt was performed. Cabergoline and pasireotide were prescribed, but discontinued after some months due to side effects. Tumor regrowth occurred in 2009 when surgery was repeated for removal of the main tumor followed by Rxt directed to cerebellar lesions, and again in 2015, when a microsurgery guided by localization systems and electrophysiological monitoring was carried out. Temozolomide was prescribed but patient refused the use. Currently, at age 55, he is doing well, working, and maintaining a stable clinical condition under HRT. Latency time from the diagnosis of pituitary adenoma to PC was 19 years, and his survival of 16 years after diagnosis of PC has no parallel in the literature to date.

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EP1014

Renal prognosis of diabetic patients with and without central diabetes insipidus

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Background
It has been suggested that higher arginine vasopressin (AVP) concentration may be associated with greater eGFR decline in diabetic patients not using inhibitors of the renin-angiotensin system (Diabetologia 2013). If excessive AVP action is detrimental to renal prognosis, then diabetic patients with central diabetes insipidus (CDI) may have relatively preserved renal function. Therefore, we aimed to compare long-term renal prognosis of diabetic patients with and without CDI.
Methods
We retrospectively identified 39 diabetic patients with CDI followed up at our university hospital for more than 4 years. Propensity matching for baseline age, sex, BMI, HbA1c, eGFR, SBP, DBP, urinary protein, and length of observation was performed to select 39 control diabetic patients without CDI in the same hospital.
Results
Baseline demographics of the CDI group were as follows: age 45.6 years, 41% female, BMI 27.2, HbA1c 7.0%, eGFR 90.4 ml/min/1.73 m^2, blood pressure 122/79 mmHg and observation of 1862 days (mean values). There was no significant difference in eGFR at the end of observation period (Control: 86.3 ± 28.1 vs CDI: 85.8 ± 33.7 ml/min/1.73 m^2) or the slope of eGFR (Control: -0.9 ± 3.6 vs CDI: -1.1 ± 10.7 ml/min/1.73 m^2/year) between groups. On the other hand, eGFR variability (standard deviation) was significantly greater in the CDI group (Control: 7.9 ± 5.1 vs CDI: 18.3 ± 13.3 ml/min/1.73 m^2, $P < 10^{-5}$). Considering that excessive fluctuations in eGFR are damaging to the kidney in general, CDI patients may exhibit milder decline in eGFR when eGFR variability and other factors, such as the use of renin-angiotensin system inhibitors, are matched between groups.
Conclusion
A simple analysis of long-term eGFR revealed no significant difference between diabetic patients with and without CDI. Nevertheless, confounding factors, such as greater eGFR variability in CDI patients, may have weakened the relationship between AVP action and decline in renal function.

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EP1015

Osilodrostat maintains normalized urinary free cortisol levels in a majority of patients with Cushing's disease: Long-term results from an extension to the LINC-2 study

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Background
In the 22-week LINC-2 study, osilodrostat (LCI699), a potent oral 11β-hydroxylase inhibitor, normalized urinary free cortisol (UFC) levels in 15 of 19 patients with Cushing's disease (CD). The most common AEs were nausea, diarrhea, asthenia, and adrenal insufficiency ($n=6$ each). Here, we report the 31-month efficacy and safety results from LINC-2 extension.

Methods
Patients receiving clinical benefit at week 22 could enter two consecutive extensions and continue on the same dose of osilodrostat; dose adjustments were allowed. Response rate: proportion of patients with UFC ≤ ULN (controlled) or UFC > ULN but ≥50% decrease from baseline (partially controlled). The maximum safety follow-up from core baseline was 40.3 months.
Results
Sixteen patients entered the extension, 12 remained on treatment at month 31. Three patients discontinued during extensions (AEs, $n=2$; consent withdrawal, $n=1$). One patient decided not to continue on to extension-2. The response rate at month 31 was 100% (controlled, 14 (87.5%); partially controlled, 2 (12.5%)) when missing values were imputed using the last available measurements and 56.3% without imputation ((controlled, 8 (50.0%); partially controlled, 1 (6.3%)). No patient had escape from response (UFC > ULN at ≥2 consecutive visits on maximum tolerated dose after initial UFC normalization) during the extension. Mean (S.D.) changes in clinical signs of CD from baseline to month 31 ($n=11$) were: SBP (mmHg), −3.4 (18.5); DBP (mmHg), −5.4 (9.9); weight (kg), −4.5 (5.7); and BMI (kg/m^2), −1.8 (2.3). The most common clinical AEs were diarrhea, hypocortisolism-related AEs ($n=6$ each), headache, asthenia, and nausea ($n=5$ each). Mean (S.D.) plasma ACTH (pmol/l; normal, 1.8–9.2) at baseline ($n=15$), week 22 ($n=15$) and month 31 ($n=10$) were 20.0 (10.4), 80.5 (145.5), and 54.0 (35.1), respectively.
Conclusion
In the majority of patients with CD, osilodrostat maintained normal UFC levels for >2.5 years with a long-term safety profile similar to that after 22 weeks; no new safety signals emerged. Two phase 3 studies are ongoing to further evaluate osilodrostat in patients with CD.

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EP1016

Acromegaly: assessing the clinical outcome through a 10-year experience at a tertiary care hospital in Pakistan

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Background
Acromegaly is due to excess Growth hormone (GH) production, usually as result of pituitary adenoma. The diagnosis is often preceded by around 5 years of active but unrecognized disease. Clinical expression of the disease in each patient depend on the levels of GH and Insulin-like Growth Factor-1 (IGF-1), age, tumor size, and the delay in diagnosis. Successful remission after Trans-sphenoidal surgery (TSS) is reported to be found in 52.5% of cases in the developed countries.
Objectives
This study was designed primarily for the evaluation of diagnostic characteristics of acromegaly and establishment of its management outcomes over a span of 10 years at a tertiary care hospital in Pakistan.
Methods
It was a Descriptive cohort study. Total 53 patients with biochemical and radiological diagnosis of Acromegaly were included in study between October, 2005 to September, 2015. Patients' medical record files were reviewed and data recorded.
Results
Of the 53 subjects, with mean age of 39.68 ± 14.35 years, 33 (62.3%) were male while 20 (37.7%) were female.The patients presented at a mean duration of 5.90 ± 4.12 years after onset of symptoms. The most frequent complaint was somatic growth features in the form of enlarged hands and feet noted by 51 (96.2%) pts. Overall, 50 (94.3%) patients underwent TSS for removal of pituitary adenoma while 3 (5.7%) patients refused to opt surgical option. Only 3 (6%) patients achieved biochemical and radiological remission after 6 months of surgery. Among 47 patients with persistent disease after TSS, 26 (55.3%) were treated with radiosurgery/radiotherapy, 12 (25.5%) underwent repeat TSS and 9 (19.1%) opted for medical treatment, mostly with Cabergoline.
Conclusion
TSS is followed by the documentation of a high rate (94%) of failure to achieve remission and majority of patients have to opt radiotherapy/repeat TSS for the persistent disease. With the continuously improving surgical skills, we expect that the figures attaining remission after primary TSS will rise in the decades to come.
Keywords: Acromegaly, Characteristics, Management Outcome

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EP1017

Evaluation of upper gastrointestinal system in acromegaly

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Background
Because of prolong exposure to elevated endogenous growth hormone (GH) and insulin-like growth factor (IGF-1) levels in acromegaly, it is resulted in multipl comorbidities such as somatic growth, hypertension, diabetes and sleep apnea. Systemic complications caused by acromegaly include gastrointestinal (GIS) involvement. In our study it was planned to evaluate the upper GIS findings by using endoscopic and ultrasonographic methods in acromegaly patients.
Subjects and methods
Thirty-nine acromegaly patients who had attended to our center for the last 6 months were recruited to the study. Upper GIS endoscopies and abdominal ultrasonography were performed to all patients.
Results
Of the patient included in the study, 23 were male and 16 were female. The mean age of the patients was 51.4 ± 11.0 years. The mean duration of acromegaly was 104.3 ± 88.6 months. Upper GIS endoscopy was performed in 39 patients and hiatal hernia, esophagitis and gastritis, duodenitis or gastric ulser were found in 3 (%7.6), 2 (%1.7) and 31 (%79.4) patients, respectively. In the pathologic evaluation of gastric antrum biopies, intestinal metaplasia was detected in 12 (%30.7) patients and helicobacter pylori was positive in 13 (%33.3) patients. Abdominal ultrasonographic evaluation revealed cholelithiasis findings in 15 (%38.6) patients.
Discussion
As a result of our study, there was no statistically significant difference between age also sex and hiatal hernia, esophagitis, gastroduodenitis, ulcer development in acromegaly patients. Preoperative GH elevation did not affect the development of hiatal hernia, whereas preoperative IGF-1 elevation significantly increased hiatal hernia development. The incidence of developing cholelithiasis was statistically significantly higher in patients with advanced age, long disease duration and no postoperative biochemical control. Limitations of our study are the lack of a control group and the low number of patients. There is a need for controlled studies involving more patients in acromegaly patients.

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EP1018

Disposition index in active acromegaly: A pilot study

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Background
Active acromegaly is characterized by decreased insulin sensitivity (ISen). However, insulin secretion (ISec) may not increase satisfactorily to compensate for the low ISen.
Aim
To assess ISen and ISec and to calculate disposition index (DI) using an intravenous glucose tolerance test (IVGTT) in patients with active acromegaly.
Methods
Twelve patients (7 men, 5 women) with active acromegaly and 2 normal subjects (2 men) underwent a standard IVGTT with a glucose dose of 0.3 g/kg of body weight. Eight patients had normal glucose tolerance (NGT) and 4 had impaired glucose tolerance (IGT). None were on medication for acromegaly of glucose intolerance. ISen was calculated as the slope of the glucose curve between 10 and 75 min (the rate of glucose disappearance) divided by the area under the insulin curve between 0 and 75 min. ISec was calculated as the acute insulin response, the delta area under the insulin curve between 2 and 10 min after glucose infusion. DI was calculated as ISen times ISec.
Results
Subjects with NGT (8 patients with acromegaly and 2 normal subjects) had a significantly higher DI than patients with IGT (801 (632, 1762) vs. 172 (98, 247); $P<0.001$). Inside the IGT group there were both patients with extremely low ISen

(0.02 L×100 000/pmol×min) and unsatisfactorily increase in ISec (3862 pmol×min/l) and patients with nearly normal ISen (1.09 L×100 000/pmol×min) but very low ISec (244 pmol×min/l).
Conclusion
Both insulin sensitivity and insulin secretion contribute to glucose intolerance in acromegaly. DI clearly differentiate glucose intolerant patients from glucose tolerant ones.

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EP1019

In well-controlled patients with acromegaly, glucose homeostasis correlates with the level of disease control rather than with the type of treatment

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Objective
Acromegaly is often accompanied by abnormalities in glucose and lipid metabolism, which tend to ameliorate upon treatment. However, few studies have investigated whether glucose homeostasis and lipid profiles are differently affected by different treatment regimens. This study aimed to compare glucose homeostasis and lipid profiles in patients with acromegaly who are well-controlled after surgery or under stable treatment with long-acting somatostatin analogs (SSA) either in monotherapy or in combination with pegvisomant.
Methods
Cross-sectional study in 21 patients with a diagnosis of acromegaly (aged 59.1 ± 10.9 years, 10 males), who were controlled (i.e. serum IGF-1 levels under sex- and age-specific thresholds) after surgery (SUR; $n=5$) or under treatment with SSA (SSA; $n=10$) or SSA + pegvisomant (COMBI; $n=6$). Glucose, insulin, total cholesterol, HDL-C and LDL-C were measured from fasting serum samples. Triglycerides were measured during a mixed-meal tolerance test (MMTT). Insulin resistance was evaluated using the homeostasis model assessment of insulin resistance (HOMA-IR); insulin sensitivity was evaluated by hyperinsulinemic-euglycemic clamp.
Results
IGF-1 levels tended to be lower in SUR (138.4 ± 54.4 ng/ml) as compared to SSA (194.5 ± 16.3 ng/ml) or COMBI (173.3 ± 52.3 ng/ml) ($P=0.056$). After adjustment for age and BMI, between-group differences were observed for HbA1c ($P=0.048$), fasting glucose ($P=0.022$), and HDL-C ($P=0.015$), with lower levels in SUR as compared to SSA or COMBI. No differences were observed in fasting insulin, cholesterol, LDL-C, HOMA-IR, glucose disposal rate during clamp, or triglyceride levels during MMTT. Independently of the treatment regimen, IGF-1 levels correlated positively with fasting glucose and insulin levels (ß = 0.52 and ß = 0.57, both $P=0.010$), with HOMA-IR (ß = 0.66, $P=0.003$), and inversely with glucose disposal rate (ß = −0.60, $P=0.006$).
Conclusion
In patients with acromegaly who are controlled after surgery or under stable medical therapy, indices of glucose homeostasis correlate with circulating IGF-1 levels, independently of the treatment regimen.

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EP1020

European observational study of long-acting pasireotide for uncontrolled acromegaly: ACRONIS study design and rationale

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Introduction
Acromegaly is a rare, serious disease caused by the presence of a pituitary adenoma secreting an excessive amount of growth hormone (GH), which leads to a consequent increase in circulating insulin-like growth factor-1 (IGF-1) levels, and excessive skeletal growth and soft tissue enlargement. It is usually managed by surgery and/or treatment with somatostatin analogs (SSA). The ACRONIS study (CSOM230CIC05) will provide real-world evidence on the efficacy and safety of the multi-targeted SSA long-acting pasireotide in uncontrolled acromegaly patients.
Methods
This non-interventional study will analyze efficacy and safety data in acromegaly patients (≥18 years) already treated (for ≥6 months) with monthly pasireotide (retrospective dataset) or about to be treated (prospective dataset). About 200 prospective patients (2-year follow-up) and 50 retrospective patients are expected to be enrolled. Outcome measures will include biomarkers (GH and IGF-1), pituitary imaging, symptom- and quality of life (QoL) scores. The primary objective is to document treatment efficacy within the prospective data subset; the endpoint will be the proportion of patients who achieve IGF-1 <1 upper limit of normal (ULN) and GH <1 µg/l after 6 months. Secondary endpoints will include the proportion of patients at 6 months (retrospective) or within 2 years (prospective) who achieve IGF-1 <1 or <1.3 ULN and GH <1 or 2.5 µg/l, change in tumor size, signs and symptoms, QoL and incidence of hyperglycemia. Safety assessments will include adverse events, hematology, clinical chemistry and physical examinations. Interim analyses will be performed once at least 50 retrospective patients have been exposed to 6 months of treatment and 100 prospective patients have been treated for at least 6 months, respectively. Descriptive statistics, as well as, absolute and relative frequencies will be reported.
Conclusion
ACRONIS will provide European real-world data to increase our understanding of the long-term efficacy and safety of pasireotide in uncontrolled acromegaly.

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EP1021

Thyrotropin secreting microadenoma – case report of a patient with goiter

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Introduction
The prevalence of pituitary thyrotropin secreting tumors (TSH-omas) is 1-2 cases per million inhabitants, most of them being macroadenomas. The differential diagnosis may be challenging, especially for microadenomas.
Case Report
A 50-year-old male was observed at the endocrinology department with multinodular goiter. He noticed progressive neck enlargement over the previous months but denied other complaints. There was no family history of thyroid pathology. He presented hot sudorific hands and a large nodular goiter. Laboratory evaluation revealed a predominantly high T3 with non-suppressed TSH (TSH 1.73 µU/ml (Reference range – RR: 0.55–4.78), T3-2.08 ng/ml (RR: 0.60–1.81), T4-11.7 µg/dl (RR:4.5-10.9), FT3-7.74 pg/ml (RR: 2.3–4.2), FT4-1.93 ng/dl (RR: 0.8–1.76)). The sonography showed an enlarged thyroid gland with bilateral nodules of 37, 50 and 70 mm. Additional evaluation revealed negative anti-thyroid antibodies, high total testosterone and SHBG, chromogranin A, alpha-subunit of glycoproteic hormones (αGS) and αGS/TSH ratio, but otherwise normal pituitary function and no evidence of other endocrine neoplasia. There was no TSH or αGS response to TRH administration and the MRI revealed a 6 mm pituitary lesion. Thyroid nodules cytology was benign. A TSH-oma was admitted and long-acting octreotide administered, with normalization of thyroid function and subsequent trans-sphenoidal tumor resection. Pathological analysis revealed an adenoma with positive TSH immunohistochemistry. Over the next months, there was TSH suppression and secondary hypothyroidism, during which levothyroxine was administered, and subsequent recovery of normal thyroid function. Slight reduction of the goiter was observed.
Discussion
Distinguishing pituitary TSH-omas from thyroid hormone resistances may be challenging, but it is important for correct therapeutic options and avoid endocrine and neurological complications. Baseline thyroid function and sonography do not adequately distinguish both entities, but the absent family history, high SHBG, αGS and αGS/TSH ratio, blunt TSH and αGS response to TRH, and FT3/FT4 normalization with long-acting octreotide, together with a small but existent pituitary adenoma, prompted a microthyrotropinoma diagnosis.

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EP1022

Non-functioning pituitary adenoma; improved endocrine outcomes with increasing surgical experience: The Manchester Cohort

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Case notes of 150 consecutive patients (58% male) who underwent pituitary surgery by a single surgeon for non-functioning pituitary adenoma and endocrine follow up at our centre between July 2005 and February 2015 were reviewed. All patients underwent endoscopic transsphenoidal surgery as the first approach. Post-operative pituitary function was assessed by measurement of baseline pituitary hormonal profile and a glucagon stimulation test to assess ACTH and GH axis. Mean age at surgery was 61 years (range 23–87 years). Pre-operatively, 63.3% of patients had evidence of hypopituitarism and vision was affected in 58% of patients. Post-operatively, hypopituitarism was detected in 70% of patients. New hormone deficiency developed in 25.3% of patients. Post-operative vision improved 46.6% of the total cohort and remained static in 47.3% of patients. During this time period, 10% of patients underwent further surgery and 28% of patients were referred for radiotherapy. To assess if increasing surgical experience affected patient outcomes, data was assessed in two time periods; patients undergoing surgery in the early years between 2005 and 2010 ($n=67$) and patients undergoing surgery in the latter years between 2011 and 2015 ($n=83$). There was no significant difference between pre-op hypopituitarism between these groups however, there was a statistically significant difference in terms of post-operatively hypopituitarism, with a lower number of patients in the latter group experiencing post-operative hormone deficiency (79.1% vs 62.7%, $P=0.033$). Furthermore, there was a statistically significant difference in terms of pre-operative visual status, with more patients in the latter group without any visual compromise (28.4% vs 51.8%, $P=0.008$). There was no significant difference in terms of post-operative visual outcomes. In conclusion, data from our cohort demonstrates improved endocrine outcome with increasing surgical experience over time. It also highlights change in clinical practice in our centre with more patients undergoing surgery prior to the development of visual symptoms.

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EP1023

Polyuria and diabetes insipidus after surgery for pituitary tumors

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Introduction
Central diabetes insipidus (DI) is a common complication after pituitary surgery, but is transient in the majority of patients. The aim of our study is to determine the incidence and course of DI in the postoperative period and to characterize the factors associated with this disease.
Methods
We performed a retrospective study of 44 patients (50% females) with a mean age of 54 years (24–83), treated with transsphenoidal (TSS) or transfrontal surgery (TFS) between January 2013 and December 2016. 26 were nonfuntioning adenoma, 7 somatotrophinoma, 6 corticotrophinoma, 2 gonadotrophinoma, 1 tirotrophinoma, 1 Rathke's cyst and 1 craniopharyngeoma. 93.2% underwent TSS (72% endoscopic) and 6.8% (3 patients) TSF. 18% were reinterventions. We consider polyuria if diuresis is >200ml/h for 3 consecutive hours and DI if the natremia is >145 mEq/l so that the patient is candidate for subcutaneous desmopresine.
Results
25 patients (56%) developed polyuria during early postoperative, 11 (25%) transient DI between 1 and 5th day and 10 (22%) SiADH between 3 and 10th day. 15% of these patients presented 2 phases Di + SiADH, none of them 3 phases. DI was permanent in only 3 patients (6.8%), all after TFS. There was no difference comparing the DI group vs no DI in tumor size, pituitary function and surgery technique. However, we found differences between transient and permanent DI groups in tumor size ($53\times36\times42$ vs $18\times16\times15$ $P<0.05$) and surgery technique (TFS vs TSS $P<0.05$), but not in age, pituitary function or number of interventions.
Conclusion
It is important to identify those patients in risk of developing permanent DI, which in our case were those with bigger tumors that required TFS.

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EP1024

Etiology and some clinical characteristics of hypopituitarism over the years of follow up

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The data of etiology and clinical characteristics of hypopituitarism in different countries differes. The aim of the study is to investigate etiology and some clinical characteristics of patients with hypopituitarism that were treated in the Clinical center of Vojvodina. The study was conducted as a retrospective study. There were 32 males and 28 female patients. Mean age was 52.2 ± 17.5 years. Data was analized before and after substitution of hypopituitarism. Patients were treated with levothyroxine, hydrocortisone, sexual steroids, growth hormone and with desmopresine depending on the type deficiency. At the time of the diagnosis, mean age was 40.2 ± 18.7 and the average period of treatment was 15.9 ± 11.4 years. The most common causes of hypopituitarism were pituitary macroadenomas (53.3%) and craniopharyngeomas (21.7%). Partial hypopituitarism with deficiency in two or more functions was diagnosed in 64.4% subjects and panhypopituitarism in 28.8%, deficiency of one function in 6,8%. Average body mass index after the treatment was 27.8 ± 6.5 kg/m^2. Blood pressure was in normal range and without changes during the treatment. High levels of total cholesterol and LDLcholesterol before the treatment showed statistically significant decrease during the treatment (6.29 ± 1.57 vs 5.32 ± 1.38 mmol/l; $P\leq0.009$ and 4.12 ± 1.45 vs. 3.20 ± 1.11 mmol/l; $P\leq0.005$ respectly). Levels of HDLcholesterol and triglycerides were not changed significantly during the treatment. Crosslaps was decreased non-significantly and bone mineral density showed absence of osteopenia and osteoporosis during treatment. Correlation analysis showed statistically significant negative correlation between LDL cholesterol and levothyroxine ($r=-0.341$). 10% of subjects had a cardiovascular event. One subject died because of sepsis. We concluded that hypopituitarism in our region is commonest in the middle aged population, the main cause being pituitary macroadenomas. Cardiovascular risk factors of untreated hypopituitarism are reversible and cardiovascular events are rare.

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EP1025

A novel *DICER1* gene mutation in a 10-month-old boy presenting with ACTH-secreting pituitary blastoma and lung cystic dysplasia

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Hypercortisolism due to Cushing disease is an extremely rare condition in children under one year of age. We present a case of a 10-month-old boy

with lung cystic dysplasia and pituitary blastoma (ACTH-secreting). The disease manifested with symptoms of hydrothorax due to cystic dysplasia of the right lung's upper lobe. Surgical resection of the affected area has been carried out. Symptoms of endogenous hypercortisolism appeared soon after lung surgery. Cushing disease due to pituitary macroadenoma has been diagnosed. Pituitary adenoma was surgically removed; pituitary blastoma with isolated ACTH-secretion was revealed by immunohistochemistry. A combination of lung cystic dysplasia and pituitary blastoma was suspicious for a *DICER1* gene defect. p.C199X mutation in *DICER1* gene was found. He has been followed up for four years after the pituitary surgery. The patient has been receiving replacement therapy with hydrocortisone, levothyroxine and growth hormone. No other DICER1-related conditions were detected during the last follow-up visit. The same mutation was found in the mother, who had a history of euthyroid multinodular goiter.

Conclusion

Combination of lung cystic dysplasia and ACTH- secreting macroadenoma should prompt to *DICER1* gene analysis. We have shown the variable clinical phenotype in *DICER1* mutation carriers within a family.

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EP1026

Pituitary insufficiency following traumatic thoracic injury in adolescent male patient-case study

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Traumatic thoracic injuries in children and adolescents are rare, but could be connected with others traumas, often with traumatic brain injury (TBI). Based on data in the current literature, approximately 15–20% of TBI patients develop chronic hypopituitarism. Growth hormone (GH) and ACTH deficiency are the most common, followed by gonadotropins and thyroid-stimulating hormone. The greatest challenge associated with endocrine complications in individuals with polytrauma injury is early recognition of these subtle problems. We present a case report of a 24-years-old male. In 2007 (when he was 15-years-old) the patient underwent a traffic accident, thoracic injury (hemothorax, dissection of the descending part of the aorta, aortic stent-graft implantation to the left subclavian artery) and concussion. During post traumatic period he had transient polydipsia and polyuria. In 2013 gonadal axis deficiency was confirmed. Testosterone replacement therapy was started. During current investigation low growth hormone level (GH) and insulin-like growth factor 1 (IGF-1) level were found to be low. Patient's hight is 160 cm, mothers 158 cm, fathers 182 cm. Mid Parental Height (MPH) = 173.5 cm. An insulin tolerance test (ITT) was performed. There was't an adequate GH response-the insufficiency of somatotropic axis was confirmed. There were no others hormonal abnormalities. Further examinations e.g. NMR of the pituitary, genetic examination and DEXA are performed.

Conclusions

Physical signs such as lack of progression through puberty, with decrease in testicular volume and libido, short stature and history of after trauma transient diabetes incipidus could suggest the presence of unrecognised hypopituitarism. Careful investigation and monitoring is necessary to unmask and treat such hormone deficiencies in the transition phase.

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EP1027

Potassium homeostasis in patients with acromegaly in comparison with hypertensive patients

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Introduction

Acromegaly is characterized by chronic growth hormone (GH) excess and leads to numerous changes in bodily functions and comorbidity. We compared potassium homeostasis in patients with acromegaly to hypertensive controls.

Methods

We prospectively assessed serum potassium, urinary potassium excretion, aldosterone and renin, acid-base balance as well as glomerular filtration rate according to the CKD-EPI formula in 71 patients with acromegaly (37 male, 34 female; age 59 ± 14 years) and 70 hypertensive age and gender matched patients (HP) in whom secondary hypertension was ruled out (37m, 33f; 59 ± 14 year). Of the acromegaly patients, 23 had active disease (AD) and 48 were biochemically controlled (BC).

Results

Serum potassium levels were more elevated in patients with acromegaly (4.2 vs 4.0 mmol/l, $P = 0.008$). Urinary excretion of potassium was also elevated in patients with acromegaly as compared to hypertensive controls (53.3 vs 35.3 mmol/l, $P < 0.001$; 69.3 vs 52.9 mmol/g Creatinine, $P = 0.004$). Analysis of variance in potassium excretion showed highly significant differences between AD, BC and HP ($P < 0.001$). Post-hoc comparison revealed higher excretion in AD (66.3 mmol/l) as compared to BC (47.1 mmol/l, $P = 0.003$) and HP (35.3 mmol/l, $P < 0.001$; BC vs HP $P = 0.012$). Mean arterial pressure was higher in hypertensive patients (110 vs 104 mmHg, $P = 0.009$). There were no statistically significant differences in GFR ($P = 0.618$), BMI ($P = 0.549$), sodium levels ($P = 0.589$), antihypertensive medications used (9 groups of antihypertensive drug classes; $0.117 < P < 1.0$), aldosterone ($P = 0.41$) and renin ($P = 0.161$).

Discussion

We observe higher serum potassium levels in patients with acromegaly compared to patients with hypertension. Still, urinary excretion of potassium is also significantly higher despite comparable characteristics of both patient groups. Higher intramuscular potassium levels have previously been shown in acromegaly. Further research is warranted to elucidate potassium homeostasis in acromegaly.

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EP1028

Russian hypothalamic and pituitary tumors registry (OGGO) data analysis: acromegaly

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Objective

To analyze registry data on patients with acromegaly.

Materials and methods

Russian hypothalamic and pituitary tumors registry database (on-line platform), which contains data on 3719 patients with acromegaly.

Results

According to the database, highest prevalence of acromegaly per 100 000 inhabitants is registered in: Penza region (7.3), Kirov region (7.3), Krasnoyarsk region (6.2). Most common clinical presentations in registered acromegalic patients were: headaches (72%) maxillofacial changes (68%), arthralgias (48%) excessive sweating (39%). Information about tumor size was available in 1543 patients: by the time of diagnosis, 516 (33.4%) had pituitary microadenomas and 1027 (66.6%) had macroadenomas. 59.5% of registered patients were prescribed medical therapy: 65.9 and 34.1% were treated with somatostatin receptor ligands (SRL) and dopamine agonists respectively. 29.9% of patients were primarily treated surgically and remaining 10.6% underwent radiotherapy. Remission is registered in 22% cases, 23% of patients have only partial disease control, 41% have an active disease and 14% of records have no data regarding disease state.

Conclusions

Russian hypothalamic-pituitary tumors registry is a promising instrument for epidemiologic and clinical data acquisition. Data suggest that multimodal treatment approach is essential to achieve higher remission rates in patients with acromegaly.

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EP1029

Adherence to hormone replacement therapy in patients with hyp-opituitarism using the Morisky 4-item scale: results of a pilot, prospective, cross-sectional study

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Objective
To investigate adherence to hormone replacement therapy (HRT) in patients with hypopituitarism in a tertiary center outpatient clinic.
Patients and methods
Prospective, cross-sectional study of patients with hypopituitarism on HRT for at least two pituitary deficiencies (independent of diabetes insipidus). Medication adherence was assessed using a validated Portuguese version of four-item Morisky scale, in which participants were asked to indicate the extent to which they agreed with each of 4 statements (two related to unintentional and two with intentional nonadherence) by rating on a 4-point scale (strongly agree, agree, disagree, strongly disagree). Patients were categorized as nonadherent if they indicated agreement (ie, reported either 'strongly agree' or 'agree') to either item of the subscale. Potential co-variables associated with adherence were tested.
Results
Ninety consecutive patients completed the survey, but five were excluded because they were on HRT with a single hormone. Of the remaining 85 patients (47 men, age 48 ± 16 year), 31 were on HRT with two hormones, 32 with three, 18 with four and 4 with five. Levothyroxine, glucocorticoids, sex steroids, growth hormone and desmopressin were prescribed to 81, 66, 64, 8 and 21 patients, respectively. Mean number of prescribed medications (excluding HRT) per patient was 3.1 (s.d. 2.4; range 0–9). The etiology of the hypopituitarism was non-functioning pituitary tumors ($n=19$), functioning pituitary tumors ($n=17$), craniopharyngeomas ($n=13$), other tumors ($n=3$), congenital ($n=14$), vascular ($n=13$), trauma ($n=2$), and idiopathic ($n=4$). Fifty-six (65.9%) patients reported unintentional nonadherence, while only 9 (10.6%) reported intentional nonadherence. Complete adherence was reported by 29.4% of the patients, while 5.9% showed both unintentional and intentional nonadherence. There were no associations of adherence to gender, age, number of pituitary deficiencies and prescribed medications.
Conclusion
Self-reported unintentional nonadherence to HRT is a common finding in patients receiving HRT for hypopituitarism.

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EP1030

Hormone and tumor responses to primary or pre-operative therapy with somatostatin analogs in acromegaly and the relation with T2-weighted MRI signal

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Objective
Study of the efficacy of SSA in the biochemical and tumour control and the relation between the T2-weighted MRI signal intensity and the response to SSA.
Material and methods
16 patients with GH-secreting pituitary adenomas (7♂/9♀) that received primary or pre-operative treatment with SSA. We classified them according to baseline T2-weighted MRI sequences as Hypo-intense (Ha) and No-Hypo-intense adenomas (no-Ha). Results expressed like media (s.d.).
Results
Median age at diagnosis was 50.6 (18.5) years. 10 patients (9 macroademonas) had pre-operative therapy with SSA during 18.58 (26.9) months, with 47.2% decrease in IGF1 levels and 24.5% of tumour shrinkage. After neurosurgery three patients required medication for hormonal control. Only one patient had postsurgical complications (hypopituitarism). Six patients (two macroadenomas) received exclusively medical treatment during 59.77(64.5) months. They showed 56.8% of reduction in IGF1 levels and 49% of tumour shrinkage. In the last consultation, 4 achieved hormonal control and two needed dose adjustment. From the whole group, ten were no-Ha and 6 Ha, showing at diagnosis: GH 20.13(16.5) vs 14.75(19.8) μg/l, IGF1 973.5(474) vs 703.7(243.5) μg/l and a maximum diameter of 15.9(11) vs 12.05(4.95) mm, respectively. After 6 months of SSA therapy there was 51.2% decrease in IGF1 levels in No-Ha vs 72.3% in Ha. Six of the No-Ha had surgery and four of the Ha. The hormonal response in No-Ha was complete in the 50% and partial in 20% of patients vs 83% and 17% in Ha, respectively. >20% of tumour shrinkage occurred in 40% of the No-Ha vs 66% of the Ha.
Conclusions
Our results show the effectiveness of the pre-operative treatment with SSA in the acromegaly, in terms of hormonal but also anti-tumoral effects. T2-signal intensity at diagnosis it's a good prognostic marker of the effectiveness of SSA therapy and it's correlated with the tumour size-invasion and hormone levels at diagnosis.

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EP1031

Abstract withdrawn.

EP1032

Does cyproterone acetate therapy contribute to the observed elevation in serum prolactin levels in trans women?

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Objective
Hormonal treatment in trans women (MtF transgender persons) in Europe usually consists of estrogens and anti-androgens, e.g. cyproterone acetate (CPA). After initiation of cross-sex hormone therapy, an elevation in serum prolactin levels is frequently observed in trans women, which was previously attributed to estrogen agents. This analysis evaluates whether CPA contributes to the elevation of prolactin in trans women receiving cross-sex hormones.
Design
This study is part of the European Network for the Investigation of Gender Incongruence (ENIGI). Belgian data were selected for this substudy. Trans women that initiated cross-sex hormone treatment (which consists of oral CPA 50 mg in combination with estrogen substitution in Belgium) and underwent orchiectomy were prospectively evaluated. Post-surgery estrogen was reinitiated in unchanged dose.
Methods
Sex steroids, gonadotropins and prolactin were compared at baseline, pre and post surgery (patients receiving orchiectomy) and after 12 and 18 months of cross-sex hormone therapy (patients not receiving orchiectomy).
Results
Data was collected of 107 trans women, with a mean age of 31.5 years. After 1 year of cross-sex hormone therapy, there was an increase in serum prolactin levels in all patients (9.65 μg/l), with a decrease after 18 months (14.10 μg/l) and after orchiectomy (10.17 μg/l). However, serum prolactin levels post orchiectomy were significantly lower than serum prolactin levels after 18 months of CPA therapy, whereas there was no difference in serum estrogen levels between both groups.

Conclusions
The observed elevation of serum prolactin levels in trans women is likely caused by CPA (independent of estrogen therapy), as prolactin levels return to normal after CPA discontinuation, independent of serum estrogen levels.

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EP1033

A rapidly resolving prolactinoma with cabergoline treatment

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Introduction
Prolactinomas are the most common pituitary tumors. Macroadenomas are rarely seen. Dopamine agonists such bromocriptin and cabergoline are the preferred treatments for prolactinomas. Herein, we report a patient with macroadenoma whose adenoma has resolved rapidly with cabergoline treatment.
Case
A 49 year old male patient evaluated for weakness and headache. After detection of central hypothyroidism he was referred to our department. His prolactin level was more than 1925 ng/ml. His laboratory tests were concordant with panhypopituitarism. Replacement therapy was initiated. A macroadenom with a size of 28 mm was detected in pituiter MRI. Cabergolin treatment (3 mg/week) was initiated. The size of the adenoma was decreased to 16 mm in the 3rd month of the therapy. In the 6th month of the treatment the size of the adenoma regressed to 5 mm.
Conclusion
Prolactinomas are tumors with a good response to medical treatment. A rapid response was detected in our patient but there is data about cabergolin resistance. So, a close follow up is required in patients with prolactinomas.

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EP1034

Pregnancy outcome in women with prolactinomas exposed to dopamine agonists at early stages of gestation

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Introduction
Medical therapy with dopamine agonists is the best treatment for prolactinomas of any size or invasiveness and restores ovulatory cycles in 80–90% of patients. Cabergoline currently suggested nearly exclusively rather than other dopamine agonists due to its excellent tolerability and long half-life. That is why the question of safety using of this drug during pregnancy and embryo-fetal development is actual.
Aim
The aim of the study is to assess the risk of pregnancy and fetal pathology in patients with prolactin-secreting tumors treated with cabergoline at early stages of gestation.
Materials and methods
The study included 24 patients from 24 to 38 years old with prolactin-secreting tumors, who become pregnant during therapy with cabergoline (Dostinex). A retrospective analysis of the outcomes of 33 pregnancies based on available medical records and questioning of the patients.
Results
Of the 33 pregnancies 26 resulted in births (78.8%), in one patient a spontaneous miscarriage was registered at 7 weeks (3.0%), six women required medical abortions due to the non-developing pregnancy on terms from 4 to 7 weeks (18.2%). In 6% of cases (two pregnant) gestational diabetes mellitus was diagnosed. The average gestational age was 39.8 weeks (36–41 weeks). Preterm delivery occurred in four women (15.3%). In total 27 children were born (in one case - twins), 26 (96.3%) of them were healthy at the time of the birth. The growth and development of the children did not differ from their peers in the general population.
Conclusions
The results of this study suggest that fetal exposure to cabergoline through early pregnancy does not induce any increase in the risk of miscarriage or fetal malformation. According the results of the study in patients with hyperprolactinemia risk of gestational diabetes mellitus is higher than in the population that require further investigations.

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EP1035

Clinical and hormonal characteristics of patients with different types hypophysitis: a single-center experience

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Background
The inflammation of the pituitary gland known as hypophysitis. It is a rare disease accounting for approximately 0.24–0.88% of all pituitary diseases. Main forms of hypophysitis are histologically classified as lymphocytic, granulomatous, IgG4 related and xanthomatous. We aim to present ourpatients of hypophysitis with clinical,laboratoryand radiological features.
Methods
We retrospectively reviewed our database of 1293 patients diagnosed with pituitary diseases between 2010 and 2017. Demographical data, clinical features, endocrinological dysfunction, magnetic resonance imaging findings, treatment courses and follow-up periods were evaluated. Primary hypophysitis diagnosis was made by the exclusion of secondary causes of hypophysitis, consequently twelve patients with hypophysitis were identified.
Results
The frequency of hypophysitis was found 0.93% in all cases of pituitary disease. Twelve patients (nine females and three males); ages ranged between 17 and 61 years were evaluated. The characteristic features of our patients tend to be female predominance and young population. Diagnosis of hypophysitis was made after pituitary biopsy in 4 patients and in 8 patients after pituitary operation due to adenoma. Headache (63%) and visual problems (18%) were the most frequent nonendocrine symptoms. Anterior pituitary hormone deficiencies (63.7%) and/or diabetes insipidus (16.7%) were seen amongpatients.According to histopathological forms, 4 had lymphocytic, 6 had granulomatous and 1 had xanthogranulomatous types of hypophtsitis.
Conclusion
Hypophysitis should be considered in the differential diagnosis of sellar masses. It can mimic pituitary adenomas in radiological and endocrinological aspects.The different patterns of anterior pituitary hormone deficiencies and diabetes insipidus may be seen in the course of disease.

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EP1036

Comparative study of different methods for monomeric prolactin determination in patients with hyperprolactinemia

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Introduction
Prolactin exists in various forms including the monomeric biologically active form (23 kDa) and a higher molecular weight form, bound most commonly to IgG, known as macroprolactin (>100 kDa). Macroprolactin lacks biological activity but can interfere in standard prolactin immunoassays and is one of the causes of false-positive results. In Russian Federation the most common method for macroprolactin determination is PEG precipitation test.
Aim
The aim of the study was an evaluation of the monomeric prolactin level measured by two methods: immunochemiluminescent (Cobas 6000) with manual PEG precipitation and immunofluorescent method (Brahms Cryptor).

Materials and methods
We had conducted a retrospective analysis of 41 samples of patients with hyperprolactinemia (3 of them were males). The mean age was 32±2.1 years. Prolactin was measured by the immune chemiluminescent (after PEG precipitation) and immunofluorescent methods.
Results
The mean values found by immune chemiluminescent method with manual PEG precipitation were 460.0 [334.0;807.2] mU/l, by immunofluorescent – 432,4 [338.8;700.0] mU/l. The number of patients with intrareference prolactin levels was 41% (17) for the first method and 48.8% (20) for the second one. At the same time, six patients with equivocal results received by immune chemiluminescent method and PEG precipitation had normal prolactin levels by immunofluorescent method. The phenomenon of macroprolactinemia without elevated level of monomeric prolactin was registered in 24.4% (10) of patients. In one person of this group with clinical features of hyperprolactinemia, the increased hormone levels was revealed by Cryptor analyzer.
Conclusion
Measurements of prolactin levels by the immunofluorescent method is useful for correct diagnosis in patients with equivocal results received by immune chemiluminescent method with PEG precipitation.

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EP1037

Pituitary Stalk Hemangioblastoma: a case report and review of the literature

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Introduction
Hemangioblastomas (HBL) in the pituitary stalk are extremely rare. Most pituitary stalk HBL reported in the literature were associated with von Hippel–Lindau (VHL) disease.
Case report
We report the case of a 34-year-old female patient with VHL disease diagnosed at the age of 18 with multiple complications (bilateral retinal and cerebellum HBL, renal cell carcinoma). Brain magnetic resonance imaging (MRI) demonstrated an hypointense suprasellar mass measuring 9×8×9 mm with marked homogenous contrast enhancement after gadolinium administration, originating from the pituitary stalk, suggesting a pituitary stalk HBL. The initial hormonal workup was normal. A visual field defect evaluation was not feasible due to severely low bilateral visual acuity. During the 4-year follow-up, a slight increase in the mass volume and prolactin level was observed; depending on the clinical, radiological and laboratory evolution, a future surgical approach cannot be disregarded.
Review of the literature
The previously reported cases of HBL in the pituitary stalk were analyzed. Seventeen cases have been reported, the majority (fourteen) being associated with VHL disease and the remaining considered to be sporadic. Ten patients had no visual symptoms or hormonal dysfunction, and therefore were kept on observation. A total of six patients were operated. Of the six surgical cases, four patients developed panhypopituitarism, and two patients had visual field disturbances preoperatively with partial recovery after surgery. None of the patients were treated with radiotherapy.
Conclusion
To our knowledge, this is the 18th case of HBL in the pituitary stalk. According to our review, pituitary stalk HBL often remain asymptomatic and do not require treatment. Surgery can be reserved until associated signs or symptoms occur.

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EP1038

Impact of glucose metabolism disorders on IGF-1 levels in patients with acromegaly

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Objective
To evaluate the presence of glucose metabolism abnormalities and their impact on IGF-1 levels in patients with acromegaly.
Methods
Ninety-three acromegalic patients (52 male/41 female) were included in this study who were seperated into three groups as normal glucose tolerance (NGT), prediabetes and diabetes mellitus (DM). Insulin resistance (IR) was calculated with homeostasis model assessment (HOMA). HOMA-IR >2.5 or ≤ 2.5 were defined as insulin resistant or noninsulin resistant groups, respectively. We compared the groups in terms of many factors that may be associated with glucose metabolism abnormalities. IGF-1% ULN (upper limit of normal)/GH ratios were used for impact of glucose metabolism abnormalities on IGF-1 levels.
Results
Frequencies of NGT, prediabetes and DM were 25% ($n=23$), 41% ($n=38$) and 34% ($n=32$), respectively. Patients with DM were significantly older and with an increased frequency of hypertension than NGT and prediabetes groups ($P<0.001$, $P=0.01$, respectively). IGF-1% ULN/GH ratio was significantly lower in prediabetes group than in NGT group ($P=0.04$). Similarly IGF-1% ULN/GH ratio was significantly lower in insulin resistant group than in noninsulin resistant group ($P=0.04$). Baseline and suppressed GH levels were significantly higher in insulin resistant group than in noninsulin resistant group ($P=0.024$, $P<0.001$, respectively).
Conclusion
IGF-1% ULN/GH ratio is a useful marker indicating glucose metabolism disorders and IGF-1 levels might be inappropriately lower in acromegalic patients with IR or prediabetes. We suggest that IGF-1 levels should be re-evaluated after the improvement of IR or glycemic regulation for the successful management of patients with acromegaly.

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EP1039

Monthly pasireotide provides clinical benefit over 12 months in patients with Cushing's disease

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Introduction
A monthly, long-acting formulation of pasireotide normalized or reduced mean urinary free cortisol (mUFC) in most patients with Cushing's disease (CD) in a multicentre, double-blind, Phase III study. The effects of long-acting pasireotide on signs and symptoms of CD are reported here.
Methods
Patients with persistent/recurrent ($n=123$) or *de novo* (non-surgical candidates; $n=27$) CD and mUFC $\geq$ 1.5–5xULN were randomized to monthly pasireotide 10 mg ($n=74$) or 30 mg ($n=76$). Dose could be up-titrated (10–30 mg/30–40 mg) at month (M) 4 if mUFC $>$ 1.5xULN and/or at M7, M9, or M12 if mUFC $>$ 1.0xULN. Primary endpoint was mUFC $\leq$ ULN at M7, regardless of dose titration. Signs/symptoms of CD were evaluated at regular intervals. All data shown are mean (95%CI).
Results
mUFC reduction was accompanied by substantial clinical improvements. Mean changes (95%CI) in clinical signs to M12 in the 10mg and 30mg groups included: weight, −3.4 kg (−4.8,−2.0) and −6.5 kg (−8.3,−4.7); BMI, −1.3 kg/m^2 (−1.8,−0.8) and −2.6 kg/m^2 (−3.3,−1.9); waist circumference, −4.5 cm (−7.2,−1.8) and −6.2 cm (−8.7,−3.6); health-related QoL score, 6.4 (1.3,11.6) and 7.0 (3.0,10.9). Clinically relevant decreases in systolic (−5.0 mmHg (−8.8,−1.3)) and diastolic (−3.1 mmHg (−5.7,−0.5)) BP were reported in the 30 mg group; downward trends were also seen with pasireotide 10 mg (systolic BP: −4.6 mmHg (−9.9,0.7); diastolic BP: −3.4 mmHg (−7.3,0.4)). A significant ($P<0.0001$) relationship was found between change in mUFC and systolic/diastolic BP, after adjusting for antihypertensive medication. Changes in other clinical parameters occurred irrespective of whether patients achieved mUFC $\leq$ ULN at M7. The safety profile of long-acting pasireotide was similar to that of twice-daily pasireotide.

Conclusion
Reductions in mUFC levels during 12 months' long-acting pasireotide treatment were accompanied by improvements in clinical signs of CD. Long-acting pasireotide is an effective treatment option for patients with CD, with a convenient monthly administration schedule.

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EP1040

Radiological study of clinically non-functioning pituitary macroadenomas: a single institutional experience

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Introduction
When facing with non-functioning pituitary macroadenomas (NFPMA), radiological invasion is determinant to surgical approach, apart from histological biomarkers of pituitary tumor aggressiveness (Ki-67; p53 and mitotic index). Invasive tumors usually need additional surgery and/or radiotherapy. There are no much studies describing epidemiological data on aggressive pituitary tumors in clinical practice. We provide information regarding the radiological findings of NFPMA in a single tertiary center during 17 years.
Material and methods
We evaluate retrospectively MR imaging of NFPMA diagnosed between 1999 and 2016 in our Hospital. Evaluation includes infrasellar invasion, Knosp's classification in both cavernous sinus, measure in three dimensions, contact with quiasm, and intensity of signal in T2.
Results
From 48 cases, we selected 41 with valuable presurgical MRI. 15 men and 26 women, mean age 61 years (24–83). Infrasellar invasion ocurred in 19 (46.34%), Knosp III or IV in 21 of 82 cavernous sinus (25.6%). 3 patients (7.3%) presented invasion of three areas. Mean craneocaudal diameter was 29.65 mm (8–52), transversal 21.5 mm (11–43) and anteroposterior 19.14 mm (11–51), with 80.5% displacing optic quiasm. 22% were giant adenomas (>40 mm) and T2 secuences hiperintense, suggesting scarcely granulated tumour, was present in 19.5%.
Conclusions
In our series, 56% of NFPMA had criteria of radiological invasión, infrasellar or cavernous sinus invasion. This finding remarks the complex management of these neoplasm and the need of a multimodal approach.

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EP1041

Idiopathic isolated acquired ACTH deficiency– a case series from the Irish National Pituitary Network

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Idiopathic Isolated ATCH deficiency (IIAD) is a rare cause of secondary adrenal insufficiency characterised by ACTH deficiency with otherwise intact pituitary function. Our objective was to describe the presentation, the autoimmune associations and diagnostic findings observed in IIAD. We present a case series of 19 cases of idiopathic Isolated ACTH deficiency which were identified from the National Pituitary Register in Ireland. A chart and biochemical review was performed to identify the presentation, clinical features, diagnostic criteria and associated diseases of people with IIAD. All patients had normal pituitary MRI imaging, (one patient refused, however he had a normal CT brain) and other causes for ACTH deficiency such as medication or traumatic brain injury were excluded. 19 patients were identified as meeting criteria (15 women and 4 men). The age at presentation ranged from 21 to 88 years, with a median age of 52 years. The majority of patients complained of fatigue and lethargy; however five patients presented with hyponatraemia. 10 of the 19 patients had autoimmune illnesses; hypothyroidism was the most common autoimmune disease with eight patients suffering primary hypothyroidism. CRH stimulation testing was available in 6 of the 19 patients, five of these patients had a rise in ACTH with CRH administration, indicating possible hypothalamic involvement. Two patients had complete recovery of their HPA axis when repeat testing was performed. IIAD is a rare, poorly defined disorder that typically presents with insidious symptoms but can present with severe hyponatraemia. It is associated with autoimmune diseases, in particular primary hypothyroidism. Two patients in this case series had complete recovery of their HPA axis, therefore repeat testing should be performed at intervals.

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EP1042

Autonomic impairment in idiopathic diabetes insipidus

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Introduction
Since DI was reported to be associated to increase mortality, the aim of this study is to evaluate the presence of autonomic dysfunction (AD) in patients with DI.
Methods
We enrolled 12 patients (six females) with central idiopathic DI and 12 controls, matched for age, sex and common cardiovascular risk factors, who were evaluated using the tilt, lying-to-standing, hand grip, deep breath, Valsalva maneuver and Stroop tests.
Results
The tilt test showed a significant more pronounced decrease in both systolic (-20.7 ± 18 vs -1.92 ± 7 mmHg, $P=0.0009$) and diastolic blood pressure (-10.5 ± 14.3 vs -1.5 ± 5.5 mmHg, $P=0.02$) in patients than in controls. Furthermore three patients with DI had to suspend the test because of the onset of syncope. The lying-to-standing test indicated a marked reduction in blood pressure in patients with DI too (1.047 ± 0.137 vs 1.533 ± 0.144, $P=0.0001$). Similar results were find in Valsalva (ratio, 1.033 ± 0.193 vs 1.431 ± 0.109, $P=0.00001$) and deep breath tests (1.075 ± 0.112 vs 1.33 ± 0.083, $P=0.00002$).
Discussion
All the principal autonomic tests performed were concordant, indicating that patients with central DI have an impaired autonomic nervous system function despite normal hydroelectrolytic balance under desmopressin therapy. This impairment may reflect both a damage in the autonomic system and the absence of the vasoactive effect of AVP on vascular smooth muscle which acts as a rescue mechanism in case of rapid drop in blood pressure. Patients with central DI should be educated on how to prevent orthostatic hypotension.

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EP1043

Salivary and serum cortisol levels by liquid chromatography tandem mass spectrometry after standard dose ACTH test in the diagnosis of central hypopituitarism

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Objective
The diagnosis of central hypoadrenalism (HPAI) is a major clinical challenge. The gold standard procedure remains insuline tolerance test (ITT). Liquid chromatography tandem mass spectrometry (LC-MS/MS) is considered the best

procedure for the evaluation of cortisol levels. This study aimed to evaluate cut-offs of serum (TM-SeC) and salivary cortisol (SaC) by LC-MS/MS and serum cortisol by ECLIA assay (E-SeC) after Standard dose ACTH test (SDCT) in diagnosing HPAI.
Design
In this study we performed SDCT in 52 consecutive patients (F/M, 33/19, age 42.9 ± 13 yrs) referred to our Center to evaluate at specific time points E-SeC, TM-SeC and SaC. In the same group of patients we also evaluated E-SeC after ITT, to diagnose HPAI (using a cut off < 500 nmol/l).
Results
HPAI was diagnosed in 8 out of 52 patients (five patients operated on for a pituitary macroadenoma, and 3 with a pituitary microadenoma). Using the diagnosis of HPAI made by ITT as reference test, we found that after SDCT an E-SeC > 348 nmol/l at 0-min, > 671 nmol/l at 30-min or > 756 nmol/l at 60-min excluded HPAI, whereas an E-SeC < 155 nmol/l at 0-min, < 436 nmol/l at 30-min or < 527 nmol/l at 60-min confirmed HPAI. By using LC-MS/MS we found that after SDCT a TM-SeC > 378 nmol/l at 0-min, > 1012 nmol/l at 30-min or > 1021 nmol/l at 60-min excluded HPAI, whereas a TM-SeC < 149 nmol/l at 0-min, < 334 nmol/l at 30-min or < 351 nmol/l at 60-min confirmed HPAI. Similarly by LC-MS/MS we found that after SDCT a SaC > 7.4 nmol/l at 0-min, > 15.8 nmol/l at 30-min or > 23.3 nmol/l at 60 min excluded HPAI, whereas a SaC < 1.7 nmol/l at 0-min, < 4.7;nmol/l at 30-min or < 7.3 nmol/l at 60-min confirmed HPAI.
Conclusions
We can conclude that even evaluating TM-SeC and SaC, after SDCT there is large gray area of indeterminate results.

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EP1044

Risk and diagnosis of hypocortisolism after transsphenoidal surgery for sellar tumors

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Introduction
Transsphenoidal surgery (TS) is used for pituitary and suprasellar tumors. It has a risk of damaging the pituitary axis and developing hypocortisolism, a potential life threating risk.
Objetive
Incidence of hypocortisolism after TS, postsurgery cortisol (PSC) levels that predict hypocortisolism and potential risk factors for hypocortisolism after TS.
Methods
Prospective study in patients who underwent TS in 2016. Glucocorticoid replacement (GR) began in surgery with hydrocortisone (HC) 100 mg tid. We defined hypocortisolism as PSC < 10 mcg/dl (discharged with HC 20 mg/day), possible hypocortisolism as PSC 10–20 mg/dl (discharged with HC 10 mg/day) and eucortisolism as PSC > 20 mcg/dl 3 days after TS. Definitive eucortisolism was defined as Cortisol > 18 mcg/dl after 100 mcg ACTH stimulation or basal cortisol > 20 mcg/dl 5 weeks after TS.
Results
Twenty-three (12 females) patients underwent TS, mean age 52 years (22–85): 56%nonfunctioning adenomas, 20%GH adenomas, 4%arachnoid cyst and 8%craniopharyngioma. *Preoperative features: tumor's* mean diameter: 25 mm (5–65), involvement of cavernous sinuses (KNOSP grade ≥ 2) 60%. Five patients present preoperative hypocortisolism. *Pituitary-adrenal axis (PAA) assessment:* After TS 9 patients were diagnosed of hypocortisolism, 13 of possible hypoC and 1 of eucortisolism. Five week after TS: 8 were diagnosis of definitive hypocortisolism and 15 of definitive eucortisolism. Mean PSC was 13.5 mcg/dl (2.28–22.5) in definitive eucortisolism patients and 8.75 mcg/dl (1.2–14.35) in definitive hypocortisolism. 75% with definitive hypocortisolism patients had PSC < 12 mcg/dl. In patients with definitive hypocortisolism: 60% presented preoperative hypocortisolism, 30% preoperatory GH deficit, 60% cavernous sinuses involvement, with KNOSP grade > 2 and 50% were > 30 mm.
Conclusions
Hypocortisolism after TS is a mayor complication; large and invasive tumors have more risk to develop postsurgery pituitary hypofunction. Three days PSC can predict development of definitive hypocortisolism, PSC ≥ 15 mcg/dl may be use to diagnose eucortisolism and avoid unnecessary replacement HC treatment in this patients.

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EP1045

Nivolumab and pembrolizumab induced hypophysitis

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Introduction
Immune checkpoint blockade in cancer treatment causes frequent adverse events of auto-immune etiology. Ipilimumab (anti-CTLA-4 antibody) causes a hypophysitis in up to 10% of patients. In contrast, during treatment with nivolumab and pembrolizumab (both anti-PD-1 antibodies), hypophysitis is rare (< 1%).
Results
In the past year, we identified 4 cases of hypophysitis in patients treated with anti-PD-1 therapy (incidence 1% out of a total group of 395 patients). Two patients (male aged 78, female aged 58) were treated with nivolumab for non-small cell lung cancer and 2 patients (male aged 61, female aged 69) received pembrolizumab for metastatic melanoma. After 8–12 cycli, all patients developed fatique, two patients developed edema and 1 patient developed nausea and a blurry vision. There was no period of transient headache as typically found in hypophysitis caused by ipilimumab. Laboratory examination revealed the diagnosis. Brain magnetic resonance imaging showed a normal pituitary gland in all patients. At diagnosis, pituitary failure was present for the thyroid and adrenal axis in 2 and 3 patients, respectively. One patient developed failure of the pituitary-gonadal axis.
Discussion
In contrast to hypophysitis after ipilimumab treatment, anti-PD-1 induced hypophysitis seems characterized by an insidious clinical course, without typical symptoms or associated MRI abnormalities. In contrast, the pattern of endocrine failure of the adrenal axis is immediately life threatening. Given the sharp increase in the number of patients treated with immune checkpoint inhibitors, more patients with this rare side effect are expected. Therefore, it is necessary to screen for central hypocortisolism and hypothyroidism and be aware of the possibility of a varied clinical presentation.

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EP1046

Heterogeneity of the patient pathway for adult growth hormone deficiency: Perspectives from a CEE Endocrinologists expert panel

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Introduction
Effective identification, diagnosis and management of growth hormone (GH) deficiency in adults are crucial for treating endocrinologists to provide the best in patient care. As such, it is important that we share our experiences to understand challenges and obstacles to enhance the patient journey. The objective of this project was to start identifying these challenges and obstacles.
Methods and findings
In November 2016, an expert panel of 10 endocrinologists from across 10 Central and Eastern European (CEE) countries met to discuss their standard of care and

journey taken by adult GH-deficient (AGHD) patients in their respective countries. Prior to the meeting the experts were asked to summarize in a systematic way, the standard of care available for AGHD patients in their countries and share this with their peers. The meeting was chaired by one of the experts and each participant had adequate time to present their perspective followed by discussion. It was uncovered that there was a substantial degree of diversity in the management AGHD patient pathway across CEE. The main variations included: initial entry to the healthcare system and referral journey; tests required to confirm diagnosis; availability of programmes to manage patients during transition to adulthood; limitations of who prescribes GH therapy, medication re-imbursement by national healthcare services and, the frequency of follow-up visits and monitoring of patients. Although most countries represented relied on international society-led, published guidelines, few countries have developed national guidelines for patient management.

Conclusion

This expert panel recognizes a high degree of diversity in the patient pathway across CEE. Sharing of local experiences with other colleagues may help in understanding areas of high heterogeneity as well as facilitating the sharing of best practice. Further work will be needed to identify differences in practice patterns and AGHD patient management among other regions in the world.

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EP1047

Considerable delays to achieve adequate control in treating patients with acromegaly

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Acromegaly is a rare disease that leads to considerable morbidity and mortality, both reversible by adequate control of the disease. However, patients that could be adequately controlled confront delays in achieving treatment targets. The aim of the present study was to estimate the time to disease control after diagnosis and the reason leading to control delays. We retrospectively studied 119 acromegalic patients (aged 46.4 ± 12.5; 71 females). Following appropriate treatment modalities all achieved IGF-1 levels within normal limits for age (43 pts had GH <1.0 ng/ml, and 76 pts had GH <2.5 ng/ml). Acromegaly was adequately controlled within 0-6 months in 19 patients (15.9%), within 6–12 in 14 (11.8%), and within 12–24 in 21 (17.6%). In 65 patients (54.6%) disease control was achieved after 24 months (25–412, median 103 months). Earlier controlled patients were older (50 ± 11.9 vs 43.5 ± 12.3, $P=0.00434$), and underwent surgery sooner after the diagnosis (8.0 ± 6.8 vs 19.8 ± 30.9 months $P=0.0324$). When under medical treatment, the main reasons for delay control were the late referral and initiation of medical therapy (5.4 ± 5.0 vs 124.6 ± 117.1 months, $P=0.0138$), and the time elapsed to modify dosage and/or implementing alternative treatment options (4.4 ± 3.7 vs 16.1 ± 11.1 months, $P=0.0138$). Tumor size or extension, GH and IGF-1 had no impact to time to control. According to our audit a substantial proportion of patients remain uncontrolled for several months despite the efficacy of available therapeutic modalities in these patients. The main reason seems to be the delay to cease early surgical intervention or to adjust the medical treatment options.

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EP1048

Hyponatremia – the other face of diabetes insipidus complications

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Diabetes insipidus is mainly associated with dehydration as a complication, hyponatremia being very rare. We report the case of a 75 years old female, from Switzerland, who presented with nausea and vomit, diarrhea, asthenia and general sickness at the emergency room, where blood tests revealed hyperglycemia of 320 mg/dl and hyponatremia of 115 mmol/l, the patient knowing to have diabetes insipidus and diabetes mellitus type II, with insulin and desmopressin. Following emergency equilibration, we recommended monitoring water intake, urine excretion in the absence of desmopressin, with control of glycemic profile every 4 hours, for the next 24 h, and a MRI scan, in order to objectivate the diagnosis. Initial cooperation was present. The anamnesis revealed diabetes insipidus diagnosed at age 30, treated with desmopressin spray 10 mcg two times a day, in the morning, and diabetes mellitus type II from age 60, treated with 4 shots of fast insulin, 42 U/day. Clinical examination revealed signs of mild dehydration. Lab tests highlighted mild hyperglycemia of 142 mg/dl and hyponatremia of 129 mol/l. Glycated haemoglobin was 7.3%. Plasmatic osmolarity was 272.3 mOsm. The patient was uncooperative to stoping or changing the schedule of desmopressin treatment, so she was discharged with natremia of 139 mmol/l. Recent medical history showed a recent emergency admission with similar clinical and biochemical futures. Moreover, it was proved that the patient had many ER admissions in Bucharest's hospitals, with same situation. In this respect, the diagnosis of diabetes insipidus itself can be put under question, complicated by the psihogenic adherence to desmopressin treatment of the patient. Frequent clinical manifestations of hyponatremia due tu desmopressin abuse in our patient is highlighting not only the complexity of psihogenic association to organic abuse, but also the need for cooperation between practitioners across EU.

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EP1049

Aggressive pituitary tumours: a multicenter study

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Introduction

Pituitary tumours are considered benign, however some exhibit an aggressive behavior. Defining a timely treatment is challenging due to absence of accurate prognostic predictors.

Objective

To evaluate radiological and histopathological features of aggressive pituitary tumours.

Methods

Multicenter and retrospective study. Criteria for aggressiveness were: invasion to sphenoid and/or cavernous sinus; growth progression after treatment (surgery/medical/radiotherapy); early recurrence ($\leq$12 months). Atypical features were Ki-67 $>3\%$, p53 positivity, mitoses >2/10xHPF or brain/spinal/systemic metastases.

Results

Forty-five patients (28 men) were collected from seven tertiary endocrine departments. Age at diagnosis was 41.2 ± 12.2 years. In 35.6% of patients first symptoms occurred before 35 years. Symptoms related to tumour expansion, hypersecretion and deficiency of hormones were the first manifestations in 73.6, 13.2 and 13.2% of patients, respectively. Our cohort comprised nonfunctioning adenomas (64.4%), somatotropinomas (9.0%), corticotropinoma (13.3%) and prolactinomas (13.3%). All were macroadenomas and 82.2% showed radiological signs of invasion. Of the 44 operated patients, 56.8% required three or more surgeries. Complementary radiotherapy was used in 66.7% of patients, medical therapy in 42.2% of patients, two of these with temozolomide. Histopathology was obtained in 42 patients. Imunohistochemichal staining was GH positive in 9.5%; PRL 14.3%; ACTH 11.9%, TSH 2.4%, FSH/LH 19%; plurihormonal 14.3%; nonsecreting and null-cell 28.6%. Elevated mitotic index was observed in 20% ($n=25$), Ki-67 labeling index $\geqq 3\%$ in 44.4% ($n=27$) and p 53 nuclear staining in 41.2% ($n=17$). During a mean follow-up of 11.5 ± 6.3 years, 8 patients died (5 ACTH-cell a*denoma*) one with extracranial systemic metastases (carcinoma).

Conclusions

In our cohort ACTH-secreting tumours presented a more aggressive clinical course. One limitation of our study was incomplete histopathological data, however, the majority of patients who died, presented atypical features. A continuous multicenter collaboration could help to identify prognostic markers and enable a different approach.

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EP1050

Effects of somatostatin analogs on glucose metabolism in acromegalic patients: a meta-analysis of prospective interventional studies

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Introduction
Glucose metabolism impairment is a common complication of acromegaly. Somatostatin analogs (SSAs) are used as both first and second line treatment. The effect of SSAs on glucose metabolism in acromegaly is still debated.
Aim
To address the following questions: 1) do SSAs affect glucose metabolism? 2) does the effect correlate with disease control? 3) do different SSAs – Lanreotide (LAN) and octreotide LAR (OCT) – affect metabolism differently?
Methods
We performed a meta-analysis of prospective interventional studies reporting the use of SSAs for the treatment of acromegaly. We searched MEDLINE, EMBASE, and SCOPUS for English-language studies. Inclusion criteria: minimum 6-month follow-up, glyco-metabolic outcomes before and after SSA treatment. The pooled estimate of a weighted mean was obtained for all outcomes using a random effects model.
Results
Forty-one studies have been included, 20 for LAN (354 patients) and 21 for OCT (569 patients). LAN treatment induced a significant decrease in fasting plasma insulin (FPI) (effect size −8.32, 95% CI: −10.44 to −6.20; $P<0.001$) and HOMAi (−2.11, 95% CI: −3.54 to −0.69; $P=0.004$), without changes of fasting plasma glucose (FPG), HbA1c, triglyceridemia, weight and BMI. OCT induced a small increase in HbA1c (+0.146, 95% CI: 0.043–0.249; $P=0.005$), a borderline rise of glucose during OGTT (0.47, 95% CI: −0.01 to 0.95; $P=0.053$) and significant decrease in FPI (−6.78, 95% CI:−9.37 to −4.18; $P<0.001$), triglyceridemia (−0.41, 95% CI −0.55 to −0.28; $P<0.001$), HOMAi (−1.44, 95% CI:−2.54 to −0.34; $P=0.010$) and HOMAβ (−36.65, 95% CI:−63.21 to −10.08; $P=0.007$), without any change of FPG. Meta-regression analysis revealed an association between the degree of GH reduction and lowering of HbA1c ($P=0.03$). Meta-regression also showed a worse post-therapy Hb1Ac outcome with increasing pre-therapy IGF1 levels ($P=0.002$). The percentage of patients at target for GH and baseline IGF1 explained up to 58% of variance of HbA1c.
Conclusions
LAN and OCT induce a significant decrease in FPI and in HOMAi, without adverse change in FPG. OCT seems to reduce HOMAβ and increase HbA1c, while reducing trygliceridemia. IGF1 and GH-response partially explain the metabolic effect of SSAs.

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EP1051

Prolactinomas diagnosed after menopause: presentation and outcomes from a large specialist centre

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Introduction
Most prolactinomas in females are diagnosed during the years of reproductive age and the majority are microadenomas. Prolactinomas diagnosed after menopause are very rare with limited published data on their presentation and outcomes.
Aim
The aim of our study was to assess the presenting clinical, biochemical and imaging findings, as well as the outcomes of women diagnosed with a prolactinoma in the post-menopausal period.
Methods
All women of this group diagnosed between 1996 and 2016 and followed-up in a large specialist centre were included in the study.
Results
We identified 17 women with diagnosis of prolactinoma after menopause (median age at diagnosis 62 years, range 52–70). Headaches and/or visual deterioration were the most commonly reported presenting signs (47%). Acute pituitary apoplexy was diagnosed at presentation or during follow-up in 18%. Two prolactinomas were detected incidentally (12%). The median serum prolactin was 18 553 mU/L (range 4153–238479). In all cases, IGF-I values were not consistent with GH hypersecretion. Macroprolactinomas comprised 94% of the tumors and 88% of them had parasellar extension. All patients with macroprolactinoma were offered dopamine agonist therapy; the median duration of their follow-up, determined by the date of starting dopamine agonist until last serum prolactin measurement, was 91 (5–186) months. Normal prolactin was achieved in 94% and adenoma shrinkage was observed in all women. Improvement or resolution of the visual disturbances documented at presentation was observed in 86% of cases.
Conclusions
The clinical phenotype of prolactinomas diagnosed after menopause differs from that of premenopausal women, possibly due to the lack of clinical signs and symptoms of hyperprolactinemia in non-menstruating patients. Most tumours were macroadenomas, with frequent parasellar extension and a relative high rate of pituitary apoplexy. In this very rare group of tumours, response to dopamine agonists is good.

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EP1052

Ipilimumab induced hypophysitis – an insight from a case series in the United Kingdom

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Aims
To assess the incidence of Ipilimumab associated hypophysitis and its common presentations.
Methods
All patients who developed Ipilimumab induced hypophysitis following treatment for Malignant melanoma at a large tertiary care centre in West Midlands, United Kingdom from 2012 to 2014 were included in the study. Patients with known pituitary disease prior to treatment and/or received other systemic immunotherapy following Ipilimumab treatment were excluded. All surviving patients were followed up to December 2016. Relevant data – clinical features, hormone profiles and radiological findings – were extracted from patients' medical records.
Results
Overall, 59 patients were treated with Ipilimumab for malignant melanoma during the period of interest. The incidence of hypophysitis in the cohort was 15.3% (9/59). The median age for patients with hypophysitis was 64 years (IQR, 60–68 years); 44.4% (4/9) were male. 66.7% (6/9) presented with mild to moderate symptoms and 33.3% (3/9) patients developed severe symptoms secondary to Ipilimumab induced hypophysitis resulting in hospitalisation. Fatigue (7/9; 77.8%) was the most common presenting symptom; headache and visual disturbance was reported by 33.3% (3/9) and 22.2% (2/9) respectively. Secondary hypogonadism (5/9; 55.6%) and secondary hypoadrenalism (4/9; 44.4%) were the most commonly affected pituitary systems. One patient developed panhypopituitarism. 33.3% (2/6) patients developed diffuse enlargement of pituitary gland. All patients had clinical recovery following adequate hormone replacement.
Conclusions
Disturbances in pituitary axis are common with Ipilimumab treatment and can present with subtle symptoms. Therefore, regular assessment of pituitary function during Ipilimumab treatment is recommended. Affected patients should be managed jointly by oncology and endocrinology teams to prevent serious complications and allow Ipilimumab treatment to continue.

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EP1053

Mammary duct ectasia due to prolactin-secreting pituitary adenoma

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Introduction
Mammary duct ectasia (MDE) is an inflammatory breast disease characterised by dilation of major ducts and periductal inflammation. MDE occurs commonly in women undergoing menopause. The etiology has not been well defined but previous studies described an association between high prolactin and MDE.
Case Report
A 42-year-old female was admitted to our hospital with complaints of galactorrhea, amenorrhea, mammary gland tenderness and breast discomfort. Tests revealed serum prolactin level of 85 ng/ml and breast ultrasound showed dilated anechoic ducts and marked cystic ectasia. A 15×12 mm complex cystic lesion in right breast and several enlarged lymph nodes were found in right axillae. Mammography revealed thickened breast tissue with diffuse MDE without any calcification. Pituitary MRI showed 5.5×5.0×2.5 mm pituitary adenoma. Treatment with cabergoline 0.5 mg twice a week, warm compress and antibiotic started. Cabergolin dose is progressively increased to 2 mg per week. Prolactin level reached to 20 ng/ml and tumor size reduced to 3×3×1.5 mm in 6 months. Although treatment with cabergoline, resulted in improvement of breast symptoms and galactorrhea, diffuse MDE was reported in repeat ultrasound. Cabergoline dose is increased and the patient is still being followed up.
Discussion
In the present case, we hypothesize that there was an association between abnormal prolactin secretion and development of MDE. Shousha *et al.* discribed three cases with marked MDE and chromophobe adenomas. Peters *et al.* concluded that MDE is due in part to increased prolactin secretion. They also concluded that MDE may cause transient hyperprolactinemia. MDE induced by sulpiride-associated hyperprolactinemia was also discussed in literature. In our case; diffuse MDE may have been developed as a result of changes in prolactin levels. We conclude that increased prolactin secretion leading to chronic inflammation and fibrosis may cause to persistence of ductal dilatation.

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EP1054

Quantitative analysis of the pituitary gland at magnetic resonance imaging in obese patients

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Background
Hypothalamic-pituitary function and adipose tissue are deeply interconnected. Obesity has been linked to morpho-functional changes in several endocrine glands (thyroid, adrenal, gonads). No study has quantified the appearance of the pituitary gland in obese subjects.
Aim
To measure pituitary signal intensity, homogeneity and texture of the pituitary gland at magnetic resonance (MR) in obese subjects free of focal pituitary disease.
Materials and Methods
Sixty-four overweight and obese patients were prospectively enrolled and underwent metabolic, hormonal, body composition (DEXA scan) and pituitary MR assessment. Texture of the pituitary gland was quantified recording pixel density and distribution at sagittal and coronal non-enhanced T1-weighted images using ImageJ software. Two operators independently placed the region of interest to entirely cover the pituitary gland, calculating mean intensity and its standard deviation. All analyses were normalized for both white and gray brain matter intensity. Pituitary volume (PV) was calculated using the ellipsoid formula.
Results
MR showed an empty sella in 12/64 (18.7%) patients. Mean PV was 384 ± 147 mm^3 (427 ± 120 mm^3, excluding the empty sella). An inverse correlation was found between PV and ultrasensitive C-reactive-protein ($P=0.004$) and a borderline association between PV and BMI ($P=0.056$). Pituitary intensity in T1-weighted images was negatively correlated with BMI ($P=0.03$) and truncal fat ($P=0.04$). Linear regression analysis revealed that, after adjusting for age and sex, the percentage of truncal fat and fibrinogen were significant predictors of the mean intensity of coronal and sagittal T1-weighted scans ($P=0.001$). The model explained up to 29% of variance of pituitary signal intensity, and in a step-wise R^2 analysis fibrinogen itself accounted for 10% of the variance. Moreover, T1-weighted coronal scans were inversely correlated with VES ($P=0.01$).
Conclusions
This study describes a reduction of pituitary volume and quantitative T1-weighted intensity in obese patients, that seems related to a low-grade inflammation. Data could be explained by a relative change in pituitary stromal tissue in this cohort of patients.

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EP1055

Hypogonadotropic hypogonadism in a patient with long-term primary hypothyroidism

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Abstract
We report the case of a 65-year-old man who presented with erectile dysfunction to an appointment in our Endocrinology department. He referred fatigue, weight gain and constipation as secondary complaints that had been steadily evolving throughout the past 4 years. He denied other symptoms such as visual impairment or headaches as well as the consumption of any medications or drugs. His past medical history was unremarkable. On examination, BMI was 25.8 kg/m^2, arterial blood pressure 112/64 mmHg, heart rate 71 BPM and temperature 36.4 °C. Neck palpation revealed a diffuse thyroid enlargement. Visual acuity and visual fields were unaltered. Blood tests revealed elevated TSH (69.8 uU/ml) with low FT4 (0.18 ng/dl), consistent with the diagnosis of primary hypothyroidism, and hypogonadotropic hypogonadism (testosterone 74.3 ng/dl). PRL levels were slightly elevated (38 ng/ml). Magnetic resonance imaging (MRI) of the pituitary showed a 17×14×12 mm sellar mass, without compression of the pituitary stalk or optic chiasm. The patient was started on levothyroxine 100 mcg per day. Three months later, the erectile dysfunction had resolved and thyroid function and total testosterone had returned to normal – TSH 0.90 uU/ml, FT4 1.16 ng/dl, and total testosterone 522.8 ng/dl. The control MRI taken one year after starting therapy revealed regression of the pituitary enlargement. This is a peculiar case of HH likely associated with pituitary hyperplasia, in the context of long standing primary hypothyroidism, successfully treated with levothyroxine.

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EP1056

Effects of pasireotide treatment on cardio-metabolic risk in patients with Cushing's disease: an Italian, multicenter study

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Patients with Cushing's disease (CD) have increased cardiovascular risk due to metabolic alterations caused by glucocorticoids excess. Pasireotide, a multi-receptor-targeted somatostatin analogue, is a therapeutic option in CD patients in whom surgery is not curative or not feasible. Pasireotide has been shown to be effective in controlling hypercortisolism and to improve metabolic features. Recently, the visceral adiposity index (VAI) has been proposed as a marker of

visceral adipose tissue dysfunction (ATD) and of the related cardio-metabolic risk. We aimed to assess the effects of 12-month pasireotide therapy on cardio-metabolic and cardiovascular risk in CD patients. In 16 CD patients (11 females), referred to the Endocrine Units of four Italian University Hospitals, we assessed anthropometric, clinical and biochemical parameters and calculated VAI, ATD severity, Framingham and Atherosclerotic CardioVascular Disease Risk Scores (FRS and ASCVD respectively), at baseline and after 6 and 12 months of therapy with pasireotide (1200–1800 mcg/daily). Before starting pasireotide therapy, ATD was present in 8/16 patients (severe in 2/16, mild in 2/16, moderate in 3/16). After 12 months of treatment: i) UFC levels ($P=0.003$), BMI ($P<0.001$), waist circumference ($P=0.001$), LDL-cholesterol ($P=0.033$), total-cholesterol ($P=0.032$), triglycerides ($P=0.03$), VAI ($P=0.015$) and ATD severity ($P=0.026$) were significantly decreased as compared to baseline; ii) ATD was present in only 1/16 patients; iii) prevalence of diabetes ($P=0.015$) and HbA1c levels ($P=0.001$) were significantly increased as compared to baseline; iv) FRS and ASCVD scores were not statistically different from pre-treatment values. In conclusion, twelve-month pasireotide treatment reduces cardio-metabolic risk in CD patients.

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EP1057

DHEA-S as a marker of the secondary adrenal insufficiency following craniospinal irradiation

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Abstract
The secondary adrenal insufficiency (SAI) is life-threatening disease. 30–50% of patients have SAI following craniospinal irradiation (CSI). The "gold standard" of SAI diagnosis is the insulin tolerance test but it is demanding for patient and medical staff. The simple and reliable test would allow to use ITT rarely. The aim was to evaluate probability of using DHEA-S in SAI diagnosis. 41 patient after CSI non-pituitary brain tumors survivor and 23 healthy were included. The mean age was $20.5\pm3,6$ years (16–30), follow-up was more than 2 years. Cortisol, DHEA-S, ACTH were determinate and then ITT was performed. The patients were divided into SAI-group and without SAI (W-SAI) after ITT.
Results
18/41 had SAI by ITT. DHEA-S was significantly lower in SAE-group 2.65 ± 1.4 μmol/l than in W-SAI and healthy (5.2 ± 2.1 and 7.6 ± 4.4 μmol/l, $P=0.001$). Cortisol in SAI and healthy was the same (326 ± 99.4 and 390.5 ± 161 mmol/l, $P=0.2$) but lower that W-SAI (495.2 ± 186 mmol/l, $P=0.05$). ACTH was not differ. DHEA-S/cortisol ratio was lower in SAI ($P=0.002$), ACTH/cortisol was the same. There was the significant correlation between SAI and cortisol ($r=0.57$, $P=0.02$) and SAI and cortisol ($r=0.49$, $P=0.02$). There was not correlation between age and DHEA-S. DHEA-S did not have gender difference within SAI and W-SAI. AUC cortisol was 0.79; AUC DHEA-S 0.9; AUC DHEA-S/cortisol 0.67. All patients who had basal cortisol lower than 200 nmol/l or DHEA-S lower than 2.0 μmol/l were in SAI-group, and who had cortisol or DHEA-S more than 500 and 3.7 respectively did not have SAI by ITT. Cut-off DHEA as 3.7 had Se 73% and SP 100%. When linear regression has applied, AUC cortisol + DHEA-S was 0.96.
Conclusion
DHEA-S had higher sensitive and specificity that cortisol for diagnosis of SAI in patients younger than 30 years following craniospinal irradiation. DHEA-S can used without gender accounting in this group. Combined examination by DHEA-S and cortisol is optimal.

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EP1058

Clinical and laboratorial reassessment of patients with isolated growth hormone deficiency during the transition phase

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Introduction
During childhood and puberty, growth hormone(GH) is essential for linear growth. Consequently, children with isolated GH deficiency(GHD) must receive replacement therapy. GH has also important metabolic actions. GHD in adults is associated with altered body composition. However, long-term consequences of GH treatment in adults is not sufficiently known.
Objective
To evaluate GH treatment during pediatric age in patients with isolated GHD.
Methods
Retrospective study of patients with isolated GHD followed in a tertiary hospital, which had undergone reassessment after finishing growth period. Anthropometric and analytical parameters before and after treatment were collected. SDS of anthropometric variables were calculated according WHO curves. IGF1 (Immulite 2000®) was analyzed considering SDS values adjusted for pubertal stage.
Results
Sample composed by 27 patients, 63% males. Before treatment: mean age was 10.5 ± 3.7 years, mean height-SDS -2.82 ± 0.77, IGF1-SDS levels -2.41 ± 1.59 ng/ml with a mean difference of 2 ± 1.5 years between chronological and bone age. All patients performed GH stimulation tests (clonidine, glucagon or insulin tolerance test) – peak values <7.0 μg/l. Three patients had abnormal pituitary MRI. Mean treatment duration was 5 ± 3 years. Mean maximal dose administered was 0.03 ± 0.01(mg/kg/day). No adverse effects were registered. At the end, final height-SDS was -1.63 ± 0.64 and IGF1-SDS -0.83 ± 2.34. Final height and target height differed in -4.72 ± 6.07 cm. Nine patients kept follow-up in Endocrinology: 3 performed insulin tolerance test, all having normal results. Only 2 patients presented IGF-1 levels <-2 SDS (one of them proposed for treatment).
Discussion
As expected, patients with isolated GHD treated at our center showed good clinical outcomes, with mean final height reaching close target height. Current recommendations consider to treat with GH, adults with documented persistent deficiency. In this series all patients with isolated GHD with normal MRI had a transitory deficit and did not required treatment in the adult age.

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EP1059

What should central diabetes insipidus and panhypopituitarism point out in a patient with lung adenocarcinoma in remission?

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Objectives
Pituitary gland is an uncommon site for metastasis of malignant tumors. Breast and lung are the most common cancer sites. Most pituitary metastases are asymptomatic, with only 7% symptomatic and central diabetes insipidus is the most common symptom.
Case presentation
A 54 year-old woman presented with nause, emesis and diplopia to emergency department. Her relatives stated that she had poliuria, nocturia, polidipsia for three months. Her history revealed that she had been operated because of lung adenocarcinoma and postoperatively had underwent adjuvant chemotherapy. She was at follow-up in remission. Laboratory tests denoted hypernatremia and MRI scan images demonstrated that hypointense contrasted hypophysis and infundibular enhacement. She possesed central diabetes insipidus and desmopressin treatment administered primarily. On observation, central hypothyroidism and secondary adrenocortical defficiency developed. Medical oncology department assesed the patient, no metastatic lesion was detected in thoracoabdominal CT additionally PET scan, so that they didn't consider pituitary metastasis. We didn't reveal any autoimmune, infectious and inflammatory diseases that can cause hypophyseal involvement. Transnasal-transsphenoidal hypophysis biopsy was occured, but histopathological sampling was insufficient. The patient refused second biopsy, so she was discharged with replacement therapy in clinical stable state. But two weeks later, the patient applied with emesis-vomitting and diplopia

and MRI scans showed progression. Also she had seizures, periferal facial paralysis and drop foot. The progression of lesions necessitated exact diagnosis and transcranial biopsy was carried out by the same neurosurgeon. After biopsy, her clinical course worsened and she lost her life. Meanwhile, histopathological examination resulted as metastasis of lung adenocarcinoma to hypophysis.
Conclusions
A past history of cancer should be kept in mind in a patient presenting with sellar mass even if the cancer is in remission. Especially, presence of diabetes insipidus and MRI scan findings are clues for metastatic disease.

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EP1060

Is there any relationship between nonfunctional pituitary adenoma and arterial stiffness?

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Introduction
In a recent study, it was determined that morbidity rates due to cardiovascular diseases were affected as a result of long-term follow-up in patients with nonfunctional pituitary adenoma. And cardio/cerebro vascular diseases were the most frequent cause of mortality when mortality rates were examined. In the literature, there are not enough studies evaluating this condition in patients with nonfunctional pituitary adenoma without traditional cardiovascular risk factors. The aim of our study was to determine the peripheral and central blood pressures and arterial stiffness by Pulse Wave Analysis (PWA) in patients with nonfunctional pituitary adenoma without traditional risk factors.
Material & methods
In ourstudy, 60 participants (30 patients with nonfunctional pituitary adenoma and 30 healthy volunteers) without traditional cardiovascular risk factors were evaluated. All participants were similar in terms of gender, age and body mass index. Peripheral and central blood pressure and PWA measurements were performed with a Mobile-O-Graph PWA / ABPM instrument (I.E.M. GmBH, Stolberg, Germany). In the nonfunctional pituitary adenoma group radiological and biochemical data were obtained retrospectively.
Results
In the nonfunctional pituitary adenoma group, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), central SBP, central DBP, augmentation index that corrected based on pulse rate of 75 bpm (Aix@75) and pulse wave velocity (PWV) were significantly higher than control group. There was no significant correlation between biochemical parameters and arterial stiffness parameters in the group of nonfunctional pituitary adenoma.
Conclusion
Peripheral and central blood pressure and arterial stiffness parameters are negatively affected in patients with nonfunctional pituitary adenoma known as cardiometabolically innocent, without traditional cardiovascular risk factors. Measurement of arterial stiffness in this patient group will lead to early detection of mortality and morbidity due to possible cardiovascular pathologies

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EP1061

A rare cause of hypophysitis: tuberculosis

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Hypophysitis is a heterogeneous inflammatory disease of pituitary gland. As it causes headache and visual defects, it mimics sellar tumors in clinical and radiological aspects. It may occur due to primary or secondary causes. Tuberculosis is one of the rare secondary causes of hypophysitis. A young male patient presented with fatigue and headache and diagnosed with tubercular hypophysitis as a result of performed tests is discussed hereby in the case report. A 30 year old male patient presented to out clinic with fatigue, malaise, somnolence and headache. It was learned that the onset of the complaints was three months before and they gradually increased since then. There was no chronic disease, medication, herbal agent or alcohol use in the patient anamnesis. Overall medical condition of the patient was moderate with 36.7℃ body temperature, 80/50 mmHg arterial blood pressure and 50/min heart rate. Physical examination revealed no abnormal finding other than icteric sclera. Due to the pathologic findings of 0.05 ng/dl free thyroxine level, 2.04 pg/ml free triiodothyronine level and 0.46 u/ml of thyroid-stimulating hormone, further tests were performed on the patient for a pre-diagnosis of central hypothyroidism. Tests performed for etiology resulted in 0.82 ug/dl cortisol, 0,1 mlu/ml luteinizing hormone, 7.97pg/ml adrenocorticotropic hormone and 2.68 mlu/ml follicle stimulating hormone. Panhypopituitarism was considered due to these results. Levothyroxine and prednisolone treatment was initiated. Diagnostic magnetic resonance (MR) imaging was performed. Imaging revealed height of pituitary gland 14 mm higher than normal. No heterogeneity was observed at pituitary gland level. Biopsy of pituitary gland was performed for establishing diagnosis and result was concordant with granulomatous hypophysitis. TORCH panel, herpes simplex virus, Brucella, Epstein–Barr, parvovirus, varicella-zoster, T. pallidum tests were negative. Adenosine deaminase (ADA) level was 45, in the upper limit. Tuberculin skin test (PPD) resulted in 22 mm induration and QuantiFERON-TB gold test was positive. Hypophysitis developed secondary to tuberculosis was considered. In addition to the current treatment, anti-tuberculosis (isoniazid, streptomycin, pyrazinamide, rifampin) treatment was initiated. The dose of administered prednisolone was gradually (24 -> 18 -> 12 -> 8 -> 75 -> 5 -> 4 mg / day) increased along the course of treatment. The need for steroid was completely eliminated by month 6 of tuberculosis treatment. In cases such as tubercular hypophysitis developing due to secondary causes, early diagnosis is very important given that panhypopituitarism may be completely eliminated in clinical terms following an effective anti-tuberculosis treatment. Therefore, tubercular hypophysitis should be kept considered for cases referred with hypopituitarism clinic and suggesting secondary hypophysitis.

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EP1062

T2-weighted MRI signal and response to somatostatin analogs in acromegaly

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Introduction
somatostatin analogs (SSA) are largely prescribed in acromegalic patients, whether as adjuvant or primary therapy. Response is variable and seems dependent of histological subtype. Intensity T2 signal in MRI has been related to granulation patern and accordingly with response to SSA.
Objective
To evaluate whether T2 MRI signal is correlated with effectiveness of SSA
Material and methods
Retrospective analysis of acromegalic patients treated with SSA and available T2 MRI. We considered response as complete (normal GH and IGF1), partial (GH and/or IGF1 reduction $\geq$50%) and no response ($\leq$50%). MRI were analysed by one neuroradiologist blinded for clinical and pathological data. Visual assessment only or direct measurements of signal intensity using ROI cursors on T2 coronal sections classified adenomas as hypointense or hyperintense, according MRI signal $\leq$ temporal lobe white matter or $\geq$ grey matter, respectively. Signal intensity between grey and white matter defined isointensity.
Results
Fourteen patients (8 males) were treated with SSA for a minimum of 6 months. All but 5 patients were surgically treated (3 refused, 1 approach failed due to bleeding, 1 is waiting surgery). T2 MRI hypointensity was documented in 8 patients (group 1) and hyperintensity in 6 (group 2). Group 1 included 3 non responders, 3 with partial and 2 with complete response. Group 2 comprised 3 non responders, 2 with partial and 1 with complete response to SSA. Considering isolated GH reduction ($\geq$ 50%), hypointensity was more often observed (62,5%).
Comments
In this cohort of acromegalic patients we observed no relationship between T2 signal intensity on MRI and hormonal response to SSA. One major limitation is the small sample analysed.

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EP1063

"Toxic" Goiter Reveals Cushing's Disease

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Case presentation
Mrs. S presented in an endocrine clinic for fatigue, weight loss, restlessness and goiter. She was obese with a BMI of 51 kg/mp, hypertensive and had a medium size, nontender goiter. Lab test revealed hyperglycaemia, suppressed TSH (<0.03mUI/L), on two separate occasions, mid-normal fT4 and T3. Thyroid ultrasound revealed multinodular goiter. A diagnosis of polynodular goiter with subclinical hyperthyroidism was made and patient was commenced on thiamazole 30 mg/day. She was also scheduled for a RAIU. Three weeks later she was admitted in the endocrine unit with a BMI of 47kg/mp. At presentation she had plethora, purpura on her breasts and bruised easily at venipuncture sites. FBC revealed neutrophilia with lymphocytopenia, normal platelets. Thyroid function tests revealed suppressed TSH (0.0164 mUI/L) with low fT4. Thiamazole was stopped. RAIU revealed low radioiodine uptake in the thyroid. Midnight plasma and salivary cortisol were high, morning plasma cortisol was borderline high, with increased ACTH. Urine cortisol was 10 fold upper limit of normal, low dexamethasone suppression test was negative. MRI of the pituitary revealed left sided pituitary microadenoma of 7,5/7 mm. Diagnosis of Cushing's disease has been made and transsphenoidal adenomectomy was perfomed. At 3 weeks postoperatively patient has returned to clinic with symptoms of cortisol withdrawal while on 30 mg of cortisone daily. She had a BMI of 42 kg/mp, no plethora and no purpura. Cortisol day curve was within the therapeutic range. Off therapy, morning plasma cortisol was 8.89 mcg/dL, normal ACTH, midnight plasma cortisol of 1.44 mcg/dL and lower normal range of urinary free cortisol. Thyroid function tests were normal.
Conclusion
Hypercortisolism is known to alter pituitary hormones, however it is not usual that mild Cushing's disease to suppress TSH to 'thyrotoxic' level. In this case of unsuspected Cushing's disease, thyroid function test alteration led to diagnosis.

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EP1064

Low incidence of hyperprolactinemia following traumatic brain injury

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Background
Traumatic brain injury (TBI) is a major cause of disability and death, and a cause of neuroendocrine dysfunction. Partial or complete pituitary dysfunction is a frequent event occurring in 25–50% of subjects after a TBI as result from damage to either the pituitary or the hypothalamus. This large variability depends on the screening methods and on the difficulty to predict the effects of the trauma on pituitary. Growth hormone deficiency and gonadotropin deficiency are the most frequently documented pituitary dysfunctions after TBI. Also hyperprolactinemia has been documented as result of hypothalamic-pituitary stalk damage.
Aim of the study
Aim of our study was to determine the incidence of pituitary dysfunctions following mild to moderate TBI.
Methods and patients
All subjects followed at the emergency room of our institution 12–6 months before were invited to a screening of pituitary function by measuring: FSH, LH, TSH, IGF-1, Testosterone (T) in (man), 17-beta-estradiol (in women) and PRL. When IGF-1 was below the reference range a GHRH + Arginine test was performed to document a GH deficency. LHRH test was performed when FSH and LH and T or 17-beta-estradiol were below the reference range to document gonadotropin deficiency.
Results
Forty-five subjects aged 18–63 years joined the screening. Single or multiple pituitary failure was found in 14 patients (31%). Hypogonadotropic hypogonadism was documented in 3 males (6.8%), low IGF-1 in 10 patients (22%) and GH insufficiency documented in 3 of 4 patients tested by GHRH + Arginine (7%). One patient displayed a concomitant GH insufficiency and low TSH level while in another subject we found GH deficit and low FSH, LH and testosterone values even if his gonadotropin response was normal after LHRH test. Surprisingly, none of the patients displayed altered PRL values.
Conclusions
Mild to moderate TBI was followed by pituitary dysfunction documented in 13.3% of subjects. Higher frailty of GH and gonadotropin secretion by pituitary was confirmed, while altered PRL secretion was not documented.

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EP1065

The pseudo-tumoral adénohypophysitis: A rare disorder of the postpartum

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Introduction
The pseudo-tumoral lymphocytic adénohypophysitis is an autoimmune disorder responsible for anterior hypophysis insufficiensy.It is a rare cause of pituitary hypofunction which predominantly affects young women in the peripartum period. We report the case of a patient in whom the pseudo-tumoral lymphocytic adénohypophysitis was the cause of a pituitary failure.
Case presentation
The patient was a 44 year-old woman, who presented with headache and vomiting without visual disturbance at the 7 th month of pregnancy. She was admitted to our institution in post-partum for secondary amenorrhea combined with the absence of lactation without diabetes insipidus.In the hormonal evaluation, we have a ante-pituitary insufficiency with: cortisol =0,01ug/dl, Estradiol=16pg/ml FSH=5.85 mUI/ml, LH=0.4 mUI/ml, TSH=0.008 uUI/ml, T4=2.19 ng/dl and a prolactin=0.15 ng/ml. Magnetic resonance (MR) imaging of the pituitary revealed a pituitary mass (18×14 mm) evoking a pituitary adenoma. The patient is maintained on oral hydrocortisone and thyroxine. The evolution was favorable and the controlled pituitary MRI, two years after, showed a normal pituitary gland with disappearance of the pituitary mass.
Discussion
The pseudo-tumoral lymphocytic adénohypophysitis is a rare and previously under-recognised disorder, most commonly affecting young females in the post-partum period. It presents clinically with symptoms and signs related to either a pituitary mass or hypopituitarism, frequently mimicking a pituitary adenoma. It is difficult to distinguish lymphocytic hypophysitis from a pituitary adenoma on pre-operative imaging and definitive diagnosis rests on histology which classically demonstrates destruction of anterior pituitary acini by an inflammatory infiltrate rich in plasma cells and T lymphocytes.

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EP1066

Clinically nonfunctioning pituitary adenoma: a case report

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Objective and importance
Clinically nonfunctioning pituitary adenomas (NFPA) are the most common pituitary tumors after prolactinomas. The absence of clinical symptoms of hormonal hypersecretion can contribute to the late diagnosis of the disease.
Clinical presentation
A 52-year-old man presented with muscle weakness, weight loss, fatigue and a long term history of depression. He had no headaches and no vision problems. Physical exam was unremarkable. Neck and thorax CT was performed because of lung malignancy suspicious. Neck CT detected a cranial mass. Cranial MRI was performed. Magnetic resonance imaging (MRI) revealed a pituitary macro-adenoma (3.5 cm high, 2.5 cm wide and 2.3 cm deep). It extended up and out of the sella turcica, stretching the optic chiasm and optic nerves. The levels of prolactin and the other pituitary hormones (except for testosterone) were normal and the lesion was given a diagnosis of a non-secreting pituitary adenoma. Endoscopic trans-nasal trans-sphenoidal pituitary adenoma resection was performed. The tumour was completely removed, identified as a pituitary adenoma with intracapsular hematoma.

Conclusion
Nonsecretory pituitary tumors are called null-cell tumors measuring a few millimeters are common and found in up to 25% of autopsies. These may grow slowly, destroying normal pituitary function, or they may compress nearby structures and cause neurologic problems. In our case report we discuss asymptomatic pituitary macroadenoma.

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EP1067

Nonfunctioning pituitary incidentaloma – delayed onset of acromegaly and concomitant primary adrenocortical insufficiency

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Introduction
Pituitary incidentaloma (PitInc), defined as an unsuspected mass observed on imaging studies performed for unrelated conditions. Most such lesions are not clinically significant at initial evaluation and current guidelines recommend periodic follow-up.
Aim
To present a rare case of delayed onset of acromegaly in a patient with a nonfunctioning PitInc, raising the question of the utility of prolonged follow-up of PitInc.
Methods
Clinical examination, biochemical and imaging studies.
Case report
Following a contrast head CT for headache, a 63 years old female presented with a 11×5 mm intrasellar pituitary mass, no clinical signs of pituitary hypersecretion and normal serum prolactin and IGF-I. Subsequent follow-up showed non-progression of mass size on CT/MRI and normal prolactin/IGF-I. 10 years from initial diagnostic, unexplained hyperkalemia prompted re-evaluation, revealing mild skin hyperpigmentation, absence of other signs of adrenal failure, a small increase in shoe size, without other acromegalic features. IGF-I was high (2.2-2.9 xULN), the GH nadir during OGTT was diagnostic for acromegaly. Review of MRI scans revealed a minimal lesion size progression and cystic changes. Visual fields were normal. The patient was offered surgery but chose to start cabergoline, dose-titrated to 3 mg/week, leading to IGF-I normalization. ACTH was elevated and increased progressively, 8 AM serum cortisol was normal, with subnormal response to Synacthen, suggesting subclinical primary adrenocortical failure. An adrenal CT scan excluded adrenal masses, but revealed a discrete left adrenal non-nodular hyperplasia. Serum 17 HO-progesterone was elevated, suggesting concomitant congenital adrenal hyperplasia. The patient is clinically well on glucocorticoid and mineralocorticoid replacement and hyperkaliemia resolved.
Conclusions
The current PitInc guideline (Endocrine Society 2011) does not specify a maximum follow-up period. Prolonged clinical and hormonal evaluation may be warranted, as delayed onset endocrine disease can occur. In our case, incidental hyperkalemia prompted endocrine re-evaluation revealing multiple endocrine abnormalities.

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EP1068

Sheehan's syndrome in clinical practice

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Sheehan's syndrome represents a rare cause of pituitary insufficiency, produced by an ischemic pituitary necrosis due to a severe haemorrhage at deliverance. Epidemiologic data indicate that, nowadays, this disease is quite rare in developed country.
Aim
To determine and evaluate the clinical and hormonal characteristics of cases with Sheehan's syndrome diagnosed and follow-up in our Clinic, during the last ten years.
Subjects and methods
We included, in this retrospective study, 13 patients, mean age 58 ± 10.9 years, diagnosed with Sheehan's syndrome. Data about medical history, routine laboratory determinations, hormonal parameters, pituitary imaging and therapy were reviewed. All the cases presented a history of severe uterine bleeding after last delivery.
Results
The age at diagnosis for these patients varied between 19 and 54 years. The period of follow-up from the moment of diagnosis was between 3 and 48 years. All except one of the cases had an assisted deliverance, but more than half of the cases (53.8%) came from rural area. Due to severe uterine bleeding, hysterectomy was performed in 7 patients (53.8%). In 12/13 subjects, breastfeeding was not possible. The diagnostic of Sheehan's syndrome was established after 0.5 to 28 years from pathological deliverance. The longest delay between the moment of delivery and those of diagnostic was 28 years. All the cases presented corticotropin, thyreotropin and gonadotropins deficiency in the moment of diagnosis. Growth hormone deficiency was documented in 2 patients and one subject was diagnosed with central diabetes insipidus. Hormonal substitution therapy with thyroxine and glucocorticoids was used in all the cases. Gonadotropins deficiency was treated with estroprogestative in younger subjects and GH replacement treatment was given in two cases. Desmopressin was given in one patient for ADH deficiency.
Conclusion
Sheehan's syndrome is still present in clinical practice, even in the condition of assisted deliverance and well-managed uterine haemorrhage.

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EP1069

Mental disorders in the hospitalized patients with Cushing's disease

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Objective
To study the frequency and features of mental disorders in hospitalized patients, suffering from Cushing's disease (CD).
Materials and methods
We studied 70 patients (59 women and 11 men) with verified diagnosis of CD, aged 41 ± 12 years. Their mental health was evaluated with ICD-10 criteria and verified by the Mini-International Neuropsychiatric Interview questionnaire (MINI 6.0). 45 patients had overt hypercortisolism (untreated CD and relapse), 25 people had remission after treatment.
Results
Majority of the patients with CD suffered from comorbid mental disorders (88.5%). 61.6% of them had different forms of affective disorders including bipolar disorder in 22/70 (38%), hypomania in 8/70 (11.2%), depressive episode in 6/70 (8.4%), mania without psychotic symptoms 3/70 (4.2%), recurrent affective disorder 3/70 (4.2%) and cyclothymia in 2/70 (2.8%) patients. The frequency of neurotic, stress and somatoform disorders was 15/70 (21%), among these, the frequency of obsessive-compulsive disorder (6/70, 8.4%) was higher than population-based, while the frequencies of social phobia (3/70, 4.2%), panic disorder (2/70, 2.8%), agoraphobia without panic attacks (2/70, 2.8%) and adjustment disorder (2/70, 2.8%) were not increased. The rest of diagnoses did not exceed population prevalence: unspecified dementia in 1 (1.4%), acute psychotic disorder in 1 (1.4%), schizoid personality disorder in 1 (1.42%). Psychiatric comorbidity with presence of two or more mental disorders in the same patient reached 37/70 (52.8%). The frequency of bipolar spectrum disorders and anxiety disorders was similar in patients with active hypercortisolism and remission, although the lack of difference may be due to the small sample size.
Conclusions
Mental disorders in patients with CD are extremely high. A prominent frequency of bipolar spectrum disorders and recurrent depression suggests, that the dysregulation of biological cycles is an important mechanism of CD development/recurrence. Besides, there are obviously specific psychological adaptation patterns and a number of typical stress responses in such patients.

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EP1070

Detailed assessment of hypothalamic damage in craniopharyngioma patients with obesity

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Background/objectives
Hypothalamic obesity (HO) occurs in 50% of patients with the pituitary tumor Craniopharyngioma (CP). Attempts have been made to predict the risk of HO based on hypothalamic (HT) damage on magnetic resonance imaging (MRI), but none have included volumetry. Qualitative and quantitative (volumetric) analyses of HT damage was performed. The results were explored in relation to feeding related peptides and body fat.
Subjects/methods
A cross-sectional study of childhood onset CPs involving 3 Tesla MRI, was performed at median 22 years after 1st operation. 41 CPs, median age 35 (range 18-56), of whom 23 had HT damage, were compared to 32 controls. After exclusions, 35 patients and 31 controls remained in the MRI study. Main outcome measures were the relation of metabolic parameters to HT volume and qualitative analyses of HT damage.
Results
Metabolic parameters scored persistently very high in vascular risk particularly among HT damaged patients. Patients had smaller HT volumes compared to controls 769 (35–1168) mm^3 vs 879 (775–1086) mm^3; $P<0.001$. HT volume correlated negatively with fat mass and leptin among CP patients ($r_s=-0.67$; $P<0.001$; $r_s=-0.53$; $P=0.001$), and explained 39% of the variation in fat mass. For every 100 mm^3 increase in HT volume fat mass decreased by 2.7 kg (95% CI: 1.5–3.9; $P<0.001$). Qualitative assessments revealed HT damage in 3 out of 6 patients with normal volumetry, but HT damage according to operation records.
Conclusions
A decrease in HT volume was associated with an increase in fat mass and leptin. We present a reproducible method with a high inter-rater reliability (0.94) that can be applied by non-radiologist for the assessment of HT damage. The method may be valuable in the risk assessment of diseases involving the HT.

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EP1071

Surgery versus expectant observation in clinically non-functioning pituitary adenomas – a 20-year single centre experience

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Background
Clinically non-functioning pituitary adenomas (NFPAs) are among the most common pituitary lesions. Its management includes surgery, radiation or observation. The authors aim to compare clinical characteristics and outcomes between patients submitted to surgery or expectant observation (EO).
Methods
Retrospective review of medical records from 1996 to 2016. In our centre, there is only 1 pituitary surgeon and NFPAs patients are referred to surgery according to the presence of neurologic symptoms, mainly visual disturbances, and tumour growth. Statistical analysis: SPSSvs20.
Results
We found 179 patients, 52% (92 females), with a median follow-up time of 5 years (IQR 3–10), 54% ($n=96$) underwent surgery. Besides indication for surgery, 2 patients refused and 3 did not have clinical conditions. Patients that underwent surgery were younger (58 vs 68 years, $P<0,001$), had more neurologic symptoms at diagnosis (62 vs 39%, $P=0.011$) and visual disturbances (64 vs 22%, $P<0.001$) than patients in EO. There were no differences in hormonal deficiencies ($P<0.001$). The surgery group presented larger adenomas (26 vs 15 mm, $P<0.001$) and further suprasellar extension ($P=0.015$), cavernous ($P=0.008$) and sphenoidal sinus invasion ($P=0.006$). Surgery occurred after a median of 12 months (IQR 0–12), since imagiologic diagnosis and 26% ($n=25$) required a second intervention. 13% ($n=12$) were submitted to radiotherapy. After surgery, 11 patients (16%) had hormonal deficiencies, while 8 (12%) improved. In the EO group, we found *de novo* hypogonadism in 3 patients and hypothyroidism in 1. No significant tumour growth was observed and none suffered apoplexia.
Discussion
Patients that underwent surgery were in average 10 years younger, had more neuro-ophthalmologic symptoms and bigger tumours at presentation. Those in vigilant observation did not present significant tumour growth, new hormonal deficiencies or apoplexy. Facing literature data, our population underwent fewer surgeries. EO may be a valuable option in selected NFPAs.

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EP1072

Risk factors for progression of the surgical remnant of non-functioning pituitary adenomas in patients treated with dopamine agonists

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Introduction
Surgery is the treatment of choice for non-functioning pituitary adenomas (NFPA), but remnants are frequently observed. Management of these remnants include observation (OBS), radiotherapy (RT) and/or dopamine agonist (DA) therapy. In this study, we evaluate the progression-free survival (PFS) of NFPA with postoperative remnant and the potential factors involved.
Methods
We performed a single-center ambispective study of a cohort of 72 patients (age 56 ± 15 years, 32 women), with NFPA and tumor remnant after transsphenoidal (TS) surgery, followed-up between 1994 and 2015. We categorized patients as stable ($n=36$) or progression ($n=21$), according to radiological criteria. No follow-up data were available for 10 patients and 5 cases died. We evaluated differences between patients according to the three postoperative approaches: OBS, DA and/or RT. Statistical analysis was performed with STATA v12.0. We present data for progression-free time medians (p 25-75), correlation coefficient (r) and Hazard Ratio (HR).
Results
Progression-free survival (PFS) of the total cohort of patients was 154 months (77-184). Subgroup analysis suggested longer PFS in OBS patients (154m) vs. RT(184m) ($P=0.07$). Univariate analysis indicates an increased risk of progression in patients without RT (HR: 3.6; [0.8–15]; $P=0.09$). Duration of DA treatment was positively correlated with PFS ($r=0.60$; $P<0.05$), and each additional month showed a favorable trend for an increased PFS (HR: 0.98; [0.95–1.00]; $P=0.06$). Sex, age, and postoperative tumor diameter were not associated with PFS. Subanalysis of the subgroup of patients who received DA($n=20$) showed that the only influencing factor for progression was female sex ($\chi^2=5.05$; $P=0.02$).
Conclusions
RT of operated NFPA seems to be associated to a higher PFS in our cohort. Prolonged treatment with DA also favored an increased PFS. Long-term follow-up and active management of patients with NFPA are important.

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EP1073

Aggressive macroprolactinoma – exception to the rule

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Background
Prolactinoma is the most frequent pituitary tumour. However, peculiar aspects may induce difficulties in their evolution and management. Malignant prolactinoma is exceptionally rare and it cannot be diagnosed on histological grounds alone. We report the case of a recurrent, possibly malignant macroprolactinoma.
Case report
46 years old female, addressed for bitemporal hemianopia, without other clinical signs. MRI confirmed a pituitary macroadenoma (22/19/35 mm) with suprasellar evolution. Hormonal profile revealed hyperprolactinemia with secondary thyroid and gonadal insufficiency, for which Cabergoline was started, with initial good evolution. Three years later she presented pituitary apoplexy with acute intracranial hypertension, solved by partial transcranial adenomectomy. Gamma knife radiation completed the treatment, with succeeding adrenal and thyroid insufficiency. After 4 years of stationary evolution under Cabergoline and substitutive treatment, an aggressive tumour progression imposed a new surgical intervention (transsphenoidal adenomectomy). One year later, intensive vertiginous syndrome enforced reinvestigations. MRI identified two cerebral tumours (meningioma?), one of them at the cranio-spinal junction, which needed urgent excision. Pathology identified pituitary adenoma cells and a Ki-67 index of 2%. Post-operatory, the patient complained of gait dysfunction, nausea and headache. Left cranial nerves paresis X, XI, and XII was objectified. The patient underwent six cycles of Temozolomide chemotherapy, with no improvement, last MRI revealing further tumour evolution.
Conclusion
Elucidating the pathogenesis of aggressive prolactinomas remains largely unknown and continues to mesmerize the physicians. The diagnosis of pituitary carcinoma is confirmed only in the presence of metastasis. After initial good response to Cabergoline, our patient developed a rapid aggressive progression of the tumour, with little effect of surgery and radiotherapy. Temozolomide was not efficient in controlling tumour evolution. In spite of the longer survival (9 years) and the low proliferation index, we believe that new markers are needed in order to assess the aggressiveness of malignant prolactinoma.

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EP1074

Body composition and bone mineral density in male patients with isolated hypogonadotropic hypogonadism

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Isolated hypogonadotropic hypogonadism (IHH) is known to decrease bone mineral density due to lack of pubertal surge of gonadotropins and deficiency of sex steroid hormone. Gonadal steroid hormones imbalance affects body composition. Nineteen Caucasian men, 22–48 year old (mean ± s.d. 33 ± 7.65) diagnosed with IHH (8 normosmic, 11 anosmic or hyposmic) were enrolled into the study. 14 patients were on hormone replacement therapy (HRT), 5 patients were started with HRT treatment. Nineteen healthy male volunteers (CON) with matched age and BMI were also included. Body composition and bone mineral density measurements were conducted with use of Air Displacement Plethysmography (BOD POD, Cosmed) and dual-energy x-ray absorptiometry DEXA (Lunar Prodigy,GE Healthcare), respectively. Hormonal status, lipid profile, calcium and phosphorus levels, 25-hydroxy vitamin D concentration were also measured. There was significant difference between fat-free-mass (FFM; kg) in IHH and matched controls (60.1 vs 66.0; $P=0.012$), related to Gynoid FFM distribution (IHH vs CON: 9.1 vs 10.3 kg; $P=0.003$). IHH patients have marked decreases in total bone mineral density compared to CON (1.21 vs 1.31 g/cm^2, $P=0.009$). Total bone mineral content, *T*-score and *Z*-score were also decreased in IHH subjects (2982 vs 3271 g/cm, $P=0.05$; 0.08 vs 1.06, $P=0.016$; −0.40 vs 0.54, $P=0.013$). High-density lipoprotein cholesterol (HDL) level was correlated with waist-to-height ratio (WHtR) ($r=-0.81$, $P<0.05$) in IHH patients. Significant correlations between insulin-like growth factor-1 (IGF-1) and WHtR were observed in IHH ($r=-0.81$, $P<0.05$; $r=-0.82$, $P<0.05$). Testosterone and 25Hydroxy vitamin D concentrations were not correlated with body composition and densitometry measurements. To conclude, IHH patient are at increased risk for osteoporosis. Long testosterone deficiency in IHH resulted in body composition changes related to fat free mass and distribution. WHtR, IGF-1 and HDL correlations in IHH patients might suggest their link with cardiometabolic dysfunctions. Susceptibility to metabolic syndrome in IHH patients on HRT should be further investigated.

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EP1075

The E in POEMS syndrome: what to expect?

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Introduction
POEMS syndrome is a rare multisystemic disorder including polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma-proliferative disorder and skin changes. We aim to describe the course of the endocrine disease in the context of this paraneoplastic syndrome.
Methods
69 patients with POEMS have been under the MDT care in our hospital. Data is currently available for 32 patients who attended the joint haematological/neurological/endocrine clinic from 06/1999 to 01/2017. All patients had regular endocrine screening including pituitary, thyroid and calcium metabolism. Median and interquartile range and mean ± s.d. were used for quantitative variables and percentage for qualitative variables.
Results
Seventy-two patients were male. The age at diagnosis was 49.4(38.2–59.8) years and the median follow-up was 4.6(2–7.4) years. At diagnosis, all patients presented with polyneuropathy, 25% had hyperhidrosis and 50% endocrinopathy. From those with endocrinopathy, 36.7% had thyroid disease, 26.7% hypogonadism, 3.3% type 2 diabetes mellitus (2DM) and 6.5% Addison disease. None of them had parathyroid disorders. 60% had more than one endocrinopathy at diagnosis. During surveillance 90.3% of patients developed endocrinopathy. 68.8% of patients had hyperprolactinemia with a fold increase 1.8 ± 0.99 above the upper limit of the normal. Hyperprolactinaemia was transient in 72.7%. One patient with hyperprolactinaemia had an empty sella on MRI. 59.4% had hypothyroidism (37.5% clinical, 21.9% subclinical). This was transient in 27.8% of patients. Addison disease was diagnosed in 18.8% of patients and none of them recovered their adrenal function. 15.6% presented with type 2DM. 78.6% had hypogonadism (19.1% secondary, 38.1% primary, 42.9% subclinical primary). Gonadal function recovered in 3 patients.
Conclusion
Endocrinopathy in POEMS was described in 90% of our cohort. The MDT team should include an endocrinologist. Patients should be systematically assessed for endocrinopathy. The most common deficiencies were hypogonadism, hyperprolactinemia and hypothyroidism. Normalisation of the endocrinopathy was common and should be considered when treating these patients.

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EP1076

Pituitary adenoma and elevated ACTH: not always corticotrophinoma

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Introduction
Hypothalamic–pituitary–adrenal (HPA) axis activation is the main neuroendocrine response to an environmental challenge. Drug abuse may activate HPA axis by interaction with neuromodulation systems.
Case report
28 year old man, was admitted in the Neurology Department for persistent headache with spinal irradiation. With suspicion of multiple sclerosis, MRI revealed pituitary macroadenoma (14 mm diameter) and subcortical, paraventricular and frontal white matter demyelinating lesions. Neurological examination

excluded multiple sclerosis and he was addressed to the Endocrinology Department. Anamnesis revealed a history of drug abuse (cocaine), alcoholism, chronic smoking (1 pack of cigarettes/day) and depression. Clinical examination revealed moderate weight excess (BMI = 27.14 kg/m^2) and normal high blood pressure (148/100 mmHg). Hormonal axes were normal, with the exception of the HPA axis: high levels of ACTH (89.2 pg/ml), DHEAS (491.3 µg/dl) and free urinary cortisol (216 µg/24 h), with normal morning and evening cortisol. 1 mg DXM overnight test was negative (cortisol = 4.28 µg/dl). It was re-evaluated after one month: persistency of normal cortisol values with constantly moderate high ACTH and good response to 1 mg DXM (1.12 µg/dl). The discordance between ACTH, DHEAS and the rest of HPA axis suggested another possible etiology than an ACTH secretion adenoma (cocaine use, smoking, depression). One year after, biological parameters were constant, with insignificant increase of adenoma (16 mm diameter). Patient denied any further cocaine use for approximately 1 year, but admits that he is still smoking.

Conclusions

The dysregulation of HPA axis may increase vulnerability to depression and numerous other psychiatric disorders, which can be puzzling for the endocrinologists in the diagnosis process. The peculiarity of the case is the association of a pituitary macroadenoma with persistent increased levels of ACTH. Investigations had not confirmed the suspicion of an ACTH secreting pituitary adenoma, and oriented to multiple ethology – drug abuse (cocaine, smoking) and depression.

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EP1077

Pituitary apoplexy – presentation, management and outcome in 35 cases

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Introduction

Pituitary apoplexy is a rare disease which results of haemorrhage and/or infarction of pituitary gland. The optimal management of this problem still remains controversial between surgery and conservative treatment.

Aims

To characterize the clinical presentation, diagnostic workup, treatment and follow up of patients with apoplexy. Methods:Retrospective study of 35 pituitary apoplexy followed in a portuguese hospital from 2006 to 2016.

Results

Thirty-five patients (21 males; mean age, 55.1(15.6) years) were identified. Three patients had subclinical pituitary apoplexy and 9(28%) had more than one emergency evaluation until the diagnosis has been correctly made. Commonest presenting features were acute headache (84.4%), visual impairment (62.5%) and vomiting (15.6%). Five patients were known to have pituitary tumour at presentation, one of them was a Cushing Disease which became cured after PA, and 3 were nonfunctioning adenomas. Nineteen patients had at least one precipitating factor with antiaggregation being the most common ($n = 4$). Twenty patients had hypopituitarism at presentation, 14 had hyponatraemia, 9 had a decreased in level of consciousness and 21 had visual impairment. 78.1% patients proceeded to pituitary surgery and 3 developed diabetes insipidus after that. When we compared those who underwent surgery and those treated conservatively, visual deficits were more common in first group (76% vs 28%, $P = 0.032$) and hyponatremia in the second one (32% vs 86%; $P = 0.027$). There were no more differences between groups in other evaluated factors, namely in Pituitary Apoplexy Score (1.68 (1.21) vs 0.86 (1.21); $P = 0.124$). During follow-up 6(3) years, 1 patient had hypopituitarism reversal after surgery and 11 patients recovered from neuro-ophthalmologic deficits. Three patients passed away and 21 have a MRI without lesion.

Conclusion

The diagnosis of pituitary apoplexy is often delayed as occurred in our population.It is associated with a high rate of anterior hypopituitarism that does not typically recover, unlike the visual symptoms. Patients with visual defects were more likely to be managed surgically.

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EP1078

Inferior petrosal sinus sampling: experience of a terciary hospital

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Introduction

Inferior Petrosal Sinus Sampling (IPSS) is the gold standard test to distinguish between Cushing Disease and ectopic ACTH secretion (EAS), mostly when the biochemical tests are discordant and/or there is no lesion in MRI.

Aim

To evaluate the results of IPSS in the diagnosis of ACTH-dependent Cushing syndrome.

Methods

Retrospective study that analysed IPSS results performed in the last decade in our centre and integrated in the clinical context of each patient. Basal central-to-peripheral ratio > 2 or after CRH test > 3 were considered diagnostic of CD.

Results

We analysed 31IPSS performed in 26 patients with biochemical diagnosis of CS. Nine patients were excluded. Seventeen patients (2 Male) with a mean age of 38.4(11.8) years were included. One patient had to repeat IPSS due to haemolysis and other had done 3 IPSS due to be on interfering medication. Eleven patients had central-to-peripheral ACTH ratio suggestive of CD(6basal and 11after CRH stimulation). The ratio was maximal at 5′ in 45.4%(5/11) patients and at 2-3′ in 36.3%(4/11). Pituitary MRI revealed microadenoma in 8 patients, macroadenoma in one and 2 patients did not present any lesion. Three patients had a lesion on the other side of pituitary when compared to the intersinus gradient. Immunohistochemical result revealed an ACTH expression adenoma in 6 patients, and expression of ACTH and GH in 2. There was no positivity for ACTH in 3 patients who had MRI lesions, but one was cured after surgery and 2 underwent adjuvant therapy. Of the remaining 6 patients, 3 had results suggestive of ectopic EAS, one of which was submitted to lobectomy and had bilateral adrenalectomy by occult ectopic, but underwent pituitary surgery with a histological result revealing ACTH expression. Of the other 3 patients, all with pituitary MRI lesion, 2 patients underwent surgery that revealed CD and in the other the result was normal and patient underwent adrenalectomy. There were no significant adverse effects.

Conclusion

This study reinforces the utility of IPSS in identifying aetiology of SC, which was obtained in more than half of the patients, with no associated adverse effects. The IPPS catheterization was not possible in 1 patient.

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EP1079

Cushing syndrome and pregnancy: a systematic review including three new cases

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Cushing's Syndrome (CS) is an uncommon disease worldwide, being characterized by an increased production of glucocorticoids, and if left untreated can lead to serious consequences and women with CS rarely get pregnant. The aim of our work is to make a systematic review of the cases of pregnancy in patients with previously diagnosed CS, being performed an extensive research of the Medline and Web of Knowledge databases, and add three new cases observed in our institution. We compared two different groups: the 'active disease' one and the 'non-active disease' and we found 17 pregnancies that were included in the first group while other 20 pregnancies were in the second category. We observed two spontaneous abortions and one ectopic pregnancy in the 'active' group, while in the 'non-active' category we found the same number of spontaneous abortions besides a placental abruption and a medical interruption of the pregnancy. Cushing disease (CD) was the main cause behind CS (28 pregnancies), with transsphenoidal surgery the preferred treatment. Within the 'active' category, we reported nine full-term and five pre-term pregnancies and in the 'non-active'

category we observed 11 full-term and three pre-term pregnancies, while two in this last group were non-specified. Hypertension was diagnosed in eight cases (six and two in the 'active' and 'non-active' group respectively) and gestational diabetes in four patients (three and one in the 'active' and 'non-active' categories). Inability to breastfeed was one of the main perinatal events reported, as a logical consequence of the treatment regimen adopted for CS. A major concern in these patients refers to the medical control of CS activity, because hypercortisolism occurs physiologically during pregnancy. This is a topic with extreme clinical significance since it is rare that a CS women conceives.

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EP1080

20-year retrospective study of clinically non-functioning pituitary adenomas – a single center experience

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Background
Clinically non-functioning pituitary adenomas (NFPA) are the most common pituitary adenomas but their treatment remains challenging. Our aim is to describe clinical, imagiological and hormonal characteristics of patients with NFPA presenting at our department.
Methods
Retrospective review of medical records of patients with NFPA at our centre from 1996 to 2016. Exclusion criteria: prolactin >100 ng/ml or histologic evidence of prolactinoma. Statistical analysis: SPSSv20.
Results
179 patients included, 52% ($n=92$) female, with a median age of 61 years (IQR 48–73) and follow-up time of 5 years (IQR 3–10). The diagnosis were more frequent in the last 10 years ($n=114$, 64%). 40% ($n=62$) had hypertension and 15% ($n=24$) were diabetic. The initial presentation was neuro-ophthalmologic symptoms ($n=87$, 52%), incidentally discovered adenomas ($n=36$, 21%), pituitary apoplexy ($n=30$, 18%) and endocrine disorders ($n=16$, 9%). Pituitary function assessment showed that half ($n=69$) had at least one hormonal deficiency, specifically; LH/FSH deficiency was detected in 45%, ACTH in 25%, TSH in 30% and GH in 15%. Hyperprolactinemia was present in 22% ($n=30$). Five patients (3%) had diabetes insipidus. The NFPA were mainly macro-adenomas ($n=146$, 89.5%) with suprasellar extension ($n=89$, 70%), 36% ($n=43$) had sphenoidal and 30.3% ($n=36$) cavernous sinus invasion. Surgery was performed in 54% patients ($n=96$), while the remaining maintained expectant observation. Immunohistochemical analyses showed 42 null-cell, 34 gonadotrophs, 1 silent thyrotroph, 2 silent corticotroph and 2 plurihormonal adenomas.
Discussion
As in other series, our patients also presented with visual disturbances and pituitary dysfunction at diagnosis, but we found and older population. We emphasize that a quarter of patients had ACTH and 30% TSH deficiency that can cause a significant morbidity and had not been suspected before. Hence, earlier diagnosis of hypopituitarism and prompt treatment are imperative.

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EP1081

Hypopituitarism and central diabetes insipidus in an HIV patient – a late complication of cerebral toxoplasmosis and/or antiretrovirals?

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Introduction
The endocrine system is often affected in the course of HIV infection. However, hypopituitarism and diabetes insipidus are uncommon disorders in these patients and have been related to drugs, infections of the central nervous system and neoplastic infiltration, in extremely rare cases.
Case report
We present a case of a 42-year-old man with HIV infection known since 2005, but undergoing antiretroviral therapy only since 2010 (emtricitabine/tenofovir and raltegravir), when he was diagnosed with hepatitis C, left parotid MALT-lymphoma, and cerebral toxoplasmosis (treated with pyrimethamine/sulfadiazine). He has also a history of smoking, drug addiction, in a methadone replacement program for 10 years, and hypothyroidism diagnosed for 1 year, medicated with L-thyroxine. The patient was referred to the Endocrinology department by bilateral gynecomastia, loss of libido and erectile dysfunction. When specifically asked he also complained of polydipsia-polyuria. Breast, testicular and thyroid ultrasonography showed no relevant changes, but the hormonal study revealed: central hypothyroidism and hypogonadotropic hypogonadism; normal prolactin levels; slightly decreased IGF-1 and GH levels; normal ACTH, cortisol and tetracosactide test; insulin-induced hypoglycemia test showed normal glucocorticoid reserve. Plasma osmolality was 300 mOsmol/kg and urine osmolality 136 mOsmol/kg. Water deprivation test confirmed central diabetes insipidus. Pituitary MRI showed lack of neurohypophyseal bright signal. He was started on testosterone therapy (250 mg, 3/3 weeks), desmopressin lyophilisate (0.06 mg bid) and maintained L-thyroxine (0.088 mg/day). Currently, he refers a global clinical improvement, but still complains of erectile dysfunction, and was recently medicated with avanafil (100 mg).
Conclusion
The authors describe a rare case of hypopituitarism and diabetes insipidus in a patient with HIV infection of possible multifactorial etiology – uncommon complication of cerebral toxoplasmosis and/or side effects of antiretroviral drugs. This case reveals the need to keep in mind the possibility of hypopituitarism in HIV-treated patients and a history of cerebral infection.

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Steroid Metabolism + Action

EP1082

Social stress stimulates glucocorticoid regeneration in lymphoid organs

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The presence of the enzymes of local metabolism of glucocorticoids in lymphoid organs and many other tissues suggests that the local glucocorticoid signal is not determined only by plasma level of glucocorticoids but also by the local activity of these enzymes. Using resident-intruder test the present study determined if chronic social stress modulates local metabolism of corticosterone and 11-dehydrocorticosterone in rats of Fisher 344 (F344) and Lewis (LEW) strains, which differ in their response to social stressors and inflammation. We demonstrated that social defeat significantly increased regeneration of corticosterone from 11-dehydrocorticosterone in thymus, spleen and mesenteric lymphatic nodes (MLN) but not pituitary of both strains. When compared with F344 strain, LEW rats showed lower corticosterone regeneration in pituitary of unstressed and stressed animals and higher corticosterone regeneration in thymic and MLN mobile cells after chronic stress. In contrast, stress-induced increase of corticosterone regeneration in stroma tissues of all lymphoid organs was similar in both strains. Social defeat was also associated with changes in expression of enzymes participating in local metabolism of glucocorticoids: 11β-hydroxysteroid dehydrogenase type 1 (11HSD1), 11β-hydroxysteroid dehydrogenase type 2 (11HSD2) and hexose-6-phosphate dehydrogenase (H6PDH). Whereas F344 rats exhibited significant upregulation of 11HSD1 mRNA, 11HSD2 mRNA and H6PDH mRNA expression in thymus and 11HSD1 mRNA in spleen, LEW rats showed an apparent insensitivity to stress in all lymphoid organs and neither of the transcripts was upregulated by stress. Our results indicate that social stress amplifies glucocorticoid regeneration in the lymphoid organs including the expression of genes involved in local metabolism of glucocorticoids and that this process is partly determined by the genetic background. *The study was supported by Czech Science Foundation.*

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Eposter Presentations: Reproductive Endocrinology

Bone & Osteoporosis

EP1083

Effects of male hypogonadism treatment on the bone mineral density

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Increased recognition of the morbidity and mortality due to osteoporosis in men are main issues of public health. Ageing and the propensity to falls are the main risk factors for osteoporotic fractures in men; moreover, hypogonadism is an important secondary cause of low bone mineral density (BMD), but very little is known about the effect of hypogonadism treatment on the BMD.
Objective
The aim was to study the impact on BMD of the treatment of male hypogonadism.
Material and methods
A group of 26 men were devided in the hypogonadotrophic hypogonadism ($n=17$) and hypergonadotrophic hypogonadism ($n=9$) groups. The BMD at several skeletal sites (assessed by DXA scans) was evaluated before and during treatment (duration from 1 to 8 years, on average 3.1 (± 2.3) years). Adequate statistical tests were used (statistical significance $P<0.05$).
Results
The treatment did not improved significantly the mean BMDs at several skeletal sites (Table 1). Moreover the BMDs were similar before and during the treatment in the hypergonadotrophic hypogonadism group; nevertheless, in the hypogonadotrophic hypogonadism group the mean BMDs were significantly higher at the lumbar spine, at the hip, at the forearm and at the whole body during therapy.
Conclusions
After more than three years of treatment there was no improvement on the BMD significantly in the total hypogonism group. The treatment of male hypogonadism has improved the BMD at several skeletal regions just in the hyponadotrophic group.

Table 1 BMD qualification in hypogonadism before and during therapy.

BMD	Hypogonadism *before* treatment $n=26$ (100%)	Hypogonadism *during* treatment $n=26$ (100%)
Normal	6 (23.1%)	8 (30.8%)
Reduced	12 (46.1%)	11 (42.3%)
Osteoporosis	8 (30.8%)	7 (26.9%)

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Cardiovascular Endocrinology and Lipid Metabolism

EP1084

The effect of hormone replacement therapy and tibolone on lipoprotein (a) concentrations in postmenopausal women: a systematic review and meta-analysis of randomized controlled studies

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Introduction
Data on the effect of hormone replacement therapy (HRT) and tibolone on lipoprotein(a) (Lp(a)), an independent risk factor for cardiovascular disease, are heterogeneous and conflicting. The aim of this study was to investigate the effect of HRT and tibolone on Lp(a) concentrations in post-menopausal women.
Methods/design
MEDLINE, Scopus, EMBASE and Cochrane databases were searched (up to February 2016). Two researchers identified randomized controlled studies and extracted data. Potential controversies were resolved by a third reviewer.
Results
In 24 eligible studies, HRT caused a significant reduction in Lp(a) concentrations compared with placebo or no treatment (mean relative difference: -20.35%, 95% CI: -25.33% to -15.37%, $P<0.0001$), with significant heterogeneity between studies ($I^2=98.5\%$), but without evidence of publication bias. No significant effect was found for tibolone ($n=7$) (mean relative difference: -23.84%, 95% CI: -63.43% to 15.74%, $P=0.238$) ($I^2=98.7\%$, but without publication bias). Oral estrogen caused greater reduction in Lp(a) concentrations than transdermal estrogen ($n=10$) (mean relative difference: 37.66%, 95% CI: 16.84% to 58.48%, $P<0.0001$), with significant heterogeneity between studies ($I^2=99\%$), but no evidence of publication bias. No difference was observed when continuous was compared with cyclical HRT, conventional with low estrogen dose, and estrogen monotherapy with combination with progestogen. No difference was observed between HRT and tibolone regarding their effect on Lp(a).
Conclusions
HRT significantly decreases Lp(a) concentrations, with oral being more effective than transdermal estradiol. The type of HRT, dose of estrogen and addition of progestogen do not seem to modify the Lp(a)-lowering effect of HRT.

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Clinical Case Reports - Pituitary/Adrenal

EP1085

CHARGE Syndrome: a rare case of hypogonadotropic hypogonadism

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Introduction
CHARGE Syndrome (CS) is a rare cause of hypogonadotropic hypogonadism (HH), usually diagnosed in paediatric age when pubertal development is compromised. Herein, we report a case that presented a major criterion and three minor criteria.
Case report
At age ten, the patient was referred to the paediatric endocrinology unit due to phenotypic alterations and psychomotor and cognitive impairment. She had no family history of consanguinity, inherited or genetic disorders. At 8 years of age she was diagnosed with semicircular channels bilateral agenesis with consequent profound bilateral deafness. At physical examination there was a normal stature and weight, facial asymmetry and dysmorphia, low ear implantation, cleft palate and dorsocifoescoliosis. Genital examination revealed normal morphology and a Tanner 2 stage. Pelvic ultrasonography was consistent with small ovaries and uterus, without evidence of follicular activity. Basal FSH and LH were below the normal range without response to LHRH stimulation. CHARGE syndrome was considered and genetic tests were performed. The karyotype was 46 XX and a missense mutation in the CHD7 gene was identified (c.484C>T/p.Q162X). The patient initiated treatment with an estradiol/norgestrel combination at the age of 15 with marked improvement of pubertal development.
Conclusion
CS should be considered in the differential diagnosis of HH particularly in presence of an abnormal phenotype. Mutations in the CHD7 gene cause more than half of all cases of CS and most of the times are new mutations as occurred in the current case. Different malformations may be present but the pattern varies among affected individuals justifying a long term follow up.

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EP1086

Combination of turner syndrome and congenital adrenal hyperplasia: a rare case report

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Combination of Turner syndrome (TS) and classical congenital adrenal hyperplasia (CAH) is rare worldwide. Incidence of CAH - autosomal recessive disorders characterized by enzyme defect of steroidogenic pathway, of which 90% ocuurs in the CYP21A2 gene coding 21-hydroxylase is 1:10000-16000. Incidencie of Turner syndrome is 1:2500 worldwide. Phenotypically, females with TS may present with a wide spectrum of clinical features. They may exhibit short stature, virilization, premature ovarian failure and compromised fertility. We present a 57-year-old women suffering from both 45X0/46XX mosaic Turner syndrome and salt wasting form of CAH. After birth she was misdiagnosed as a male. She had short stature and ambiguous genitalia – presence of the phallus with perineoscrotal hypospadias and incomplete urogenital opening. Laparoscopy at age of six showed female sex organs. After this examination clitoroplasty and vaginoplasty was done. Karyotyping revealed a 45X0/46XX pattern without sex determining region Y on gene analysis. The presence of virilizing feature at puberty could not explain the diagnosis of Turner syndrome. She had amenorhea, marked hirsutism and was of short stature (height 130 cm). Laboratory tests revealed elevated level of 17-hydroxyprogesterone, dehydroepiandrosterone and low cortisol concentrations. Congenital adrenal deficiency was then suspected. With the genomic analysis, CYP 21A2 mutation in IN2G and united deletion/conversion was detected. She was treated with hydrocortisone. In adolescent hydrocortisone was replaced by dexamethasone. Fludrocortisone was added to the treatment, because laboratory tests revealed increased plasma renin concentration. Under a continuous treatment, her state improved.

Keywords: Turner syndrome, congenital adrenal hyperplasia, 21-hydroxylase deficiency, CYP21A2

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EP1087

A rare case of short-term postpartum primary adrenal insufficiency

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Aims
Polyglandulare Autoimmune Sydnrome (PAS) is a rare disease and the development during pregnancy is seen even less often. PAS Type II presents with autoimmune adrenalitis and thyroiditis. Symptoms of adrenalitis such as hypotension and hyperpigmentation are overlapping with physiological manifestations during pregnancy making the diagnosis difficult.
Clinical presentation
We are reporting the case of a 28-year old prima para prima gravida presenting two weeks postpartum (spontaneous preterm birth at 36 completed weeks of pregnancy) with hypotension, orthostatic presyncopal events and adynamia. Laboratory tests showed a low cortisol level, while adrenocorticotropic hormone was augmented. Steroid-21-hydroxylase-antibodies and active renin were increased. The medical history was significant for chronic lymphocytic thyroiditis with subclinical hyperthyroidism under L-thyroxin substitution. Synopsis of all findings led us to the diagnosis of PAS type II.
Conclusion
The aim of this case report was to show that during pregnancy or postpartum we should take symptoms of adrenalitis in women with known autoimmune thyroiditis seriously and test for PAS.

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EP1088

Hypogonadotropic hypogonadism, functional and transitory

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Functional hypogonadism has been described in association with acute severe medical or surgical illness, subacute recovery and chronic disease. We present a case of transitory hypogonadism manifested during a peri-surgical period. A 42-year-old patient was sent to the endocrinology clinic due to hypertension and a solitary adrenal mass. He was treated with bisoprolol and telmisartan, that he maintains until today. The evaluation favoured non-functional adenoma but during the follow-up new complaints arose. He was diagnosed heart failure NYHA class-I related to aortic valve dysfunction and thoracic aortic aneurysm with surgical indication. He had recently visited the urologist due to complaints of erectile dysfunction and mentioned a normal scrotal US evaluation and the prescription of a phosphodiesterase inhibitor. These complaints started during the pre-surgical period. He mentioned timed puberty (13 years old) and one daughter but declared reduced libido, reduced spontaneous erections, reduced turgor and reduced need of shavings. He had BMI 21 kg/m^2, no gynecomastia, normal sense of smell and adult volume testicles. His previous total testosterone (TT) evaluations were within reference range (265 and 310 ng/dl). The new laboratory analyses showed low TT on two separate evaluations, 104 and 181 (RI 249–836) ng/dl with inappropriately normal LH 3.12 U/l and FSH 5.18 U/l. Prolactin, IGF1 and ACTH were normal. MRI could not be performed because of the new prosthetic valve. He was started on monthly testosterone enanthate achieving normal TT levels (267 ng/dl) and remission of clinical complaints. After a period of 5 months, approximately 2 months after the heart surgery the patient felt he had regained shaving frequency and sexual turgor, withdrawing both the phosphodiesterase inhibitor and the testosterone substitution. After 5 months of no therapy he revisited the clinic and laboratory tests were performed with the finding of normal TT 295 ng/dl, normal FSH and LH.

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EP1089

Congenital adrenal hyperplasia: case series, describing results of initial dexamethasone therapy

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Introduction
Congentital adrenal hyperplasia (CAH) comes to adult endocrinologist wheather as transition from pediatritian (Case 3) or as still without diagnosis (Case 1, 2, 4). The aim of this work is to describe typical forms of CAH initially sucessfuly treated with dexamethasone therapy.
Case descriptions
Case 1: female, 1972y., presented in 1995y. (23y.) as severe hirsutism and infertility managed by team of gynecologists. She refused any additional investigations and was severily depressed. Ex iuvantibus 0.5mg dexamethason therapy was followed with pregnancy. **Case 2**: female, 1990.y, presented in 2008.y.(18y.). Non-classic CAH. Hirsutism, primary amenorrhoea. Dexamethasone therapy 0.5 mg at night. After 4 month estabished menstruation, after 18m. became pregnant with healthy male baby born. **Case 3**: female, 1994y, presented 2012.y. (18y.) Classic CAH, salt wasting form. At birth classical low sodium, high potassium. Established therapy with fludrocortison and hydrocortison, at night dexamethason 0.5 mg. Still primary amenorrhoea. On CT sevear vaginal stenosis. **Case 4**: male, 1980y, presented in 2014.y.(34y. old), when he was diagnosed for the first time! Classic CAH, simple virilising form and glucocorticoid-remediable aldosteronism, suprarenal hyperplasia on one gland and incidentaloma on the other. Unilateral testicular adrenal rest tumour (TART), azoospermia. Therapy hydrocortisone and dexamethasone at night. Soon he normalised aldosterone, ACTH, 17-OH progesterone but lowered testosterone. After 2y. CT of testes confirmed enlargement and the regression of TART.
Discussion
We have described two cases of CAH which solved the problem of fecundity (Cases 1 and 2). One treatment confirmed the need for additional surgical treatment of developmental abnormality on external genitalia(Case 3). Finally the problem of TART has been solved without any invasive intervention (Case 4), wheather diagnostic or therapeutic, which are not the rare case even in these years.

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Clinical Case Reports – Thyroid/Others

EP1090

A rare cause of a 46, XY disorder of sex development diagnosed in an adult patient

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The defective conversion of testosterone to dihydrotestosterone due to a steroid 5-alpha-reductase 2 deficiency results in a unique form of 46, XY disorder of sexual development (DSD). Dihydrotestosterone is essential for the embryonic differentiation of the external male genitalia and the prostate. Steroid 5-alpha-reductase 2 deficiency is an autosomal recessive disorder in which genetic males have a predominantly female phenotype with female external genitalia but male internal urogenital tract. We describe the case of an adult patient having migrated from Pakistan to Switzerland in whom a steroid 5-alpha-reductase 2 deficiency was diagnosed at the age of 29. Molecular genetic analysis identified a homozygous point mutation in exon 4 of the 5-alpha-reductase 2 gene, leading to an amino acid change from glutamic acid to lysine. To our knowledge, this is the second case of this mutation in the steroid 5-alpha-reductase 2 gene (SRD5A2) which was first described in 1997 (Anwar *et al.*).

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EP1091

Association of short stature, microcephaly, secondary amenorrhea and consanguinity: clinical case report

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Background
In 1985, Mikati et al., described a new syndrome, which included microcephaly, hypergonadotropic hypogonadism, short stature, mental retardation and minor anomalies in four out of nine siblings of consanguineous parents. No genetic disorder was associated to the disease. No further references to this syndrome have been found in literature. The authors present a new possible case of Mikati-Naijjar and Sahli syndrome (MNJS).
Clinical case
Forty-two-year-old female referred to the Endocrinology Department due to secondary amenorrhea for 6 years. History of menarche at eighteen with regular menstrual cycles. No access to prenatal and neonatal history. Personal history of primary hypothyroidism medicated with levothyroxine 50 µg. She was able to help in some household duties, but lacked capabilities for satisfactory results at school. Parents are 1st degree relatives. Two healthy brothers and one other with microcephaly, not further investigated. Physical examination Microcephaly (46 cm), weight 50 kg, height 129 cm. Also, narrow forehead, synophrys and micrognathia. Tanner V. Unremarkable neurological exam. No relevant findings in biochemical study besides hypergonadotropic hypogonadism. She had normal prolactin, dehydroepiandrosterone sulphate, delta-4-androstenedione, sex hormone-binding globulin and total testosterone. Normal uterus and ovary ultrasound. Karyotype 46, XX.
Discussion
The patient presented with multiple congenital abnormalities, which do not occur in any known syndrome to our knowledge, besides MNJS. However, our patient presented with secondary amenorrhea unlike the female patient in MNJS kindred with primary amenorrhea and Tanner II. Like the genetic defect was not studied in MNJS it will be challenging to ascertain if it is the same syndrome.

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Developmental Endocrinology

EP1092

Age and developmental stage dependent relationship between plasma concentrations of leptin, luteinizing hormone, follicle stimulating hormone, prolactin, testosterone and inhibin B in boys between the age of 1 and 20 years

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Leptin is regarded as an essential adipokine for controlling energy homeostasis, caloric intake reduction and increase of caloric expenditure by negative feedback mechanisms via receptors in the hypothalamus. Puberty is said to be triggered by leptin, which signals the hypothalamus that adequate fat reserves are available for initiation of energetically costly process of reproduction. Leptin activates gonadotropin releasing hormone (GnRH) system, which stimulates luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion from pituitary gonadotropes and subsequent secretion of testosterone (T) from testes. Nevertheless, it is not clear whether leptin has any association with the secretion of FSH, prolactin (PRL) and inhibin B during puberty. This study examined possible associations between plasma concentrations of leptin and LH, FSH, PRL, T, and inhibin B at different ages and developmental stages in boys between 1 and 20 years (27 boys/age group). The concentrations of leptin, LH, FSH, PRL, T and inhibin B were determined using specific ELISA. Data were analyzed using Student's *t*-test, ANOVA and Pearson correlation *r*. The concentrations of leptin and LH were positively correlated at 1st, 4th−10th, 12th, 16th, 20th year and at infancy and early puberty. Leptin and FSH concentrations were positively correlated at 1st-3rd, 8th−10th, 12th, 13th, 15th, 16th, 18th, 20th year and at infancy, pre-puberty and early puberty. Leptin and PRL levels were positively correlated at 1st, 3rd, 5th, 6th, 9th, 10th, 12th-14th, 19th year and at infancy, pre-puberty and early puberty. Leptin and T concentrations were positively correlated at 1st, 3rd, 6th, 7th, 9th, 10th, 12th and 16th year and at infancy and early puberty. Leptin and inhibin B levels were positively correlated at 1st, 3rd−8th, 10th, 12th, 15th-19th year and at infancy, early and late puberty. Thus, leptin and LH, FSH, PRL, T and inhibin B are positively correlated only at early puberty.

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Endocrine Tumours and Neoplasia

EP1093

Molecular mechanisms underlying progesterone-enhanced breast cancer cell proliferation

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Previously, we demonstrated that progesterone (P4) could enhance breast cancer cell migration through increasing formation of the p27-RhoA complex and RhoA activation caused by the cSrc/AKT-mediated phosphorylation of p27 at T198. Here, we further examined the effect of P4 on breast cancer cell proliferation. Our results show that P4 (12.5–100 nM) concentration-dependently enhanced proliferation in breast cancer cell lines (T47D and MCF-7). We also found that increases of cytoplasmic p27 localization are responsible for the P4-enhanced breast cancer cell proliferation. Our results demonstrated that P4 activated the cSrc/PI3K/AKT signaling pathway, subsequently activating RSK1, which in turn increased phosphorylation of p27 at T198. PI3K/AKT activation also increased phosphorylation of p27 at T157. Both p-p27T157 and p-p27T198 caused cytoplasmic mislocation of p27 protein. In addition, P4 induced KIS activation, which in turn increased phosphorylation of nuclear p27 at S10, subsequently causing p-p27S10 translocation from the nucleus to the cytosol. The decreased level of nuclear p27 protein reduced its inhibition in the cyclin-CDK2 system, subsequently increasing phosphorylation of CDK2 at T160 and p27 at T187, hence causing translocation of p-p27T187 from the nucleus to the cytosol. In the cytosol, both p-p27S10 and p-p27T187 were degraded by the ubiquitin-proteasome pathway. Importantly, the P4-enhanced proliferation in breast cancer cell lines was abolished when p27 was knocked-down or phosphorylation of 27 was inhibited. Taken together, our results demonstrated that P4 enhanced breast cancer cell proliferation through increasing p27 degradation due to its

cytoplasmic mislocation. The findings from the present study highlight the molecular mechanisms underlying P4-enhanced proliferation in breast cancer cell lines.

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EP1094

Study of CYP17 and PSA G158A polymorphisms in prostate cancer

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The relationship between the level of genetic variation in CYP17, PSA genes and prostate cancer has been extensively studied but the results are still unclear. A 450c17a (CYP17) polymorphism A1/A2 was described to be significantly associated to prostate cancer. A SNP in the promotor PSA gene is an A to G substitution at position −158 (G158A) was proposed to interact differently with AR, thereby modifying the expression pattern and occurrence of prostate cancer.
Objective
The aim of the study was to investigate the association between CYP17 and PSA gene polymorphisms with advanced prostate cancer.
Subjects and methods
The study was conducted on 48 patients with advanced prostate cancer (Gleason score > 7) and 13 benign prostate hyperplasia subjects. Patients were enrolled after they gave their informed consent. DNA was isolated from prostatic tissue with PureLink Genomic DNA (Invitrogen). Genotyping of the A1/A2 and G/A polymorphisms in the promoter region of CYP17 and the PSA, respectively, were determined by a PCR–RFLP assay. PCR product was digested with restriction enzyme NheI (PSA G-158A) and MspA1I (CYP17). Preoperatory serum PSA was assayed by immunochemiluminescence.
Results
Genotype distribution differ for PSA G-158 between the prostate cancer and the control group (25% GG, 25% AA, 50% AG vs. 8% GG, 23% AA, 69% AG) and for CYP 17 (36% A1, 45% A1A2, 19% A2 vs. 22% A1, 64% A1A2, 14% A2). The frequency of A1 allele was 0.41, and 0.59 for A2 allele. In control group the frequency of A1 allele in population was 0.46, for A2 allele the frequency was 0.54. Neither CYP17 nor PSA polymorphisms associated with prostate cancer. Serum levels of PSA did not differ between genotypes.
Conclusion
In our study groups CYP17 and PSA gene polymorphisms did not significantly associated with prostate cancer or serum PSA levels. Further studies are needed on larger cohorts.
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Female Reproduction

EP1095

Administration of first line anti-tuberculosis drugs induces ovarian and uterine oxidative stress and disruption of endocrine balance in rats

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The first line anti-tuberculosis (anti-TB) drugs; isoniazid (INH), rifampicin (RIF), ethambutol (EMB) and pyrazinamide (PZA) were effective in the treatment of pulmonary tuberculosis. However, the toxicity of these drugs has been of great concern in clinical settings. This study was designed to evaluate the toxic effects of anti-TB drugs on reproductive system in female rats. Thirty-five female Wistar rats were assigned into five groups of seven animals each. The control received normal saline, while others received INH (5 mg/kg), RIF (10 mg/kg), EMB (15 mg/kg) and PZA (15 mg/kg) via gavage thrice in a week for eight consecutive weeks. Results showed that anti-TB drugs significantly ($P < 0.05$) reduced both uterine and ovarian weights, and relative weight of uterus relative to controls. In addition, anti-TB drugs increased the activities of alanine aminotransferase (ALT) and levels of total bilirubin. Furthermore, treatment with INH, RIF and PZA significantly ($P < 0.05$) reduced the levels of luteinizing hormone, estrogen and prolactin. In contrast, there were no significant differences ($P > 0.05$) in the levels of follicle stimulating hormone and progesterone in rats treated with anti-TB drugs when compared to controls. Moreso, INH, RIF, EMB and PZA caused significant ($P < 0.05$) increase in the uterine malondialdehyde (MDA) levels by 281, 214, 273 and 190%, respectively, while INH and EMB increased the ovarian MDA levels by 111% and 129%, respectively. All the anti-TB drugs significantly ($P < 0.05$) decreased the activities of ovarian glutathione-S-transferase and uterine glutathione peroxidase, superoxide dismutase and catalase. Histopathological examinations showed severe erosion of uterine mucosa, cellular debris in lumen of uterus and under-developed follicles in ovary of the rats. These results confirmed that the first line anti-TB drugs elicited reproductive toxicity in female rats via mechanism that involved oxidative stress.

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EP1096

Development of hepatic steatosis and inflammation by chronic insulin and hCG exposure in female rats: possible implications in PCOS patients with NAFLD

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Accumulating clinical data suggest that women with polycystic ovary syndrome (PCOS) are at high risk for nonalcoholic fatty liver disease (NAFLD). However, it is not clear whether hyperinsulinemia and hyperandrogenism act concomitantly or independently to induce hepatic steatosis and inflammation, and the molecular mechanisms behind the interactions between insulin resistance and hyperandrogenism in the female liver remain largely unexplored. To achieve hyperinsulinemia, insulin resistance, and hyperandrogenism, we treated rats chronically with insulin, human chorionic gonadotropin (hCG), or a combination of insulin and hCG. We showed that the different treatments induced varying degrees of hepatic steatosis in rats. While hCG-treated rats had strongly aggravated hepatic inflammation, insulin + hCG-treated rats exhibited the hallmarks of metabolic alterations and hepatocyte cell damage. Further mechanistic study revealed that the expression of a number of genes (Srebp-1, Srebp-2, Gpam, Ppara, Pparg, Lxrα, E2f1, Il-6, Mcp1, Tgfb, and Ctgf) and proteins (AceCS1, p-ACL, IRβ, p110-PI3K, p-Akt (T308), AS160, p-GSK3β, p-JNK, TNFα, and IL-1β) was significantly different in the liver between treatment and control groups. In parallel, we observed that expression of genes in adipose tissues that are related to M1/M2 macrophages was differentially regulated by the different treatments. In summary, our study presents several lines of in vivo evidence that hyperinsulinemia and hyperandrogenism, either alone or in combination with insulin resistance, alter hepatic lipid metabolism, liver and adipose tissue inflammatory responses, and cellular function and that the effects of the different conditions are distinct from each other. By deciphering the metabolic, endocrine, and molecular alterations along with morphological changes, our findings offer a new understanding of how hyperandrogenism itself or combined with insulin resistance contributes to liver damage in women with PCOS.

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EP1097

Frequency of nodular goiter and autoimmune thyroid disease and association of these disorders with insulin resistance in polycystic ovary syndrome

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Background and aim
Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder in women with reproductive age. Nodular goiter and autoimmune thyroid

disease (AITD) are frequently seen endocrinological abnormalities. The aim of this study was to identify the prevalence of AITD and nodular goiter in PCOS patients and investigate whether PCOS related hormones and metabolic factors affect these thyroid disorders.
Methods
Ninety-seven with PCOS and seventy-one healthy female volunteers were recruited in the present study. Serum free thyroxine (fT_4), thyroid stimulating hormone (TSH), anti-thyroperoxidase antibody (anti-TPO Ab), and anti-thyroglobulin antibody (anti-Tg Ab) were measured. Thyroid ultrasonography was performed and thyroid volume (TV) was calculated.
Results
The BMI, waist/hip ratio, fasting blood glucose, fasting insulin, HOMA-IR, TG and LDL-C were significantly higher in PCOS patients ($P<0.05$). HDL-C were significantly higher in control group ($P=0.005$). The mean thyroid volume was 11.4 ± 4.7 ml in PCOS patients while 9.9 ± 2.8 ml in controls ($P=0.022$). Twenty nine PCOS patients (29/97; 29.9%) had thyroid nodule whereas only eleven control subjects had thyroid nodule (11/71; 15.5%) ($P=0.043$). The frequency of AITD was significantly higher in PCOS patients ($P=0.001$). Statistically significant relationship was found between thyroid volume and age, BMI, fasting glucose, fasting insulin, HOMA-IR ($P<0.05$). Participants with thyroid nodule were older and had higher BMI, fasting glucose, fasting insulin and HOMA-IR values compared to participants without thyroid nodule ($P<0.05$).
Conclusion
Our study showed that TV and frequency of nodular goiter were increased in PCOS patients. This result has been associated with insulin resistance. Therefore we recommend PCOS patients must be monitored for the development of nodular goiter and AITD.

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EP1098

Association of basal and post-synacthen stimulated 17-hydroxyprogesterone levels with insulin resistance in polycystic ovary syndrome

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Objective
17-alpha-hydroxyprogesterone caproate therapy during pregnancy has been associated with insulin resistance. The aim of this study was to highlight any possible association of 17OHP with insulin resistance in women with PCOS.
Design
Forty-five women with PCOS underwent 75 g OGTT test and short Synachten test with sampling of stimulated 17OHP. Women were divided into two subgroups according to basal 17OHP cut-off level of 0.8 ng/ml.
Results
Women with basal 17OHP more than 0.8 ng/ml had significantly higher glucose levels at 60′ min: Glu_{60}: 111.36 ± 22.37 mg/dl vs 133.11 ± 32 mg/dl, $P=0.047$, and at 90′ min Glu_{90}: 93.50 ± 13 mg/dl vs 113.50 ± 27 mg/dl, $P=0.038$ and more often polycystic ovarian morphology in ultrasound compared to those with basal 17OHP levels below 0.8 ng/ml. The mean percentage increase of 17OHP at 60′ after Synachten test was 223%. According to this, women were subdivided into two categories depending on whether the intraindividual percentage increase of post-Synachten 17OHP levels was higher or lower than the mean percentage increase. A total of 26 women with hyperresponsiveness of 17OHP at 60′ minutes appeared with significant higher insulin resistance and post glucose challenge hyperinsulinemia when compared to 19 women with lower percentage increase of 17OHP, i.e. their mean insulin levels at 30′ minutes were: Ins_{30}: 130.9 ± 98.7 vs 59.3 ± 30.9 μU/ml, $P=0.05$, at 60′ minutes: Ins_{60}: 182.4 ± 124.9 vs 74.4 ± 32.1 μU/ml, $P=0.01$, at 90′ minutes: Ins_{90}: 177.2 ± 128.2 vs 67.9 ± 34.1 μU/ml, $P=0.01$, and at 120′ minutes: Ins_{120}: 121.6 ± 65.2 vs 67.1 ± 45.8 μU/ml, $P=0.05$.
Conclusions
17OHP could possibly be related to the metabolic abnormalities in women with PCOS and this should me taken into account especially during pregnancy when insulin resistance increases.

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EP1099

Serum sclerostin and dickkopf-1 levels in polycystic ovary syndrome patients

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Introduction
Polycystic ovary syndrome (PCOS) is the most common endocrine pathology in premenopausal women and it is a complex syndrome affecting various systems. Numerous studies have been made about how the PCOS effects on bone metabolism, but currently there is no clear information. Wnt pathway plays important role in the regulation of bone metabolism. The sclerostin(Scl) and Dickkopf-1 (DKK1) inhibit this pathway and they has recently become a therapeutic target of osteoporosis. In this study, we aimed to show the Scl and DKK1 levels in women with PCOS.
Methods
This study was conducted in Çanakkale Onsekiz Mart University Endocrinology department. Thirty-six women with PCOS and 35 healthy volunteers were examined in this study. Both groups were compared in terms of respect demographic, anthropometric, biochemical and Scl and DKK levels.
Results
PKOS grubunda sklerostin düzeyi 42.68 ± 13.28 pg/ml, kontrol grubunda ise 45.69 ± 11.79 pg/ml olarak ölçülmüş olup iki grup arasında istatistiki anlamlı fark olmadığı tespit edilmiştir. DKK1 düzeylerinin ise PKOS'lularda 1444.73 ± 611.30 pg/ml, kontrol grubunda 1204.26 ± 660.88 pg/ml olduğu gösterilmiş olup iki grup arasında anlamlı fark olmadığı saptanmıştır. The proportion of clinical hirsutism ($FGS\geq8$) in PCOS group were significantly higher than the control group. PCOS group compared to the control group in BMI and WHR were found to be high, although the difference is not statistically significant.
Conclusions
This is the first study on this subject. Çalışmamızda PKOS'lu kadınlarda sklerostin ve DKK1 düzeylerinin değişmediği gösterilmiştir. PKOS'lu hastaların KMY ölçümleriyle olan çalışmalarda da çelişkili sonuçlar çıkmıştır. Her ne kadar amenore bu hastalarda kemik kaybına yol açıyorsa da, hiperandrojenemi ve hiperestrojenemi gibi durumlar kemik üzerine olumlu etkiler yaparak bu etkiyi dengeliyor görünmektedir.

Keywords: Polycystic Ovary Syndrome, Osteoprosis, Sclerostin, Dickkopf-1
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EP1100

Phthalates induce ovarian failure through disturbance in folliculogenesis and steroidogenesis

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Introduction
Phthalates are chemicals used to improve the plasticity of industrial polymers and used in commercial products such as toys, paints, packaging materials, medicals devices and personal care items. Phthalates, endocrine disrupting chemicals, have been documented to cause adverse effects to the human health such as breast cancer in female, reduced uroogenital distance and changed the expression of steroidogenesis and folliculogenessis. In this study, we investigated the impact of di(2-ethylhexyl) phthalate (DEHP), di-n-butyl phthalate (DBP), and butyl benzyl phthalate (BBP) on loss of ovarian function through folliculogenesis and steroidogenesis. 4-Vinylcyclohexene diepoxide (VCD), a disruptor of ovarian small pre-antral follicles, was used as a positive control.
Methods
Female Spargue-Dawley rats (8 weeks of age, 160–180 g bodyweight) were administered VCD (80 mg/kg) by intraperitoneal, DEHP (25 mg/kg), BBP (250 mg/kg) and DBP (250 mg/kg) by oral gavage in 0.3 ml of corn oil at LOAEL during 6 weeks. Vaginal smear was collected at 9 a.m every day to check estrus cycle. Blood, pituitary, uterine and ovaries were collected after 24 h final injection.
Results
There was significantly increased in body weight of DEHP groups compared to other groups. Estrus cycle in DEHP and DBP groups showed no difference comparing with vehicle group. However, diestrus phase in VCD and BBP groups drew out compared to vehicle group. The transcriptional levels of

folliculogenesis-related genes (Foxl2, Kitl and Amh) and steroidogenesis-related genes (Star and Cyp11a1) were changed.
Conclusion
Our findings suggest that these phthalates can induce premature ovarian failure by disturbance in folliculogenesis and steroidogenesis and failure in hormone regulation.

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EP1101

Efficacy comparison of oral rosuvastatin versus oral progesterone and bevacizumab on regression of surgically endometriotic implants in rats

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Aim
Thirty female Wistar albino rats with surgically endometriotic implants were randomly randomized into three treatment groups: oral rosuvastatin (20 mg kg per day; oral rosuvastatin group 1; $n=10$), oral progesterone (Dienogest group 2; $n=10$), and intraperitoneal bevacizumab (2.5 mg/kg of single intaperitoneal injection of bevacizumab; group 3; $n=10$) respectively, for 10 day and post-treatment variables were compared.
Results
The endometrium foci as were measured on days 1 and 10. Rosuvastatin group showed higher reduction for the glandular epithelium and uterine vessels of histopathological scores values than progesterone group (both, $P<0.017$; respectively). The median glandular epithelium and uterine vessels and histopathological scores values did not show statistically significant difference among group 1 and group 3 ($P>0.017$). No significant different reduction was observed in between the three groups for the myometrium, endometrial stroma, in histopathological scores ($P>0.017$). Endometrial thickness and uterine volume values analyzed in all treatment groups. Endometrial thickness values and uterine volume values was more significantly reduced in the oral rosuvastatin medication than oral progesterone group (both, $P<0.017$; respectively). Moreover, endometrial thickness and uterine volume values were not different in groups I compared with group 3 ($P>0.017$).
Conclusion
In conclusion, rosuvastatin and intaperitoneal injection of bevacizumab may causes more significant regression of surgically endometriotic implants in rats than oral progesterone medications.

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EP1102

The relation between sex hormones and sexual function in women with Turner syndrome

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Objectives
To evaluate sexual function in women with Turner syndrome (TS) in the relation with sex hormones.
Methods
The study was undertaken in Lithuanian University of Health Sciences. 65 women with genetically confirmed TS (18–45 years) were enrolled and compared with 65 age-matched healthy controls. Sexual function was evaluated using The Female Sexual Function Index (FSFI). Risk for sexual dysfunction was defined as FSFI score $\leq$ 26.55. BMI, waist-hip ratio (w_h), concentrations of estradiol (E2), testosterone (T), sex hormone binding globulin (SHBG) were evaluated. TS patients were divided into 3 groups: natural estrogens users (NE2), combined oral contraceptives users (COCs) and untreated (no_E).
Results
38% ($n=27$) TS had sexual intercourse and filled out FSFI. 33% ($n=9$) of TS and 42% ($n=25$) of controls were at risk for sexual dysfunction ($P>0.05$). No difference in FSFI score depending on karyotype (classic or mosaicism) was found. No significant relation between age, BMI, w_h, E2, T, SHBG concentrations, duration of E2 use and FSFI domains in TS patients was detected. 41% ($n=11$) of TS used NE2, 26% ($n=7$) were on COCs and 33% ($n=9$) were in no_E group. NE2 or COCs users had higher total FSFI score (25.36 ± 9.10 vs 17.89 ± 13.62; $P=0.008$) and reported better lubrication (4.60 ± 1.84; $P=0.031$), satisfaction (4.83 ± 1.72 vs 3.20 ± 2.57; $P=0.008$), pain (4.67 ± 1.69 vs 2.97 ± 2.46; $=0.03$) during sexual intercourse compared with no_E. NE2 users had better desire (3.81 ± 1.36 vs 2.01 ± 2.15, $=0.005$), lubrication (4.58 ± 1.78 vs 2.35 ± 2.48; $P=0.014$), arousal (4.03 ± 1.63 vs 2.37 ± 2.33; $P=0.009$), orgasm (3.85 ± 1.86 vs 2.20 ± 2.37; $P=0.05$), satisfaction (4.54 ± 1.81 vs 2.71 ± 2.83; $P=0.001$), pain (4.90 ± 1.73 vs 2.26 ± 2.46; $P=0.011$) and total FSFI score (25.74 ± 9.33 vs 14.09 ± 14.38; $P=0.001$) when compared with COCs users.
Conclusion
Sexual function in TS did not differ compared with controls. Higher FSFI score was found in E2 users compared with untreated patients and in NE2 users compared with COCs users.

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EP1103

BMP8 sustains expansion and survival of cumulus cells *in vitro*

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Cumulus cells are a group of specialized granulosa cells that surrounds oocytes and are critical for female fertility. During ovulation, cumulus cells need to be expanded systematically in order to support the maturation, ovulation and fertilization of oocytes, whereas their apoptosis will result in the decline of fertilization rate and pregnancy outcome. However, the molecules as well as their signalings involved in the control of cumulus cell-oocyte complex (COC) expansion are complicated and await more studies. By analyzing several microarray and RNA-seq datasets, we intriguingly noticed that *BMP8* expression in cumulus cells was positively correlated to human oocyte maturation and zygote developmental competence. Using a rat superovulation model, we found that *Bmp8* transcripts were up-regulated by the luteinizing hormone signaling and were abundant in cumulus cells of pre-ovulatory follicles. Furthermore, BMP8 treatment can induce COC expansion as well as the expression of COC expansion-related genes. Hoechst-propidium iodide double staining further revealed that BMP8 can decrease cumulus cell apoptosis in ovulated COCs. BMP8 can induce the phosphorylation of both SMAD1/5/8 and SMAD2/3 in isolated COCs. Signaling dissection by inhibitors further indicated that blockage of SMAD2/3 pathway can impair BMP8-induced COC expansion, whereas blockage of either SMAD1/5/8 pathway or SMAD2/3 pathway dampens the protective role of BMP8 against cumulus cell apoptosis, indicating that both pathways are needed for BMP8-mediated cumulus cell survival. Taken together, our data demonstrated that BMP8 sustains both expansion and survival of cumulus cells through different SMAD downstreams. With these capabilities, BMP8 can contribute to the maintenance of oocyte quality and this may have clinical applications when doing *in vitro* fertilization.

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EP1104

Serum concentrations of betatrophin and its association with indirect indices of insulin resistance and beta cell function in women with polycystic ovary syndrome

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The accumulated data underline the role of betatrophin in glucose homeostasis. Polycystic ovary syndrome (PCOS) is characterized by insulin resistance and high risk of developing prediabetes and diabetes. The aim of our study was to investigate the relationship of serum betatrophin concentrations with indirect indices of insulin resistance and insulin secretion in women with PCOS, comparing to the control group. The study group comprised 43 women with PCOS and 16 controls matched for BMI and age. An oral glucose tolerance test (OGTT) with estimation of serum betatrophin concentrations was performed. Insulin resistance was assessed by HOMA-IR and Matsuda index. Insulin secretion was evaluated by HOMA-B. Glucose load resulted in an increase of serum betatrophin concentrations only in the control group ($P=0.02$). Consequently, serum betatrophin concentrations at 120′ of OGTT were lower in women with PCOS in comparison to the control group ($P=0.02$). We observed a positive relationship between baseline serum betatrophin concentrations and baseline serum insulin concentrations ($r=0.42$, $P=0.004$) in PCOS group. Additionally, correlations between baseline serum betatrophin concentrations and HOMA-IR ($r=0.39$, $P=0.008$), HOMA-B ($r=0.38$, $P=0.01$) and Matsuda index ($r=-0.31$, $P=0.004$) were observed in women with PCOS. We found relationship between Δ betatrophin and serum total testosterone concentration in the entire group ($r=-0.32$, $P=0.01$). Multiple regression analysis revealed that HOMA-B ($\beta=0.47$, $P=0.001$) was an independent factor connected to serum betatrophin levels in women with PCOS. Serum concentrations of betatrophin is connected with insulin resistance and beta cell function and did not change after glucose load in women with PCOS.

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EP1105

Short term intervention with liraglutide and metformin increased fertility potential in a subset of obese PCOS proceeding IVF

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Objective
Obese PCOS have poor IVF outcomes. The aim of this study was to evaluate the impact of weight reduction with metformin alone or in adjunct with liraglutide on oocyte maturity and embryo quality in infertile obese PCOS population.
Design/participants/main outcome measure
A 12-week prospective randomized study was conducted with 40 infertile PCOS (30.77 ± 3.742 aged years, BMI 36.69 ± 3.51 kg/m^2, mean ± SD) who had been previously poor responders to lifestyle intervention. They were assigned to metformin (MET) 1000 mg BID or MET 1000 mg BID and liraglutide 1.2 mg QD s.c. (COMBI) or to controls (CON). CON direclty proceeded with ovarian stimulation protocol, whereas MET and COMBI started with stimulation after 4 weeks medication free period.
Results
Eleven women on MET, 13 on COMBI and 11 CON completed the study. Patients in MET lost 6.70 ± 6.70 kg (P?0.001) compared with 7.68 ± 3.74 kg loss in COMBI ($P<0.001$), COMBI not being superior to MET ($P=0.103$). COMBI resulted in a reduction of visceral adipose tissue area (−20.65 ± 7.40 cm^2; $P=0.028$). More than 5% of weight reduction was achieved in 76.9% in COMBI and 45.5% of patients in MET. In high responders who lost more than 5% of body weight numbers of blastocysts/patient were greater in both treatment arms than in CON (3.67 ± 4.82 in COMBI; 3.60 ± 6.95 in MET; vs 2.09 ± 2.07 in CON). High responders in COMBI had the highest numbers of oocytes/patient 14.67 ± 9.59 and of mature oocyte 11.22 ± 9.27 (P=NS). In COMBI 3 patients became spontaneously pregnant before IVF in medication free period.
Conclusion
Women who lost more than 5% of body weight before IVF had increased fertility potential. COMBI resulted in the highest number of high responders and was associated with the highest number of blastocysts/patient. The high rate of spontaneous pregnancies in COMBI implies the potential role of GLP-1 in reproduction.

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EP1106

The functional state of hypophysis – gonad axis in patients with polycystic ovary syndrome (PCOS)

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The aim
To study the functional state of axis of hypophysis-gonads for women with PCOS.
Material and methods of investigation
Under our supervision in the department of neuroendocrinology of The Center of Endocrinology of PHM of Republic of Uzbekistan ambulatory in a period from September 2015 for July, 2016 120 patients of fertile age were inspected with polycystic ovary syndrome (PCOS). Middle age of patients – 25.5 ± 4.3 years. The remoteness of disease hesitated in limits from 7 months to 9 years. 20 healthy women of corresponding age made a control group. The complex of researches, including clinical, biochemical hormonal, ultrasound investigations of uteri/ovaries, pituitary MRI was executed all patients.
Results
Patients were divided into two groups: 1 g – patients with primary sterility are 94 cases, 2 r. – patients with secondary sterility are 26 cases. In a 1 group of patients with primary sterility the reliable decline of both pituitary and ovarian hormones was marked on a background hyperandroenemiya and hyperprolactinemiya. In the second group of patients the reliable decline of pituitary hormones was also educed on a background hyperandroenemiya and hyperprolactinemiya. While an ovarian function was within the limits of norm.
Conclusions
In both groups of patients took place hypogonadotropinemiya combining moderate hyperprolactinemiya and hyperandrogenemiya.Thus, the most expressed violations of the system of pituitary – ovarian function were found out in the first group of patients with PCOS with primary sterility, at that the reliable decline of the functional state of pituitary-gonads was marked, namely decline of LH, FSH, estradiol and progesterone of plasma of blood on 14 day of menstrual cycle.

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EP1107

Efficacy of FSH alone, FSH + LH, hMG or FSH + hCG on ART outcomes in the 'personalized' medicine era: a meta-analysis

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Background
Luteinizing hormone (LH) and human chorionic gonadotropin (hCG) act on the same receptor, activating different signal transduction pathways. The role of LH or hCG addition to follicle stimulating hormone (FSH) as well as menopausal gonadotropins (hMG) in controlled ovarian stimulation (COS) is debated.
Aim
To compare FSH + LH, or FSH + hCG or hMG vs FSH alone on COS outcomes.
Design
A meta-analysis according to PRISMA statement and Cochrane Collaboration was performed, including prospective, controlled clinical trials published until July 2016, enrolling women treated with FSH combined with other gonadotropins. Trials enrolling women with polycystic ovarian syndrome were excluded.
Results
Considering 70 studies, the administration of FSH alone resulted in higher number of oocytes retrieved than FSH + LH or hMG. The MII oocytes number did not change when FSH alone was compared to FSH + LH, FSH + hCG or hMG. Embryo number and implantation rate were higher when hMG was used instead of FSH alone. Pregnancy rate was significantly higher in FSH + LH-treated group versus others. Only twelve studies reported live birth rate, not providing protocol-dependent differences. Patients' stratification by age (median = 32.5 years) and/or by GnRH agonist/antagonist identified patient subgroups benefiting from specific drug combinations.

Conclusion
In COS, FSH alone results in higher oocyte number. However, hMG improves the collection of mature oocytes and embryos and increases implantation rate, although the final increased pregnancy rate is evident only in GnRH agonist protocol. On the other hand, LH addition leads to higher pregnancy rate. This study supports the concept of a different clinical action of gonadotropins in COS, reflecting previous *in vitro* data.

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EP1108

May thiol/disulfide homeostasis predict adult PCOS?

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Purpose
The purpose of this study was to evaluate the relation polycystic ovarian syndome (PCOS) and the thiol/disulfide balance, used as a marker of oxidative stress, by measuring that exchange using a novel technique.
Material/methods
Fourty nine subjects diagnosed with PCOS and 44 healthy were included in the study. Thiol/disulfide homeostasis concentrations were measured by a newly developed method. After native thiol, total thiol and disulfide levels were determined; measures such as disulfide/native thiol, disulfide/total thiol, and native thiol/total thiol were calculated.
Results
Lipid accumulation product (LAP) index ($P<0.001$), total testesterone ($P<0.001$), insulin ($P=0.003$), total cholesterol ($P=0.02$), triglyceride ($P=0.004$), disulfide ($P=0.007$), disulfide/native thiol ratio ($P<0.001$) and disulfide/total thiol ratio ($P<0.001$) were significantly higher and native thiol ($P=0.01$), total thiol ($P=0.04$) and native thiol/total thiol ratio ($P<0.001$) were sig-nificantly lower in patients with PCOS compared to control subjects. Correlation analysis reveals negative correlation of FGS, cycles, WC, LH: FSH ratio and Tg with native thiol and total thiol in cases. Also there was a significant negative correlation between LAP index, BMI and native thiol. DHEA-S had a positive correlation between disulphide. Stepwise logistic regression model showed that significantly high disulfide levels, disulfide/native thiol ratio and disulfide/total thiol ratio in patients with PCOS were found to be independent of age and BMI. Receiver operating characteristic curve analysis showed that areas under the curve for native thiol, total thiol, native thiol/total thiol ratio and disulfide, disulfide/native thiol ratio, disulfide/total thiol ratio were 0.660 ($P=0.008$), 0.601 ($P=0.096$), 0.714 ($P<0.001$), 0.663 ($P=0.007$), 0.701 ($P=0.001$), 0.701 ($P=0.001$), respectively.
Conclusion
It can be concluded that oxidative stress is increased in patients with PCOS, can play a pathophysiological role in the development of PCOS and this increase is not associated age and BMI. However, studies with larger sample sizes are needed in this area.

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EP1109

Effects of cigarette smoke extracts on proliferation, migration, and hCG-β protein expression of JEG-3 human placental cancer cells

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Maternal smoking during pregnancy is known to be related to adverse pregnancy results associated with trophoblast proliferation and cell cycle progression. Moreover, many previous studies have shown that cigarette smoke is correlated with human chorionic gonadotropin beta (hCG-β) subunit produced from syncytiotrophoblasts during pregnancy. Thus, we further investigated whether cigarette smoke extract (CSE) affects the cell proliferation, migration and endocrine hormone activity of JEG-3 human placental cancer cells. JEG-3 cell proliferation was significantly reduced by all CSEs in a concentration-dependent manner. Moreover, CSEs decreased proliferating cell nuclear antigen (PCNA) levels in JEG-3 cells in western blot. Increased migration or invasion ability of JEG-3 cells following CSE treatment was also confirmed by a scratch or fibronectin invasion assay in vitro. Additionally, protein levels of E-cadherin as an epithelial maker were down-regulated, while the mesenchymal markers N-cadherin, snail and slug were up-regulated in a time-dependent manner. The metastasis marker, cathepsin D, was also down-regulated by CSE. Finally, CSEs significantly reduced the expression of hCG-β protein in JEG-3 cells. Overall, these results indicate that exposure of placental cells to CSE deregulates the cell cycle by altering the expression of cell cycle-related proteins and stimulates cell metastatic ability by altering EMT markers and cathepsin D expression. CSE exposure may also decrease hCG-β production as an endocrine marker, implying that cigarette smoke has adverse effects during pregnancy. (This research was supported by a grant (14182MFDS977) from the Ministry of Food and Drug Safety, Republic of Korea, in 2016.)
Keywords: Cigarette smoke extract, placental cells, cell cycle, metastasis, human chorionic gonadotropin beta subunit

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EP1110

Hyperandrogenism and overweight/obesity, independently and interactively, increase the risk of metabolic syndrome and type 2 diabetes in women – a Prospective, Population-based Cohort Study

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The significance of hyperandrogenism (HA) as a metabolic risk factor in women is controversial. HA can be defined as either clinical (hirsutism) or biochemical (elevated androgen levels). We aimed to investigate whether HA at age 31 associates with metabolic syndrome (MetS), type 2 diabetes mellitus (DM2) or carotid intima media thickness (CIMT) by age 46. In a prospective, general population-based follow-up birth cohort ($n=5889$ women) blood samples were collected at age 31 in 3127 women and at age 46 in 3280 women. HA was defined as presence of hirsutism, serum testosterone >2.3 nmol/l (determined by LC-MS/MS) or free-androgen-index (FAI) >5.6 at age 31. MetS was defined according to IDF criteria. An oral glucose tolerance test (OGTT) was performed at age 46 in 2780 women. Glucose metabolism was defined according to the WHO standards. Diagnosis of DM2 was also verified and completed from the national drug and hospital discharge registers. Regression models were used to study if HA associates with cardiovascular risk factors at age 46. As expected, women with HA had significantly greater BMI at age 46 (27.54 ± 6.2 vs 26.58 ± 5.23 kg/m^2, $P=0.018$), compared to controls. HA at age 31 was significantly associated with MetS (OR = 1.5, 95%CI: 1.1–2.0) and DM2 (OR = 3.1, 95%CI: 1.8–5.2) at age 46. The significance remained in the multivariate regression analysis including BMI at age 31 (for MetS: HA: OR = 1.4, 95%CI: 1.1–2.0; BMI: OR = 4.0, 95%CI: 3.1–5.2; for DM2: HA: OR = 2.7, 95%CI: 1.6–4.6; BMI: OR = 4.1, 95%CI: 2.4–7.0). There were no significant differences in the CIMT between women with HA compared to controls. These results indicate that HA *per se* may increase the prevalence of MetS and DM2 in a general population. However, BMI seems to have a greater impact on the presence of these metabolic risks, with two-fold higher odds ratios than HA.

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EP1111

Natural history of the Swyer Syndrome

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We present a case of a eighteen-year-old woman admitted to the Gynecological and Endocrinological Department because of primary amenorrhea. Physical examination showed excessive pubic hair and clitoral hypertrophy. Laboratory tests showed the increased level of foliculotropina (FSH) 90 mIU/ml (normal range 3.5–12.5 mIU/ml) and the estradiol level below 10 pmol/l (normal range 46–607 pmol/l). An ultrasound-imaging of the abdomen and pelvis showed the uterus of normal size and shape. Bands of connective tissues were present at the site of ovaries. Because of the clinical presentation a genetic test was done which revealed the XY karyotype. Based on the results the Swyer syndrome was diagnosed. A hormonal substitution therapy was introduced and the surgical removal of the streak gonads was planned because of the risk of malignancy. The patient did not give consent for the operation and did not report for the follow up visits. Three years later, the woman reported back to the Clinic because of acute pain in the lower back, dyspnoea and increasing abdominal circumference. The computer tomography of the minor pelvis showed the presence of lumpy mass in the pelvic cavity. The patient underwent an operation. Intraoperatively numerous metastasis were found in the abdomen and pelvis. Radical hysterectomy was performed. Histopathological examination of the streak gonads showed dysgerminoma and gonadoblastoma on the left gonad and dysgerminoma on the right one. After operation the patient was given 4 cycles of chemotherapy. This case presents the natural history of the Swyer syndrome.

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EP1112

Biological activity mediated by sfingosine-1-phospate receptors in human primary granulosa cells and immortalized granulosa cell line *in vitro*

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Introduction
Sphingosine-1-phosphate (S1P) is a sphingolipid mediating proliferative signals in human ovarian follicles, acting through five receptors (S1PR1-5). We characterized the effects of S1PR1 and S1PR3 *in vitro*, as those mostly expressed in human primary granulosa cells (hGLC) and immortalized, tumor-like granulosa cell line (hGL5).
Methods
The S1P-mediated signaling, as well as the activity of S1PR1- and S1PR3-specific agonists (SEW281 and CYM5541, respectively), was evaluated in hGLC and hGL5 cells. Dimethyl-sulfoxide-, cholera toxin- and phorbol-12-myristate-13-acetate (PMA)-treatments served as controls. The kinetics of pERK1/2, pAKT and pCREB activation were evaluated over 2 h by Western blotting, while total cAMP production was measured by ELISA. The downstream cell viability was measured by MTT assay over 72 h, ±FSH. Differences were significant for $P<0.05$ (two-way Anova; $n=2$–12).
Results
Dose-response experiments revealed that 0.1 μM S1P, 1.0 nM SEW2871 and 1.0 nM CYM5541 are the most effective concentrations, in terms of pERK1/2 and pAKT activation. In hGLC, pERK1/2 activation occurs within 5–60 min by S1P, and, in a lesser extent, within 15–30 min by SEW2871 and CYM5541. In hGL5 cells, SEW2871- and CYM5541-dependent pERK1/2 activation is prolonged until 2 h. We describe for the first time S1P- and, to a lesser extent, SEW2871/CYM5541-mediated pCREB activation in both cell models, occurring in spite of no pAKT and cAMP recruitment. All the agonists increased cell viability in hGL5 cells, an effect reverted in the presence of 50 nM FSH. Only S1P mediated anti-apoptotic effects in hGLC, while the treatment by SEW2871 and CYM5541 impacts negatively cell viability.
Discussion
We found S1PRs-mediated cAMP-independent steroidogenic potential and different signaling kinetics in hGLC and hGL5 cells, revealing opposite effects on the downstream cell signaling, depending on the cell model.
Conclusion
Our study suggests that S1PRs play a role in ovarian follicle growth and oocyte maturation.

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EP1113

Polycystic ovary syndrome and euthyroid hashimoto's thyroiditis: possible influence of thyroid autoantibodies

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Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common endocrine disorders in general population. Autoimmune thyroid diseases are common autoimmune disorders that affect about 5% to 20% of women in childbearing age. In this study, we evaluate the comorbidity rate of euthyroid Hashimoto's Thyroiditis (HT) in PCOS patients and possible influence of thyroid autoantibodies on clinical and laboratory findings of PCOS. This study includes 285 PCOS patients attending to our outpatient Endocrinology Clinic at Erzurum Region Training and Research Hospital. The control group include 32 age and body mass index matched healty women. In PCOS group 88 of 285 (%30.87) patients have euthyroid Hashimato's disease where as in control group 2 of 32 (%6.25) have disease. These findings are statistically significant ($P=0.003$). None of the euthyroid Hashimato's patients take L-thyroxine replacement therapy. Anti-TPO and anti-TG were significantly higher in patients with PCOS ($P=0.000$; $P=0.01$; respectively). Anti-TPO had a significantly positive correlation between PCOS presence ($r=0.119$; $P=0.036$), and clinical indicators of PCOS such as cycle time ($r=0.709$; $P=0.000$), Ferriman-Gallwey score ($r=0.376$; $P=0.001$), DHEAS ($r=0.132$; $P=0.04$), testosterone ($r=0.124$; $P=0.043$), and LH/FSH ($r=0.136$; $P=0.025$). TPO was seen to be an independent risk factor from body mass index, age and TSH in PCO patients. Anti-TPO and anti-Tg were also sensitive and spesific in diagnosing PCOS. AUC value of Anti-TPO was 0.843 ($P=0.000$) and Anti-Tg was 0.843 ($P=0.000$). In ROC analysis, TPO $\geq$ 4.9 had 99.6% sensitivity and 71% specificity, anti TG $\geq$ 18 had 94.8% sensitivity and 75% specificity in predicting PCOS. In our study thyroid autoantibodies were significantly higher in patients with PCOS. We think that thyroid autoantibodies can affect the clinical and laboratory course of PCOS. We have found that the euthyroid HT may be observed at higher rates in PCOS patients, independent of the thyroid function tests.

Keywords: polycystic ovary syndrome, Hashimoto's Thyroiditis, thyroid autoantibodies

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EP1114

Novel insulin resistance index using C-peptide is reliable predictor of insulin resistance in women with PCOS

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Introduction
Recently, it was suggested that insulin resistance index using C-peptide (CIR) could be a better marker of insulin resistance than homeostasis model assessment (HOMA-IR) in patients with type 2 diabetes mellitus. The aim of this study was to investigate performance of CIR index in PCOS subjects.
Methods
We evaluated 187 PCOS women (PCOS: 25.38 ± 6.32 kg/m^2; 26.01 ± 5.16 years) diagnosed using ESHRE/ASRM criteria and 42 healthy women (Controls: 22.56 ± 5.46 kg/m^2; 28.33 ± 5.62 years). In follicular phase of menstrual cycle total testosterone, SHBG, lipids, glucose, insulin and C-peptide were determined.

Novel CIR index (20/(fasting C-peptide×fasting plasma glucose)) and HOMA-IR (fasting plasma glucose× fasting insulin)/22.5 were calculated in all subjects. Euglycaemic hyperinsulinemic clamp (EHC) was performed in PCOS group and the whole body disposal rate (M, mg/kg per min) was determined as the mean of the glucose infusion rate during the last 30 min of EHC. Insulin sensitivity index (M/I) was calculated by dividing M by the steady state plasma insulin level during the last 30 min of EHC. All analyses were adjusted for BMI and age.

Results

In comparison to controls, PCOS had significantly lower CIR index (14.72±2.21 vs 9.65±1.02, respectively; $P=0.040$) and higher HOMA-IR (2.91±0.36 vs 3.70±0.16, respectively; $P=0.047$). CIR index strongly correlated with HOMA-IR ($\rho=-0.447$, $P<0.001$), M/I ($\rho=0.461$, $P<0.001$), BMI ($\rho=-0.381$, $P<0.001$) and waist circumference (WC)($\rho=-0.335$, $P<0.001$). HOMA-IR correlated with M/I ($\rho=-0.404$, $P<0.001$), BMI ($\rho=0.349$, $P<0.001$), WC ($\rho=0.348$, $P<0.001$) and, unlike CIR index, also with SHBG ($\rho=-0.411$, $P<0.001$).

Conclusion

Novel CIR index could be a good surrogate marker of IR in PCOS. The absence of liver clearance of C-peptide is the reason for stronger correlation of CIR index with M/I in comparison to HOMA-IR.

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EP1115

Omentin-1, a potential link between chronic low grade inflammation, metabolic and reproductive features of polycystic ovary syndrome

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Background

Polycystic ovary syndrome (PCOS) is associated with features linked to metabolic syndrome including visceral adiposity, dyslipidemia and impaired glucose homeostasis. Adipose tissue produces adipocytokines which contribute to regulation of insulin sensitivity and reproduction. Omentin-1 is an adipokine with anti-inflammatory and insulin sensitizing roles produced by adipocytes. The exact role of mentin-1 in PCOS remains unclear as studies have reported reduced or unchanged levels in PCOS.

Methods

To determine the relationships between PCOS status, adipocytokines including omentin-1 and etiological features of PCOS we measured serum omentin-1, interleukin-6 (IL-6), high sensitivity CRP (hs-CRP), androgens, SHBG, fasting glucose and insulin levels in an observational study of community recruited PCOS and controls.

Results

49 women with PCOS (age 29.8±5.9 years, BMI: 29.0±5.4 kg/m^2) and 25 healthy controls (age 37.6±7.8 years, BMI: 28.9±4.0 kg/m^2) were recruited. Homeostatic model assessment for insulin resistance (HOMA-IR) ($P=0.006$), free androgen index (FAI) ($P=0.01$) and Ferriman-Galway score ($P<0.001$) were higher in PCOS. Women with PCOS had lower omentin-1 (median (IQR): 68.76(67.17) vs 112.45(67.42)) ($P=0.005$) independent of obesity. Omentin-1 correlated significantly with hs-CRP, IL-6, HMW-adiponectin, BMI, percentage of body fat, insulin, low density lipoprotein (LDL), triglycerides and total ovarian volume in women with PCOS. Multiple regression analyses revealed omentin-1 was explained by triglycerides (Beta: −0.177, $P=0.03$) and total ovarian volume (Beta: −0.009, $P=0.025$).

Conclusion

Omentin-1 is significantly lower in women with PCOS and correlates significantly with other inflammatory markers, metabolic parameters and total ovarian volume. This finding suggests omentin-1 as a potential link between metabolic and reproductive features of PCOS and chronic low grade inflammation.

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EP1116

Hirsutism in reproductive aged Korean women

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Hirsutism, excessive terminal hair growth in a male-like pattern as a marker of hyperandrogenism, affects 5–10% of reproductive-age women worldwide. The frequency of hirsutism seems to decrease in Asians and the lower cut-off modified hirsutism score is suggested. We performed the study to estimate the frequency, bio-metabolic characteristics, correlates and determinants of hirsutism in reproductive aged Korean women. A total of 2682 female volunteers of reproductive age (15–39 years) were recruited for the genetic study of PCOS. Menstrual history was taken and hirsutism was diagnosed when modified Ferriman-Gallway (mFG) score ≧8 was noted. Anthropometric features, hormones (total testosterone, SHBG, 17OH progesterone, prolactin, and TSH) and metabolic parameters (glucose, insulin and lipids) in blood were measured. The frequency of hirsutism is 133 (4.96%) in a total 2682 subjects. Fifty nine % (1582) of subject had m-FG score of zero; 30.0% (805) had m-FG score between 1 and 4; 6.0% (162) were between 5 and 7. The m-FG values of 25th, 50th, 75th, and 95th percentiles were 0, 0, 2, and 7 respectively. m-FG score significantly correlated to age, waist circumference, serum total and free testosterone, SHBG, postprandial plasma glucose, fasting and postprandial plasma insulin, and HOMA-IR. Logistic regression analysis showed younger age, increased fasting insulin and free testosterone levels were associated with mFG score. In conclusion the estimated frequency of hirsutism among reproductive aged Korean women was 4.96%, which is comparable to other races. Hirsutism is associated with fasting plasma insulin, serum free testosterone level and younger age.

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EP1117

Pharmacokinetics and bioavailability of non-polar phytocomponents of Aloe vera gel and their role as an endocrine modulator in letrozole induced PCOS rat model

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Background and aim

Polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age with an estimated prevalence of 5–10%, is one of the most common causes of female infertility. The therapeutic options for PCOS are limited. Thereby, traditional knowledge of Ayurveda has been exploited to identify an herbal therapeutic target for PCOS. Pharmacokinetic (PK) studies on bioactive constituents of herbal drugs provide valuable information on bio-transformed metabolites, dosage form, doses and potential herb–drug interactions. Thereby, the aim of the study was to study the pharmacokinetics and bioavailability of the non-polar phytocomponents of *Aloe vera* gel and their role as an endocrine modulator in PCOS pathology.

Methodology

PCOS was induced in rat using letrozole and validated for structural and metabolic characteristics of PCOS. Blood and tissues (ovaries, adrenal, hypothalamus, pituitary, uterus and liver) were collected upto 48 h after petroleum ether extract of dried *Aloe vera* gel (1.0 g) were administered orally to rats. Metabolites of Phytosterols were identified using GC/MS and quantified using HPLC. Progesterone and estradiol were analysed using ELISA. Steroidogenic enzymes as well as important enzymes responsible for biotransformation were evaluated along with the toxicity parameters.

Results

PCOS animals demonstrated altered estrus cyclicity, serum testosterone levels and oral glucose tolerance test profile when compared to controls. An increase in the estradiol ($P<0.01$) and progesterone levels ($P<0.05$) were observed in the plasma after 24 h. Several phytosterols and their modified oxysterols were identified in the plasma and tissues which could be well-correlated with the functional changes observed in hormone profile.

Conclusion

This study elucidates the bioavailability and functionality of phytosterols/oxysterols obtained from Aloe vera gel towards management of PCOS. This study will be helpful in identification of a naturally derived drug target and add to its economic viability at national and international level.

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EP1118

Influence of peroxisome proliferator-activated receptor (PPAR)-γ exon 2 (Pro12Ala) and exon 6 (His447His) and Gly972Arg insulin receptor substrate (IRS)-1 polymorphisms on insulin resistance (IR) and beta cell function in Southern Mediterranean women with polycystic ovary syndrome (PCOS)

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The Pro12Ala and His447His polymorphisms of PPAR-γ, and Gly972Arg polymorphism of IRS-1 have been implicated in insulin resistance (IR) and adiposity. In this study, we investigated the possible influence of these polymorphisms on metabolic features of 53 PCOS women compared with 26 healthy women (controls). All women underwent a clinical, anthropometric and biochemical evaluation, including a 75-g oral glucose tolerance test; insulin secretion and sensitivity indices were calculated. In the two groups, frequencies of PPARγ polymorphisms did not differ from those predicted by the Hardy-Weinberg equilibrium. Instead, the IRS-1 Gly972Arg allele was significantly more frequent in the PCOS group compared to controls. The frequency of different allelic combinations was unequal in the two groups, with IRS1^{+}/exon2^{-}/exon6^{-} detected in 66% of PCOS and IRS-1^{-}/exon2^{-}/exon6^{-} in 73% of controls. In PCOS women, the IRS-1 Gly972Arg allele was associated with lower E_2 levels ($P=0.030$), while the PPARγ Pro12Ala allele with lower free-testosterone levels ($P=0.021$). No other relationships were noted. When compared with wild-type women, in PCOS group, IR was: 1) trendwise greater in carriers of the variant allele in IRS-1 gene (borderline higher HOMA-IR, insulinogenic and disposition indices); 2) trendwise lower in carriers of the variant PPAR-γ exon6 allele (lower HOMA-IR and higher Matsuda index, lower insulinogenic and disposition indices); 3) lower ($P<0.01$) in carriers of the PPAR-γ exon2 variant (lower HOMA-IR values and higher insulinogenic and disposition indices). Furthermore, within the IRS-1^{+}/PPAR-γ-exon2^{-} PCOS women, PPAR-γ- exon6^{+} women had higher Matsuda index ($P=0.03$) compared with the noncarriers (PPAR-γ-exon6^{-}). Our data support the protective influence of PPAR-γ-exon2 and exon6 variants on IR and beta-cell function, whereas IRS-1 polymorphism is associated with a more unfavorable metabolic profile. However, these associations do not fully explain the high metabolic risk PCOS-associated.

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EP1119

Hormonal disturbances and adipokines levels in girls with oligomenorrhea

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Aim
The aim of this study was to evaluate hormonal disturbances and adipokines levels in girls with oligomenorrhea.
Materials and methods
The study comprised a group of 46 girls, aged 16–18 years, who were diagnosed with oligomenorrhea, and a control group with 37 healthy girls, aged 16–18 years, with no diagnosed menstrual disorders. In the first stage of the study, all girls had their medical history assessed. Subsequently, anthropometric measurements (height, weight) were measured, severity of hirsutism -according to the Ferriman-Gallwey score – was assessed and a pelvic ultrasound was conducted. In the blood serum, the following parameters were determined: LH, FSH, estriadol, TSH, SHBG, total and free testosterone, androstenedione, DHEA-S, prolactin, insulin and glucose. Assessment of adipokines in plasma included: leptin, adiponectin and apelin-36. Insulin resistance was assessed using the indirect method, setting HOMA-IR and on the basis of a standard model, free androgen index (FAI) was also calculated.
Results
The incidence of hyperprolactinemia in the study group is 32%, while there was no disturbance among any of the girls from the control group. Furthermore, among the group of girls with oligomenorrhea, a significantly greater increase in clinical symptoms of hyperandrogenism was observed – hirsutism, assessed according to the Ferriman-Gallwey scale, as compared to the control group ($P=0.048$). Full-blown PCOS was diagnosed in 6.52% of the girls from the study group, whereas none of the patients from the control group met all the criteria for the diagnosis of PCOS ($P<0.05$). There were no significant differences in plasma concentrations of leptin, adiponectin and apelin-36 between the study and control groups.
Conclusions
Hormonal disorders such as hyperprolactinemia, hyperandrogenaemia and PCOS are more frequently diagnosed in girls with oligomenorrhea. In girls with oligomenorrhea, elevated levels of leptin and decreased levels of adiponectin may be considered as new biomarkers for insulin resistance and hyperandrogenaemia.

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EP1120

Global methylation pattern and endocrine-metabolic profile during early infancy and puberty in sons born to women with polycystic ovary syndrome (PCOS)

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Prenatal and postnatal environment can regulate gene expression through multiple epigenetic mechanisms, being DNA methylation among the most relevant. Metabolic and reproductive function may be modified by this mechanism. Sons born to women with PCOS show altered markers of metabolic and reproductive function during childhood and adulthood. However, these functions have not been studied during puberty. The aim of the present study was to assess the global methylation pattern and its possible association with anthropometrics, endocrine and metabolic variables in a cohort of early infants and peripubertal boys born to women with PCOS. Global DNA methylation was measured from blood leucocytes, in 21 sons born to control women (C-Sons) and 15 born to women with PCOS (P-Sons) at early infancy (2-3 months old). In addition, 50 P-Sons (12 prepubertal (Tanner I), 28 pubertal (Tanner II-IV) and 10 late pubertal (Tanner V)) and 61 C-sons (13 prepubertal, 30 pubertal and 18 late pubertal) were studied. Weight, height and waist circumference were determined. A 75-gr oral glucose tolerance test with insulin and glucose measurements was performed. HOMA-IR and ISI composite were calculated. In the fasting sample circulating AMH, 17-OH-Progesterone, androstendione, testosterone, estradiol and lipids were measured. P-Sons showed lower global methylation at early infancy ($P=0.027$), whereas at pubertal age a higher global methylation was found ($P=0.035$). No differences were observed during pre and late puberty. At early infancy, no differences were observed in anthropometric variables between C-Sons and P-Sons. In prepubertal age, fasting and 120-min glucose were higher in P-sons compared to C-Sons ($P=0.038$ and 0.046, respectively). At puberty, waist circumference and androstenedione levels were higher ($P=0.032$ and 0.006, respectively) and cholesterol tended to be higher ($P=0.06$) in P-Sons compared to C-Sons. At late puberty, no differences were observed between groups. These results suggest that the methylation pattern can be modified from early infancy to the pubertal age in sons born to PCOS women. During puberty, global methylation increased concomitantly with circulating androstendione levels and waist circumference suggesting that the endocrine and metabolic milieu may be associated with DNA methylation in these boys.

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EP1121

Natural history of autoimmune primary ovarian insufficiency progresses through several stages from normal ovary function to clinically overt ovary dysfunction

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Context
Women with autoimmune Addison's disease with normally ovulatory cycles but positive for steroid cells antibodies (StCA) have been considered at risk of premature ovarian insufficiency (POI).
Design
Thirty-three women younger than 40 years, with subclinical-clinical Addison's disease but with normally ovulatory menses, were followed-up for 10 years to evaluate the long-term time-related variations of StCA, ovarian function and follicular reserve. All patients and 27 control women were investigated at start and every year for the presence and titer of StCA (by indirect immunofluorescence), serum concentrations of anti-Mullerian hormone (AMH) and ovarian function along four consecutive menses every year.
Results
At start of the study StCA were present in 16 women (group 1), at low/middle titer ($\leq$1:32) in seven of them (43.75%, group 1A), at high titer ($>$1:32) in the remaining nine patients (group 1B, 56.2%), while they were absent in 17 patients (group 2). During the follow-up period, all women in group 1A persisted StCA positive at low/middle titer with normal ovulatory menses and normal gonadotropin and AMH levels, while all patients in group 1B showed a further increase of StCA titers (1:128–1:256) and progressed through three stages of ovarian function. None of patients in group 2 and controls showed appearance of StCA or ovary dysfunction during the follow-up.
Conclusions
The presence of StCA at high titers could be considered a good predictive marker of subsequent development of autoimmune POI. To single out the stages of autoimmune POI may allow a timely therapeutic choice in subclinical and early clinical stage.

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EP1122

Relationship between anabolic hormones and benign lesions in different organs in premenopousal women

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Objective
We aim to detect co-occurence of uterine myomas, thyroid nodules and breast lesions in premenoposual women with menstruel disorders and investigate association between these benign tumors with anabolic hormon levels.
Design
Records of 8008 premenopausal women were analyzed who had been admitted to the hospital for routine breast image investigation which was performed by the same radiologist in between 2010 and 2015.
Study and Methods
251 patients who had both Thyroid Ultasound (US), Pelvic Ultrasound (US) and Breast Imaging Reporting and complain about menstruel disorders in the same year, were extracted from 8008 premenapousal woman. All data were obtained from file records and ICD-10 diagnosis code of electronic database of the hospital. For breast examination, Breast Imaging Reporting and Data System (BIRADS) terminology had been used. Tiroid stimulating hormone (TSH) and Estrodiol (E_2) levels were recorded for investigate of situation of anabolic hormon levels, which had been taken from premenopousal women at the time of third day of menstruel cycle.
Results
The mean age of the patients at the admission to the hospital was 32 ± 5.7 years. From 251 patients only 9 patients had benign lesions in all three organs, whereas 63 patients had both thyroid nodules and breast lesions and 5 patients had thyroid nodules and uterine myoma, and seven patients had BIRADS 2,3 lesions and uterine myoma, respectively. There was only found a relationship between age and existence of myoma uteri and thyroid nodule. ($P = 0.008$, for both). Only TSH levels were found lower in patients with BIRADS 2,3 lesions than with BIRADS 1 ($P = 0.017$).
Conclusion
Our study indicate that no association between E2 levels and existence of benign lesions in different organs according to the radiologic investigations in premenopausal women. And, TSH levels were found related to upper BIRADS grades in premenopausal women.

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EP1123

Heterogeneous hCG and hMG commercial preparations result in biased intracellular signaling but induce similar progesterone response in vitro

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Human chorionic gonadotropin (hCG) is the pregnancy hormone marketed as a drug for assisted reproduction technologies to support follicle-stimulating hormone action. Several hCG formulations are commercially available, differing in source, purification methods and biochemical composition. In this study, we investigated the molecular features and the intracellular signaling mediated by five urinary and recombinant hCGs. The drug comparisons were performed by quantifying the hormones by immunoassay, calibrated against the hCG standard (5th IS; NIBSC 07/364). Immunoreactivity pattern, isoelectric point and oligosaccharide content of hCGs were evaluated by reducing and non-reducing Western blotting, capillary isoelectric-focusing immunoassay and lectin-ELISA, respectively. Functional studies were performed in order to evaluate intracellular and total cAMP, progesterone production, as well as β-arrestin two recruitment by ELISA and BRET, in both human primary granulosa lutein cells (hGLC) and LH/hCG receptor (LHCGR)-transfected HEK293 cells stimulated by increasing hormone doses. Heterogeneous profiles were found among preparations, revealing hormone-specific molecular weight patterns (20–75 kDa range), isoelectric points (4.0–9.0 pI range) and lectin binding (Two-way ANOVA and Bonferroni post-test; $P < 0.05$; $n = 5$). These drug-specific compositions are linked to different potencies on cAMP production (EC_{50} 1.0–400 ng/ml range) and partial agonism on β-arrestin 2 recruitment (EC_{50} 0.03–2.0 μg/ml) in hGLC and transfected HEK293 cells (Mann-Whitney's U test; $P < 0.05$; $n = 3$ or 5). However, the treatment of hGLC with hCGs resulted in similar progesterone production after 24 h of exposure (Mann-Whitney's U test; $P \geq 0.05$; $n = 3$). Therefore, although hCG preparations consist of different glycosylated isoforms and mediate drug-specific early signaling, they result in similar downstream steroidogenesis *in vitro*. Commercial gonadotropins calibration relies on their *in vivo* activity (Pharmacopea), which can be reached with different mixtures of isoforms with various half-lives and receptor binding activities. Here, we demonstrate that commercial hCG preparations, likely with different assortments of isoforms, exhibit similar steroidogenic activity in vitro, by triggering biased intracellular signaling pathways.

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EP1124

Etiopathogenetical aspects of endocrine infertility

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Urgency
According to WHO the frequency of infertile unions is high amount 25–30% in developed countries. There are following reasons of infertility by women: 1) tubal

infertility; 2) endocrine infertility-it takes the 2nd place among the reasons of infertility; 3) anomalies of the vagina and uterus; 4) immunological reasons, that are caused by sensibilisation of female organism, also there are patients, the reason of infertility of that is not 'explainable', when there not obvious violations of reproductive system, it is called 'unexplained infertility' – 8–10% and an emotional form of infertility.
Research aim
Studying etiological and pathogenetic mechanisms of infertility's development by women.
Materials and methods
Retrospective analyses of scientific literature from 2010 to 2016 years.
Results of the research
Endocrine infertility- complex of hormonal disorders, that follow irregular ovulation or its absence. By every 3rd infertile woman the reason is the pathology of endocrine system. These are: 1) unovulation; 2) hypothalamic-pituitary dysfunction; 3) hyperandrogenism of ovarial or adrenal henesis; 4) function disorders of thyroid; 5) estrogen and progesterone deficiency; 6) severe somathic pathology; 7) obesity; 8) resistance ovary syndrome, when there is an insensivity to the gonadotrophini, that stimulates an ovulation, that is manifested with amenorrhea; 9) premature menopause in younger women to 35–38 y.o; 10) mutations of sex chromosomes. Abortions and infections, that cause tube-peritoneal forms of infertility among to 50% of all patients with infertility. According to WHO more than 20% of patients with infertility have expressed anatomical changes of fallopian tubes. Obstruction of FT we can see by 11–15% of observing, 30% of cases-endometrioid heterotopia.
Conclusions
For prophylaxis of endocrine infertility: 1) preventing of child infections, chronic tonsillitis, rheumatism; 2) preventing the developing of patholodical birth, abortion, inflammatious infections of women reproductive system; 3) proper maintenance of pregnancy, judicious use of hormones during the pregnancy.

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EP1125

Prenatal androgen exposure alters gene expression and promoter methylation of two ovarian follicle maturation factors

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Background
Follicles imaturation, as the hallmark of polycystic ovarian syndrome caused by prenatal androgen exposure, is suspected to be effected through expression changes of related genes. The aim of this study was to evaluate gene expression and promoter methylation of GATA6 and Follistatin (FST), two factors involved in follicle maturation, in adult female rats prenatally exposed to androgen excess by comparing them with non-treated rats.
Material and methods
Eight pregnant Wistar rats in the experimental group were treated by subcutaneous injection of 5 mg free testosterone on day 20 of pregnancy, while controls ($n=8$) received 500 ml of solvent. DNAs and RNAs were extracted from ovarian theca cells of adult female off-springs of PNA ($n=24$) and controls ($n=24$). Relative expression and promoter methylation levels were measured using Cyber-green Real-Time PCR and bisulfite sequence PCR (BSP) methods, respectively.
Results
Compared to the control group, the relative expression of GATA6 and FST genes in the treated group was 2.08 fold (95% CI: 1.62–2.55; $P<0.0001$) for GATA6 and 0.85 fold (95% CI: 0.73–0.97; $P=0.058$) for FST. Along with decrease in the methylation percentage of 11 CpG sites of GATA6 promoter in the PNA group in comparison with controls, the methylation of -480 position, was significantly decreased by 6.72 ± 4.66 and 41.69 ± 15.78 percent for PNA and the controls, respectively ($P=0.03$). No significant difference was seen in methylation of FST promoter although the percentage of 17 CpG sites increases slightly in PNAs.
Conclusions
These results reveal that manifestation of PCOS-like phenotype following prenatal exposure to excess androgen is associated with alteration in the expression and promoter methylation of the particular CpG sites of follicle maturation involved genes.

Keywords: GATA6, FST, Gene Expression, Promoter Methylation, Prenatal androgenisation
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EP1126

Graduated response to pulsatile GnRH therapy in hypothalamic amenorrhea

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Introduction
Pulsatile GnRH therapy is currently used to restore LH pulse and induce physiological ovulation, with effectiveness demonstrated in all types of hypothalamic amenorrhea (HA). Anorexia nervosa (AN) is characterized by self-starvation-induced undernutrition leading to functional hypothalamic amenorrhea (HA). Weight recovery does not always restore menses despite no apparent clinical and biological undernutrition residual signs. Only few specific studies on persistent amenorrheic weight-recovered AN (Rec-AN) have evaluated pulsatile GnRH therapy, including small number and under nourished patients. Comparison data on hormonal response of the different causes of HA (weight-recovered AN, primary and secondary HA non-related to eating disorders) is also lacking. Therefore, this study was designed to evaluate hormonal and clinical responses to GnRH pulsatile treatment in three groups of HA patients: weight-recovered anorexia nervosa patients (Rec-AN) with persistent functional hypothalamic amenorrhea (HA), secondary and primary HA.
Patients and method
This retrospective, observational ambulatory study included 41 females: 15 secondary HA without any eating disorders patients (SHA), seven primary HA patients (PHA), and 19 Rec-AN (BMI$>$ 18.5 kg/m^2 without menses recovery), who underwent GnRH pulsatile therapy. Baseline Estradiol (E), LH and Progesterone plasma level and their changes during induction cycles were evaluated. Ovulation, follicular recruitment and pregnancies rate were also studied.
Results
Rec-AN displayed higher basal E and LH plasma levels after GnRH injection compared to SHA and to PHA. WE observed higher E and LH levels during induction cycles in Rec-AN compared to SHA and PHA. PHA displayed the lowest hormonal plasma levels. Follicular recruitment was higher in Rec-AN. Ovulation rate was higher in Rec-AN and SHA compared to PHA.
Conclusions
This study showed increased gonadal status and higher Estradiol response to pulsatile GnRH therapy in persistent amenorrheic weight-recovered AN compared to SHA and PHA. Pulsatile GnRH therapy seems less efficient in primary hypothalamic amenorrhea.

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EP1127

Relationship between steroid hormones and metabolic profile in women with polycystic ovary syndrome

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Background
There is evidence that polycystic ovary syndrome (PCOS) is commonly associated with higher cardiometabolic risk. *Aim of the study* was to compare various sex streoids in PCOS women with overweight or obesity (BMI >27) and those with lower BMI. Second aim of the study was to determine the relationship of various sexual setroids to cardiovascular risk in PCOS women.

Subjects and methods
Study included 64 Caucasian women with PCOS. Fasting blood samples were collected in an early follicular phase and were analyzed for metabolic parameters and sexual steroid hormones (androgens, estrogens and adrenal androgen precursors).
Results
Women with BMI $\geq$ 27 had worse metabolic profile and higher serum free testosterone (FT), free androgen index (FAI), estrone (E1) ($P=0{,}014$ for FT, $P=0.02$ for FAI and $P=0.01$ for E1) and slightly higher dihydrotestosterone (DHT) with borderline significance ($P=0.06$). There were no significant differences in total testosterone (TT), androstenedione (ASD) and dehydroepiandrosterone sulphate (DHEAS). E1 positively correlated with BMI ($P=0.0067$), serum insulin ($P=0.0046$) as well as HOMA IR ($P=0.0125$) and negatively correlated with HDL-cholesterol ($P=0.009$). FAI was in positive correlation with total cholesterol ($P=0.0457$), TAG ($P=0.0001$), HOMA IR ($P=0.037$), serum insulin ($P=0.0428$) and glycemia ($P=0.0001$) and negatively correlated with HDL cholesterol ($P=0.029$). In multiple linear regression model E1 most significantly predicted HOMA IR, whereas FT predicted HDL-cholesterol and BMI.
Conculsion
We conclude that PCOS women with marked overweight or obesity have significantly worse cardiometabolic profile than those with lower BMI. They also have higher FT, FAI, E1 and slightly higher DHT. Among steroid hormones E1 and FT predicted cardiometabolic risk, whereas other sexual steroids were not in relationship to CVD risk.

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EP1128

Secondary amenorrhea after bone marrow transplantation and adjuvant chemotherapy misdiagnosed as disorder of sex development: a case report

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Introduction
Disorders of sex development (DSD) is a congenital condition in which the development of chromosomal, gonadal or genital sex is atypical. A female appearance patient with secondary amenorrhea and 46 XY karyotype seems to be solid evidences to diagnose Y-chromosome-related DSD diseases, while it is not necessarily the accurate diagnosis. We here report a case of a 16- year-old girl with secondary amenorrhea and 46 XY karyotype after bone marrow transplantation (BMT) and adjuvant chemotherapy misdiagnosed as DSD.
Case report
A 16-year-old lady who gets her first *period* at *age 13*, was referred with a 3 years history of secondary amenorrhoea. The patient presented female appearance. She had normal female genitalia and *she* was at *Tanner stage 3*. Her medical history included BMT and chemotherapy because of acute leukemia (AL) when she was 13 years old. So far there is no sign of AL recurrence. Laboratory examination showed a 46 XY karyotype, elevated follicle stimulating hormone and luteinizing hormone, low estrogen, and normal prolactin. Perineal and pelvic ultrasound scans showed developed uterus and vagina, and two small ovaries with no follicular activity. Furthermore, we found that she received BMT from her brother and adjuvant chemotherapy 3 years ago. Her karyotype changed from normal female to a karyotype of donor (her brother) origin after BMT. Adjuvant chemotherapy for AL may impair her ovarian function and finally bring about primary ovarian insufficiency.
Conclusion
The present case serves as a reminder that a correct diagnosis depends on the comprehensive collection of present and past medical history, complete physical examination, and careful evaluation of related adjuvant tests.

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EP1129

NCAH prevalance with novel CYP21A2 and CYP11B1 mutations in hirsut turkish women

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Introduction
Hirsutism affects 5–8% of the whole female population. In most patients, hirsutism is associated with hyperandrogenemia and the most common cause of androgen excess is polycystic ovary syndrome; however, the clinical presentation of non-classical congenital adrenal hyperplasia(NCAH) in females is often indistinguishable from other hyperandrogenic disorders because of common clinical signs with hirsutism and poly cystic ovary syndrome(PCOS).
Objective
The aim of the study is to evaluate the prevalence of NCAH in woman presenting with hirsutism and distinguish the underlying causes.
Subject and Method
122 women admitted to the Endocrinology Clinic at Erciyes University Hospital with hirsutism enrolled the study voluntarily between January 2013 and December 2014. All protein encoding exons and exon-intron boundaries of CYP21A2, CYP11B1, HSD3B2 and CYP21A2 promoter changes determined by direct gene sequencing from genomic DNA isolated from peripheral blood leukocytes.
Results
Detailed clinical, hormonal and DNA sequencing analyses of the volunteers have resulted in 91 (74.6%) PCOS, 12 (9.8%) IHA, 14 (11.4%) IH and 5 (4.1%) NCAH. All NCAH were steroid 21-hydroxylase deficient and there was neither 11B-hydroxylase nor 3-beta-hydroxysteroid dehydrogenase deficient NCAH. Sequencing analyses revealed 5 novel mutations; A89V (c.266 C>T), M187I (c.571 G>A) and G491S (c.1471 G>A) located on CYP21A2 and V188I (c.562 G>A) and G87A (c.260 G>C) located on CYP11B1 gene in homozygous and heterozygous states.
Conclusion
NCAH prevalence in Turkish woman with hirsutism found higher compare to similar studies. It might be because of not only doing sequencing analyses of CYP21A2 but also promoter region since 3 of them have promoter changes in addition to protein coding. However, the study confirmed that promoter region of the CYP21A2 should be sequenced as well for true genetic diagnosis and genetic counselling.

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EP1130

Effects of photoperiod on estrous cycle in the Mongolian gerbil (*Meriones unguiculatus*)

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Gerbil (*Meriones unguiculatus*) a non traditional laboratory model with reproductive state influenced by photoperiod, was used to analyze those photoperiodic mechanisms involving reproductive regulation. The 14:10 photoperiod has been widely used for reproductive research since 1950 (Everett). As is well known gerbils locomotor activity cycle has been reported to be crepuscular and reproductive cycle presents two annual peaks. As for the estrous cycle (EC), it has been analyzed mainly under a12hr:12hr light (L)dark(D) photoperiod, and reported as mostly irregular. In this research, female gerbils were exposed to 8:16, 12:12, 14:10 and 16:8 LD conditions. The EC were monitored by cytology via vaginal smears every four hours (ZT) for 3 consecutive cycles, where ZT2 was the first (ZT0 was the light onset). Under the 14:10 photoperiod, the EC was the most stable. Cycles lengthen in between to five and four days and stable phase duration. When the other photoperiods were analyzed the EC showed not only less stability (3–9 days) but also variability in the phase duration, i.e. diestrus increased its duration under 8:16 and12:12 LD, meanwhile at 16:8 photoperiod diestrus and estrus, showed a significant increase when compared with 14:10 LD. In a period of 15 days an average of 2 cycles on 16:8, 12:12 and 8:16 and 3 EC for 14:10 were presented. Proestrus and metaestrus did not show a significative variance under any condition. A shift in the time of the day when estrus phase become settled was reported; vaginal smear showed predominantly cornified cells under 12:12 and 14:10 LD at ZT6; for 6:8 LD ZT2, and under 8:16 photoperiod a shift to the dark phase was found starting at ZT22. As cytological examination of vaginal smears is a good indicator for endocrine condition of the female, the estradiol and progesterone level are being analyzed by ELISA.

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EP1131

The regulation of LHCGR-dependent signaling is linked to circadian gene expression

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Introduction
Reproduction exhibit a regular cyclicity and is regulated by complex interactions between circadian signals, gonadotropins and sex steroid hormones. Peripheral circadian rhythm is generated upon cyclic transcription of clock genes expressed in several cells, e.g. granulosa cells in the ovary. Here we investigated whether cyclic intracellular events occurring in response to gonadotropins are linked to expression of clock genes.
Methods
Primary human granulosa cells (hGLC), naturally expressing luteinizing hormone (LH)/chorionic gonadotropin (hCG) receptor (LHCGR), were maintained under continuous exposure to LH/hCG over 24 h, and the expression of clock genes (*PER1*, *PER2*, *ARNTL*, *CLOCK*), gonadotropin receptors (*LHCGR* and *LHCGR-exon 6A* variants, *FSHR*) and genes regulating steroidogenesis (*STARD1*, *CYP19A1*, etc.) was analysed by real-time PCR. Cyclicity of cAMP production, G proteins and β-arrestins and ERK1/2 phosphorylation were evaluated by ELISA, Western blotting and immunofluorescence.
Results
Treatments by gonadotropins de-synchronize *CLOCK* and *ARNTL* gene expression, as well as *LHCGR* mRNA isoforms, *STARD1* and *CYP19A1* gene expression (two-way Anova; $P<0.05$; $n=3$). Immunostainings revealed a 4–5 h-rhythmic, up- and down-regulation of Gαs protein and β-arrestin1/2, as well as G protein coupling/uncoupling to LHCGR upon gonadotropin treatment. 17 h-treatment is linked to rounded shape of the cells and intracytoplasmic vacuoles, LHCGR internalization and translocation of Gαs protein to cytoplasm. These gonadotropins-induced changes are accompanied by 3–5 h-oscillatory intracellular cAMP production over 24 h, in spite of LHCGR internalization.
Discussion
We found a link between circadian rhythm, LHCGR up-/down-regulation and interaction with Gαs protein and β-arrestin1/2, resulting in the modulation of cAMP-dependent signalling.
Conclusions
These data suggest that the kinetics of LHCGR activation and downstream events are influenced by circadian rhythm, which modulates the cell response to gonadotropins and secondary waves of cell signalling activation.

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EP1132

High dose metformin effect on weightloss, androgen levels and thyroid function in obese hypothyroid patients with PCOS

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Objective
to evaluate the effects of metformin use on weight loss, improvement of ovarian and thyroid function in obese women with polycystic ovarian syndrome.
Material and Methods
30 obese (BMI 30–34.99 kg/m^2) hypothyroid (TSH 6–10 mIU/ml) women of age 25–35 years old were included. The patients received appropriate levothyroxine treatment according to TSH levels and body weight. A number of 15 patients added metformin gradually increased from a starting dose of 500 mg/day to a final dose of 3000 mg/day over a period of 6 months. Baseline levels, 3 months and 6 months levels of TSH, fT4, T3, AMH, LH/FSH ratio, testosterone, along with BMI and ultrasound ovarian volume and antral follicle count were determined. No adverse events that might have led to discontinuation of the treatment were recorded. Mild nausea was registered in 8 patients after 2 weeks of treatment with 3000 mg/day of metformin, respectively softer stools (but no diarrhoea) in 5 patients in the first week of treatment (500 mg/day), but the symptoms relieved with disappearing within the mentioned time frame.
Results
BMI levels decreased significantly in the first 3 months in metformin group (32.5+/-1.65 kg/m^2 vs. 28.4+/− 1.95 kg/m^2). BMI variation in the non met-group was smaller. BMI levels have reached a plateau after 3 months of metformin treatment. TSH levels decreased (7.2+/− 1.6 mUI/ml vs. 4.8+/− 2.2 mUI/ml) significantly in the metformin group, compared to a smaller decrease in the non-metformin group (5.6+/−2.2). Significant decrease was registered for the LH/FSH ratio (5,10+/−0.9 vs. 2,1+/−0.45), AMH (9.80+/−1.6 vs. 7.9+/−1.2 ng/ml) and testosterone levels; antral follicle count and ovarian volume improved in met-group (in a similar fashion to the gross ultrasound appearance), while in non-met group, the 3 and 6 months values were similar to baseline.
Conclusion
Metformin treatment administered in high doses (3000 mg/day) on a 6 months period was useful for weight loss, improvement of ovarian function and decrease of androgen levels in obese PCOS patients with hypothyroidism. It also improved supplementary the thyroid function parameters. AMH can be used a prognostic marker for metformin response in PCOS obese patients with thyroid dysfunction, especially if (transvaginal) ultrasound scanning is not available.

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EP1133

Influence of thyroid stimulating hormone (TSH) level in in-vitro fertilization (IVF) success

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Introduction
Prevalence of hypothyroidism is 2–5% in women in the reprodutive age group. Hypothyroidism can affect fertility due to anovulatory cycles, luteal phase defects, hyperprolactinemia and sex hormones imbalance. Some data also report that TSH levels are inversely proportional to the fertilization rate at ART (assisted reproductive technologies).
Objective
To evaluate if a relationship exists between pregnancy rates in women undergoing *in vitro* fertilization (IVF) and their basal thyroid stimulating hormone (TSH) levels.
Study design
We performed a retrospective cohort study in which women with known TSH level who were submitted to IVF in our Hospital during 2014 and 2015 were included. They were divided in two groups, according to their initial TSH level: $>$ or $<$ 2.5 mU/l. Pregnancy was defined by ultrasound visualization of gestational sac.
Results
A total of 132 women met inclusion criteria. The mean age was 34.6 years old. 75.7% of women with TSH data had oligomenorrhea. Thyroid autoantibodies were requested only in 6 cases. 36.3% of the patients had a TSH $>$2.5 mU/l. In that group 39% of the women had pregnancy compared to 42.8% in the group with TSH $<$2.5 mU/l ($P=0.636$).
Conclusion
No statistically significant difference was observed between the two groups concerning pregnancy rates after IVF. We cannot exclude that it is the presence of thyroid autoantibodies and not the TSH value *per se* that is associated with lower pregnancy rates. Further studies are needed to confirm this hypothesis.

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EP1134

The efficiency of metformin in polycystic ovarian syndrome is not necessarily attributable to the improvement of insulin resistance

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Insulin resistance has a pivotal role in the pathogenesis of polycystic ovarian syndrome (PCOS), thus insulin sensitizer therapy is beneficial. Purpose. Our purpose was to study the effectiveness of metformin in PCOS women, including those without insulin resistance. Matherials and methods. This study was conducted on 24 pacients (12 obese or overweight and 12 lean women), aged 21–31 years, diagnosed and treated with PCOS at the Clinical Department of Endocrinology Targu-Mure, during January 2013-March 2015. All patients received metformin therapy, including those without insulin resistance.

Results
Menstrual cycle disturbances (anovulation, bradi-oligomenorrhoea) before metformin therapy appeared in 91.6% of the obese or overweight women, and 83.3% of the lean women (21 cases from the 24). In 15 cases insulin level, glycaemia were measured, and HOMA-IR calculated. Mean insulin level was 13.06 ± 14.53 mIU/l in the obese group, and 6.82 ± 1.92 mIU/l in the lean group, and the corresponding mean HOMA-IR was 4.23 ± 3.42 vs. 1.29 ± 0.43. Among the 21 women (11 obese and 10 lean) with menstrual disturbance before metformin therapy these disturbances improved or pregnancy occurred in 11 cases (5 obese and 6 lean) during metformin treatment alone, which means a significant improvement ($P = 0.0085$, RR = 3.16, 95% CI = 1.12–8.87). During metformin treatment alone, 14 women from the 24 presented normal menstrual cycle, normalized progesterone level or pregnancy occurrence ($P = 0.002$, RR = 3.83, 95% CI = 1.33–11.03). Conclusion. Metformin therapy might resolve menstrual cycle disturbances not only in insulin resistant obese PCOS women, but also in those with normal weight and/or without insulin resistance.

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EP1135

Serum Vitamin D status in women with the polycystic ovary syndrome

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Objective
To measure the levels of 25-hydroxyvitamin D (25(OH)D) and vitamin D binding protein (VDBP) and assess their relationships with metabolic features in patients with the polycystic ovary syndrome (PCOS).
Methods
267 women, aged 20–35 years (24.7 ± 4.9): 167 with PCOS, 100 healthy women as a control group were studied. Study groups were divided according to body mass index (BMI). Biochemical and hormonal parameters, 25(OH)D, VDBP were measured. Free and bioavailable 25(OH)D were calculated using the mathematical equations. The percentage of body fat and visceral fat deposit were assessed by DXA.
Results
In the normal weight control group total, free and bioavailable 25(OH)D were significantly ($P < 0.001$ for all) higher than in its overweight/obese counterpart. In women with PCOS both total 25(OH)D ($P < 0.001$), and VDBP ($P < 0.001$) were lower in the overweight/obese subgroups than in the normal weight one. VDPB was negatively correlated with fasting insulin, positively with SHBG in control group. In PCOS group, VDPB was negatively correlated with abdominal fat deposit, BMI, fasting glucose and insulin and positively with HDL and SHBG.
Conclusions
Despite lower total 25(OH)D in obese PCOS women, all women with PCOS (lean and obese) had comparable free and bioavailable 25(OH)D which might be a result of concomitantly lowered serum VDBP levels in obese PCOS women. VDBP might play important role in the regulation of availability of active fractions of 25(OH)D in PCOS women. VDBP is strongly associated with cardio–vascular risk factors such as BMI, waist circumference, visceral fat, fasting insulin in women with PCOS.

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EP1136

Abstract withdrawn.

EP1137

Oxidative status imbalance in patients with polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is one of the most frequently encountered endocrine pathologies in women of reproductive age, being regarded as a chronic systemic disease instead of the simple local one. It is frequently associated with insulin resistance, hyperandrogenemia and chronic inflammation. PCOS reunites multiple and diversified pathological combinations like: ovulatory functional disorders directly impacting on the reproductive system, carbohydrate and lipid metabolism disorders which can be explained at least partially through an increased oxidative stress. Oxidative stress occurs due to an imbalance between the generation of reactive oxygen species (ROS) and the antioxidant defense systems. In women, oxidative stress may be a major cause of infertility. In this clinical study, comprising 55 PCOS patients and age-matched healthy subjects, we aimed to assess the relationship among different metabolic risk factors, such as triglycerides, cholesterol and glycaemia, and the reactive oxygen species levels in patients diagnosed with polycystic ovary syndrome. For an accurate determination of the biochemical markers, diagnostic kits (Dialab, Austria) have been used, whereas for the determination of the reactive oxygen species (ROS) concentration, the chemiluminescent method was chosen. The triglycerides, glycaemia and cholesterol levels were significantly higher in the group of patients compared with the control group ($P < 0.05$), suggesting a considerable imbalance in patients with polycystic ovary. The serum concentration of the reactive oxygen species (ROS) represents a marker of the global oxidative stress. The experimental results obtained following the assessment of the ROS concentration revealed a significantly higher value in the patient group with polycystic ovary as compared to the control group, which translates into an enhanced oxidative stress in patients diagnosed with polycystic ovary syndrome. Correcting oxidative stress with antioxidants along with monitoring the antioxidant status could have a beneficial effect on oxidative stress induced insulin resistance and hyperandrogenism in the PCOS diagnosed women.

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EP1138

Utility of oral glucose tolerance test (OGTT) in patients with polycystic ovary syndrome (PCOS)

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Background
PCOS patients associate an increased risk of glucose metabolism abnormalities. Although Hb A1c was suggested as a good diagnostic test for prediabetes/diabetes, in PCOS patients its diagnostic value could be inferior to OGTT as previously suggested. Aim of the study was to evaluate which are the clinical and paraclinical parameters associated with impaired glucose tolerance (IGT) in order to identify the profile of the patients that will benefit from OGTT.
Material and methods
449 patients (mean age years, mean body mass index (BMI) kg/sqrm) diagnosed with PCOS based on Rotterdam criteria evaluated with OGTT were retrospectively selected from our PCOS database.
Results
From the 449 patients included in the study 23 (5.1%) had impaired fasting glycemic (IFG) and 28 (6.2%) IGT. Patients with prediabetes (IGT and IFG) were older, had higher BMI, waist circumference (WC), insulinemia (fasting and 2 h), HOMA-IR in comparison to patients with normal glucose. Patients with IFG were not different from those with IGT with respect to age, clinical and biochemical hyperandrogegism, adiposity, HOMA-IR, fasting insulinemia and metabolic parameters, except the 2 h insulinemia and serum FSH level which were higher and lower respectively in patients with IGT ($P < 0.05$).
Conclusion
Our patients with IGT and IFG were similar in terms of clinical and paraclinical baseline parameters, making impossible their identification without an OGTT.

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EP1139

Diagnostic performance of non-invasive markers for the presence of nonalcoholic fatty liver disease in premenopausal women with and without polycystic ovary syndrome

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Introduction
Several markers based on anthropometric and biochemical parameters like fatty liver index (FLI), lipid accumulation product (LAP) index and visceral adiposity index (VAI), have been proposed for the detection of nonalcoholic fatty liver disease (NAFLD).
Objective
To evaluate the diagnostic performance of FLI, LAP and VAI as markers of NAFLD in premenopausal women with and without polycystic ovary syndrome (PCOS), assessed for hepatic steatosis (HS) by ultrasonography.
Design
Prospective, cross-sectional study.
Patients and methods
Anthropometric measurements, biochemical testing and abdominal ultrasonography after excluding causes of secondary liver disease were performed in 145 premenopausal women with PCOS (Rotterdam criteria) and 145 BMI-matched healthy controls. The three markers VAI, FLI and LAP were calculated and their diagnostic performance for predicting HS was evaluated with receiver operating characteristic (ROC) analysis.
Results
HS by ultrasonography was detected in 132/290 (45.5%) women, while the prevalence of HS was increased in PCOS women compared to controls [78/145 (54%) και 54/145 (37%), $P=0.01$]. FLI, LAP and VAI values were higher in HS(+) compared to HS(−) women [68.7±26.7 vs 26.5±24.8, $P<0.001$, 61.1±39.3 vs 23.7±15.2, $P<0.001$ και 2.4±1.8 vs 1.2±0.6, $P<0.001$), respectively] as well as in PCOS women compared to controls. The area under the curve (AUROC) for FLI, LAP and VAI were 0.87±0.02, 0.84±0.02 and 0.77±0.03, respectively, in the whole group of women. When AUROCs of the three indices were calculated separately for PCOS women and controls, no statistical differences were observed.
Conclusions
FLI, LAP and VAI can detect NAFLD in premenopausal women with a similar diagnostic performance. The presence of PCOS has no effect on the diagnostic performance of these indices.

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EP1140

Complementary effect of Vitamin D supplementation and lifestyle modification on anthropometric and metabolic parameters in young polycystic ovary syndrome women with Vitamin D deficiency: a 3-month prospective interventional study

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Background
PCOS women usually have metabolic disturbances particularly insulin resistance. Previous studies suggest that vitamin D deficiency may contribute to the development of insulin resistance. Our aim is to study the effect of vitamin D supplementation on clinical and biochemical parameters in vitamin D deficient PCOS women.
Methods
At baseline, 50 PCOS women were enrolled (37 vitamin D deficiency and 13 vitamin D sufficiency). Thirty-seven PCOS women on LSM (low-calorie diet 1000–1200 kcal/d and aerobic exercise walking 3.2 km/d, 5 days/wk) received 60 000 IU cholecalciferol weekly for 8 weeks followed by once a month. Clinical, anthropometric and biochemical parameters were performed at baseline and after 12 weeks.
Results
Thirty PCOS women completed the study. 25(OH) D levels significantly increased from 7.55±4.10 at baseline to 34.16±4.14 ng/ml at 3 months. Following vitamin D supplementation for 3 months, significant improvement of BMI and metabolic parameters like FPG, 2 hr glucose, HOMA IR, HOMA B, TG levels and TC was observed in women who followed LSM. However, there was no change in serum testosterone.11/30 patients in the supplementation group who did not comply with LSM also showed significant decrease in FPG, 2 hr PG, and HOMA IR.
Conclusion
Vitamin D supplementation has beneficial effect on insulin resistance and metabolic parameters in vitamin D deficient PCOS women. Both vitamin D supplementation and LSM have complementary effects in improving BMI and HOMA indices, glucose and lipid metabolism in the setting of PCOS with vitamin D deficiency, suggesting a role of vitamin D in the management of PCOS.

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EP1141

Epigenetics of female hypogonadotropic hypogonadism: analysis of mRNA expression of engaged in IHH genes

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Hypogonadotropic hypogonadism is a syndrome which may be manifested clinically by low sex steroids because of low (or inappropriately normal) gonadotropins. To date, more than 30 genes were reported as possible reason for this condition, but genetic basis is still unknown for ∼60% of HH cases. Due to this fact we decided to analyze mRNA expression of several HH-related genes which can be found in leukocytes of peripheral blood: GNRHR and GNRH1 (which are necessary for adequate biological effect of GnRH); PROK2 and CHD7 (which are responsible for the migration of GnRH neurons), WDR11 and DUSP6 (which are involved in normal sexual development). A quantitative determination of mRNA expression of these genes were comlpeted in the fresh peripheral blood sample by PCR in real time.
Examined patients
Ten women with hypogonadotropic hypogonadism (age from 18 to 53 y.o.); 4 of them suffer from amenorrhea I and 6 – amenorrhea II. Reasons of amenorrhea II were: stress, excessive exercises, rapid body weight loss, past use of oral contraceptives. The control group: 19 healthy women; age from 19 to 37 y.o.; with regular ovalutory menstrual cycle, some of them have children.
Results
mRNA expression of examined genes differed from normal patterns in each case of hypogonadotropic hypogonadism. Changes in GNRHR, GNRH1 and DUSP6 mRNA expression were found in most of cases. However variations of mRNA expression were multidirectional in each case and there was no similarity among expression profiles of patients according to anamnestic factors; but some affinities were found among patients who suffer from primary amenorrhea. According to our preliminary results, in women with hypogonadotropic hypogonadism the functional activity damage of 'reproductive-responsible' genes could be found in each case. Probably mRNA expression measuring could be a perspective method for proving hypothalamo-pituitary level of reproductive disorders and may help to determine which genes should be tested for DNA impairment.

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EP1142

How far is possible to make a diagnosis of infertility

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Introduction
Chemotherapy may be an important cause of primary infertility, especially in girls submitted to this therapy at very young ages.

Clinical case
A 20-year-old female was diagnosed with *acute* lymphoblastic leukaemia at the age of 1. She was submitted to chemotherapy: intrathecal methotrexate and cyclophosphamide and i.v. doxorubicin, vincristine, mercaptopurine, asparaginase and bone marrow transplantation at the age of 2. She was referenced to Endocrine Rehabilitation Clinics at the age of 6.75 years-old. Her auxology evidenced: height 109.8 cm (p3-10); predicted adult stature: 155 cm (p10); and identical bone and chronological ages. In terms of puberty, her Tanner stages were A1P1B1. Blood analysis evidenced IGF1 of 344 ng/ml (p90) and normal thyroid and gonadal axes. At the age of 11, she remained pre-pubertal, with increased levels of FSH (76.3 mUI/ml) and LH (17.2 mUI/ml). Her bone age was 11 years. At this time, we started inducing puberty with oestradiol. After 2 years, Tanner stages were A4P4B3. Menarche was achieved at 13.41 years old. At the age of 18, she reached A5P5B5, after 7 years of estradiol + norgestrel. She withdrawal this therapy when she was 20 and scarce menses were observed. Blood tests evidenced FSH of 84.1 mUI/ml and LH of 26.7 mUI/ml and pelvic ultrasound was normal. At this age, given her desire to become pregnant, she underwent ovarian stimullation, which was unsuccessufull. However, 12 months later she became pregnant.
Discussion
This case reports the complex and not fully understood process of gonadal function after chemotherapy gonadotoxicity. We believe that the fortunate pregnancy result in our patient was probably due to previous gonadotrophins stimulation performed in a very young woman, which enabled the reactivation of the gonadic axis.

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EP1143

Physiological changes of adipokines and selected steroids during the menstrual cycle

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Context
The cyclical effects of hormones during the menstrual cycle (MC) are responsible for driving ovulation. The information about roles of adipokines within the scope of MC are not definite. Leptin plays a role in sexual function and regulating the onset of puberty. Thin girls often fail to ovulate or release an egg from an ovary during menstruation cycles. Leptin also acts on specific receptors in the hypothalamus to inhibit appetite. Levels of leptin are increased in women suffering from premenstrual syndrome. The aim of our study was to describe physiological changes of selected steroids and adipokines at healthy women during the MC.
Methods
Twenty-seven women with regular menstrual cycles were included in the study, and their hormonal spectrum and adipokines were measured in regular intervals starting from the first day of their MC.
Results
Classical changes in gonadotropins, estrogens and progesterone during the menstrual cycle are accompanied by less striking but significant changes in 17-hydroxyprogesterone and testosterone. No significant changes show dehydroepiandrosterone and its 7-oxygenated metabolites. Adipokines show a tendency to increase during ovulation, while ghrelin and resistin decrease. There is also a remarkable association of sex hormone-binding globulin on the day of the cycle.
Conclusion
Our results demonstrate that changes to adipokines dutiny the menstrual cycle are not substantial, but nonetheless can play a role in the changes of food intake described in the literature. Precise descriptions of physiological changes in healthy women are important in helping us understand the significance of the changes accompanying various pathological states.

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EP1144

Serum activities of dipeptidyl peptidase-4 and adenosine deaminase and parameters of oxidative stress in polycystic ovary syndrome: association with obesity

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Dipeptidyl peptidase 4 (DPP-4) is thought to play a role in the pathophysiology of metabolic and inflammatory diseases. Increased ADA activity has been suggested to induce insulin resistance and inflammation. We investigated DPP-4 and ADA activities, serum nitric oxide (NO) level and nitric oxide synthase (NOS) activity which are the oxidative stress parameters in patients with PCOS. Fifty two women with PCOS and 41 healthy women were included in this study. Serum ADA activity (0.33 (0.17–0.67) vs 0.26 (0.12–0.60) IU/l; $P=0.006$), NO level (24.5 (13.25–58) vs 12.25 (6–24.50) μmol/l; $P<0.001$) and NOS activity (5.46 (3.38–12.71) vs 4.54 (2.55–10.13) IU/ml; $P<0.001$) were significantly higher in PCOS group while there was no difference in serum DPP-4 activity (19.54 ± 7.01 and 18.24 ± 6.73 IU/l; $P=0.369$) between the groups. The groups were divided into subgroups as obese and nonobese. In obese PCOS group; ADA, NO and NOS were significantly higher than obese controls ($P=0.044$, $P<0.001$ and $P<0.001$), while there was no difference in DPP-4 activity ($P=0.356$) between the groups. In nonobese PCOS group; NO and NOS were significantly higher than nonobese controls ($P<0.001$ and $P=0.006$), while there were no differences in DPP-4 and ADA activity ($P=0.802$ and $P=0.128$). There was a negative correlation between ADA and DPP-4 activity in PCOS group ($P=0.047$). A positive correlation was observed between ADA and BMI in the whole group ($P=0.022$). In conclusion, we found that there was no significant change in serum DPP-4 activity in women with PCOS. However, we demonstrated increased serum ADA activity as well as its association with obesity in PCOS. Also, our finding that increased NO level and NOS activity in PCOS which is independent of obesity may result from a compensatory mechanism for the oxidative stress in PCOS.

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EP1145

Oocyte donation in women with Turner's syndrome: successful outcome can be achieved with a specialist multidisciplinary approach

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Introduction
Although oocyte donation (OD) is increasingly utilised in women with Turner's syndrome (TS) few data are available. Reported clinical pregnancy rates following OD range from 17 to 40%. Complications of 2% death from aortic dissection and severe hypertension are reported.
Aim
To analyse the OD-pregnancy success rate and materno-fetal outcomes in women followed in a TS-dedicated centre.
Methods
A retrospective study of 114 adult TS patients analysed cardiovascular risk factors, feto-maternal morbidity and mortality in women undergoing OD (1997–2015). Data were compared with spontaneous pregnancy (SP) 14/114 patients, mean age 24 years (Calanchini *et al*. 2016, for SP data comparison).
Results
Eleven patients underwent egg donation cycles (total 27) using fresh (16) or frozen (3) donated eggs or embryos frozen and stored from a previous egg donation cycles (8). Endometrial preparation achieved endometrial thickness ≥ 7.3 mm, mean 10.2 mm. 1 or 2 embryos were transferred between day 2 and 5. Mean recipient age at first IVF was 32.5 years (24–41) and at delivery 33.8 years (26–41). 3/11 were 45X, 3/11 were 45X/46XY and 5/11 other TS-karyotypes. Five had cardiovascular malformations (4 bicuspid aortic valve, 1 treated aortic

coarctation), four treated hypertension, and two pre-existing aortic dilatation. 12/27 (44%) cycles had positive pregnancy-tests and 5/27 (19%) resulted in live births. The cumulative live birth rate per patient undergoing treatment was therefore 5/11(46%). Increased aortic diameter occurred in 1/5, and gestational-diabetes 1/5. No patient developed gestational-hypertension compared with 7% SP. No cardiovascular or fetal complications were noted. One emergency caesarean section (37 + 1w, twin pregnancy).
Conclusions
OD showed a 19% live birth rate per cycle and 46% per patient in TS, was safe even in women with cardiac risk factors, and unassociated with increased feto-maternal complications compared with TS SP. This emphasises the importance of early discussion of assisted reproductive technology and alongside monitoring in a TS-dedicated multidisciplinary centre.

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EP1146

The features of young women reproductive health with type 1 diabetes

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Background
Leading position among endocrine pathology of adolescence and young women is type 1 diabetes (T1D), which in recent years had been proved to have a strong association with reproductive dysfunction among such patients. The purpose was to investigate the features of reproductive health in 120 young women (18–22 years old) with T1D.
Methods
Retrospectively we studied the features of puberty and prospectively examined level of blood glucose and HbA_{1c}, levels of gonadotropin (LH, FSH) and sex hormones (prolactine, estradiol, progesterone, testosterone) (ELISA, France) and determined antibodies to ovarian tissue (Euroimmune, Germany) in peripheral blood, held pelvic ultrasonography (MyLabSeven, Italy).
Results
The proportion of patients with delayed puberty and physical development of type 1 diabetes with the debut in the pre-puberty was in 62.5%, in the early puberty (3-7 years) – 15.0%, in the active adolescence (11–14 years) – 11.7% of post-puberty (over 14 years) – 10.8%. Ovarian failure occurred in 76.7% of the patients, and was expressed in the increased LH, estradiol and free testosterone levels. The positive correlation relationships were detected between blood levels of estradiol ($r=0.77$, $P<0.05$), testosterone ($r=0.56$, $P<0.05$) and level HbA_{1c}; negative correlation relationship were revealed between progesterone blood level ($r=0.67$, $P<0.05$) and level of HbA_{1c}. Fiction revealed correlations between the levels of sex hormones and the regime of insulin therapy. Autoimmune ovarian failure was detected in the 4.2% cases. The presence of ovarian insufficiency was accompanied by an increase in ovarian volume and number of antral follicles in them.
Conclusion
Type 1 diabetes adversely affect the formation of future reproductive health of girls, realized at hormonal dysfunction, ovarian failure and pathological changes in the structure of the ovaries.

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EP1147

The determinants of thyroid autoimmunity in patients with polycystic ovary syndrome

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It was suggested that polycystic ovary syndrome (PCOS) patients have an increased risk for autoimmune thyroid disease. However the mechanisms underlying this association are incompletely clarified. The aim of the present study is to evaluate the factors associated with thyroid autoimmunity in patients with PCOS. We performed a retrospective study which included 126 PCOS patients (mean age 24 ± 4.5 years, mean body mass index, BMI 27 ± 7.33 kg/sqm) diagnosed based on Rotterdam criteria between January 2015 and January 2016. We found that anti-thyroid peroxidase antibodies (ATPO) serum levels were positively correlated with HOMA-IR ($r=0.234$, $P=0.019$), fasting insulin ($r=0.218$, $P=0.025$), waist circumference (WC, $r=0.267$, $P=0.007$) and BMI ($r=0.203$, $P=0.04$). We found no association between ATPO and total testosterone, free androgen index, gonadotropins, TSH, leptin and adiponectin serum levels. In a multivariate linear regression model with ATPO as dependent variable only HOMA-IR was an independent predictor of ATPO values after adjustment for adiposity markers. In conclusion, in PCOS patients insulin resistance seems to be the main factor involved in thyroid autoimmunity.

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EP1148

Metformin treatment decreased free androgen index among PCOS women

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Hyperinsulinemia is one of biochemical features of polycystic ovary syndrome (PCOS). Metformin is a common drug used in PCOS. Recent studies have shown that metformin has impact on clinical and biochemical parameters in PCOS patients. The aim of our study was to assess retrospectively the influence of metformin on total testosterone, sex hormone binding globulin (SHBG) and free androgen index (FAI) in women with PCOS in polish cohort. A total of 54 patients with PCOS and irregular menses were examined. The duration of metformin treatment between the baseline and final blood results was about six months. There were statistically significant differences in the total testosterone (1.9 (1.4–2.6) vs 1.2 (0.6–2) ng/ml), SHBG (34.8 (27.2–53.1) vs 49.4 (35.9–81.7) nmol/l) levels and FAI (5.3 (3.2–9.8) vs 2.3 (1.3–4.3) before and after the metformin administration (all $P<0.0001$). In addition the patients were divided into two groups according to FAI. There was no difference in age (29 (26–32) vs 28 (25–31) years, $P=0.7$) and BMI (22.5 (19–24.1) vs (22 (20.7–28.1) kg/m^2, $P=0.35$) between group with FAI < 5 and group with FAI > 5, respectively. Our study showed that metformin therapy ameliorates the total testosterone and FAI both in women with FAI greater and lower 5 but improves SHBG levels only among patients with FAI > 5. The groups did not differ in difference between baseline and final testosterone and SHBG levels but differed in FAI change. Our study suggest that metformin effectiveness could differ between PCOS patients according to the phenotype.

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EP1149

Abstract withdrawn.

EP1150

Biochemical and clinical characteristics of polysystic ovarian syndrome (PCOS) in women with and without type 1 diabetes (TID)

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Abstract
PCOS prevalence is reported to be increased in reproductive-age women with type-1 diabetes (T1DM) but measurement of androgens, crucial for diagnosis, has been with inaccurate immunoassays. No studies have been reported using liquid-chromatography-mass-spectrometry (LCMS). Reproductive-age T1DM women attending a single centre were evaluated for PCOS (NIH criteria). Women with T1DM and PCOS (T1/PCOS) were compared to T1DM women without hyperandrogenism (T1/no HA), and to two groups of non-diabetic women with PCOS – one group BMI-matched (PCOS-lean) and the other overweight (PCOS-overweight). 16 (18%) of T1DM women had PCOS. TIDM women with PCOS compared to the overall group were younger (26.5 vs 29) and had a lower BMI (23.4 vs 25.3). Compared to T1/no HA, testosterone (1.3 vs 0.8 nM, $P=0.004$) and androstenedione (7.1 vs 4.6 nM, $P=0.0016$) were elevated but no differences in DHEA-OX, DHEAS, SHBG or free testosterone was noted. They had an older age of menarche (13 vs 12.5 years, $P=0.024$), and were more likely ($P=0.024$) to have a positive family history of PCOS. There were no differences in androgen levels between T1/PCOS and PCOS-lean women, but both of these groups demonstrated greater androstenedione levels (7.1 vs 5.5 nM, $P=0.0247$) than PCOS-overweight women. In summary, PCOS is common in T1DM. Women with T1/PCOS are leaner than T1 women without PCOS but are more likely to have a family history of PCOS. They have a similar biochemical phenotype to lean women with PCOS but differ from overweight women with PCOS. The mechanisms underlying PCOS in T1DM and its clinical significance are unknown.

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EP1151

A case of polycystic ovary syndrome (PCOS)

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Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women of reproductive age. It's a heterogeneous functional disorder of unclear etiology. The features of PCOS are disorders of ovulation, androgen excess, polycystic ovaries; it's associated with presence of associated risk factors for cardiovascular disease (obesity, glucose intolerance, dyslipidemia). The diagnosis of PCOS is made using the Rotterdam 2003 criteria. 23yo female patient was evaluated for oligomenorrhea. At the age of 17, she consulted for the first time her gynecologist because of irregluar menstrual cycles since the menarche (age 14) and excessive hair growth. A diagnosis of PCOS was made and oral contraceptives (OC) were introduced in therapy. After 1.5 yrs, OC were excluded because of undetectable levels of LH and FSH. Without them, the menstrual cycle length was 40–120 days. Examination revealed high BMI 25; normal BP; excessive hair on chin, forearms and lower abdomen; no striae, no acanthosis nigricans, normal thyroid. High levels of insulin, LH, total testosterone, androstendione and low levels of SHBG and progesterone in the luteal phase were found. An oral glucose tolerance test, fasting lipid profile and concentrations of TSH, prolactin, 17OHP were normal. A pelvic ultrasound confirmed polycystic ovaries. The clinical and lab. tests were consistent with PCOS. Therapy with life style changes (weight reduction) and metformin was started (500 mg bid). After 10 months of treatment, she lost 8 kg, menstrual cycles were regular (26–28 days), concentrations of LH, testosterone, progesterone and insulin were normal. The patients with PCOS are treated according to their symptoms, risks and desire for pregnancy. The OCs are the mainstay of pharmacologic therapy for women with PCOS for managing hyperandrogenism and menstrual dysfunction. The case has showed impact of the OC on the pituitary-ovarian suprresion. There are relatively few publications examining the effect of the OC on ovarian function in women and it's less clear whether the pituitary–ovarian suppression induced by the OCs has any impact on functional ovarian reserve, so we need further evaluation. Although, the use of metformin in the treatment of PCOS is off-label, in this case, metformin had showed as safe and effective. Benefit was made on oligomenorrhea, fertility and obesity.

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EP1152

Does radioactive ıodine therapy affect fertility?

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Introduction
Thyroid carcinoma is common in young women. Radioactive iodine (RAI) therapy has been confirmed as a useful treatment in the management of differentiated thyroid carcinoma (DTC). For women with DTC, the effect of RAI therapy on gonadal and reproductive function is an important consideration. We aimed to evaluate effects of RAI therapy on ovarian function.
Method
Women younger than 40 years old and diagnosed with thyroid cancer that required RAI treatment were enrolled in this study.Patients with ovarian insufficiency were excluded. *Early follicular phase* serum follicle stimulating hormone (FSH) and anti-müllerian hormone (AMH) levels were measured before and 3–6 months after RAI therapy. Friedman test is used to detect changes in FSH and AMH levels by RAI therapy with time.
Results
Eighteen patients with a mean age of 31.9 ± 4.9 years were enrolled in this study. Median AMH levels were 4.2 (2.96–17.42) ng/ml, 2.21 (0.84–3.69) ng/ml, 2.08 (0.86–6.12) ng/ml before and 3–6 months after RAI therapy, respectively. Median FSH levels were 5.5 (3.78–15.5) mIU/ml, 5.32 (4.19–35.36) mIU/ml, 6.07 (4.24–13.69) mIU/ml before and 3–6 months after RAI therapy, respectively. AMH levels before RAI were higher than after RAI ($P=0.021$).AMH levels after RAI at 3 and 6 months were not different. FSH levels were similar before and after RAI.
Conclusion
Anti-müllerian hormone (AMH) is considered an important marker of ovarian reserve. Ovarian reserve decreases in first 6 months after RAI therapy. Further large prospective studies are necessary to determine its predictive interest for post-treatment residual fertility.

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EP1153

Androgen profiling by liquid chromatography-mass spectrometry (LC-MS) in reproductive-age women with and without diabetes

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Abstract
The prevalence of hyperandrogenism has been reported to be increased in reproductive-age women with type-1 diabetes (T1DM). This observation however is based on findings using inaccurate immunoassays. No studies have been reported in diabetes using liquid-chromatography-mass-spectrometry (LCMS). We compared LCMS-measured androgens in T1DM-women with age-/ BMI-matched normal women, and compared findings with those in women with type-2 diabetes (T2DM) also compared to a matched control group (Table Below). Compared to non-diabetic women, androstenedione and SHBG were greater in T1DM while estimated free-testosterone was lower. In contrast, compared to non-diabetic women, androstenedione, DHEA-OX and SHBG levels were lower in T2DM while free-testosterone and DHEAS were greater. Total testosterone did not differ between groups in either comparison. T1DM and T2DM are associated with differing effects on androgen levels. These differences are likely to reflect differences in insulin sensitivity and differing effects of exogenous insulin administration. Their clinical significance requires further investigation.
Mean (± SEM); *P*-value vs matched non-diabetic.
Median (range); *P*-value vs matched non-diabetic.

	TID (*N*=63; median age =32; median BMI=25.5)	Non-diabetic (*N*=42; median age =34.5; median BMI=27.4)	T2D TID (*N*=32; median age =38; median BMI=36)	Non-diabetic (*N*=55; median age =34; median BMI=35.1)
Androsten-dione (nM)	5.1 (1.4–13.1) *P*=0.0005	3.6 (0.0–16.9)	2.5 (0.0–14.1) *P*=0.0035	3.8 (0.4–15.5)
DHEA-OX (nM)	10.1 (2.0–44.0)	12.0 (1.3–43.7)	5.7 (0.0–15.3) *P* <0.0001	13.5 (1.1–51.0)
DHEAS (uM)	5 (1.3–14.3)	5.0 (1.1–14.7)	6.0 (2.2–13.9) *P*=0.0045	4.3 (1.3–13.1)
FT (%)	1.1 (± SEM 0.05) *P*=0.0015	1.4 (± SEM 0.07)	2.0 (± SEM 0.11) *P*=0.0005	1.6 (± SEM 0.056)

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EP1154

Anti-mullerian hormone a marker for metformin therapy efficacy in PCO: a pilot study on Egyptian population

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Background
Polycystic ovarian syndrome (PCO) is the most common endocrinopathy in adult women, and is emerging as a common cause of menstrual disturbance in the adolescent population. Insulin resistance, which is considered one of its underlying causes, has increased substantially in the past decade, putting more adolescent girls at risk for PCOS and its complications. *Anti – Mullerian hormone (AMH)* is secreted by the granulose cells of ovarian follicles and correlated with count of small antral follicles and it is expressed throughout folliculogenesis.
Objective
Evaluation of AMH in Egyptian women with PCOS and if it might serve as a prognostic marker for treatment efficacy with metformin.
Patients and methods
The study included 30 women with PCOS (group 1) and 30 healthy women without PCOS (group 2). AMH is measured in both groups and before and after treatment with metformin (2550 mg) for 3 months in group I.
Results
AMH levels was higher in PCO groups before (3.54±0.58 ng/ml) and after treatment (2.79±0.39 ng/ml) than the control group (2.14±0.49 ng/ml) with $P<0.01$. In PCO group, it was higher before (3.54±0.58 ng/ml) than after treatment (2.79±0.39 ng/ml), with $P<0.01$.
Conclusion
AMH is higher in PCO subjects and its levels decreases significantly with the insulin sensitizer metformin and it can be used as a marker for treatment efficacy with metformin.
Keywords: PCO, Anti-Mullerian hormone (AMH), Metformin.
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EP1155

Influence of BMI in response to ovarian stimulation and live birth in IVF

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Introduction
The deleterious effects of obesity on spontaneous reproduction are well recognized, although the literature on obesity and assisted reproductive technology outcome remains heterogeneous and inconsistent.
Objective
To estimate the effect of BMI on ovarian stimulation response and live birth in women underwent *in vitro* fertilization (IVF).
Methods
Retrospective observational study that included women submitted to a first IVF cycle in an infertility center of a public hospital in 2015.
Results
We included 102 women with a mean age of 33.2 years (±3.7). 69 (67.6%) were in normal weight range, 22 (21.6%) were overweight and 11 (10.8%) were obese. The mean values of basal serum FSH and LH were 6.6 mIU/ml (±2.7) and 5.9 mIU/ml (±3.8) respectively. The antral follicles count (AFC) on day 2–3 of the cycle was on average 14.2 (±6.9). 46 (45.1%) women underwent IVF cycle and 56 (54.9%) underwent IVF with intracytoplasmic sperm injection. The average duration of stimulation and dose of FSH administered was 9.8 days (±2.3) and 1622.1UI (±647.7) respectively. There were no statistically significant differences in the 3 groups of BMI in relation to the women's age, FSH levels, AFC and neither in relation to the number of oocytes obtained. In our sample, age and AFC were the factors that correlated with the number of oocytes ($P<0.001$). Obese women had significantly fewer live births than overweight women ($P=0.027$) and this last BMI group (average BMI 26±0.9) had more live births. There were no differences in embryo quality or number of embryos frozen in these three groups.
Conclusions
Increased age and decreased AFC are negative determinants in the number of oocytes obtained. Although BMI groups had no difference in the number or quality in the oocytes collected, obese women had a significant lower probability of having a live birth after IVF.

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EP1156

Anti-Mullerian hormone level is independently affected only by the ovarian factor among clinical and endocrinological factors in polycystic ovary syndrome

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Polycystic ovary syndrome (PCOS) is an endocrine disorder that affects 6–10% of women. We evaluated the correlations between the serum AMH level and various endocrine and metabolic features in PCOS. Serum AMH level was compared between 114 PCOS patient (PCOS group) and 95 normal menstrual cycle women (Control group). Correlations between serum AMH level and various endocrine

and metabolic factors were analysed in PCOS group. The serum AMH level was significantly higher in the PCOS group (8.35 ± 8.19 ng/ml) than in the Control group (4.99 ± 3.23 ng/ml). The serum AMH level was independently affected by age and the presence of PCOS on multiple regression analysis. Ovarian volume per ovary (OPVO) showed the strongest positive correlation ($r = 0.62$) with the serum AMH level among clinical factors. OPVO was the only independent factor that affected the serum AMH in PCOS on multiple regression analysis. Serum AMH level is determined only by ovarian morphological factor and the other pathophysiological factors such as androgen, severity of anovulation and insulin resistance are not determinant factors in PCOS even if significant relationship exists.

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Male Reproduction

EP1157

Analysing by decade, testosterone undecanoat depot injectable does not increases prostate volume. Study during up to 9 years on hypogonadic patients. (December 2016)

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Aim
Re-analyzing (study starting in 2007) the effect of injectable testosterone undecanoat depot (TUD) in hypogonadic patients.
Materials and Methods
A. Patients: at onset 231 men with hypogonadism (median: 62 y). B. Distribution: by decade (starting with 20y); no = 4, 14, 24, 61, 63, 49, 17, 1. C. TUD (Nebido^R-Bayer) 1000 mg injected one/3 months i.m. D. Prostate volume (PV) appreciated by per-abdominal ultrasound: 3.5–5 MHz probe, elliptical/3D (cm^3). E. 12 patients were opperated before starting testosteron, 2 patients were opperated during treatment. F. Analysis Time: before starting testosterone (T0), after 1/2 month (T1 = 231), 3m (T2 = 182), 6m (T3 = 149), 1y (T4 = 123), 2y (T5 = 90), 3y (T6 = 62), 4y (T7 = 48), 5y (T8 = 40), 6y (T9 = 33), 7y (T10 = 22), 8y (T11 = 11), 9y (T12 = 4). G. Maximum increment from T0 noted **Δ** M %. Average increment noted **Δ** A %. H. Statistical analysis: Student test.
Results
I. All average prostatic volume for decade – tabulated (see pdf). Maximum increment (**Δ** M %) per decade, including the moment (**Δ** M % at) and average increment (**Δ** A %) – tabulated (see pdf). II. PV at T0 increases with age, from minimum 15.38 (19–29y) to maximum 45.5 (80–89y), $P = 0.0007$. III. Considering all observations, TUD did not increase PV significantly; in fact the average of increment in all patients was negative = −22.38%. **Δ** M % per decade: 45.95; 31.82; 56.41; 55.77; 45.45; 64.41; 42.11; 20 IV. Inside a specific decade *no significant increased in PV* was registered: all $P > 0.05$; exception: 80–89 decade, $P = 0.002$, from 3 to 5 y. V. In some patients, especially from 40-79 years, TUD could decrease slightly prostatic volume.
Conclusions
Considering the risk for prostate (in elderly), testosterone undecanoat 1000 mg depot injectable is a safe treatment, even after 9 years of administration. Precautions should be accorded to men over 80 y old, after the 2nd year administration.

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EP1158

After 9 years observation, testosterone undecanoat 1000 mg at 3 months did not increased Prostatic Specific Antigen level (December 2016)

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Aim
Has testosterone undecanoat 1000 mg injection (Nebido^R; Bayer), 1/3month negative effect on prostate?
Material and method
i) PSA (ng/ml) was registred retrospective (from files) and prospective analysis (onset 2010). ii) Patients: PSA analysis was done before treatment and recorded at T1 to T12 [2 weeks to 9 years] (see Pisoschi, this Congress). iii) Statistical analysis: Student test, simple correlation, multiple regression.
Results
A. Patients at onset: 160 men, 18–96 years, average: 60.38; median: 60; no prostatic cancer. B. Prostatic volume (cmc): average: 34.81. C. Average PSA (no patients): before treatment = 1.60 (160); 1y = 1.69 (110); 2y = 1.4 (83); 3y = 1.85 (57); 4y = 2 (46); 5y = 1.86 (34); 6y = 1.51 (30); 7y = 2.86 (2); 8y = 1.99 (11); 9y = 1.90 (4). D. Statistical difference of increasing average: nonsignificant for all times from 2 weeks to 9 years. E. Correlation between age and PSA was 1. significant at: T0: $r = 0.29$; 1y: $r = 0.35$; 2y $r = 0.28$. 2. nonsignificant for 3 to 9 years ($r = 0.14$–0.73). F. Correlation between PSA and prostatic volume was *significant*, both before and after treatment (depending on group size). G. Observations: 7 patients died; 1 during treatment, Klinefelter, 41 y, cerebral tumor; remaining 6 after 2 years stoping tretament, 60& 83–91 y, most cardiac stop. H. Multiple regression test shows p values $\ll 0.001$ for all years (examples): 1y: $R^2 = 0.58$, $F = 50.24 \rightarrow$ 9y: $R^2 = 1$, $F = > 1000$.
Conclusions
i) Testosterone undecanoat 1000 mg injectable i.m. at 3 months did not increased PSA level after up to 9 years administrations. ii) PSA level post testosterone does not depend on testosterone administration but on age, prostatic volume, before and after treatment, and initial PSA level, i.e. before testosterone administration.

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EP1159

Induction of male puberty in patients with hypogonadism hypogonadotrope with subcutaneous gonadotropin

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Objective
The most used therapeutic guidelines for the induction of male puberty in hypogonadotropic hypogonadism (HH) are GnRH in subcutaneous pulsatile infusion and HCG in monotherapy or combined with FSH in intramuscular injection. The objective of this study was to evaluate the efficacy of subcutaneous HCG with or without FSH in induction of male puberty in patients with HH.
Patients and methods
Descriptive study of patients with HH treated with HCG subcutaneously (s.c.) with or without FSH, for induction of male puberty (2004–2015). The Treatment was initiated with HCG 500 UI/72h s.c., periodic monitoring of testosterone, testicular volume and semen analysis was realized, adjusting doses up to 2500 UI/72h. If no answer obtained after one year, combined treatment with FSH s.c. was started.
Analyzed data
Cause of HH, age, testosterone levels, testicular volume, semen, dose of HCG and FSH treatment. Pubertal development assessed by testosterone levels, testicular volume and normalization of spermatogenesis.
Results
Nine patients. 17.2 ± 1.8 years old (15–20). Cause of HH: four Idiopathics, four craniopharyngiomas and one adenohypophysis hypoplasia. Dose of HCG: 1666 ± 821.6U/72 h. Two patients required combined treatment with FSH. Treatment period: 32.2 ± 9.5 months. Testosterone levels were normalized in 100% of cases (7.34 ± 5.1 ng/ml). 95% increased testicular volume: 13.5 ± 4.4 ml (10–20). The spermiogram was performed in 80% of cases at the end of treatment, with oligospermia in all cases. No presence of side effects.
Conclusions
Subcutaneous gonadotropin therapy is effective in induction of male puberty in HH. Treatment with subcuataneous HCG alone is successful. No presence of side effects.

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EP1160

Semen quality in young, healthy men is not related to serum concentration of vitamin D (AndroLS)

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Introduction
Relationships between vitamin D and male fertility are not fully elucidated. Studies in infertile/subfertile subjects suggest that vitamin D status may be associated with semen parameters (1, 2). Data from healthy men is inconclusive (3, 4). Our purpose was to evaluate the andrological status and a range of biochemical, dietary and lifestyle variables in healthy men aged 18–35, living in the region of Lower Silesia (Poland) (AndroLS).
Material and methods
We invited 5000 subjects to participate in the study. From among 500 respondents, we acquired necessary material (semen and blood) from 177 men. The specimens were collected in autumn and winter. The semen samples were evaluated according to WHO 2010 criteria by a single experienced medical analyst.
Results
Only minority of the studied subjects (18%) had serum $25(OH)_2D_3$ concentration above the lower limit (20 ng/ml). 39% had severe vitamin D deficiency (<10 ng/ml). Mean (±S.D.) $25(OH)_2D_3$ was 13.7±8.9 ng/ml. Mean (±S.D.) semen volume in the volunteers was: 3.1±1.5 ml, sperm concentration: 60±44×10^6/ml, total sperm count: 170±137×10^6/ejaculate, percent of normal forms: 14.7±6.5%. None of the studied semen parameters correlated with serum concentration of $25(OH)_2D_3$. We did not observe any correlations after adjustments for: alcohol consumption, cigarette smoking, carrying a mobile phone in pants' pockets, body mass index, caffeine consumption and physical activity, either.
Conclusions
Our data suggest that serum concentration of $25(OH)_2D_3$ cannot indicate semen quality in healthy men.

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EP1161

Semen quality in patients with newly diagnosed lymphoma's

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Objective
To analyse the semen quality in patients with newly diagnosed lymphoma's before starting the treatment.
Materials and methods
We evaluated semen quality in 131 patient with lymphoma who underwent sperm banking in our clinic over a 14-year period. 102 patients had Hodgkin's lymphoma, and 29 had non-Hodgkin's lymphoma. Semen samples were collected by masturbation after 2–7 days of sexual abstinence. Age at banking, semen volume, sperm concentration, and total and progressive sperm motility were recorded. Semen parameters were compared to established World Health Organisation (WHO) reference values (WHO Laboratory Manual for the Examination and Processing of Human Semen, Fifth Edition, 2010).
Results
The median age of these patients was 26 years (range 17–43); median semen volume was 2.0 ml (range 0.1–6.5); median sperm concentration was 63.8×106 per ml (range 0–413); median total and progressive sperm motility were 40% (range 0–84) and 24% (range 0–69), respectively. According to the reference values of the WHO 34 patients (26%) in this series had a semen quality within the normal range, and 97 patients (74%) had abnormal semen quality. In 2 patients (1.5%) the semen samples were not frozen because of azoospermia (no spermatozoa in the ejaculate). 69 patients (52.7%) had single damages (oligozoospermia or asthenozoospermia) and 26 patients (19.8%) had combined damages (oligoasthenozoospermia).
Conclusion
Patients with lymphoma have an increased risk for poor semen quality before any treatment. 74% of these men in our study had abnormal semen parameters according to the WHO. Generally, all patients with newly diagnosed lymphoma's need counselling about their reproductive function and semen cryopreservation should be offered before undergoing gonadotoxic treatment.

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EP1162

Abstract withdrawn.

EP1163

Gonadal profile in men with early-onset androgenetic alopecia: does a male PCOS-equivalent syndrome exist?

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Importance
Early-onset androgenetic alopecia (AGA) has been suggested as a phenotypic sign of the male polycystic ovary syndrome (PCOS)-equivalent since men with this feature have a PCOS-like hormonal pattern. No study has evaluated the gonadal function of these men.
Objective
To study the gonadal function of men with early-onset AGA and to identify suggestive criteria of male PCOS-equivalent.
Design
This case-control study was conducted from January 2014 to June 2016.
Setting
The study was carried out on patients referring to hospital for andrological check-up.
Participants
Forty-four men with early-onset AGA (19–30 years) and 37 aged-matched healthy men (controls) were enrolled. A subgroup of patients was assumed to have the male PCOS-equivalent (sAGA) when at least one of the following parameter was present: BMI >25 kg/m^2, insulin-resistance (IR) (HOMA index >2.5), SHBG <25 nmol/l. The remaining patients were considered to have AGA alone (aAGA).
Main outcome(s) and measure(s)
The primary outcome was to evaluate the gonadal function and the metabolic/hormonal features of men with early-onset AGA. The secondary outcome was to identify which parameters may be used to suspect the male PCOS-equivalent syndrome among men with early-onset AGA.
Results
Patients had higher mean (±S.D.) BMI (25.5±3.8 vs 23.7±3.0 kg/m^2; $P<0.05$) and 17αOH-progesterone (2.05±0.90 vs 1.51±0.62 ng/ml; $P<0.05$) compared to controls. sAGA had higher levels of insulin (11.8±1.7 vs 6.0±0.4 μU/ml; $P<0.01$) and LH (4.9±2.1 vs 3.8±1.4 mIU/ml; $P<0.05$), lower total testosterone (TT) levels (5.2±1.7 vs 6.3±1.6 ng/ml; $P<0.05$) and left testicular volume (TV) (12.3±2.8 vs 15.4±4.1 ml; $P<0.05$) compared to aAGA. sAGA also had higher fat-mass percentage (17.6±4.1 vs 13.2±5.3%; $P<0.05$), DHEAS (323.3±112.6 vs 257.8±107.1 μg/dl; $P<0.05$) and seminal fluid volume (4.2±2.8 vs 2.8±1.3 ml; $P<0.05$), lower TT (5.16±1.70 vs 6.47±4.30 ng/ml; $P=0.016$) and left TV (12.3±2.8 vs 15.0±4.3 ml; $P<0.05$) compared to controls.

Conclusion and relevance
Men with early-onset AGA and at least one among the following parameters BMI >25 kg/m^2, IR, SHBG <25 nmol/l had a borderline-low left TV and a impaired gonadal steroidogenesis. Hence, they might have a greater risk to develop a gonadal dysfunction later in life. These criteria may be used to suspect the male PCOS-equivalent.

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EP1164

Improved conception of the normative values of testosterone in men with type 2 diabetes

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Background
Men with type 2 diabetes mellitus (T2DM) have significantly lower levels of testosterone (T) than nondiabetic controls. But androgen deficit symptoms may be detected in males with normal T levels.
Aim
To analyze parameters of lipid, carbohydrate metabolism and endothelial function in diabetic males with low normal and middle-to-high normative T levels.
Patients and methods
We examined 86 men with T2DM and serum T levels higher than 12.1 nmol/l. Parameters of total T, lipid metabolism, HbA1c, biochemical markers of endothelial function – NO, endothelial NO synthase type 3 (NOS3) were analyzed. The patients were divided into two groups: 1–23 men with T levels 12.1–14.9 nmol/l, 2–63 patients with T levels $\geqq 15.0$ nmol/l. Statistic analysis was performed using Mann-Whitney U-test and Spearmen rank correlation method.
Results
The HbA1c value was 8.7% (6.7; 9.8) in 1st group and 7.7% (6.4; 9.2) in 2nd group ($P>0.39$), but the proportion of patients with HbA1c level $>7\%$ was higher in group 1 (71% vs 58.6%) as compared to group 2 ($P=0.002$). In patients with T levels lower than 15.0 nmol/l, higher levels of serum cholesterol (38.1% vs 27.6%), triglycerides (40.0% vs 24.1%) and low density lipoproteins (26.3% vs 17.2%) as compared to the 2nd group were found ($P<0.01$). There was a significant correlation in the T concentrations with NOS3 levels $|r|=0.350$ in 1st and $|r|=0.266$, ($P<0.05$) in 2nd group. Vascular endothelial dysfunction as assessed by ultrasonographic measurement of the dilatation of the brachial artery was more frequent in patients of group 1 compared to group 2 (55.6% vs 23.8%, $P=0.02$).
Conclusion
Males with T2DM and low-normal T level are at higher risks of dyslipidemia, endothelial dysfunction and progression of T2DM as compared to men with serum T higher than >15 nmol/l.
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EP1165

Endothelial dysfunction, inflammation and insulin resistance in patients with Klinefelter Syndrome

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Introduction
The prevalence of cardiometabolic disorders such as type 2 diabetes mellitus, dysipidemia and metabolic syndrome is increased in patients with Klinefelter syndrome (KS). The mechanism by which cardiometabolic risk increases in patients with KS remains to be completely elucidated. We investigated the presence of inflammation, insulin resistance and endothelial dysfunction in an unconfounded population of KS.
Methods
A total of 31 patients with KS (mean age 21.59 ± 1.66 years) and 33 healthy control subjects (mean age: 22.15 ± 1.03 years) were enrolled. The demographic parameters, Asymmetric dimethylarginine (ADMA), high sensitive C reactive protein (hs-CRP) and homeostatic model assessment of insulin resistance (HOMA-IR) levels were measured in patients and controls.
Results
The patients had higher insulin, HOMA-IR and ADMA levels ($P<0.001$ for all) and lower HDL-C ($P=0.002$) and total testosterone ($P<0.001$) levels, compared to the healthy controls. There were significant negative correlations between the total testosterone levels and ADMA ($r=-0.479$, $P<0,001$), hsCRP ($r=-0.291$, $P=0.034$), and significant positive correlation with HDL-C ($r=0.429$, $P=0.001$) levels. The multivariate analysis has shown that total testosterone ($\beta=-0.412$, $P=0.001$) and TG ($\beta=0.332$, $P=0.009$) levels were the significant independent determinants of the plasma ADMA levels.
Conclusion
The results of the present study show that endothelial dysfunction and insulin resistance are prevalent even in the very young subjects with KS, who have no metabolic or cardiac problems at present.

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EP1166

Testosterone is poorly related to erectile dysfunction in young/middle aged human immunodeficiency virus-infected men

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Background
human immunodeficiency virus (HIV)-infection is strongly associated to erectile dysfunction (ED) in men. Preliminary data suggests that ED is poorly associated with serum T in HIV+ men.
Aim
To investigate in HIV-infected men the relationship between sexual function as assessed by the validated International Index of Erectile Function (IIEF-15) and T deficiency using Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS).
Methodology
Prospective, cross-sectional, observational study on HIV-infected male patients with ongoing Highly Active Antiretroviral Therapy (HAART), attending the Clinic of Infectious Diseases. IIEF-15 and IIEF-5 questionnaires were used to define ED, while LC-MS/MS was used for hormonal assays.
Results
233 consecutive HIV-infected patients were enrolled (mean age 45.29 ± 5.33 years). Eight patients (3.4%) had total T <300 ng/dl, while 142 patients (61.5%) had ED (score ≤ 25). Age, hormonal data and duration of HIV-infection and HAART did not differ among groups of patients according to the degree of ED. The direct comparison of each ED cluster showed that months of infection were significantly higher in men with severe ED compared to mild ED ($P=0.037$). The erectile function domain at IIEF-15 was directly correlated with IIEF-5 score (0.778, $P<0.001$), as expected. Moreover, the IIEF-15 score was inversely related to months of infection (-0.147, $P=0.026$), but not to months of HAART therapy (-0.121, $P=0.071$).
Conclusions
To the best of our knowledge, this is the first, properly-designed prospective study aiming to investigate the relationship between erectile function and serum T, assessed by LC-MS/MS in HIV-infected men. In our cohort, i) IIEF-5 is reliable as IIEF-15 for ED diagnosis, ii) ED is not associated with serum T, iii) erectile

function is not influenced by T and HAART, but only by HIV-infection duration. In conclusion, several specific factors, such as the duration of HIV infection, are involved in erectile function in HIV-infected men and should be carefully considered in this setting, while hormonal status seems to be less important.

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EP1167

Early arterial stiffness and chronic inflammation in male equivalents of polycystic ovary syndrome

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Introduction
There is some evidence that a rise in the androgen hormone levels increases the risk for the development of a cardiovascular disease, obtained from the studies conducted on women with polycystic ovary and on men with androgenic alopecia. Inflammatory substances tend to increase in polycystic ovary syndrome and in androgenic alopecia. On this basis, we conducted a study that aimed to evaluate the early cardiovascular and metabolic effects in male patients with androgenic alopecia.
Methods
A total of 81 people, of whom 41 were patients with androgenic alopecia and 40 were healthy controls, were included in the study. Aged from 25 to 45, none of them had any cardiovascular risk factors, malignancy, any active infections and any liver or kidney diseases. Ambulatory blood pressure was measured for 24 h and sensitive CRP and galectin-3 were studied so as to assess the cardiovascular and metabolic risk.
Results
There were no differences between the patient and control groups in terms of ambulatory blood pressure of 24 h, sensitive CRP and galectin-3. A positive correlation was found in the patient group between sensitive CRP and waist and neck circumferences. While there was a positive correlation in the patient group between galektin-3 and HOMA-IR, waist and neck circumferences, a negative correlation was seen with free testosterone. Alopecia level correlated positively with daytime pulse wave velocity and night time reflection magnitude.
Conclusion
We did not find any difference in our study in terms of arterial stiffness and chronic inflammation in the early period when the control and androgenic alopecia groups were compared; however, a positive correlation between alopecia level and daytime pulse wave velocity and night time reflection magnitude may be considered as an early signal for atherosclerosis.

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EP1168

Abstract withdrawn.

EP1169

Can salivary testosterone be used in the monitoring of men using transdermal testosterone replacement therapy?

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In community-dwelling men, salivary testosterone (Sal-T) concentrations are thought to represent tissue hormone levels and correlate strongly with serum free-T levels. Measurement of salivary glucocorticoid concentrations is a non-invasive and objective means of assessing cortisol exposure in users and non-users of hydrocortisone therapy. We assessed relationships of Sal-T with transdermal testosterone replacement therapy (TD-TRT) and with markers of testosterone exposure. In 40 men aged 50.7 ($\pm$13.9) years who were attending a university hospital endocrinology clinic, we measured serum and salivary androgen concentrations by immunoassay and liquid chromatography tandem mass spectrophotometry (LC-MS/MS) respectively. In our unit, TD-TRT (Tostran 2% Gel at an initial dose of 30–60 mg of testosterone once daily) is offered to men with sexual symptoms and low fasting serum testosterone (Ser-T) concentrations on at least two consecutive occasions. Ser-T concentrations did not differ between users ($n=23$) and non-users ($n=17$) of TD-TRT (16.6$\pm$10.2 vs 11.4$\pm$4.4 nmol/l, $P=0.131$). Sal-T concentrations, however, differed greatly (17.14$\pm$15.25 vs 0.23$\pm$0.15 nmol/l, $P<0.001$) as did salivary androstenedione (Sal-A4) concentrations (2.57$\pm$4.50 vs 0.17$\pm$0.04 nmol/l, $P<.001$) and Sal-T/Sal-A4 (16.26$\pm$14.25 vs 1.45$\pm$0.94, $P<0.001$). Haematocrit and serum prostate specific antigen concentrations (PSA) did not differ significantly between the two groups (0.44$\pm$0.05 vs 0.43$\pm$0.05 l/l, $P=0.563$ and 1.06$\pm$0.66 vs 0.79$\pm$0.53 ng/ml, $P=0.170$ respectively). With TD-TRT, there was a rise in blood testosterone (4.7$\pm$4.2 to 7.9$\pm$5.7 nmol/l, $P=0.162$), haematocrit (0.42$\pm$0.05 to 0.44$\pm$0.04 l/l, $P=0.049$) and PSA (0.68$\pm$0.33 to 1.06$\pm$0.76 ng/ml, $P=0.021$) levels. Two hours after a dose of TD-TRT, Ser-T rose modestly (10.5$\pm$13.2 to 16.6$\pm$11.0 nmol/l, $P=0.003$) and Sal-T rose tremendously (7.7$\pm$8.1 to 17.0$\pm$16.9 nmol/l, $P=0.004$). Despite normal Ser-T, haematocrit and PSA concentrations, Sal-T concentrations are 75-fold greater than normal in men using TD-TRT. This is unlikely due to contamination (Sal-A4 concentrations are also high) and may be due to a conduit between skin, the lymphatic system and salivary ducts. Measurement of Sal-T is unlikely to be useful in the monitoring of men using TD-TRT.

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EP1170

Changes of dihydrotestosterone within the life in men

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Abstract
Dihydrotestosterone (DHT) is the most powerful naturally occurring androgen with three to six times higher biopotency than testosterone. Time onset of benign prostatic hyperplasia and alopecia in middle life could be the result of an imbalance between androgens. The decline of testosterone during lifespan is well known, controversial data can be found concerning the age dependence of DHT levels. We analysed the levels of testosterone, dihydrotestosterone and SHBG from 3076 men and we observed changes of their relationship and the ratio of total and free fraction of T and DHT, depending on age in men. We found that the DHT/T and fDHT/fT ratios during the life of adult males are constant, and that there is no evidence of a reversal in ratios of these hormones after puberty. Given that the ratio DHT/T remains constant during the age, the role in the development of androgenetic alopecia and benign prostatic hyperplasia is rather unlikely. The question remains, however, local status in androgen-dependent tissues, which would change the expression of enzyme, it could be caused just by local change in this ratio. This study was supported by the project MZCR for conceptual development of research organization 00023761 Institute of Endocrinology and grant 17-28692A.

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EP1171

Male pseudohermaphroditism with 45,X/46,X,idic(Y) karyotype: a case presenting with dysgenetic testis on one side and almost normally sized testis on the other side

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Dicentric Y chromosome [idic(Y)] is the most common structural abnormality of this chromosome, and generally results from altered meiotic breakage and reunion of sister chromatids. Since this rearrangement is unstable, idic(Y) may be lost in subsequent cell cycles, resulting in a mosaic 45,X cell line. Variable are the phenotype and gonads (from streak gonads to ovotestes or dysgenetic testes). Few cases of 45,X/46,X,idic(Y) male pseudohermaphroditism with testes have been reported. We report the case of a 26-yr-old 45,X/46,X,idic(Y) male born at 38 weeks' uncomplicated gestation who consulted us for infertility. At 3 years, he presented with cryptorchidism, micropenis and scrotal hypospadias. Congenital adrenal hyperplasia was excluded (17OH-progesterone 0.7 ng/ml, testosterone $<$20 ng/ml). Scrotal ultrasound revealed the absence of the right testis (RT). RT was eventually found in the pelvis, where uterus and ovaries were absent. Hypospadias repair was performed. The undescended RT, which histologically was described as testicular tissue with fibrosis, was surgically fastened inside the scrotum. At age 26, the patient was slightly overweight (BMI 25.8 kg/sqm), with a male phenotype, normal androgenization and no gynecomastia. He had a satisfactorily engagement with her partner. The RT was hardly palpable, while the left testis was reduced in volume and consistency. At ultrasound, RT was atrophic (1.4 ml), while the left was 10 ml, and both had a hypoechoic and inhomogeneous texture. FSH, androstenedione and 17OH-progesterone were high (30 mU/ml, 4.1 and 3.4 ng/ml), LH high-normal (9.6 mU/ml), total testosterone low-normal (348 ng/dl), and calculated free-testosterone low (6.1 ng/ml). The response of 17OH-progesterone after cosyntropin stimulation was normal. E2, progesterone, and SHBG were within the female reference range (53 pg/ml, 3.4 ng/ml, and 37.7 nmol/L). Azoospermia was detected at semen analysis. Considering the risk of malignancies within the dysgenetic gonad (10–15%), we advised right gonadectomy.

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EP1172

Effects of anabolic androgenic steroids on the reproductive system of athletes

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Background
Anabolic androgenic steroids (AAS) are widely used to improve performance and/or enhance appearance. The aim of this study was to assess the impact of AAS on the reproductive system of athletes.
Methods
An electronic literature search was conducted, using the databases MEDLINE, CENTRAL, Scopus and Google Scholar. Studies including AAS use in any type, dose, form or duration of intake were included in the review. Main outcomes were AAS effects on the reproductive system of athletes, as assessed by medical history, clinical examination, hormone analysis and/or semen analysis.
Results
Twenty-six studies were included in the review, involving 963 participants, with the median (25th-75th percentile) duration of AAS intake being 16 (8–100.8) weeks. Most studies showed that gonadotropin and testosterone levels decreased during the period of AAS intake, whereas following AAS cessation, they gradually returned to normal levels. The majority of AAS users demonstrated prolonged hypogonadism with persistently low gonadotropin and testosterone levels, lasting for several weeks to months after AAS withdrawal. Most studies have also shown that AAS use results in structural and functional sperm changes, reduction of testicular volume, as well as clitoromegaly and menstrual irregularities. Only 2 out of 26 studies determined AAS effects on fertility and only 2 studies involved female athletes.
Conclusion
AAS use results in profound and lasting effects on the reproductive system of athletes and potentially on fertility. Targeted education about AAS abuse and thorough monitoring are needed to prevent negative long-term effects.

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EP1173

Gonadal status in males with acute coronary syndrome and the extent of coronary artery disease: a comparative cross-sectional analysis

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Introduction and aims
Association between coronary artery disease (CAD) and male gonadal status has been previously suggested, but still remains inconclusive. Aims of our study in males with recent acute coronary syndrome (ACS) were to evaluate the prevalence of hypogonadism, to compare their gonadal status with non-ACS matched controls and to evaluate gonadal status by the extent of CAD.
Subjects and Methods
A cross-sectional retrospective study included all consecutive males with recent ACS and age and BMI matched non-ACS controls. Basic demography and standard CAD risk factors were recorded as well as fasting serum levels of total testosterone (TT), sex hormone binding globulin (SHBG), estradiol, follicle-stimulating and luteinizing hormone (FSH and LH) and calculated free androgen index (FAI). First, we evaluated the prevalence of hypogonadism (TT $<$ 7 nmol/l and FAI $<$ 24%). Second, we compared patients and control group for ACS associated factors on univariate and multivariate analysis. Third, using the same analysis in patients undergoing coronary angiography we aimed at identifying factors associated with CAD extent (0–1 vessel vs 2–3 vessel disease).
Results
96 patients and 49 controls were included. Hypogonadism was confirmed in 20.8% of patients. Patients had lower levels of TT (12.638 ± 6.138 vs 15.702 ± 4.903, $P < 0.01$), FAI (30.292 ± 12.489 vs 36.902 ± 9.816, $P < 0.01$) and higher levels of LH (5.58 IQR 4.4–8.21 vs 5.0 IQR 3.64–6.35, $P = 0.04$) compared with controls. In multivariate analysis, smoking, hypertension, dyslipidemia and FAI were identified as factors independently associated with ACS. 73 patients underwent coronary angiography, 43 had findings of 2-3 vessel disease. Hypertension, BMI and FAI were found as associated factors with CAD extent and FAI as its single independent risk factor.
Conclusion
Lower gonadal status was found common (20.8%) in males with recent ACS. It was independent on standard ACS risk factors and was independently associated with CAD extent.

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An unusual karyotype in a young adult with a clinical phenotype suggesting a Klinefelter syndrome

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Introduction
46 XX testicular DSD (disorder of sex development) is a rare syndrome characterized by 46 XX karyotipe, male external genitalia, azoospermia, sterility and usually hypergonadotropic hypogonadism in adulthood. Approximately 85% of individuals present after puberty with normal penile size, small testes and gynecomastia.
Case report
We present a 34-year-old male who was referred for endocrine evaluation due to slightly high prolactin levels. He underwent surgical correction of bilateral inguinal hernia at the age of 1.8 years old. Three years later, surgery was needed to descend trapped right testicle, showing testicular atrophy. At age 33, the patient requested medical evaluation after one year unsuccessfully attempting to father a pregnancy. Erectile dysfunction and lack of libido were not present. Semen analysis revealed azoospermia. Serum hormone evaluation detected high gonadotropines, low-normal testosterone and normal prolactin levels: LH 13,9 mIU/ml, FSH 32.11 mIU/ml, prolactin 15 ng/ml [4–15], testosterone 311.20 ng/dl [250–836]. Physical examination revealed a descended left testicle of 12 cm^3 and a right testicle unnoticed to palpation. There was no hypospadias and penile size was within the normal range. Patient's height and weight was 177 cm and 70 kg, respectively. Klinefelter syndrome was suspected. Cytogenetic procedures demonstrated a 46 XX kariotype, and the presence of SRY gene on one of the X comosomes was detected by fluorescent *in situ* hibrydization.
Conclusions
46 XX testicular DSD SRY-positive should also be considered in the differential diagnosis of adult hypergonadotropic hypogonadism with small testes and sterility. Adult diagnosis can be challenging because of normal sexual development and phenotypic similarities between patients with 46 XX DSD and Klynefelter syndrome, althought the latter are usually taller and show less incidence of cryptorchidism.

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EP1175

A case with taurodontism and Klinefelter syndrome

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In this paper we present an 18-year-old patient with Klinefelter syndrome who has taurodontism. Klinefelter syndrome is the most common abnormality of sex chromosomes. It is characterized by hypogonadism, gynaecomastia, azoospermia or oligospermia, and increased levels of gonadotropins. Associated medical disorders can be categorized as follows; cancer, autoimmune disorders, intellectuel and psychiatric disorder, osteoporosis, endocrine disorders, venous disease and taurodontism. Taurodontism is a developmental anomaly of a tooth characterized by large pulp chamber and short roots. It affects 0.5–3% of the general population. Taurodontism is observed with several syndromes and anomalies including Klinefelter syndrome. Endodontic treatment of taurodont teeth is tend to be complex and difficult because of the complexity in the tooth morphology, extraction of the taurodont teeth may be difficult and these teeth have risk for early decay. This feature can be seen in permanent and primary teeth, in a single tooth, or in several molars, and can be unilateral or bilateral. Taurodontism must be the part of comorbidity evaluation and patients with Klinefelter syndrome should have regular dental examination and care in order to provide long term oral health and improve quality of life of patients with Klinefelter syndrome.

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EP1176

Methylation of the CPG islands from MTHFR promoter in male infertility

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A large number of studies are now focused on the causes of male infertility. Among these are epigenetic modifications, which are important contributors to reproductive pathology in the male by providing dynamic changes of the phenotype according to the environmental and metabolic factors. The most known epigenetic modification is DNA methylation and alterations in this pattern in several genes could induce male infertility. Alterations in DNA methylation patterns in several genes may lead to abnormal male sexual development and infertility. MTHFR is an enzyme involved in the folate pathway and in de novo nucleotide biosynthesis but also a good example for gene-environment interaction in phenotype development. This study investigates the promoter methylation status of MTHFR in infertile men from by quantitative methylation-specific PCR in order to investigate possible correlations with sperm abnormalities. Our study includes patients ($n=27$, median age 31 years, range 26–41 years) recruited from men seeking advice for couple infertility and control group ($n=11$, median age 30.5 years, range 24–37 years). DNA was isolated from sperm samples and promoter methylation of MTHFR was quantified in qMS-PCR using bisulphite treated DNA samples (EpiTect Bisulfite Kit – Qiagen). Were detected significant correlations that indicate a tendency towards promoter hypermethylation in spermatozoa with low motility ($P=0.0130$, $r^2=0.3886$), poor morphology ($P=0.0138$, $r^2=0.3833$) and with low sperm count ($P=0.0092$, $r^2=0.4184$). Our data suggest that the methylation patterns of the promoter of MTHFR is linked with sperm anomalies of motility, morphology and sperm count, which could lead to male infertility.

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EP1177

How relevant are the complications associated with testosterone treatment in men with hypogonadism?

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Introduction
Testosterone treatment in patients with hypogonadism has been associated with cardiovascular and prostatic complications.
Objective
To describe the evolution of analytical parameters associated to the complications of testosterone treatment in a male population with hypogonadism treated with testosterone. Methods A retrospective, longitudinal study in which the clinical data of male adults with hypogonadism under intramuscular testosterone therapy were analysed in 2 tertiary centres. The duration and doses of testosterone were recorded. Haematocrit (Hct), total cholesterol (TC), LDL cholesterol (c-LDL), total prostate-specific antigen (PSA) and total testosterone levels were assessed at the beginning and at the end of follow-up. Paired-*t*-test was used to compare means and the results are shown in mean and standard deviation.

	Hct (%)	TC (mg/dl)	C-LDL (mg/dl)	PSA (ng/ml)
First measurement	42.9±5.0	194.3±41.5	114.1±37.3	1.4±1.7
Final measurement	44.0±4.4	191.7±30.2	110.8±28.3	1.7±2.4
Difference	1.1±4.4	−2.6±38.2	−3.4±34.8	0.3±1.6
P-values	0.01	0.68	0.60	0.30

Results
We analysed 128 patients, 35% primary and 65% secondary hypogonadism. The mean age was 49.6 ± 17.3 years. The follow-up time was 2.6 years (0.6–9.4 years). The mean interval between injections was 4.4 ± 2.3 weeks. The final testosterone was 392.0 ± 112.7 ng/dl. The results are summarized in the table below: Treatment with testosterone resulted in increased Hct and PSA values, however only the Hct difference proved statistically significant. Spearman correlation test revealed a positive and statistically significant correlation between the increase of testosterone levels and the increase of Hct ($r = 0.21$; $P = 0.03$). No hospitalizations for cardiovascular events were reported.
Discussion
The rise of Hct, although statistically significant, was low. The remaining parameters did not show statistically significant increases so testosterone therapy appears to be safe from a cardiovascular and prostatic perspective.

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EP1178

Evolution of healthcare demand in a public gender identiy clinical center in Valencia (spain)

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Introduction
The prevalence of transsexuality in Europe is uncertain in absence of epidemiological studies, so it's difficult to implement public healthcare strategies.
Aim
To describe healthcare demand evolution in a gender identity clinical service in our country.
Methods
Our center is a public university hospital placed in Valencia (Spain). It is a reference center on gender dysphoria from two provinces (Valencia and Castellon), with a target population of 2.646.801 inhabitants ≥14 years old (50.8% women and 5.5% adolescents). We reviewed medical records of patients referred from 2008 to 2016, excluding gender-non conforming people without demand of hormonal or surgical intervention.
Results
We attended 331 transsexual people with eligibility criteria for pubertal block, cross hormonal treatment or surgery; 41.7% transsexual men (FxM) and 58.3% transsexual women (MxF). 6% in FxM and 30% in MxF had previously started any kind of treatment. 82% FxM and 56% MxF were living in desired role at the initial evaluation. Before 2011 no adolescent was referred while between 2012 and 2016 were attended 82 of them. In adolescents, sex ratio was favoring natal males before 2014 (2.9:1) and it changed in 2015 and 2016 (1.7:1–1:1.5, respectively) favoring natal female. Minors represented 16% of patients in 2012–2014 and 52% nowadays. We performed 34 hysterectomies (34.6% of patients older than 18 years), 25 mastectomies (25.5%) and implanted 20 breast prosthesis (13.1%), surgeries preformed in private centers were not accounted. For genitoplasty surgery they were referred to another national surgery center.
Conclusions
Demand for transexual care shows an important increase in our geographical area. This increase is due to adolescent population. There is a significant variation of sex ratio favoring transsexual men. This results can be explained by sociocultural phenomena. Only one-third of FxM choose to perform hysterectomy and adnexectomy.

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EP1179

Leptin modulates Sertoli cells mitochondrial function and biogenesis with implications for the nutritional support of spermatogenesis

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Current lifestyle, characterized by physical inactivity and a poor diet, is heavily linked with an increased incidence of metabolic diseases. One of the most serious silent co-morbidities of those diseases is infertility. The hormonal link between food intake and energy homeostasis is mediated by the leptin ghrelin axis. Compelling evidence suggests that direct leptin's action regulates cellular glucose homeostasis and mitochondrial biogenesis. We have recently shown that leptin modulates the nutritional support of spermatogenesis, which may be related with obesity-related male subfertility/infertility. Herein, we hypothesized that leptin directly affects mitochondrial function, dynamics and biogenesis of Sertoli cells (SCs). Rat Sertoli cells (Ser-W3) were treated ($n = 5$ for each group), during 24 h at 37°C 5% CO_2, with different concentrations of leptin (5 ng/ml as reported in normal mice, 25 ng/ml as reported in obese mice and 50 ng/ml as a supraphysiological concentration) and the results were compared to a condition without leptin. Western Blot was performed to determinate protein levels of mitochondrial complexes. qPCR was performed to determinate expression levels of several genes involved in mitochondrial biogenesis and to assess mitochondrial DNA copy number. Mitochondrial membrane potential was determined by JC-1. Direct leptin exposure did not alter SCs proliferation rate, though all leptin concentrations decreased SCs metabolic activity. That was accompanied with alterations in the expression levels of the different mitochondrial complexes and also of genes involved in mitochondrial biogenesis. In addition, the highest concentration of leptin decreased mitochondrial membrane potential. Finally, mitochondrial DNA copy number was not sensitive to the treatment with the different leptin concentrations. Overall, the results show a direct action of leptin on Sertoli cells mitochondrial function and biogenesis with implications in the nutritional support of spermatogenesis, which is a novel mechanism by which leptin can affect the reproductive potential of males.

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EP1180

Study of CDX-2 VDR gene polymorphisms in male infertility

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The CDX2 VDR polymorphism (rs11568820) is located in the promoter region of exon 1 in the 5′-untranslated region of the VDR gene.
Objective
The current investigation examines the association between CDX2 VDR polymorphism and male infertility.
Subjects and methods
The study was conducted on 69 infertile men, aged between 20 and 50 years, divided into three groups, based on spermatic parameters: group with azoospermia (19 subjects), group with severe oligospermia (38 subjects), group with oligospermia (12 subjects), and 37 age-matched controls. CDX-2 VDR gene polymorphisms were performed by PCR-RFLP. Vitamin D was assessed by electrochemiluminiscent method.
Results
The evaluation of Vitamin D levels was found to be significantly decreased in infertile patients group versus controls ($P = 0.0198$). The lowest Vitamin D levels were characteristic for azoospermia patient group (median = 18.34 ng/ml, range = 14.89–19.6 ng/ml), than controls (median = 24 ng/ml, range = 18.2–36.10 ng/ml). The analyses for CDX2 VDR polymorphism in infertile patients showed that six cases were homozygote (GG), 28 heterozygote (GA) and 35 homozygote (AA). The frequency of G allele was 0.29, and 0.71 for A allele, $\chi^2 = 0.014$. In control group the analyses of CDX2 VDR polymorphism revealed that 10 cases were homozygote for G allele (GG), 19 were heterozygote (GA) and 8 were homozygote (AA). The frequency of G allele in population was 0.53, for A

allele the frequency was 0.47, $\chi^2 = 0.033$. The controls and infertile groups were compared using χ^2-test and the difference was significant ($P = 0.0229$). The GG genotype was found in a low percentage in patients group than controls (8.7% vs 27.03%), and the percentage of AA genotype was higher in infertile group (50.72% vs 21.62%).
Conclusion
Despite numerous publications, the influence of Vitamin D on reproductive health remains ambiguous. Our study showed that infertile patients present low levels of Vitamin D. According the results the A allele may represents a potential risk for male infertility.

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EP1181

CHARGE syndrome – late diagnosis in adulthood

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Introduction
CHARGE syndrome is a rare autossomal dominant genetic disorder with an estimated birth incidence of 1:10000. It affects multiple organ systems and can have a variable phenotypic expression.
Case report
34-years-old man, referred to Endocrinology in the context of bilateral gynecomastia. He had an acute corneal hydrops which was treated by ophthalmology. Physical examination showed short stature (149 cm), obesity (BMI 31.5 kg/m^2), micropenis and cryptorchidism. He presented other problems: coloboma of the iris, bilateral hearing loss, anosmia, craniofacial dysmorphisms (abnormal ear shape, microstomia) and intellectual disability. Patient's investigation included among others: breast ultrasound which revealed bilateral gynecomastia; testicular ultrasound that demonstrated an empty scrotal sac with the atrophic testes in the inguinal canals; biochemical evaluation showed hypogonadotrophic hypogonadism (FSH 0.42 mUI/ml (*n*:1.5–12.4), LH < 0.10 mUI/ml (*n*:1.7–8.6), total testosterone 0.08 ng/ml (*n*:2.8–8.0) and a low IGF-1 12 ng/ml (*n*:140–405). Pituitary had a 3 mm height on MRI; Karyotype result was normal male (46, XY); He started monthly 250 mg/ml enanthate testosterone with poor compliance. Otolaryngology evaluation excluded choanal stenosis/atresia (peri-nasal sinuses CT showed only exuberant deviation to the left of the nasal septum) and confirmed moderate sensorineural hearing loss (audiogram with about 50 dB hearing threshold bilaterally and normal tympanogram) but the patient refused auditory prosthesis. His echocardiogram was normal. Family history was irrelevant for congenital malformations, intellectual disability, deafness or vision loss and endocrinological problems. CHARGE Syndrome was suspected and molecular study of *CHD7* gene was requested. A heterozygous pathogenic variant was identified [c.3106C > T, (p.Arg1036Ter)] and clinical suspicion was confirmed.
Conclusion
CHARGE acronym stands for C–*coloboma, H–heart disease, A–atresia choanae, R–retarded growth and retarded development and/or CNS anomalies, G–genital hypoplasia, and E–ear anomalies and/or deafness*. Diagnostic criteria currently combined *major* and *minor* features are used. Pathogenic variants in CDH7 gene are found in around 80% of CHARGE patients. We present CHARGE Syndrome referred to our clinic due to gynecomastia. Most of CHARGE syndrome patients are diagnosed in childhood infancy and rarely in adulthood. With this clinical report we would like to alert that in the presence of hypogonadotrophic hypogonadism associated with suggestive features, this diagnosis should be considered.

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EP1182

Azoospermia revealing the uncommon Jacob's syndrome

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Introduction
Dysgonosomies are abnormalities of the number of gonosomes X and Y. They have fewer Phenotypic repercussions than the aneuploidies involving autosomes, and are mostly viable. The 47 XYY are generally boys with normal phenotype. The prevalence is around 1 per 1000 birth boy but undoubtedly under diagnosed given the often normal phenotype associated with this chromosomal formula, in addition to the lack of large-scale studies. There is no gonadal dysgenesis and often no infertility or criminality in the past.
Case report
Our case is a 48 years old patient consulting for primary hypofertility. The anamnesis finds a type 2 diabetes, High blood pressure, orchi-epididymitis at the age of 34 and bilateral unaccompared varicosele and hydrocele. The patient is an active smoker. Clinically, he is an over weighted patient (BMI: 27 kg/m square) with 180 cm height. No other dysmorphia is noted. In the Spermogram, we find an azoospermia (00 SPZ), with 1 CC of ejaculation volume. Scrotal ultrasound shows a normal-sized testicles with micro calcifications in the epididymis tail with varicocele and bilateral hydrocele. An Epididymis Cytoponction recovering SPZ (without cryopreservation).
The hormonal status is:
FSH: 1.65 mIU/ml (0.95–11.95)
LH: 2.40 mIU/ml (0.57–12.07)
Testosterone: 5.65 ng/ml (1.42–9.23) or a correct gonadal assessment
Inhibin B 215.4 ng/ml (11.5–368.9) predicting the presence of SPZ in the biopsy
Caryotype 46 XY/47 XYY
The clinical examination and the exploration of the 31 years old partner is without anomalia. The patient is programmed for testicular biopsy in the optic of a possible ICSI.
Conclusion
It appears that many men with 47, XYY syndrome will likely have decreased fertility potential. These patients may ultimately require assisted reproductive techniques in order to achieve pregnancy.

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Neuroendocrinology

EP1183

Prenatal intervention by P271 reduces LH pulsatility and testosterone levels in PCOS condition

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Background
Polycystic ovary syndrome (PCOS) is a frequent endocrine and metabolic disorder and the most common cause of infertility occurring in 5–10% of women of reproductive age. The characteristic endocrine abnormalities of PCOS involve hypersecretion of androgens and LH (as a consequence of increased GnRH frequency). Although PCOS signs generally become obvious at puberty, clinical and experimental evidence suggests an intrauterine origin for the syndrome. On the other hand, kisspeptin antagonists have been shown to reduce LH pulse frequency and amplitude.
Methods
RNAs were extracted from hypothalamus of prenatally androgenized (PNA) ($n = 18$) and non-PNA female rats ($n = 14$) thought estrus cycle. The ability of prenatal administration of kisspeptin antagonist P271, to alter GnRH mRNA expression and gonadotropin and steroid hormone levels, was tested using Cyber-green Real-time PCR and ELISA methods, respectively.
Results
Hypothalamic GnRH mRNA levels fluctuated in a cyclic-dependent manner, with a robust increase in the afternoon of proestrus phase. P271 treated animals showed reduced GnRH expression and gonadal steroid and gonadotropin levels.
Conclusion
PNA animals had increased GnRH mRNA expression and LH levels in diestrous phase than controls, which reduced in response to prenatally administered P271. This pilot study, for the first time, shows that prenatal intervention by P271 reduce LH pulsatility and T levels associated with PCOS.
Keywords: Kisspetin, P271, Gene Expression, Prenatal androgenisation

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EP1184

Prenatal testosterone exposure increases anxiety-like behavior in female rats

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Polycystic ovary syndrome (PCOS) is characterized by excessive androgen secretion and women with PCOS are at risk of developing anxiety disorders. Maternal testosterone levels in humans have been shown to affect brain development and to be correlated to mental function. During pregnancy, women with PCOS display high circulating androgen levels that may affect the fetus and increase the risk of mood disorders in offspring. This study investigated whether maternal androgen excess causes anxiety-like behavior in offspring. Ten pregnant Wistar rats were injected s.c. with 100 mg/kg testosterone undecanoate (TU) on gestational day 20, while control (C) rats received only solvent. To investigate the presence of anxiety-like behavior in female offspring of TU and C dams, the elevated plus maze (EPM) and open field (OF) test was performed. In the EPM test, offspring of TU dams displayed decrease in the number of open arm entries and in the percentage of time spent on open arms. OF test showed altered pattern of locomotor activity in female TU offspring. Numerous data demonstrate that the early life environment, including *in utero* plays a key role in later life behavior. The results of our research suggest that prenatal testosterone exposure increases anxiety-like behavior in female offspring.

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Obesity

EP1185

Placental maternal and fetal vascular circulation in healthy non obese and metabolically healthy obese pregnant women

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Background
Obesity in pregnancy is associated with hyperinsulinemia, impaired endothelial function, inflammatory up-regulation and higher risk of placental pathological lesions. However not all obese individuals demonstrate similar metabolic profiles. The present study was designed to investigate placental histopathology in lesions that are associated with maternal and fetal circulation abnormalities, in nonobese and obese women with and without metabolic alterations.
Methods
332 pregnant women were divided into three groups according to presence of obesity and metabolic risk factors: Group 1 included 163 non-obese metabolically normal (NOMN); Group 2 included 106 obese metabolically normal (OMN); Group 3 consisted 63 obese metabolically abnormal (OMA) subjects.
Results
Placental weight was significantly higher in OMN compared to NOMN ($P<0.000$). Maternal vascular supply (MVS) abnormalities of the placental bed differed significantly across groups, and increased from Group 1 to Group 3 in a continuous fashion (31, 38 and 54% respectively, $P<0.005$). Fetal vascular supply (FVS) abnormalities rate increased from group 1 to group 3, and was significantly higher in obese subjects with and without metabolic abnormalities, compared to non-obese subjects (9, 20 and 22% respectively, $P<0.021$). Willous maturation defect (WMD) rate was higher in OMN subjects compared to NOMN ($P<0.018$). In the logistic regression analysis, obesity emerged as a significant predictor of fetal vascular supply abnormalities ($P=0.001$) and WMD ($P=0.011$).
Conclusion
We demonstrated that obesity, per se, is associated with an increased rate of fetal vascular malperfusion abnormalities, Willuos maturation defect, as well as higher placental weight and lower FPR, compared to non-obese subjects.

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EP1186

The dynamics of anthropometric data in fertile age women by various types of the treatment

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The aim
To study efficiency of pathogenetic therapy and dynamics of anthropometric indexes for women with obesity of fertile age at different endocrinopathies to and through 6 months after treatment.
Material and research methods
On the etiologic factor of patient with obesity were up-diffused on three groups: 1 g. are patients with obesity at the polycystic syndrome of ovaries (PCOS) – 30 patients, 2 g. are patients with hypothalamic obesity – 21 cases and 3 g. – patient with endocrine obesity (at a primary hypothyroidism) – 20 patients. Age of patients in a 1th group hesitated 39 from 20 to and 28.3 ± 0.64 averaged year. To all patients have been conducted spectrum of investigations, which include clinical, biochemistry, hormonal analysis of the blood. Besides of this, electrocardiography, ultrasound investigation of uteri and ovarium during 11–14 days of periods, and MRY of pituitary. For the 1 g. we administered combination of Syofor 1000 mgs + spironolacton 100 mgs + yodmarinum 100 mgs +L-thyroxine 50 mgs in the morning + antiandrogens + antidepressants. For the 2 group: combination of Syofor 1000 mgs + spironolacton 100 mgs + Yodmarin 100 mgs +L-thyroxine 50 mgs i+ methaboliks + Reduxine (Sibutramin) 15 mgs + antidepressants. For the 3 groupo: combination of Yodmarin 100 mgs +L-thyroxine 50 mgs.
The results
In 1 and 2 groups of patients marked reliable decline of BMI 1 and 2 degrees after 6 months of treatment, while for patients 3 groups of reliable changes of BMI through 6 months of treatment were not attained at none of degree of BMI Thus, for patients 1 and 2 groups with BMI 3 degrees through 6 months a tendency was attained to the decline of BMI. In addition, renewal of fecundity and pregnancy was attained for the patients of a 1 group – in 19,5%% cases (at 10 patients).
Conclusions
Optimization of treatment of obesity for the women of reproductive age is based on drafting of the individual programs, the choice of that is determined by the values of anthropometric indexes, state of hormonal and metabolic status, features of food behavior and personality-emotional sphere, state of menstrual and reproductive function.

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EP1187

The disorder of secretion of somatotropic hormone in women with obesity in the polycystic ovaries syndrome (PCOS) by comparison to patients with the non-functional pituitary adenomas (NFPA)

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Aim
To study the disorder of secretion of growth hormone for women with obesity in PCOS by comparison to patients with NFPA.
Materials and methods
Under our supervision in the department of neuroendocrinology of the Center of Endocrinology of PH Ministry of RUz ambulatory in a period from September 2015 for December, to 2016, 15 adult patients of fertil age were observed with obesity in PCOS and 15 – with NFPA. Middle age of patients to make 25.5 and 28.9 accordingly. The remoteness of disease hesitated in limits from 7 months to 9 years.
Results
It was set that in both groups there were neuroendocrine violations peculiar to each of pathologies. So, in a 1 group of patients with PCOS such violations, as obesity, met most often, strium, acanthosis, acne, hyperandrogenemiya. hyperpolymenorheya, and in the second is secondary amenorrheya, hyperprolactinemiya, pahhypopituitarism. In both groups there was anovulation, and also decline of secretion of STH, IGF- 1. In addition, in the group of patients with NFPA the most for certain mionectic basale levels of trope hormones of hypophysis were educed - STH, LH, FSH on a background hyperprolactinemiya and normal values of IGF- 1, while for patients with PCOS the decline of STH, LH, FSH, was marked on a background hyperandrogenemiya and declines of IGF- 1.

Conclusions
1) It is set that in the group of patients with PCOS the most reliable decline of basale levels of IGF- 1 was educed, while the deficit of STH met rarer.
2) For patients with NFPA took place panhypopituiarism, namely combined deficiency of STH, LH, FSH, TSH, while the deficit of IGF- 1 met rarer.
3) The secretions of STH and IGF- 1 educed in our research of violation confirm these literatures that for patients with PCOS the decline of levels of STH and IGF-1 takes place on a background of hyperinsulinemiya and hyperandrogenemiya, that requires further research.

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Paediatric Endocrinology

EP1188

17alpha-hydroxyprogesterone in non-CAH children and adolescents at different ages

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17α-hydroxyprogesterone (17OHP) is currently used as a diagnostic parameter in children and young adults when a milder form of congenital adrenal hyperplasia (CAH, late-onset) is suspected. A basal serum level of 17OHP (2 ng/ml; 6.0 nmol/l, respectively) has been discussed as cut-off for suspected late-onset disease. We analysed 17OHP in a cohort of children and adolescents without CAH and in confirmed CAH patients to define reference ranges for these age groups. For the analysis of 17OHP, we used a novel automated immunoassay in 506 anonymized samples from children and adolescents with a previous exclusion of CAH by conventional hormone measurement. 302 girls and 204 boys in two age groups from 1–11 and 12–18 years were included. In a subgroup of 49 probands, follow-up samples within one year were available, as well as in 17 out of initially 38 children with genetically confirmed CAH. In prepubertal children at the age of 1–11 years, mean 17OHP serum concentrations were 0.99 ng/ml ± 0.86 (STD) (reference limits 0.31–4.62) for girls and 0.85 ± 0.59 (reference limits 0.31–2.60) for boys, which was not statistically different ($P = 0.852$). There was also no difference in mean 17OHP serum concentrations at the age of 12–18 years between female 1.39 ± 0.70 (reference limits 0.37–3.26) and male adolescents 1.38 ± 0.67 (reference limits 0.32–2.93) ($P = 0.95$). Repeated measurements in follow-up samples showed a mean coefficient of variation (CV) for non-CAH samples of 14.2 and 20.8% in CAH patient samples. In our study, baseline 17OHP was a useful marker for the exclusion of late-onset CAH in the majority of samples. Based on the established reference ranges, an overlap with confirmed CAH patients was very small. In suspicious cases, additional hormonal tests as well as stimulation tests of 17OHP have been defined as the standard of late-onset CAH diagnosis and therapy monitoring.

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Steroid Metabolism + Action

EP1189

Effects of estrogen and progesterone on the protein expression of EMT- and pluripotency-associated markers in human embryonic stem cells

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Embryonic stem (ES) cells are pluripotent stem cells derived from a developmental stage of preimplanted embryos. In this study, we investigated the effect of female sex steroid hormones on the characteristics of human ES cells by using a feeder-free culture protocol. In a feeder-free condition without sex hormones, human ES cells assumed the form of tightly packed cells that grow in a monolayer. The cells also displayed clean and defined edges with no evidence of differentiation and expressed several markers specific for undifferentiated ES cells such as POU5F1, SOX2, and NANOG. Next, we investigated whether female sex steroid hormones such as 17β-estradiol (E2) and progesterone (P4) could alter the protein expression of epithelial-mesenchymal transition (EMT) related markers as well as pluripotency markers such as POU5F1, SOX2, and NANOG in human ES cells. The protein expressions of N-cadherin, SNAI1, and SNAI2 were increased while E-cadherin expression was decreased by treatment of E2 or P4 and that the expressions of POU5F1, SOX2, and NANOG were decreased by the treatment of E2 or P4. When E2 and P4 were treated in the combination with estrogen receptor inhibitor (ICI 182,780) and progesterone receptor inhibitor (RU486), respectively, their effects on EMT and pluripotency of ES cells were restored to the control levels. Collectively, these results suggest that E2 and P4 may regulate EMT and pluripotency of human ES cells by mediating their receptors. The present study might be useful to understand the roles of sex steroid hormones in cellular biology of human ES cells. (This research was supported by a grant from the Next-Generation BioGreen 21 Program (no. PJ011355-2015), Rural Development Administration, Republic of Korea.)
Keywords: sex steroid hormones, human embryonic stem cells, pluripotency, epithelial-mesenchymal transition

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EP1190

Homo-dimerisation of cytochrome P450c17 resolves the conundrum of the dual activities of cytochrome P450c17

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Reproduction requires the temporal and spacial control of specific and exact signals, delivered by locally regulated hormonal flux. In the case of androgen biosynthesis, cytochrome P450 17α-hydroxylase, 17,20-lyase (P450c17) is the key enzyme. However, P450c17 is a multi-functional P450, so, it synthesizes cortisol in the zona fascicula of the adrenal cortex and also androgen precursors in the adrenal zona reticularis and the gonads. The regulation of this dual activity has been the focus of research studies over many decades and remains unresolved. Functionally, it is known that each of these reactions of P450c17 require electrons transferred by the electron donor cytochrome P450 oxidoreductase (CPR). The first reaction, the 17α-hydroxylation of its substrate, occurs in all cells where P450c17 is expressed. Remarkably, a second, subsequent reaction, namely the 17,20-lyase activity, only occurs in the zona reticularis and gonads. The specificity of the second reaction is due to a non-redox 'allosteric' interaction with the haem-protein cytochrome b5. Surprisingly, cytochrome b5 and cytochrome P450 oxidoreductase have overlapping binding sites on the surface of the P450c17 enzyme. This poses the question as to how cytochrome b5 and cytochrome P450 oxidoreductase interact with P450c17 - structurally, functionally and physiologically? This conundrum can be rationalized based on the observation that P450c17 can homodimersise. A homodimer would allow cytochrome P450 oxidoreductase to bind to one P450c17 of the P450c17 homodimer, whilst cytochrome b5 could bind to the other P450c17 simultaneously, at the surfaces distal to the dimer interface. We present our molecular modelling data that predicts that the P450c17 homodimer is a stable structure and the CPR and cytochrome b5 proteins can assemble on the P450c17 dimer to form a tetrameric 'CPR:P450c17:P450c17:cyt b5' assembly, predicted to be the functional complex required for androgen biosynthesis. This model is fully consistent with extensive experimental data published over the last two decades. Predictions derived from this model are currently being tested by a range of *in vitro* and *in vivo* experimental approaches.

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EP1191

Non-alcoholic fatty liver disease and its relation with sex steroids in men

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Background
Obesity associates with co-morbidities as non-alcoholic fatty liver disease (NAFLD). Obese men often present with low testosterone (T) levels. As sex steroids undergo hepatic metabolization and their serum levels depend on hepatic sex hormone binding globulin (SHBG) secretion, NAFLD could contribute to this phenomenon. Previous studies however were contradictory and not based on state-of-the-art technology as mass spectrometry or biopsy-proven NAFLD.
Objective
To assess the relation between biopsy-proven NAFLD and sex steroid levels in obese men undergoing gastric bypass surgery (GBS).
Methods
This cross-sectional study included 56 obese men (mean age 44 ± 11 years; BMI 41.6 ± 4.6 kg/m^2) and 56 healthy, age-matched control men (mean age 44 ± 11 years; BMI 23.5 ± 1.8 kg/m). T and estradiol (E2) measured using LC/MS-MS, SHBG by immunoassay and free hormone fractions were calculated. Surgical liver biopsies scored using NAFLD activity (NAS) and Steatosis, Activity and Fibrosis (SAF) scores.
Results
Obese men showed lower T, free T (FT) and SHBG levels, lower (F)T/(F)E2 ratio (all $P < 0.001$) and higher FE2 ($P = 0.019$) compared to controls. Within the GBS patients, no significant differences were found for sex steroid levels according to NAS-based NAFLD severity. However, with increasing grade of steatosis, trends towards lower T and FT levels, and lower (F)T/(F)E2 ratios were observed ($P < 0.059$). No associations between sex steroid levels and other NAFLD features were detected. Using SAF, we found that lower (F)T levels correlated with steatohepatitis ($P = 0.014$). These correlations were independent from age, BMI, HOMA-IR and SHBG. Remarkably, no differences in SHBG or (F)E2 levels according to NAFLD severity were found.
Conclusion
This study confirmed lower T levels in obese as compared to normal-weight men. In these obese men, overall NAS-based NAFLD severity was not associated with these lower T levels although presence of steatohepatitis and increasing grade of steatosis was related to lower (F)T levels and FT/FE2 ratios.

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Eposter Presentations: Thyroid

Clinical Case Reports – Thyroid/Others

EP1192

An adverse outcome in a thyrotoxic lady with propylthiouracil induced necrotising leukocytoclastic vasculitis

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A 37 year old lady with relapsing Graves' thyrotoxicosis initially managed on a 'block and replace regime' with propylthiouracil and levothyroxine for 7 years had her medication changed to carbimazole after a relapse from non-compliance but developed agranulocytosis. She was then restarted on an increased dose of propylthiouracil alone. Two weeks later, she developed tender purpuric lesions and was admitted after developing painful bullous lesions to her lower limbs. She had previously noted haemorrhagic lesions on her limbs but these would resolve within a week. Investigations revealed positive MPOANCA antibodies, skin biopsy confirmation of necrotising leukocytoclastic vasculitis and no evidence of systemic involvement on imaging. She had rheumatology and dermatology input regarding the vasculitic rash. Initial treatment involved stopping propylthiouracil, starting beta blockers, short course of pulsed high dose methylprednisolone and wound care. Within a few weeks, her skin lesions were improving, but she was becoming progressively more thyrotoxic. She was commenced on potassium iodide therapy in preparation for a total thyroidectomy. Unfortunately, her temperature increased and she rapidly went into septic shock due to pneumonia requiring inotropic and respiratory support on the intensive care unit before dying a few days later.

Discussion

Necrotising vasculitis remains a rare complication of propylthiouracil therapy. It is classically, as in our patient, strongly associated with positive MPO-ANCA antibodies. Clinical presentation is variable. Treatment includes discontinuation of the drug, immunosuppression and good wound care. The prognosis in the absence of major organ vasculitis as in our patient is usually good, and our patient seemed to be making good progress whilst being worked up for thyroidectomy. However, her low grade tachycardia and raised inflammatory markers masked the early onset of sepsis. Our case highlights the importance of clinical vigilance for sepsis in patients with the rare complication of propylthiouracil induced necrotising leukocytoclastic vasculitis.

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EP1193

Synchronous papillary thyroid carcinoma and primary hyperparathyroidism: a rare association

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Introduction

Although the association between parathyroid and thyroid diseases is not uncommon, the coexisting of parathyroid adenoma causing primary hyperparathyroidism (PHPT) and papillary thyroid carcinoma (PTC) is rare. Probably this can be partially explained by different embryologic origin of thyroid and parathyroid cells. Herein, we report a case of PHPT associated with synchronous bifocal PTC.

Observation

A 65-year-old woman was referred to our department with incidental hypercalcaemia and biochemical PHPT. A Technetium (99mTc) sestamibi scintigraphy showed a distinct functioning nodule in the lower right pole of the thyroid. Ultrasonography of the neck revealed parathyroid adenoma at the inferior pole of the right thyroid lobe and bilateral thyroid nodules. The patient was subjected to uncomplicated right inferior parathyroidectomy and synchronous total thyroidectomy. Postoperative histopathological examination confirmed the diagnosis of parathyroid adenoma with coincidence of papillary thyroid carcinoma. After surgery, serum parathormone and calcium returned to their normal values and patient was referred to the department of Nuclear Medicine for a radioactive iodine ablation therapy.

Conclusion

Concomitant papillary thyroid carcinoma and primary hyperparathyroidism is rare. It still remains controversial whether these two pathologies happen coincidental or are caused by specific risk factors or genetic changes.

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EP1194

A case with langerhans cell histiocytosis having papillary microcarcinoma of thyroid: two birds in one nest

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Introduction

Langerhans cell histiocytosis (LHH) is an idiopathic, clonal, pleomorphic, neoplastic disorder characterized by the presence of atypical histiocytic cells which are locally or commonly seen in bone, lung, hypothalamus, liver, lymph nodes, mucocutaneous tissues with damaging them.

Case

58 year-old male patient applied to our clinic due to fatigue. On his physical examination, lymphadenopathy and hepatosplenomegaly were absent. In his history, he had an operation owing to Large-cell neuroendocrine carcinoma in 2014. He took chemotherapy but no radiation. In surveillance, a thyroid nodule was detected in PET-CT. Thyroid US revealed a nodule 5 cm in diameter in the right lobe. He underwent bilateral total thyroidectomy. In pathological examination, left lobe was reported as thyroid papillary microcarcinoma, follicular variant and langerhans cell histiocytosis, right lobe was reported as follicular nodular disease. The focus of papillary microcarcinoma in 0.2 and 0.1 cm diameter was seen in the left lobe and langerin positive focus was observed in the morphology of langerhans cell histiocytosis consisting of langerhans cells and eosinophils. Bone marrow biopsy and abdominal MR were normal. On his laboratory examination urine dansity was normal. FSH: 5.44 mlU/ml (1.5–12.4), LH: 4.74 mlU/ml (1.7–8.6), total testosterone: 2.35 ng/ml (2.8–8), prolactin: 5.87 ng/ml (4.6–21.4), TSH: 0.37 μIU/ml (0.35–5.50), tyroglobulin $<$ 0.9 ng/ml (1.6–60) were detected. In pituitary MRI, nodular focus with different contrast enhancement according to pituitary gland referred as intermediate lobe was detected in the middle posterior of pituitary gland

Discussion

In LHH and papillary thyroid carcinoma coexistence, papillary microcarcinoma was frequently encountered.Gold standard treatment for limited LHH is surgical resection and it has usually good prognosis. Diffuse goitre (59%) or nodules (25.8%) can be detected in patients with LHH having thyroid gland involvement. Large cell neuroendocrine carcinoma of the lung is rarely seen and has poor prognosis.

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EP1195

Amiodarone and refractory thyrotoxicosis in a patient with complex arrhythmia

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Background
Amiodarone is a potent antiarrhythmic drug used to treat tachyarrhythmias. However, is linked to a number of adverse effects, including thyroid dysfunction. It is the main cause of drug-induced thyrotoxicosis. Here we report a clinical case of amiodarone-induced thyrotoxicosis (AIT) in a patient with complex ventricular dysrhythmia.
Case report
A 23 years-old women with dilated cardiomyopathy, severe depression of ejection fraction of left ventricle and complex ventricular dysrhythmia under amiodarone treatment 200 mg id since June of 2013, presented asthenia and weight loss since march of 2016, with worsening of heart failure. TSH was <0.008 μUI/ml (0.4-4.0), Free T_4 (FT_4) 3.4 ng/dl (0.8–1.9) and Free T_3 (FT_3) 6.1 pg/ml (1.8–4.2). Autoimmunity was negative. Thyroid ultrasound: normal dimensions, without nodularity or increased vascularity at doppler study. ^{99m}Tc-sestamibi thyroid scintigraphy: signal in lower limit of normality. It was started methimazole 30 mg/day and prednisolone 40 mg/day. After 3 months, she presented undetectable TSH, FT4 2.4 ng/dl and FT_3 4.0 pg/ml. Methimazole was increased to 40 mg/day and prednisolone to 60mg/day and amiodarone was suspended. After 2 months, TSH was still undetectable and FT_4 2.2 ng/dl, with development of steroids side effects. So thyroidectomy was performed, without complications. After surgery, started levothyroxine 75 μg/day, steroids were tapered and amiodarone was restarted. Three months after surgery, normal thyroid function and improvement of her clinical condition were observed.
Conclusion
In this case, a type 2 AIT was diagnosed, resistant to medical therapy and with steroids side effects. This uncommon scenario illustrates the difficulty of controlling thyrotoxicosis in a patient of high risk of sudden death, requiring an invasive procedure to its resolution. Thereby, when thyrotoxicosis is uncontrollable and patients are at high cardiovascular risk, thyroidectomy should be considered for the resolution of AIT. This could be lifesaving by controlling the disease, avoiding iatrogeny and maintaining the possibility of amiodarone therapy.

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EP1196

Relapsed Graves' thyrotoxicosis following total thyroidectomy 20 years earlier

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We report a 55-year-old non-smoker with a history of Graves' disease diagnosed in 1990 at age 29 years old. Due to poor compliance to therapy, she underwent a total thyroidectomy within 1 year of diagnosis. She remained well controlled on thyroid hormone replacement for over 20 years with Levothyroxine 100 μg daily. However, in the two years before referral to the Endocrine Clinic, she had difficult to treat hypothyroidism with persistent over-replacement; at the time of referral she was taking Levothyroxine 25 μg daily. She reported no symptoms of over-replacement. She had no evidence of thyroid associated orbitopathy. Taking Levothyroxine 25 μg daily, TSH remained suppressed at <0.01 mIU/l, Free T_4 14.5 pmol/l and Free T_3 4.3 pmol/l. Thyroid autoantibodies were both positive: thyroid peroxidase 285 unit/ml and TSH receptor 2.9 unit/ml. Ultrasound of the thyroid bed confirmed three hypervascular thyroid nodules measuring 8, 27 and 16 mm. Thyroid hormone replacement was discontinued. Subsequent NM Thyroid scan with uptake Technetium demonstrated three toxic nodules and therefore concordant with the ultrasound. Graves' disease is an autoimmune condition characterised by the production of autoantibodies against the thyroid-stimulating hormone receptor: TSH-receptor antibodies (TRAb). TRAb stimulates target organs with the majority developing hyperthyroidism from stimulation of follicular cell production of thyroid hormone and about half developing thyroid associated orbitopathy. Total thyroidectomy removes target tissue for TRAb and controls hyperthyroidism. Surgical thyroid resection is usually followed by a reduction of TRAb levels in variable degrees; the degree of reduction remains controversial. The median TRAb value half-life has been estimated at 93.5 days after total thyroidectomy in patients without orbitopathy or smoking, such as our patient. This case therefore demonstrates that remnant thyroid cells after total thyroidectomy in Graves' disease can become stimulated under the mediation of TRAb causing recurrent thyrotoxicosis. Revision surgery would be challenging and therefore radioactive iodine necessary.

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EP1197

Where is the thyroxin disappearing?

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Introduction
The most common cause of loss of adequate substitution on a stable dose of replacement therapy is noncompliance. Impaired absorption and weight gain are also possible. We present a rare case of renal loss of thyroxin in severe nephritic syndrome.
Case report
We present a 46 year old female after total thyroidectomy for Graves-Basedow disease. From 2005 she was euthyroid on a stable dose of L-thyroxin (100 μg/day). On physical examination she had oedemas of the lower extremities. A marked hypercholesterolemia (17.49 mmol/l, normal range 0–5.2 mmol/l) and a very high TSH value (92.5 mU/l, normal range 0.27 - 4.2 mU/l) were found. Celiac disease was excluded, abdominal ultrasound was performed with a normal finding. During examination proteinuria (6.19 g/day, normal range to 0.14 g/d) and thyroxin loss in urine (50 μg/l) were found. Renal biopsy was performed with the finding of membranous glomerulopathy (glomerulonephritis). Treatment will be started in nephrology department. After increase of L-thyroxin dose (300 μg/den) normalisation of TSH was established.
Conclusion
Nephrotic syndrome increases L-thyroxine requirements because of urinary loss of free and protein-bound thyroid hormones. Physical examination, careful history taking and laboratory findings are the key to the accurate diagnosis. After treatment of membranous glomerulopathy reduction of L-thyroxin dose is expected.

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EP1198

Hyalinizing trabecular tumor of the thyroid gland

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Hyalinizing trabecular tumor is an uncommon, controversial lesion of thyroid gland. Hyalinizing trabecular neoplasm share similarities with medullary thyroid carcinomas (MTC) and exhibit nuclear features resembling papillary thyroid carcinoma (PTC). However, the clinical behaviour unclear. We aimed to present a rare case of hyalinizing trabecular tumor of thyroid gland and ten-year follow up. A 54-year-old woman who was being followed up because of multinodular goiter on examination of neck, the thyroid gland was nodular, measured 20 mm$\times$ 10 mm and non-tender. Serum FT3, FT4 and TSH were within normal limits. Ultrasonography showed a hypoechoic nodular lesion of 12 mm$\times$6 mm in the right lobe and 29 mm$\times$11 mm hypoechoic nodular lesion in the left lobe. Fine needle aspiration cytology the diagnosis was suspicious due to cells similar to papillary carcinoma cells. She underwent a total thyroidectomy. Histopathological examination showed the nuclei were oval, slightly pleomorphic, trabecular growth pattern, intratrabecular hyalinization and nuclei with grooves and cytoplasmic pseudoinclusions. Immunohistochemically the tumor was thyroglobulin positive, and calcitonin and HBME-1 negative, galectin 3 and TTF-1 focal

positive.The pathological diagnosis was hyalinizing trabecular tumor with lympositic thyroiditis. L-thyroxine 0.1 mg/day therapy was started. The patients treated was found to be euthyroid over the ten year follow-up period. Hyalinizing trabecular tumor is a unique neoplasm of follicular derivation. Most authors consider this tumor to be benign. The differentiation of hyalinizing trabecular tumor from other thyroid tumors such as PTC and MTC, based on overlapping nuclear features. Cytological diagnosis of hyalinizing trabecular tumor has a characteristic trabecular growth pattern and hyalinizing stroma. The prognosis of hyalinizing trabecular tumor is favorable.

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EP1199

Riedel thyroiditis presenting with pleuro-pericardial involvement

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Riedel thyroiditis (RT) is a rare kind of chronic thyroiditis which may be a part of a multifocal systemic fibrosis syndrome. When it is generally accepted as a thyroid manifestation of IgG4 related systemic disease. We hereby present a 54 year old woman who was suffering from shortness of breath because of a mass lesion originating from thyroid and invading neck and upper mediastinal structures, leading to dyspnea and dysphagia, as shown by CT, 15 years ago. After an isthmectomy and decompression surgery she was diagnosed as RT. Corticosteroid therapy was given as the firstline agent and she responded well to the therapy, the dose was tapered off in about 6 months. However she was readmitted with severe dyspnea and chest pain with no large mass lesion at neck. Investigations revealed an exudative pleural and pericardial effusion and mediastinal enlargement. The detailed evaluation of pleuropericardial effusion, did not point out any spesific etiology. Glucocorticoid theraphy was restarted along with colchicines and azathioprine. Alleviation of the symptoms were achieved. She was followed by tamoxifene and colchicines on the long term. She is now symptom-free with loss of the soft tissue mass and effusions for more than 15 years. This case is interesting because of reporting pleuropericardial involvement and the success of being in remission for more than 15 years. Although the etiology and definite treatment of the IgG4 related thyroid diseases are unclear; expanding knowledge about IgG4 related diseases will further clarify the optimal approach to RT.

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EP1200

A Novel Thyroid Hormone Receptor Beta Gene Mutation: p.L450F (c.C1633T) in a family with Resistance to Thyroid Hormone

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Introduction
Resistance to thyroid hormone (RTH) is a rare autosomal dominant (AD) condition caused by mutations of the Thyroid Hormone Receptor Beta (TR-β) gene, resulting in generalized tissue resistance to thyroid hormone. Euthyroidism is usually maintained at the expense of increased levels of thyroid hormones and with non-supressed TSH.
Case report
A 61 year-old-woman was evaluated for increased free T4 index: 2.29 ng/dl (normal, 0.9–2.1) and free T3 index: 4.59 pg/ml (normal, 2.57–4.43) and normal TSH levels:3.22 μUI/ml (normal, 0.3–5)). Analysis were repeated and laboratory error was excluded. The patient was asymptomatic. A physical examination detected a moderate diffuse goitre and a normal resting heart rate. Thyroid antibodies were negative. Sex hormone binding globulin and gonadotrophin α-subunit were within the normal range and pituitary magnetic resonance imaging ruled out a pituitary adenoma. Thyroid ultrasound showed a multinodular goitre with micronodules (<6 mm size). Thyroid scintigraphy demonstrated a diffuse goitre with increased technetium uptake. A diagnosis of RTH was suspected. Molecular genetic studies showed a change in exon 10 of the TR-β gene: p.L450F (c.C1633T). Later, our patient's daughter was also diagnosed of RTH and AD inheritance was demonstrated in family segregation studies.
Conclusions
The rare finding of increased thyroid hormones (T3 and T4) with normal or increased TSH level presents a differential diagnosis between a TSH secreting pituitary adenoma and RTH. Mutational analysis of the TR-β gene enables both definitive diagnosis of RTH and family screening. We present a novel mutation of this gene that has not been previously reported. Although, there have been reported mutations affecting another aminoacid substitution at this position (L450P) in cases of RTH.

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EP1201

Tuberculosis of the thyroid gland: a case report

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Introduction
The involvement of the thyroid gland by tuberculosis is extremely uncommon even in countries in which tuberculosis is endemic. In the majority of the reported cases, thyroid function was preserved. Herein we report a case of thyroid tuberculosis in a patient with a primary hypothyroidism.
Case report
A 52-year-old woman was referred to our department for a gradually growing goiter without compressive symptoms. She presented with a productive cough. Her Past medical history included type 2 diabetes mellitus, goiter and primary hypothyroidism in the last fifteen years. On examination, she had a plunged multinodular goiter. The rest of the clinical examination and laboratory tests were normal. Chest radiography showed a nodule located in the right lung upper lobe. Cervical ultrasonography revealed an enlarged heterogeneous multinodular thyroid gland. Total thyroidectomy and lung nodule biopsy were performed to the patient. Thyroid histopathological examination showed benign multinodular hyperplasia with epithelioid cell granulomas and giant cells. The histopathological examination of the lung biopsy showed foci of granulomatous inflammation along with caseous necrosis. The diagnosis of tuberculosis involving the lungs and the thyroid gland was established. Then, patient was put on antitubercular drugs with a good recovery.
Conclusion
Although thyroid tuberculosis is a rare condition, it should be considered as differential diagnosis of thyroid masses especially in an endemic country. In this case, the use of fine needle aspiration biopsy can help to avoid unnecessary surgical interventions.

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EP1202

Follicular variant of papillary thyroid carcinoma with lung, bone, and soft tissue metastases

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We report on a case of a 63-year-old male patient with a history of metastatic DTC, with both lung and bone metastases and an additional paravertebral mass. The patient presented with enlargement of the left thyroid lobe. FNA was positive for malignancy and subsequent CTs were negative for distant metastases, whereas laboratory tests showed elevated thyroglobulin (Tg>500 ng/ml). The patient underwent total thyroidectomy and the pathology report revealed a multifocal, follicular variant of papillary thyroid cancer, with localized extrathyroidal extention. He was then referred to the Endocrinology Department. After withdrawal of levothyroxine (preablation laboratory results: TSH: 52.6 μIU/ml, Tg: 9900 ng/ml) the patient received 80 mCi of I^{131} (RAI uptake: 7,6%). A subsequent SPECT/CT scan revealed lung and bone metastases (ribs with adjacent soft tissue mass). Thoracic CT showed bilateral, scattered lung metastases with lymph node enlargement of the hili as well as a paravertebral soft tissue mass 6.2×3.8 cm of diameter which metastasize to the 7th rib and the

respective thoracic vertebra. $Tc99^{m}$ bone scan showed metastases in the ribs (6th, 7th) as well as the 7th thoracic vertebra. The patient 6 months later received 150 mCi I^{131}. The post-therapeutic scan revealed radioiodine avid metastases in both lungs without response to the previous therapy as well as uptake in the right maxillary area. The latter blood test (6 months after the 2nd RAI) showed biochemical improvement (Tg: 403 ng/ml, anti-Tg <42 IU/ml), while the last thoracic CT (6 months after the 2nd RAI treatment) revealed radiologic improvement on the lung metastases and the paravertebral mass (5.6×3 cm), as well as disappearance of the right maxillary area lesion. The case presented is about the management of a patient with DTC and distant metastases, without objective benefit showed by the postablation scan, but followed by decreasing Tg and radiologic improvement revealed by computed tomography.

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EP1203

Severe acute hepatitis associated with thyrotoxicosis

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Liver dysfunction related to hyperthyroidism encompasses abnormalities associated with the effects of thyroid hormone excess, drug-related hepatic injury, and the presence of concomitant liver disease. Mild liver abnormalities such as hypoalbuminemia and increased serum level of liver enzymes may be seen in 45–90% of patients with hyperthyroidism. Nevertheless, there are a few case reports of thyrotoxicosis associated with severe acute hepatitis. A 37 year old woman presented to the Emergency Department with abdominal pain associated with diarrhea for 2 weeks and new-onset jaundice for 2–3 days. She had been diagnosed with hyperthyroidism 6 months before and it was prescribed treatment with methimazole but she decided to stop the treatment one month later. On initial physical examination there was significant jaundice and tachycardia. Blood pressure and body temperature were normal. There was no exophthalmos and the thyroid gland was diffusely enlarged. There were no findings of heart failure, chronic liver disease, lymphadenopathy or hepatosplenomegaly. Laboratory workup showed hyperthyroidism and abnormal liver function tests: FT3 was 21.59 pg/ml (normal 2.57–4.43), FT4 7.77 ng/dl (normal 0.9–2.1), TSH 0.01 mU/l (normal 0.3–4.2). Total bilirubin 8.47 mg/dl (normal 0.1–1), direct bilirubin 7.7 mg/dl (normal 0.05–0.2), ALT 674 IU/l (normal 0–31), AST 664 IU/l (normal 0–31), GGT 42 IU/l (normal 5–36), albumin 2.9 g/dl (normal 3.4–4.8). After excluding other etiologies for her liver injury, she was treated with antithyroid medications. One week after starting treatment we observed an important decline in FT3 to normal values, bilirubin and liver enzymes dropped to half of maximal values. One month later normalization of thyroid hormones and near normalization of bilirubin and liver enzymes was documented. In conclusion, severe acute hepatitis is rarely associated with thyrotoxicosis. Hyperthyroidism should be rule out in patients with acute liver failure of unknown origin.

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EP1204

Isolated ocular Miasthenia Gravis and Graves' disease – a challenging ophtalmopathy

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We report the case of a Caucasian woman presenting with a challenging differential diagnosis of ophtalmopathy. The patient was diagnosed with Graves' disease during postpartum at the age of 28 (TSH <0.001 U/ml; FT3 6.7 ng/dl; FT4 2.2 ng/dl; TSAb 15 U/l). Besides 16 pack-year smoking history, no other previous disease was known. At examination, exophthalmos grade I/III with bilateral lid retraction was evident. Persistency of the disease despite optimal use of medical antithyroid therapy led to radioactive iodine ablation (10 mCi) at the age of 34.Three months afterwards, hypothyroidism was detected on blood tests results (TSH: 12 U/mL; Free T4: 0.7 ng/dl) and therapy with 100 µg of L-thyroxine was initiated. Two months after therapy, thyroid function was normalized (TSH: 1.3 U/ml; Free T4: 1.1 ng/dl). Exophthalmia persisted, even though TSAb title was virtually undetected (0.6 U/l). At the age of 45, there was onset of binocular vertical diplopia and blurred vision. Upon administration of 500 mg ev Methylprednisolone, symptoms were only transiently relieved and thereafter rapidly worsened. Persistent diplopia and mild exophthalmos were confirmed in ophthalmology appointments. The patient was clinically euthyroid, thyroid function tests were normal under Levothyroxine replacement and TSAbs remained negative. Computed tomographic scan and magnetic resonance imaging of the orbits showed symmetric bilateral exophthalmia (grade I/III) with inferior rectus muscle thickening on the right eye, consistent with Graves' disease. However, the single fiber electromyography revealed a moderate defect in neuromuscular transmission. Anti-acetylcholine receptor antibodies were 14 times the reference value, compatible with the diagnosis of Myasthenia Gravis. Moreover, the patient denied fatigue, movement disorders or other neurological symptoms. By reporting this case, we would like to draw attention for a possible, although rare, association of myasthenia gravis and Graves' ophthalmopathy and stress the importance of a clinical judgment.

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EP1205

Pleiotropic function of vitamin D and goiter

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Objective
Among women over 40 the prevalence of goiter in Poland is over 40% and the prevalence of vitamin D deficiency is over 80%. There have not been any previous studies that investigate the vitamin D level in women with and without goiter.
Methods
152 women-96 with and 56 without nontoxic goiter were examined in 2014. In US examination we calculated the volume of the thyroid gland and volume of nodules. Blood samples for 25-(OH) D total were taken. We made statistical analysis of correlation between volume of the thyroid gland, volume of the nodules and levels of vitamin D.
Results
96 women with goiter size from 5.67 ml to 68.85 ml – mean 19.7 ml, median 15.6 ml, the total nodules volume varied from 0.1 to 39 ml mean 4.59 ml, median 0.94 ml and the control group of 50 women with thyroid volume in normal range from 5.1 to 19.9 mean 11.2, median 11.2 ml. The 25(OH) total levels varied in control group from 5.3 to 31.8 ng/ml, mean – 14.4, median 12.95, and in goiter group from 4.7 to 39.8 ng/ml, mean 15.00, median 13.3 ng/ml. Only 14% in control and 22% in goiter group had vitamin level over 20 ng/ml. We found no correlation between vitamin D level and volume of thyroid gland in goiter group and no correlation between vitamin D level and summary volume of the thyroid nodules. There is negative correlation between vit. D level and thyroid volume in healthy subjects.
Discussion
As vitamin D deficiency affects majority of both groups and can result in osteoporosis, osteomalacia, and increased risk of fragility fractures, our study demonstrates the importance of screening and educating a broader age group of women with goiter disease but also in the 'healthy' population.
Conclusion
There is an unacceptably high level of vitamin D deficiency among women in both examined groups. The pleiotropic effects of vitamin D seems to be insignificant in development of goiter, but may play a role in healthy thyroid.

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EP1206

Amyloid goiter secondary to Crohn's disease

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Introduction
Amyloidosis results from deposition of insoluble proteins in the extracellular space. It can be both primary or secondary to chronic inflammatory diseases. Although microscopic thyroid involvement is common, cases in which it becomes clinically evident (amyloid goiter) are rare.
Case report
Woman, 45 years. In 2009, she was diagnosed with Crohn's disease after Bartholin's gland abscess excision and evaluation for weight loss, anemia and renal failure. In 2010, during hospitalization in Gastroenterology department, an euthyroid diffuse goiter was identified (without compressive symptoms, except easy choking) and she was oriented to endocrinology consultation. Due to chronic kidney disease, she underwent renal biopsy (Jan/2011), that established the diagnosis of renal amyloidosis. Because she presented hepatic cytolysis a liver biopsy was also done, which revealed amyloid deposits in the wall of some portal arteries. She has been followed in Endocrinology since 05/2011, being asymptomatic, with diffuse goiter. Thyroid function tests and calcitonin are normal with negative thyroid antibodies. Thyroid ultrasound has shown an enlarged gland (LD 16×25×58 mm, LE 18×20×57 mm T×AP×L), with increased echogenicity and diffuse heterogeneity, but without dimensional progression. Considering the imaging findings and the presence of systemic amyloidosis, she underwent thyroid core biopsy, which confirmed the amyloid goiter diagnosis.
Discussion
In the majority of cases of amyloid goiter there is a rapid thyroid growth (in weeks to months), although in the case described there was no progression. Despite the widespread involvement of the thyroid by the disease, patients are usually euthyroid. Since amyloid deposits can also be found in association with medullary thyroid carcinoma, this possibility must always be excluded. In conclusion, the diagnosis of amyloid goiter should be considered in patients with systemic amyloidosis or chronic inflammatory disease who present with bilateral and rapidly progressive enlargement of the thyroid, even in the presence of normal thyroid function.

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EP1207

Two case reports of amiodarone induced thyroid dysfunction: thyrotoxic and myxedematous crisis

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Introduction
Amiodarone is a well-established antiarrhythmic drug frequently used in tachyarrhythmias. Side effects include hypothyroidism and hyperthyroidism. Extreme cases such as myxedematous and thyrotoxic crisis are very uncommon. Here we report one case of each of these presentations.
Case Report no.1
A 73-year-old woman with history of atrial fibrillation under treatment with amiodarone presented to the emergency department with headache, nausea and chest pain. On admission, she was tachycardic - atrial fibrillation with heart rate of 127 bpm. Her free T4 (fT4) and TSH were 31.5 ρmol/l and <0.01 mU/l, respectively and her antithyroid antibodies were all negative. Thyroid ultrasound demonstrated a micronodular gland with increased Doppler sign. Amiodarone was discontinued and she was started on propylthiouracil, propranolol, hydrocortisone, cholestyramine and Lugol's iodine, without laboratorial or clinical improvement - sustained tachycardia and coma. As such she was thyroidectomized. Her thyroid function tests and heart rate improved, however she died due to sepsis secondary to MRSA on the 18th post-operative day.
Case Report no.2
A 90-year-old woman with history of atrial fibrillation under treatment with amiodarone presented to the emergency department with a 12-h history of diminished consciousness level. On admission, she was myxedematous, hypothermic, bradycardic and with bradypnea. Laboratory studies revealed respiratory acidemia, increased creatinine, toxic benzodiazepine levels, TSH 80.2 mU/l and fT4 4.47 ρmol/l (antithyroid antibodies were negative). She was started on IV fluids, non-invasive ventilation and antibiotherapy due to suspected pneumonia. Amiodarone was discontinued and IV L-thyroxine (250 μg) and hydrocortisone (200 mg) were administered and continued orally on the following days. She showed dramatical clinical improvement and was discharged after 10 days on oral L-thyroxine 75 μg/day.
Conclusion
Although uncommon, extreme cases of thyroid dysfunction can occur in patients on amiodarone therapy, underlining the importance of thyroid function monitoring.

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EP1208

Hashimoto's thyroiditis in a patient with ectopic thyroid tissue

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Introduction
Abnormalities in the development and migration of the thyroid gland are known to produce ectopic thyroid tissue, usually in the midline between the tongue base and the diaphragm. Hashimoto's thyroiditis involving ectopic thyroid tissue is particularly unusual. Herein we report a case of Hashimoto's thyroiditis developing in a midline thyroid cervical mass.
Observation
A 55-year-old man was referred for hypothyroidism. His physical and psychomotor development was completely normal. His thyroid gland was not palpable in its normal pretracheal position. Elevated thyroid-stimulating hormone levels (TSH = 19.8 μIU/ml, range 0.35–4.5) with low free serum thyroxine (0.64 ng/ml) value were found. In addition, high titers of antiperoxydase antibodies (295.8 IU/ml) were detected. The neck ultrasound revealed a left lobar hypoplasia and a midline cervical mass representing aberrant thyroid tissue due to migration defects. A Tc-99 m pertechnetate marked isotope showed accumulation at the left thyroid lobe and at the midline cervical mass with no uptake at the right thyroid lobe.
Conclusion
Ectopic thyroid tissue itself is not known to demonstrate a predilection for Hashimoto's thyroiditis. Despite its rarity, the presence of ectopic thyroid should be considered in the differential diagnosis of all tongue, neck and trachea masses. The ectopic tissue may be functional and affected by the same pathological processes as the thyroid gland.

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EP1209

Autoimmune thyroid disease occurring as a possible late complication after a non-occupational HIV Postexposure Prophylaxis

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Introduction
Nonoccupational postexposure prophylaxis (nPEP) is a three-drug antiretroviral regimen used to decrease the risk for HIV infection after less than 72 h from nonoccupational exposure to body fluids that might contain HIV. The most frequent side effects concern the gastro-intestinal intolerance, renal and hepatic toxicity, with no hormonal imbalance to have been yet reported.
Case report
24 years old male patient, consulted for palpitations, hoarseness, shortness of breath, laryngeal tightness, weight loss (4 kg /3 months), fatigue, insomnia, recurrent panic attacks and anxiety-symptoms progressively installed since 3 months. Patient's previous history contains a nonoccupational exposure to body fluids containing HIV 8 months previously, treated with nPEP (Lamivudine, Zidovudine and Kaletra- Lopinavir/Ritonavir), with a negative serology at the check-ups. He presented high blood pressure and tachycardia, tremor, hyperhidrosis and excessive preoccupation concerning his illness. Thyroid tests found an autoimmune thyroiditis with subclinical thyrotoxicosis: ATPO = 57.5 IU/ml (*N*: 0–35), TSH = 0.09 μIU/ml (*N*: 0.4–4), FT4 = 1.35 ng/ml (*N*: 0.89–1.76), TRAb- negative, normal thyroid at the ultrasound. Cardiac evaluation was normal so the patient was advised to start betablocker and anxiolitic treatment, along with psychological counselling. At the one month follow-up, the blood test has shown persistence of the thyroid autoimmunity with normalisation of the

function: TSH = 0.602 μIU/ml, FT_4 = 1.38 ng/dl, without any other abnormalities.
Conclusions
The occurrence of the autoimmune thyroid disease after a 6 month period post nPEP has not yet been cited. It may be a result of either the autoimmune system rebound after the antiretroviral therapy or an inflammatory imbalance induced by the treatment with consecutive immune reconstitution syndrome.

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EP1210

Recurrent Thyroiditis in an Amiodarone treated patient: An Illustrative Case Demonstrating the Spectrum of Abnormalities

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A 65 yo gentleman was referred to the endocrinology department with thyrotoxicosis. He had a history of IHD and recurrent VT necessitating amiodarone for 8 years. Routine TFTs had shown TSH undetectable, fT_4 34.1, fT_3 8.7. There were no symptoms or signs of thyrotoxicosis or cardiovascular compromise. He had been treated with carbimazole by his GP for the previous 3 weeks, this was discontinued at the initial evaluation due to recurrent vomiting. TPO antibodies were negative, a thyroid uptake scan showed normal uptake (2.86% at 20 mins) with a hot nodule in the isthmus. The thyroid function normalised over a period of 2 months with no medication. It was felt unsafe to discontinue the amiodarone. Sixteen months later there was a further episode of thyrotoxicosis, again asymptomatic with no CV compromise. A repeat thyroid uptake scan showed a cold thyroid. This episode too was managed conservatively. This was followed by a further two self-resolving episodes (2 and 3 years later); subsequently the patient developed permanent hypothyroidism treated with levothyroxine 100 μg. Amiodarone induced thyrotoxicosis (AIT) comes in two forms: type 1 (iodine-induced excess thyroid hormone production) and type 2 (thyroiditis), though in some patients an overlap is thought to exist. Differentiation of these types can be difficult. Our case seems to demonstrate both forms; initially type 1, then three episodes of type 2. Recurrent thyroiditis has been reported with suppurative thyroiditis and postpartum thyroiditis. Whilst there are reports of recurrence of thyroiditis with ongoing treatment with amiodarone, to our knowledge this is the first case to show four episodes of AIT with ongoing administration of this drug. The continuation of amiodarone is sometimes clinically necessary, but can lead to a longer time to cure if treated with steroids. Thyroidectomy and perhaps radioiodine are options in troublesome cases.

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EP1211

Thyroid storm subsequent to amiodarone-induced thyrotoxicosis

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Introduction
Thyroid storm is a rare medical emergency with high mortality, which usually results from acute exacerbation of hyperthyroidism. Amiodarone is a highly used class III antiarrhythmic drug and amiodarone-induced thyrotoxicosis is an infrequent effect of this medication, whose treatment may be difficult.
Case study
A 20-year old male with congenital cardiomyopathy (Fallot tetralogy and Ebstein anomaly), chronically medicated with amiodarone 200 mg/day since age 2, was admitted to the emergency room with palpitations, diaphoresis, nausea, vomiting and diarrhea. EKG showed atrial fibrillation with rapid ventricular response (HR 160 bpm). Blood analysis showed hyperthyroidism – TSH < 0.005 μUI/ml; FT_3 7.83 pg/ml (2.57–4.43) and FT_4 5.50 ng/dl (0.93–1.70). Burch-Wartofsky's score was 55. He started tiamazol 30 mg/day and prednisolone 40 mg/day, but because of his cardiac disease, amiodarone could not be withdrawn. Despite adequate treatment, there was no clinical response and patient remained hypotensive, taquicardic and at risk of cardiogenic shock. Potassium perchlorate was initiated at 400 mg 8/8 h with subsequent normalization of heart rate and hemodynamic stability. He was discharged after radiofrequency ablation of an abnormal signal pathway with EKC in sinus rhythm and amiodarone was suspended. Thyroid ultrasound showed thyroid goiter (24.5 ml) with heterogeneous structure. There was a lack of 99 mTc uptake in scintigraphy (0.5%). Normalization of hormones was reached after eight months of onset of the disease, with tiamazol 70 mg/day and prednisolone 20 mg/day.
Conclusions
Amiodarone-induced thyrotoxicosis occurs in 5–10% of patients and may cause significant morbidity, especially in patients with significant cardiac disease and when it cannot be discontinued. Differential diagnosis between type 1 and type 2 is not always easy and sometimes mixed forms occur, adding more challenges and difficulty to the treatment, particularly when antithyroid drugs and corticosteroids are ineffective.

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EP1212

Atrial flutter with 1:1 atrioventricular conduction: An uncommon cardiac manifestation of hyperthyroidism

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Introduction
Atrial flutter (AFL) is a rapid, regular atrial tachyarrhythmia that occurs most commonly in patients with underlying structural heart disease. Patients with tachyarrythmias as a result of thyroid storm have been typically treated with beta-blockers to decrease the heart rate and alleviate beta-receptor mediated symptoms. We report an unusual case of AFL with 1:1 atrioventricular (AV) conduction.
Case report
Patient H, M 45 years old was admitted to our hospital with Graves Disease. He presented with typical symptoms which included tiredness, shaking, palpitations and opthalmopathy. He had lost 36 pounds over 3 months. He had a heart rate of 280/min, blood pressure of 130/80 mmHg, a moderate sized goitre without signs of right heart failure. An electrocardiogram revealed atrial flutter with 1:1 (AV) conduction. The echocardiogram showed a preserved internal dimension and overall normal systolic function. The diagnosis of hyperthyroidism was confirmed: Thyroid stimulating hormone: 0.002 mIU/l, Free T_4: 3.52 ng/dl (0.7–1.5). He was treated with propranolol 60 mg/day and thiamazole 40 mg/day. He was placed on anticoagulation with warfarin for a target INR of 2–3. We performed a linear radiofrequency ablation and he reverted to sinus rhythm. His symptoms improved and he was discharged 1 week later.
Conclusion
This case report shows that AFL with 1:1 AV conduction may be observed in patients with hyperthyroidism and rapid supraventricular tachycardia.

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EP1213

Pharyngeal Irritation, Incidental Neck Masses; A difficult journey

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This is a case of a 48-year-old lady initially referred to respiratory clinic with symptoms of breathlessness. She had a high-resolution CT thorax where an incidental finding of a right para-oesophageal 2.4-cm soft tissue density at the level of the thyroid gland identified. A CT neck was performed for further evaluation again showed the soft tissue mass (26 mm × 37 mm) situated to the right of the oesophagus and another mass (16 mm × 26 mm) left of the oesophagus. Discussion at the Lung MDT felt they may represent thyroid nodules but given location and relative normality of the rest of the thyroid parenchyma, parathyroid adenomas were possibilities hence she was referred to the endocrine surgeon. She then described symptoms of irritation in her throat on swallowing over the previous 6 weeks but no subsequent breathing problems. On neck examination, the thyroid lobes were just palpable, with no cervical

lymphadenopathy. She was clinically and biochemically euthyroid with a normal calcium and parathyroid hormone level. Ultrasound thyroid reported hypoechoic heterogenous solid masses posterior to the thyroid; 3 cm on the right and 2 cm on the left. These masses appeared separate from the thyroid with minimal internal vascularity, likely representing parathyroid adenomas. MRI soft tissue neck could not differentiate between parathyroid and thyroid origin. Following Endocrine multi-disciplinary team discussion, the patient had a thyroid technetium scan and technetium MIBI scan with findings concordant that it was probably thyroid in origin rather than parathyroid adenomas. Endoscopic fine needle biopsies found small foci of follicular tissue with immunochemistry showing strong nuclear positive staining with positive thyroglobulin antibodies, suggesting thyroid tissue, not parathyroid.

Conclusion

This case highlights the difficulty differentiating between thyroid and parathyroid masses found incidentally. Dedicated imaging and biopsies may be the only way to confirm the nature of these masses.

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EP1214

Papillary thyroid microcarcinoma in struma ovarii tissue: a case report

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Introduction

Struma ovarii is an uncommon ovarian neoplasm that more than half of itself is made up of thyroid tissue. In clinical trials about the disease, malign transformation has been detected at the rate of 0.5–5%. Because of the disease's rareness, there is no absolute agreement about diagnosis and treatment of the disease.

Case report

A 33-year-old woman admitted to gynecology department with abdominal pain. Her pelvic MR revealed 147×99 mm multiseptated cyst in right over which may compatible with teratoma. On laboratory evaluation, her CA-125 level was 43.8 U/ml (normal range: 0–35). The cyst was excised and frozen section analysis was performed. The frozen section showed stuma ovarii so no additional surgical procedure was performed. Diameter of 300 micron papillary thyroid carcinoma was determined at the histopathological examination. At postoperative evaluation, there was no metastasis on thoracic and abdominal imaging. There was no nodule on thyroid USG. In the second operation, omentectomy, excision of paraovarian palpable lymph nodes and right oophorectomy were performed. Pathologic examination revealed no over invasion or lymph node metastasis. Preoperative and postoperative thyroid function tests were measured in normal range; on the other hand postoperative thyroglobulin level was 0.071 ng/ml (normal range: 1.4–78) and anti-thyroglobulin value was 427 IU/ml (normal range: 0–115). Postoperative CA-125 level of the patient was found to be regressed to 12.9 U/ml. Because of the diameter of the tumor tissue, thyroidectomy or adjuvant radioactive iodine therapy treatment was not performed. There has been no recurrence in 1 year follow-up.

Conclusion

There is still no consensus on the diagnosis and treatment of malignant SO. The general approach is that low-risk cases can be followed without adjuvant radioactive iodine therapy such as primary thyroid papillary carcinoma. However, further studies are needed to determine the effect of this approach on recurrence and mortality rates.

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EP1215

Simultaneous occurrence of RET-negative Medullary Thyroid Carcinoma (MTC) and extrathyroidal B large cell Non-Hodgkin Lymphoma (NHL)

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The simultaneous occurrence of MTC and extrathyroidal B large cell NHL are very rare. MTC may be sporadic or part of a MEN and NHL is not reported in association with MEN. A woman of 76 year old with a history of cholelithiasis and hepatitis B, is admitted for left abdominal pain. On examination it is detected inguinal, axillary and clavicular lymphadenopathy, splenomegaly and also a multinodular thyroid disease. The thyroid function was normal, antithyroid antibodies were negative and calcitonin (Ct) serum levels were moderately elevated (28.9 pg/ml). The thyroid ultrasound will detect bilateral hypoechoic areas the largest to the right of 2.4 cm with hypoechoic halo and peri- and intranodular vascularization. Total body CT scan showed splenomegaly almost breaking and so was made of splenectomy. The histology showed splenic localization of lymphoma diffuse large B cell. The PET/CT scan with F18 FDG was positive of upper- and subdiaphragmatic lymph nodes and a right thyroid nodule. Immunochemotherapy was initiated according to the R-COMP protocol and at the end a new PET/CT F18FDG detects activities only to the lower right thyroid pole. A control of Ct showed an increase to 45.1 pg/ml and the calcium gluconate infusion test was suggestive of MTC (peak Ct $>$2.000 pg/ml). Total thyroidectomy and lymph node draining was performed. Histology showed a MTC bifocal, 2.5–1.5 cm to the right and left respectively, with all node-negative. Screening for MEN 2 was negative. Seven months after surgery Ct levels are $<$1.0 pg/ml; molecular analysis of the RET gene showed no pathogenetic variants. In conclusion, the two neoplasms appear to be independent and not correlated to a multiple cancer syndrome; moreover also in the NHL detect on palpation of the neck and then the morphological examinations a thyroid nodule suggest the dosage of Ct.

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EP1216

miRNAs microarray differential profile in papillary thyroid carcinoma

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Introduction

The deregulation in miRNA expression has been described in thyroid tumors, and is considered an important factor in thyroid carcinogenesis. mRNA expression profiling in cancer allows identifications of signatures associated with diagnosis, staging, prognosis, and response to treatment.

Objective

We aimed to detect miRNAs species differentially expressed between tumor and peritumoral tissue in papillary thyroid carcinoma.

Materials and methods

After informed consent and study approval by ethics committee, 24 patients were included in the study: seven patients with classic papillary thyroid carcinoma (cPTC), 14 patients with follicular variant of papillary thyroid carcinomas (fvPTC) and three patients with insular and sclerosing variant of PTC, using intra-operatively obtained tumor and peritumoral normal tissue. RNA was isolated from thyroid tissue using Trizol (Invitrogen, Life Technologies). miRNA microarray analysis was performed using miRNA Microarray System with miRNA Complete Labeling and Hyb Kit and SurePrint G3 Human miRNA r21 Array Kit (Agilent Technologies). SureScan Microarray Scanner Agilent (G2600D) with Feature Extraction v11.0 and Agilent GeneSpring GX v14.5 were used for data extraction and analysis.

Results

Our analysis showed that 2570 miRNA species differ between normal and tumor tissues. From all these, a fold change (FC) $>$ 1.1 identified 2516 species, with 276 having a FC $>$ 2. Applying an asymptotic P value below 0.05 and Benjamini-Hochberg correction for false-discovery rate we found eight miRNAs significantly different between normal and tumor thyroid tissues, namely hsa-miR-181c-5p, hsa-miR-181d-5p, hsa-miR-221-3p, hsa-miR-34a-5p, hsa-miR-34b-5p, hsa-miR-5703, hsa-miR-630 and hsa-miR-744-5p, 6 of them up-regulated and two of them downregulated in tumor vs normal tissue.

Conclusion

miRNA microarrays expression profile using a specific platform allowed a very good differentiation between tumor and normal thyroid tissue, providing an important tool for the individualized, specific variant-based management of thyroid cancer.

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Simultaneous papillary and medullary thyroid carcinoma in siblings with RET 611 mutation. More than a coincidence?

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Germinal mutations of the oncogene RET originate the development of medullary thyroid carcinoma (MTC) in carriers with phenotypic expression depending on the mutated codon and other unknown factors. Simultaneous detection of differentiated thyroid carcinomas is considered a casual phenomenon (collision tumours). We communicate two brothers with double heterozygous mutation of maternal inheritance at codon 611 of RET, TGC to TTT, changing to encode phenylalanine (C611F), with a simultaneous papillary thyroid carcinoma (PTC).
Case 1
A 42-year-old male who underwent through total thyroidectomy and bilateral central dissection (TT + BCD) after genetic diagnosis in 2006. Basal preoperative calcitonin was 6.0 pg/ml and stimulated, 34 pg/ml. Histology showed a bifocal MTC, the bigger of 3 mm, and a classic infiltrative PTC of 3 mm with intense desmoplastic stromal reaction and four metastatic lymph nodes out of five in central compartment, two with extranodal extension. BRAFV600E mutation was positive. He received 100 mCi of I^{131} with stimulated thyroglobulin of 1.9 ng/ml. Ten years later, he has undetectable calcitonin and excellent therapeutic response.
Case 2
A 48-year-old male received TT + BCD after genetic diagnosis in 2016, with basal calcitonin of 25.2 pg/ml and stimulated of 124.5 pg/ml. Histology showed a bifocal MTC, 6 and 5 mm, and two foci (5 + 2 mm) of well limited not encapsulated follicular variant of PTC, BRAFV600E negative. There was no involvement by any of the two tumours in six resected nodes. After 3 months, basal calcitonin is 0.8 pg/ml, and basal thyroglobulin, without radioiodo, reaches 0.31 ng/dl. We are remarking simultaneous occurrence of MTC and PTC, originated from different thyroid cell types, in siblings bearing the same RET mutation. This coincidence raises the possibility of an underlying common genetic drive in both PTC, although with different mutational events added that explain distinct differentiation, among them BRAF V600E mutation.

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EP1218

Thyroid nodule size at ultrasound as a predictor of malignancy

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Introduction
Most thyroid nodules are benign. Some studies have shown largest nodule size, specially > 4 cm, can predict malignancy and reduce fine needle aspiration (FNA) accuracy. Recent studies, however, have shown conflicting results as to whether nodule size may be used to distinguish at risk-lesions. We attempt to determine whether nodule size predicts thyroid malignancy and to examine accuracy of fine needle aspiration (FNA) by size.
Material and methods
A multicenter, retrospective analytical study was performed on a total of 882 patients with thyroid solitary nodules and put underwent partial or total thyroidectomy between 2010 and 2013. We compared nodules by size cutoffs using Chi-squared and Fisher exact test where appropriate. Binary logistic regression analysis was used to identify the independent factors associated with thyroid malignancy. All data were analyzed using SPSS software for Windows (version 18.0).
Results
Of the 882 nodules, 664 (73%) were benign and 238 (27%) malignant. Nodules < 2 cm had the highest malignancy rate (49.2%). Decreasing malignancy rates (23.1, 16.8, 4.6, and 6.3%) were observed with increasing size (2–3 cm, 3–4 cm, 4–5 cm, > 5 cm). Thyroid nodule size > 4 cm was associated to less risk of malignancy (OR O.589 (0.421–0.824)). After adjusting for patient age and gender, nodules that measured > 4 cm had a greater malignancy risk compared to those measuring < 4 cm (OR 2.031 (*P*:0.001)). In nodules with a benign FNA diagnosis (Bethesda II), the overall malignancy rate (false negative rate) was 10% (35/349). The highest false negative rates (15%) were in nodules < 2 cm. There was no significant difference in the false negative rates for nodules > 4 cm (8%) or < 4 cm (10%) respectively.
Conclusions
After adjusting for patient age and gender, nodules that measured > 4 cm had a greater malignancy risk. The false negative rates were not higher for nodules > 4 cm. Thyroidectomy should not be recommended based solely on nodule size.

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EP1219

Struma ovarii – A report of thirteen cases

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Introduction
Struma ovarii (SO) is a rare ovarian teratoma characterized by the presence of thyroid tissue in > 50% of the tumour. Malignant transformation is rare and defined by the same histological criteria as for thyroid cancer. There is few data on the literature and treatment is controversial. The objective of this study was to describe the clinical, pathologic and treatment characteristics of women diagnosed with SO in our centre.
Methods
Retrospective analysis of the SO followed in our Institution between 2000 and 2015.
Results
A total of 13 patients were identified with a median age at diagnosis of 46 years (range 19–85). No patient had previous history of thyroid disease. In nine cases the diagnosis was made by routine imaging exams and in three cases by associated symptoms (mostly pelvic pain). CA 125 and HE4 serum levels were normal in every patient tested (four and three patients respectively). Seven patients underwent bilateral oophorectomy plus hysterectomy (with or without omentectomy or external iliac lymphadenectomy) and in six the surgical procedure was a unilateral oophorectomy. Three cases were diagnosed as malignant SO. In these cases thyroidectomy followed by radioactive iodine was performed and papillary thyroid cancer (PTC) was diagnosed in two.131I-WBS performed after surgery, showed no uptake in the pelvis in any patient. In one benign SO case, thyroid imaging and fine-needle biopsy disclosed PTC as well. During a median follow-up of 14 months (range 1–78), nine patients remained with no evidence of disease, one died with a non-related cause and one was lost to follow-up. Two of the malignant SO patients were found to have biochemical evidence of disease.
Conclusions
SO was frequently asymptomatic. Patients with malignant SO had often persistence of disease, although they had a good overall survival rate. An important proportion of these patients developed thyroid cancer.

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Diagnosis of medullary thyroid carcinoma at early stage

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Medullary thyroid carcinoma (MTC) is a rare neuroendocrine tumor derived from the thyroid C cells producing calcitonin, ac-counts for 0.6% of all thyroid cancers. It occurs either sporadically or in a hereditary form (RET mutation). MTC can be cured only by complete resection of the thyroid tumor and any loco-regional metastases. Calcitonin (CT) measurement is crucial to the early diagnosis and the follow-up of MTC. If the evaluation of stimulated CT levels is required, a provocative test can be performed. We report the case of a 52-year-old woman presenting with multinodular goiter, positive *TPO* antibody and basal CT in repeated samples 42.92, 38.15, and 33.99 pg/ml respectively. The patient was euthyroid. Plasmatic

metanephrines and PTH were in normal ranges. The thyroid ultrasound showed an isoechoic nodule 6 mm in size with a punctate calcification in the left lobe and two hypoechoic nodes on the right lobe 19 and 9 mm in size, with central and peripheral vascular signal. After a provocative test with high dose Ca was performed, stimulated CT level was 96.6, 98.10 and 82.10 pg/ml at 2, 5 and 10 min respectively. The patient underwent total thyroidectomy. The histology showed multifocal medullary microcarcinoma (max 5/5 mm in the left lobe), pTN: pT1a(m) Nx and positive immunohistochemistry for calcitonin. Postoperatively calcitonin level <0.2 pg/ml and CEA was negative. The mutations of RET protooncogene was tested, too.

Conclusion

We have to pay attention for patients with bCT >10 pg/ml and, a high-dose Ca test is reliable for the identification of MTC.

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EP1221

Clinicopathological characteristics and outcomes of differentiated thyroid carcinoma in children and adolescents

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Introduction

Differentiated thyroid carcinoma is a rare entity in pediatric population, with particularities in diagnosis, management and outcomes.

Methods, aim

Retrospective noninterventional study describing clinical presentation and outcomes of children with DTC.

Results

Between 2011 and 2017 54 children and adolescents aged 7.8–18 years (mean age at diagnoses 14.4 years) with DTC were diagnosed/followed up in our Institution. The female to male ratio was 3.5:1. In 70% cases unilateral thyroid nodule was the first manifestation of the disease, in 25.9% cases the DTC was diagnosed during the follow-up for chronic thyroid pathology, whereas in 3.7% cases cervical lymph node enlargement was the first clinical sign. 29.6% patients had cervical node involvement at diagnosis, 9.3% had pulmonary metastases. The initial tumour size (over 4 cm diameter), the diffuse sclerosing form of papillary cancer were independent risk factors for initial metastasis. A total thyroidectomy was performed in 58.5% cases, a total thyroidectomy with central neck dissection in 41.5% cases. 57.4% patients were classifies as low risk, 18.6% as high risk patients. The follow-up period was between 1 and 98 month, with an average of 30.4 months. At the last visit 36.3% patients had a good response to therapy, 28.5% were in complete remission of the disease and 9.5% had stable persistent disease.

Conclusion

DTC in children and adolescents has good prognosis even in loco-regionaly advanced forms of the disease.

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Nuclear Receptors and Signal Transduction

EP1222

The human TRα variants affect the specification of haematopoietic stem cells during zebrafish haematopoiesis

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Anaemia in RTHα patients correlates with documented abnormal erythropoiesis and reduced haematocrit in TRα-null or mutant mice, but the underlying mechanisms and characterization of the defect remain elusive. In a previous work, we described that the injection of several hTRα variants in zebrafish eggs caused a marked reduction of circulating erythrocytes at later stages of the erythropoiesis. To characterise the involvement of TRα during erythrocyte development, we analysed by qRT-PCR and *in situ* hybridization (ISH) the expression of different haematopoietic markers. We microinjected the zebrafish eggs at 1–2 cells stage with 80pg/embryos of the purified mRNAs of several hTRα variants, and from the 6-hpf, the injected embryos were treated with the control vehicle, or with 20 μM-T3, added in the harvested water. By qRT-PCR, the expression of genes involved in the specification of lateral mesoderm (*cdx4*, bmp2b, smad5, *chd*), induction and proliferation of haematopoietic stem cells (HSC) (*tal1*, lmo2, gata1, gata2) and proliferation of erythrocytes (*zin*, grx5, cia, cha) appeared significantly reduced in all hTRα-injected embryos. Consistent with previous results, the treatment with high T3 doses can rescue the DN-activity of the missense variants D211G and A263V, whereas the truncated receptors A382PfsX7, E403X and F397fs406X are unaffected by TH treatment. Furthermore, we analysed the specification of HSC in embryos at 8-somite stage, by ISH. The vast majority of the hTRα-injected embryos showed a reduced or undetectable expression of early erythropoiesis markers, such as c-myb, pu.1, *tal1* and *gata1* in anterior or posterior lateral mesoderm. At 36-hpf, we also observed a dramatic reduction of *gata1* in the intermediated cell mass of hTRα-injected embryos. Therefore, our results highlight a relevant role for TRα during the early phases of the primitive haematopoiesis, when the HSC start to proliferate and differentiate.

Research founding

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Paediatric Endocrinology

EP1223

An interesting etiology in childhood choreoathetosis; autoimmune hyperthyroiditis

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Introduction

Neurologic symptoms due to autoimmune encephalopathy related to autoimmune hyperthyroidism (AEAH) cases are very rare in childhood. The reason why hyperthyroidism causes this situation is still unknown. In this case we discussed the diagnosis, treatment and follow-up of a case with choreoathetosis in the review of literature.

Case

15 years old female admitted to hospital with the complaint of nervousness, discomfort for last 3 weeks. There was not any particular feature in personal and family history. In physical examination, heart rate was 110/min, goiter, exophthalmos, dysarthria, involuntary hand-foot movements, and decrement of fine motor skills was observed. Laboratory results were sT3: 12.59 ng/dl, sT4:3.6 ng/dl, TSH:0.007 μU/ml anti-TPO 591.4 595 IU/ml, ani-Tg:357.9 IU/ml, TRAb: positive. In thyroid ultrasonography volume $>+2$S.D., and parenchymal heterogeneity were observed. History of beta streptococcus infection was negative, mitral valve prolapse and non-rheumatologic mitral regurgitation was seen on echocardiography so Sydenham's chorea was not considered. Lupus antibodies were negative; C3, C4, cranial MR and MR spectrogram were normal. Anti-thyroid and beta-blocker treatment were started. *On the 14th day of the treatment major recovery in patient's walking and talking were observed.* Recovery of the fine motor skills was evaluated comparatively with weekly video records. On the first month of the treatment fine motor skills were definitely normal.

Discussion

Cranial hypoperfusion due to cerebral vasculitis, autoimmunity specific to cerebral tissues and primary demyelination secondary to neuronal dysfunction were blamed in pathogenesis of AEAH. Plasmapheresis and corticosteroids are used in addition to anti-thyroid drugs in the treatment. *The best aspect of is our patient responded anti-thyroid drugs well*. Our case is very challenging since *it reminds us the autoimmune thyroiditis in the etiology of major neurologic symptoms in children and adolescents*.

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EP1224

Thyroid pathology and breasts diseases in adolescent girls

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Several studies have noted that there is a connection between thyroid pathology and breast diseases.

Purpose

The study was undertaken to estimate the frequency of the breasts diseases in adolescent girls with thyroid pathology.

Patients and methods

The study included 2371 girls (aged 10–18 years). Thyroid diseases were diagnosed on the basis of hormonal analysis and typical picture of examination and thyroid ultrasound. Breast diseases were diagnosed on the basis of signs and typical picture of breast ultrasound. We have identified the two groups: girls ($n=618$) with thyroid pathology (group I) and girls ($n=30$) without thyroid pathology (control group). Statistical analysis was performed using Mann-Whitney Test, P value of <0.05 were considered statistically significant. This study has been carried out in accordance with the Helsinki Declaration.

Results

The endemic goiter was diagnosed in every forth girls. Autoimmune thyroiditis was found in 30 girls, nodul goiter in 4 and congenital hypothyroidism (later form) in 2 adolescent girls. The investigation shows that every adolescent girl with thyroid diseases had breast disorders. Breast cysts (cystic dysplasia) was diagnosed in 42% cases, fibrous mastopathy (dysplasia) – in 35%, adenosis mastopathy – in 18%, breast secretion – in 5% and fibroadenoma in 4 patients. All girls with breast dysplasia and fibroadenoma complained of mastalgia. The average level on the visual analog pain scale in cases of mastalgia amounted 6.9 ± 2.1 points (in group I). The investigation shows that only 2 girls without thyroid pathology had breast diseases (predmenstrual mastalgia) (<0.001). The average level on the visual analog pain scale in control group was 3.8 ± 1.4 points ($P=0.02$).

Conclusions

This study has shown a high frequency of the breast diseases among the adolescent girls with thyroid pathology. Thyroid diseases are risk factor for breast disorders and show the necessity of for observation and examination of breast.

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EP1225

Age and development stage dependent association between thyroid hormones and growth hormone and linear growth velocity in boys between the age of 1 and 20 years

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During the time of puberty, thyroid hormones (THs), thyroxin (T_4) and triiodothyronine (T_3), influence growth and developmental processes by working in association with growth hormone (GH), insulin like growth factor-I (IGF-1), glucocorticoids, insulin and gonadal steroids. THs have a direct effect on GH secretion, which stimulates IGF system. It has been suggested that THs control increase in bone length through synergy with GH. This investigation determined age and developmental stage dependent association between circulating concentrations of T_4, T_3, GH and linear growth velocity (LGV). Blood samples were collected from 540 normal healthy boys (27 boys/age group) between 1 to 20 years of age and plasma concentrations of T_4, T_3 and GH were determined using specific ELISA; LGV was measured by calculating changes in height in cm/year. Data were analyzed using Student's t test, ANOVA and Pearson correlation r. The concentrations of T_4 and GH were positively correlated at 3rd, 7–9th, 14–16th and 18th and 19th year. T_4 and GH concentrations were positively correlated at pre-puberty and early and late puberty. The concentrations of T_4 and LGV were positively correlated at 3rd, 4th, 7th, 14–16th and 18–20th year. There were positive correlations between plasma T_4 levels and LGV at pre-puberty and late puberty. There were positive correlations between plasma T_3 and GH concentrations at 1st, 3rd, 6th, 7th, 10th-15th and 18th and 19th year. The plasma T_3 levels were positively correlated with plasma GH concentrations during infancy, pre-puberty, early and mid-puberty. The concentrations of T_3 and LGV were positively correlated at 1st, 3rd, 4th, 7–15th and 18–20th year. The plasma concentrations of T_3 were positively correlated with LGV at infancy, pre-puberty, early and mid-puberty. In conclusion, the present study shows negative correlations between T_4 and GH and LGV and positive correlations between T_3 and GH and LGV at infancy and mid-puberty.

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EP1226

Pediatric case of Autoimmune Polyglandular Syndrome type IIIC: autoimmune thyroid disease and severe autoimmune thrombocytopenia

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Introduction

Association between autoimmune thyroid disease (AITD) and other autoimmune disorders is common and known as autoimmune polyglandular syndrome (APS). It may involve hypoparathyoridism with Addison disease (AD) and mucocutaneous candidiasis – APS type I, AD with Diabetes mellitus type 1 (DM1) or AITD- APS type II, AITD associated with other autoimmune diseases (excluding AD): DM1- type IIIa, pernicious anemia- IIIb, or alopecia and/or vitiligo and/or other autoimmune disorder- IIIc, any other combination being classified as APS type IV. We report a case of a 15-year old patient diagnosed simultaneously with Graves disease (GD) and severe autoimmune thrombocytopenia (AIT).

Clinical case

A 15-year-old female patient was admitted to hospital with palpitations, weight loss, petechiae on lower limbs, during menstruation. Physical examination revealed tachycardia, goiter, thyroid bruit, fine distal tremor, petechiae of trunk, upper and lower limbs. Abnormalities in laboratory studies: thrombocytopenia-platelet count: 4.0×10^3/ul, clinical hyperthyroidism with positive TSH receptor antibody. Myelogram: normal. Thyroid ultrasonography: enlarged thyroid gland, colour Doppler: increased blood flow. She was treated with intravenous immunoglobulin (IVIG), platelets concentrate and started methimazole. During follow-up she had 4 more episodes of severe thrombocytopenia, with good however temporary response to therapy with IVIG or intravenous corticosteroids. Meanwhile vitamin B12 deficiency was detected and vitamin B12 replacement therapy started. After normalization of thyroid function, maintaining low dose of methimazole, thrombocytopenia persisted (platelet count $>20\times10^3$/ul). Anty-glutamic acid decarboxylase(GAD) antibodies were tested: positive, without hyperglycemia.

Comments

Although some autoimmune diseases may coexist, combination of AIT and GD is rarely reported. Moreover it was unusual because of juvenile onset, severity of thrombocytopenia, simultaneous diagnosis of GD, concomitant presence of GAD antibodies and vitamin B12 deficiency. The patient needs to be monitored closely for early detection of other autoimmune disorders or glandular failure and initiate hormone replacement therapy if it is established.

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EP1227

Pediatric thyroid nodule: cytologic and histopathologic correlation

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Background

Thyroid nodule in the pediatric age group is rare, but the rate of malignancy is much higher than adult population. Fine needle aspiration biopsy (FNAB) is an

accurate test commonly used to determine whether thyroid nodules are malignant in adults. However, less is known about its diagnostic accuracy for this purpose in children.
Aim
To characterize the outcomes of FNAB of nodular thyroid disease at a pediatric tertiary-care institution and to correlate cytopathology with histopathology.
Materials and methods
Retrospective analysis to identify children who underwent FNAB of the thyroid between 2000 and 2016. Epidemiological, clinical, radiological, cytologic and histopathologic data were analysed. The smears were categorized according to The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) into six categories – Nondiagnostic, benign, atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS), suspicious for follicular neoplasm (SFN), suspicious for malignancy (SM), and malignancy.
Results
Out of 32 cases, 87.5% were females. Patients ranged in age from 6.8 to 17.9 years (mean $\pm$ S.D., 14.8 $\pm$ 2.6 years). Seven individuals underwent more than one FNAB. Histological follow-up was available in 50%cases. The diagnosis according to TBSRTC included 3 (9.4%) nondiagnostic, 22 (68.8%) benign, 1 (3.1%) AUS/FLUS, 0SFN, 2 (6.3%) SM, and 4 (12.5%) malignancy cases. On histological follow-up ($n=16$), the rate of malignancy was 50%.There was no difference in the ecografic size of the nodule of benign versus malignant lesions ($P=0.27$) or diagnostic versus non-diagnostic lesions ($P=0.61$). No difference was found in benign versus malignant lesions ($P=0.97$) or diagnostic versus non-diagnostic lesions ($P=0.60$), concerning mean age. Diagnoses at cytopathology and surgical pathology were concordant in 9/14 (64%) nodules. Overall sensitivity of FNAB was 66.7% and specificity was 75%.
Conclusion
Due to the limited sample size our FNAB sensitivity and specificity are lower than the previous reported on literature (90.6–100% and 76.2–100%, respectively). In patients whose cytology was reported as inadequate or benign, is important to maintain follow-ups.

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Thyroid (non-cancer)

EP1228

Thyroid autoimmunity in beta thalassemia minor

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Background-aim
Tendency to autoimmune diseases has been reported to be increased in beta thalassemia minor (BTM). Our aim was to examine the prevalence of thyroid autoimmunity in BTM.
Method
Eighty six adults with BTM and 93 age and gender matched controls were included in the study. The two groups were compared cross-sectionally in terms of anti-thyroid antibodies (anti-TG and anti-TPO) and thyroid hormones. Patients with known autoimmune disorders other than autoimmune thyroid disease were not included in the study.
Results
In the BTM group, serum TSH, FT4, FT3 levels were statistically indifferent from the control group. Serum anti-TG and anti-TPO antibody levels were found to be similar in the two groups. BTM and control groups were similar in terms of anti-thyroid antibody positivity prevalence. In the BTM group, anti-TG was 11.6% and anti-TPO was 14% positive, while these were respectively 14% and 12.9% positive in the control group ($P=0.806$ and $P=0.989$, respectively). The proportion of anti-TG and/or anti-TPO antibody positive subjects was found to be 20.9% in the BTM group, and 20.4% in the control group ($P=0.919$). Ratios of subjects with euthyroidism, hypertiroidism and hypothyroidism were similar in both group.
Conclusion
Because thyroid autoimmunity prevalence in the BTM group is not increased compared to the control group, we consider that there is no necessity for routine anti-thyroid andibodies and thyroid hormone testing in subjects with BTM.

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Thyroid disorders and type 1 diabetes

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Introduction
Type 1 Diabetes is an auto-immune disease caused by a disturbance of the immune system, damaging the Beta-cells. The association with other auto-immune diseases was frequently described, and dysthyroidism represents an important part of these associations. In type 1 diabetes, the hormonal profile can be disturbed regardless of auto-immunity. The goal of our study the thyroid hormonal profile in type 1 diabetes, as well as the prevalence of auto-immune dysthyroidism associated with it.
Material and methods
This is a retrospective cross-sectional study based on the observation of patients admitted for diabetes with insulin deficiency. The positivity of anti-pancreas antibodies testified to the auto-immune characteristic; anti glutamic acid decarboxylase GAD and/or anti tyrosine phosphatase IA2. The goal is to determine the type 1 diabetic patients' thyroid hormonal profile, and the auto-immune dysthyroidism profile.
Results
Our series was conducted with 359 patients: 209 men and 150 women, aged between 10 and 69 years with an average of 28.75 years. The clinical picture was ketotic in the majority of cases: 336 (93.6%), with inaugural ketosis in 313 cases (87.2%). Insulin deficiency varied between one week an 36 months, with an average of 3.75 months and a standard deviation of 6.8 months, exceeding 6 months achieving a slow form and a previous oral treatment in 24% of cases. Regarding weight, the average BMI was 22 (extremes: 15 and 39), over 30 in 22 patients. Upon admission, average blood sugar levels were 16.40 mmol/l with an average glycosylated hemoglobin HbA1C of 12.32%. Average TSH levels were of 3.23 mUI/l and the average T4 levels = 12.43 pg/l in 242 patients who had thyroid function tests. Auto-immune thyropathies were frequent: 54 patients (71% of cases). Hashimoto's disease dominated the etiologic profile and was confirmed by the presence of anti-TPO antibodies found in 37 patients (48.6% of cases). Basedow's disease was found in 17 other patients (22.3% of cases) with positive anti-TSH receptor antibodies.
Conclusion
Type 1 Diabetes is common in adults and children, and the association with auto-immune diseases is frequent, hence the necessity of looking for these diseases when patients are diagnosed with diabetes.

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EP1230

Keep calm and put on the emergency list: total thyroidectomy for refractory thyrotoxicosis

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The standard management for Grave's thyrotoxicosis includes the use anti-thyroid drugs, surgery and radioactive iodine treatment. In certain -situations,alternative methods including bile acid sequestrants and therapeutic plasma exchange (TPE) have proven effective especially when other treatment modalities fail. We describe a case where conventional and alternative non-invasive measures failed to restore an euthyroid state and resorted to emergency thyroidectomy. A 49 years old female was referred signs and symptoms consistent with Grave's thyrotoxicosis. She was already started on pulse IV methylprednisolone for active thyroid eye disease. Her thyroid functions tests showed a suppressed TSH of <0.05 mIU/l (0.27–4.2),free T4 of 52.7 pmol/l (10.0–21.0) and free T3 of 18 pmol/l (3.5–6.5). Her Thyroid receptor antibodies were high of >100 IU/l (1.0–1.8). She was started on anti-thyroid drugs which were stopped due to side effects. She had active thyroid eye disease so radioiodine was not appropriate and surgery considered the best option. She failed to block on Potassium iodide, and surgery was cancelled due to hyperthyroidism. She was started on Steroids and Cholestyramine but failed to respond with worsening symptoms and biochemistry. As a last resort, therapeutic plasma exchange was initiated with improvement in her thyroid biochemistry but no resolution despite seven sessions. An emergency total thyroidectomy was rearranged as the final resort with steroid and B-blocker cover. Fortunately, the surgery was uneventful and she made an uneventful recovery with subsequent improvement in her thyroid

functions and clinical symptoms. This case demonstrates how Graves's thyrotoxicosis can pose a clinical challenge when it is refractory to all medical therapies including plasma exchange. Total thyroidectomy remains the best and only option, a comprehensive multidisciplinary approach involving an endocrinologist, a surgeon and an anaesthetist is crucial to optimize the outcome and reduce the risk of thyroid storm.

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EP1231

Screening with TSH and anti-TPO antibodies of patients with vitiligo

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Aim
The aim of the study was to evaluate the relation of vitiligo with thyroid autoimmunity.
Materials and methods
A cross sectional study was done on 75 patients clinically diagnosed (old and new) with different types of vitiligo. Patients with known thyroid disease were excluded from the study. Serum TSH and anti-TPO antibodies were measured in all patients.
Results
The prevalence of anti-TPO antibody positivity was found in 23 of 75 patients (30.6%).
Conclusion
Although none of vitiligo patients enrolled in the study had symptoms or signs of thyroid disease at the time of clinical examination anti-TPO antibodies proved to be positive and with high values in almost one third of the patients. Multidisciplinary approach for patients diagnosed with vitiligo and screening with anti-TPO antibodies are strongly recommended.

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EP1232

Clinical aspects of cardiothyreosis in patients with Graves' disease

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Introduction
Cardiothyreosis (CT) is the most frequent and dangerous complication of hyperthyroidism (HT). It is defined as an association of HT with severe heart abnormalities such as: rhythmic troubles, heart and/or coronary insufficiency. The aim of our study was to describe the frequency and the clinical characteristics of CT in Graves' disease (GD).
Methods
Patients with GD were enrolled into a retrospective study. The prevalence and the clinical characteristics of CT were described.
Results
Out of 90 participants with GD, 12.2% patients presented with cardiothyreosis. Their sex ratio (M/F) was 9/2 and their mean age was 46.72 ± 15.11 years. CT was the circumstance of discovery of GD in 2.2% of cases. Its clinical manifestations were palpitation in 75.5%; dyspnea in 24.4% and anginal pain in 5.6%. Different modes of presentation of CT were found: ten cases of atrial fibrillation (ACFA) (90.9%); five cases of Heart failure (45.45%) and three cases of coronary insufficiency (27.27%). Systolic blood pressure was on average 128 ± 11.6 mmHg and mean diastolic blood pressure was 76 ± 19 mmHg. Mean heart frequency was measured at 106 ± 20 beats/min. Underlying mitral valvulopathy was found in two cases. Six out of 11 patients presented anemia (54.5%) and 90.9% had severe hyperthyroidism. Arrhythmia was reduced in 72.7% of the cases, after treating with betablocker.
Conclusion
CT, although rare, remains a serious life-threatening complication of GD. The ACFA is its most common clinical form and underlying cardiac disease is often present.

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EP1233

Risk factors associated with the severity of Graves' ophthalmopathy

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Introduction
Graves' ophthalmopathy (GO) is an autoimmune disorder affecting the retro-orbital tissues. It represents the main extra- thyroidal expression of Graves' disease (GD). Its onset and progression are influenced by several factors that are potentially modifiable. The aim of this study was to identify risk factors for severe GO.
Methods
Patients with GD were enrolled into a retrospective study. We compared possible risk factors and various clinical findings between patients with mild to moderate GO and those with a severe form.
Results
Of 90 participants with GD, 59 patients (65.8%) presented with GO. Their mean age was 35.15 ± 12.25 years and their M/F ratio was 31/28. GO was the circumstance of discovery of GD in 11% of cases. Its clinical manifestations range from mild findings such as tearing (25.6%), conjunctival injection (16.7%), gritty eyes (10%) and photophobia (8, 9%) to more significant findings including exophthalmos (65.6%), eyelids retraction (41.1%), palpebral edema (18.9%), Oculo-palpebral asynergy (17.8%), exposure keratopathy (7.8%), diplopia (6.7%), reduced visual acuity (5.6%) and strabismus (2.2%). GO was mild in 64.4%, moderate in 16.9% and severe in 18.6% of cases. On multiple logistic regression analysis, smoking status ($P = 0.005$) and male gender ($P < 0.001$) were predictive factors associated with the severity of GO. Other factors such as age, initial free T4 level, TSH-receptor antibodies and a history of diabetes were studied but were not predictive of severe GO.
Conclusion
Although various factors may influence the severity of GO, our study showed that smoking and male gender were the major and the more significant risk factors for developing severe GO. Therefore it is important for patients with GD to stop smoking.

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EP1234

Determination of plasma cortisol levels in women with dysthyroidism

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Activation of the corticotropic axis seems to affect the thyroid axis at the central level and/or by a direct effect on the thyroid gland. The aim of this study is to investigate a possible disruption of the adrenal cortical function that would cause dysthyroidism in a population of women by assaying plasma cortisol. The study was carried out in a human population divided into three subpopulations according to plasma levels in TSH, FT4 and FT3: the subpopulation with euthyroidism (control), the subpopulation with hyperthyroidism (Hyper) And the subpopulation with hypothyroidism (Hypo). Hormone levels were determined by radioimmunoassays (FT3, FT4 and cortisol) and radioimmunometric (TSH). Variations in plasma cortisol content in subpopulations with dysthyroids have been observed and are in favor of an interrelation between the two glands. These results could be explained by the fact that factors responsible for the activation of the corticotropic axis are capable of causing structural and functional changes in the thyroid as a function of the nature of the stimulus, Its intensity and its duration.

Keywords: Glucocorticoids, thyroid, hyperthyroidism, hypothyroidism, cortisol.
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EP1235

Therapeutic plasma exchange in the treatment of hyperthyroidism

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Preoperative preparation of the hyperthyroid patient for thyroidectomy is imperative to avoid perioperative complications due to severe thyrotoxicosis. 24-years old woman was admitted at our clinic for uncontrolled Graves' disease. In our case, agranulocytosis introduced by propylthiouracil. Therefore, surgery was the only chance of an effective therapy. In cases when the patient is unresponsive to medical therapy or when such therapy is contraindicated, therapeutic plasma exchange (TPE) could be useful for preparing patients for surgery. After 13th TPE, our patient both FT4 and FT3 levels remained above the normal limits but the sign and symptoms of thyrotoxicosis improved In the literature, number of plasmapheresis sessions done were usually less than 13 except a case of Jod Basedow with 17 sessions We observed a moderate decrease in FT3 and at least decrease in FT4 levels after thirteen session. Total thyroidectomy was performed successfully. In cases when the patient is unresponsive to medical therapy or when such therapy is contraindicated, TPE could be useful for preparing patients with thyrotoxicosis for surgery. It is still unclear why some patients achieve the maximum benefit from TPE, regardless of their etiology. Our patient both FT4 and FT3 levels remained above the normal limits but the sign and symptoms of thyrotoxicosis improved and maybe reduced the risk of thyroid storm in the perioperative period. We continued to use the β-blocker and systemic steroid therapy in order to avoid thyroid storm during the operation and a few days after surgery. These findings suggested that TPE ameliorates the clinical symptoms of thyrotoxicosis rather than thyroid hormone status. It is unclear which elements are responsible for determining patient response to TPE.

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EP1236

Adult outcome of congenital hypothyroidism

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Introduction
It is because of the heavy somatic and especially intellectual impact of congenital hypothyroidism that its systematic screening from birth has been proved to be essential. Numerous publications have already reported the considerable improvement in the prognosis of this condition but still few relate to adults. This preliminary work proposes to report the adult outcome in a cohort of 12 patients followed for congenital hypothyroidism.
Patients and methods
Descriptive study of 12 patients, seven girls and five boys, followed for congenital hypothyroidism in the pediatric department of Mahdia and who reached an age of 18 years.
Results
The mean age at diagnosis was 4.5 months. The average term was 38 SA. The mean birth size was 49.5 cm. The mean birth weight was 3700 g. Regarding statural development: the average final size was 153.5 cm (128–174). The difference between final size and target size was –0.7 DS. The last average BMI was 21.35 kg/m^2 (16–27). Regarding pubertal development: In girls, the onset of breast development (S2) appeared at the average age of 9 and a half years, the average age of menarche was 12 years. In boys, the onset of increased testicular volume (G2) appeared at the average age of 13 years, the onset of pubic hair (P2) at 12 years. For the school curriculum: in primary school, all children were admitted to the normal age of 6 years. Only one patient redoubled in primary. Four patients redoubled in secondary, only nine patients reached the baccalauréat and three left the high school.
Discussion
An improvement in the results is still possible by acting on the different prognostic factors: age at onset of treatment, higher dose of thyroxine in the neonatal period, psychological monitoring with appropriate aids if necessary and above all compliance in adolescence.
Conclusion
It is impossible to draw definitive conclusions from this study, given the small number of patients studied. This is a preliminary study of work to be continued in the adult sector. For this these patients were oriented in the service of adult endocrinology.

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EP1237

Asymptomatic riedel thyroiditis presented in a patient with thyroid storm and polyglandular autoimmune disease

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Riedel Thyroiditis is a rare form of infiltrative and fibrotic disease of the thyroid that is characterized by compressive symptoms resulting from a rapidly enlarging goiter. The association with Graves Thyroiditis and autoimmune diseases is very rare. The aim of this presentation is to report a patient with asymptomatic Riedel Thyroiditis associated with Thyroid Storm and Polyglandular Autoimmune Disease. A 54-year-old female patient with recent diagnosis of Grave's Disease was admitted to our hospital with congestive heart failure, abdominal pain, vomiting and diarrhea. Her medical history was remarkable for dilated myocardiopathy, cholecystectomy and precocious ovarian failure. At physical examination ascites, bilateral pleural effusion and a 50 g goiter with a 19 mm nodule were present. Thyroid Storm was diagnosed according to Burch-Wartofsky Score. A 10 miCu I131 dose was administrated given the impossibility to prescribe antithyroid drugs because of severe liver disease associated. Due to persistent hyperthyroidism a second dose of 12 miCu I131 was administrated. After achieving euthyrodism on L-thyroxine treatment a hepatic biopsy was indicated due to chronic intrahepatic cholestasis with negative antibodies and confirmed a stage 2 Primary Biliary Cirrhosis. Later on the patient presented impaired fasting glycaemia. A pancreatic, adrenal and ovary autoimmune panel was asked and only GADA resulted positive. Histocompatibility study showed HLA DQ9 and DQ4. Three fine needle aspirations (FNA) were performed during follow up due to changes in the vascular flow of the nodule. After a negative first result the second FNA leads to III Bethesda diagnosis. Given the insufficient material obtained during the third a total thyroidectomy was indicated. Histopathological examination revealed a 1.5 cm Follicular Adenoma surrounded by Riedel Thyroiditis. To our knowledge asymptomatic Riedel Thyroiditis associated with Thyroid Storm and Polyglandular Autoimmune Disease has not been described.

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EP1238

Congenital hypothyroidism in children with down syndrome

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Introduction
Congenital hypothyroidism is 30 times more frequent in newborns with Down syndrome (DS) than in the population of healthy children. Mild isolated TSH elevation with normal thyroxine (T4) levels is the most commonly seen pattern of thyroid dysfunction in these children.
Patients and methods
A retrospective study was carried out on eleven patients with DS in the pediatric department of Mahdia who were followed for congenital hypothyroidism.
Results
The average age of diagnosis of hypothyroidism was 3 months. Trisomy 21 was free in 10 patients and secondary to a translocation (46, XY, t rob (14;21), +21) in a single patient. Four patients had interventricular communication, 3 patients had atrial septal defects, 2 patients had arteriovenous communication and only one patient had cleft palate. Renal ultrasound was normal in all patients except one patient who had a moderate left pyelocalicial dilatation. Thyroid hormone tests were done after the discovery of an umbilical hernia in one patient and a neonatal jaundice in 3 patients; the thyroid assessment was then requested before the genetic confirmation of trisomy 21 by the karyotype. For the remaining 7 patients, hypothyroidism was discovered during a biological assessment requested as part of the systematic follow-up of these patients. The mean TSH value was 13.72 μU/ml. Hypothyroidism was subclinical in 4 patients (with normal T4 value). Cervical ultrasound showed a thyroid gland in place in all patients. No patients developed goiter. The initial mean dose of L-thyroxine was 7.25 μg/kg/d. After 3.25 years of follow-up, hypothyroidism proved to be transient in one patient while it was permanent in the others.
Conclusion
Newborns with DS have often subclinical hypothyroidism at birth. Systematic screening at birth and subsequent repeat screening is necessary because L-thyroxine administration will improve growth, hypotonia and psychomotor functions in these patients.

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EP1239

Retrospective audit: To investigate the long-term outcome of fixed dose 300 MBq of radioiodine (131-I) treatment for Autonomous Toxic Thyroid Nodule

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Introduction
Radioiodine (131-I) treatment for benign thyroid disease has a 70 year history. Among the radioactive isotopes, (131-I) can be used successfully. The intention of radioiodine treatment is primarily to induce a euthyroid or hypothyroid state, but in the case of large multinodular goitres, shrinkage represents a secondary aim of therapy. The optimal method for determining iodine-131 treatment doses for Toxic Thyroid nodule is unknown, and techniques have varied from a fixed dose to more elaborate calculations based upon gland size, iodine uptake, and iodine turnover. Historically, UK prescribing has varied widely according to local custom and practice. The range of activities currently prescribed varies between 200–800 mega Becquerel (MBq), with the majority of patients receiving 400–600 MBq. Toxic adenoma, usually mild hyperthyroidism required 500 MBq of 131-I radioiodine.
Data/Method
We collected data from nuclear medicine department and hospital electronic and paper patient records. In this retrospective audit we had total 10 patients (8-female and 2 male) who received a single fixed dose radioiodine (131-I) for autonomous toxic thyroid nodule in the 10-year period from 2007–2016. Patients' age were between 20 to 75 years. All patients had suppressed TSH at <0.05 nmol/l, with mildly raised thyroid hormones, and thyroid antibodies (TPO and TR) were negative which tended to excluded thyroid immune disorders.
Results
We checked their Thyroid function tests at 3, 6, 12 and 24 -month periods. There were significant improvements in thyroid function tests, with 4/10 patients achieving results within the euthyroid range and 6 patients becoming hypothyroid. All nodules shrank down to become non-palpable and no patient required a repeated dose of 131-I.
Recommendations
Though, 500MBq of 131-I radioiodine is recommended for toxic thyroid adenoma in the UK, our data showed that a smaller fixed dose is 100% effective and probably associated with lower rate of hypothyroidism (60%) at 2 years. **Ref; Radioiodine in the management of benign thyroid disease Clinical guidelines, Royal College of Physicians, UK.**

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EP1240

Assessment of thyroid functions, thyroid autoimmunity and insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease

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Introduction
Non-alcoholic fatty liver disease (NAFLD) is a common cause of impaired liver functions. It is associated with hepatic and adipose tissue insulin resistance (IR) as well as decreased whole-body insulin sensitivity. Thyroid hormones are important for the intrahepatic metabolism of lipids. Thyroid disorders have been associated with IR due to various mechanisms such as altered insulin secretion and lipid levels.
Aim
The aim of our study was to assess thyroid functions, thyroid autoimmunity and IR in non-diabetic patients with NAFLD.
Material and methods
The study was conducted on 90 non-diabetic subjects (60 patients with NAFLD and 30 subjects with normal liver). Both groups were sex matched. Ultrasonography was used to categorize the study subjects into NAFLD and normal liver groups. Thyroid functions and thyroid peroxidase antibody (TPO-Ab) were assessed in all subjects. Homeostatic model assessment (HOMA-IR) was used to assess IR in the study population.
Results
Our study showed a highly-significant positive correlation between NAFLD and IR ($P<0.001$). It also showed a significant positive correlation between NAFLD and thyroid functions with higher prevalence of subclinical thyroid dysfunction in NAFLD patients ($P=0.02$). Thyroid functions didn't show any statistically significant correlations with IR, but TPO-Ab showed significant positive correlation with IR ($P=0.02$) within the total study population.
Conclusion
In non-diabetic patients, IR and thyroid dysfunction have strong correlations with NAFLD. The role of thyroid autoimmunity in this relationship needs further assessment.

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EP1241

Two pseudomalabsorbtion cases successfully treated with parenteral levothyroxine

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Hypothyroidism is a common endocrine disorder which is easily treatable by an appropriate thyroid hormone replacement therapy in the majority of patients. In some patients, hypothyroidism is refractory to oral levothyroxine substitution. Common causes of lack of response to levothyroxine replacement comprise non-compliance and impaired absorption. We report a case of pseudomalabsorption of levothyroxine. Here, we report two female patients with hypothyroidism who had multinodüler goiter and thyroid papillary carcinoma with total thyroidectomy, despite the use of levothyroxine sodium at very high doses (800 mcg/day to 1100 mcg/day). Desired blood TSH and fT4 levels were reached soon after the days of administration of levothyroxine by parenteral routes(intramusculer-intravenosus) to the patient who had malabsorption but no detectable etiology. By investigation during hospitalization in the endocrinology department. Symptoms of the patients have declined. Clinical and laboratory improvement in pollinic follow-ups continued in these two patients. With these findings, these two patients were diagnosed as pseudomalabsorbtion.

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EP1242

Follow-up observations on nodular goiter in Japanese – Progression and related factors

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Nodular goiter (ND) is increasingly found by image analysis. The long-term course of ND, however, is not necessarily clear and may differ in locality. The present study analyzed the changes of ND in Japanese, taking iodine-rich foods, during follow-up periods.
Patients and methods
Patients ($n=4,229$) were followed up to 28 years (3.4 ± 5.8 years). Volume of nodules (VOL) by ultrasonography (US) and laboratory data, including thyroid hormones (TH), thyroglobulin (Tg), autoantibodies (Ab) and thyroid stimulating hormone (TSH), were examined. Increase rates of VOL (VIR, start from 100%) and Tg were compared in 5 periodic intervals; B-period (<2 years), C (2- yrs), D (3- yrs), E (5- yrs) and F (10- yrs).
Results
1) VIR in 5 periods: In 6 scales (-50% to 400%-), NOD (%) of VIR $<150\%$, clinically 'unchanged', decreased in A (81%) to F (43%), while NOD (%) of VIR $>200\%$, 'visible enlargement' increased; A (11%) to F (46%). 2) Analysis in solitary nodules ($n=1,314$): a) VIR increased; B ($119\pm82\%$) to F (176 ± 140) ($P<0.05$). b) Serum Tg showed mild increase; B ($105\pm82\%$) to F (134 ± 131). c) US detected fluids, 'cystic', more in F (78%) than in B (32%). 3) Pathology: VIR of adenomatous goiter (AG) was 15% higher than that of non-AG ($P<0.05$). 4) Factors related to VIR: Initial VOL, Abs and length of follow-up periods were significantly related to VIR. Use of ethanol or TH-drugs also influenced VIR. 5) Late surgery (after 2 years): VIR of surgical cases ($n=24$, $159\pm133\%$) was higher than that of non-surgical cases ($n=572$, $129\pm96\%$, $P=0.14$).
Conclusions
NOD remained unchanged (VIR $<150\%$) in 40% of patients over 10 years. Progression of NOD seemed to be associated with pathology, TSH and Abs. Late surgery tended to be performed in patients with higher VIR.

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EP1243

Aggravation of thyroid dysfunction in a case of thyroid hormone resistance after near total thyroidectomy for multinodular goiter

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Introduction
Resistance to thyroid hormone (RTH), a syndrome reduced end-organ responsiveness to thyroid hormone.
Case report
A 42 year old woman underwent near total thyroidectomy due to her enlarged thyroid with multiple nodules. At that time she had sligthly elevated values of plasma FT4, FT3 and normal TSH values and had no sign and symptoms of thyrotoxicosis or hypothyroidism. After thyroidectomy she recieved L-T4 treatment but her TSH levels remains elevated although FT4 was high. She was reffered endocrinology polyclinic when she began to have symptoms of hypothyroidism like fatique, fibromyalgia. The results were FT4: 1.93 ng/dl (*n*: 0.61–1.12), FT3: 2.2 pg/ml (*n*: 2.5–3.9) TSH > 100 uIU/ml (*n*: 0.27–4.2) under 150 mcg L-T4 treatment. There were no detectable anti-thyroid autoantibodies. Alpha subunit of TSH level was 0.8 IU/l (*n*: 0–0.8) normal. No pituitary adenoma was determined in pituitary MRI. She has no family history of thyroid disease. Genetic test is not available in our hospital. We performed TRH stimulation test after taken off levothyroxine for 14 days and TSH diluted up to 20 times during test. After intravenous bolus injection of TRH (200 mcg) serum TSH concentration increased from 269 uIU/ml (basal value) to a peak of 1330 uIU/ml at 30 min. As a result RTH was considered and LT4 initiated again. After L-T4 titrated up to 175 mcg a day L-T3 added 12.5 mcg two times a day. Six weeks after this treatment FT4: 2.58 ng/dl (*n*: 0.61–1.12), FT3: 3.99 pg/dL (*n*: 2.5–3.9), TSH: 14 uIU/ml s*n*: 0.27–4.2). Her complaints were reduced. Blood pressure was 120/80 mmHg, pulse 74/min. She was clinicaly better.
Conclusion
Treatment with L-T3 would be more appropriate for reducing goitre size than attempting thyroidectomy in that patient. In patients with RTH thyroid gland ablation tends to aggravate thyroid dysfunction and multinodularity. Large glands have been successfully treated by administration of a single high dose of L-T3 given every other day. Symptoms of thyrotoxicosis usually respond to the administration of the beta bloker, atenolol.

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EP1244

Thyroid function and weight loss after Roux-en-Y gastric bypass: observational study

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Background
TSH seems to be positively related to the degree of obesity and weight loss seems to induce a reduction in the TSH levels and T3Total. TSH is the first regulatory mechanism of total energy expenditure and T3 regulates energy metabolism and thermogenesis (1)
Objective
The aim of this study was to investigate the association between thyroid function and body mass index (BMI) in obese population. And evaluate the influence of weight reduction after gastric by-pass on thyroid hormone levels.
Design
Retrospective observational study
Setting
A single center study in Curitiba, Brazil.
Methods
We studied 215 obese patients (BMI 35–58.5 kg/m^2), age between 18–65 years, baseline, 3, 6, 12, 24 months after laparoscopic Roux-en-Y gastric bypass (RYGBP). Participants with thyroid disorders were excluded.
Results
Baseline TSH concentration was not associated with baseline BMI (Pearson = 0.003; $P = 0.971$). There were a significantly decrease in serum TSH after RYGBP until 24 months ($P = < 0.001$) (Figure 1), but did not correlate with weight loss (Pearson = 0.08; $P = 0.303$). Subclinical hypothyroidism prevalence was 9.3% ($n = 20$) before RYGBP. At 12 months, 8.7% ($n = 17$) of this patients had TSH < 4.5 ($P = 0.003$).

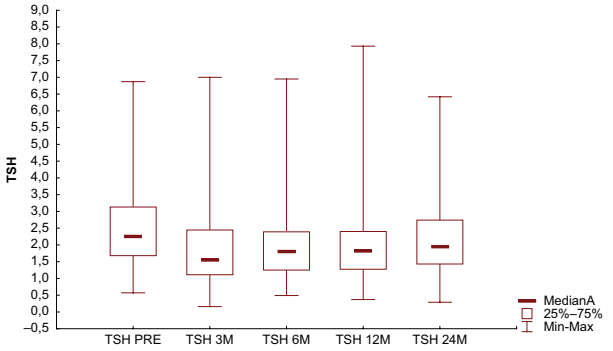

Figure 1

Limitations
This study is a retrospective review and did not employ controls, blinding, or randomization. Additionally, the thyroid antibodies did not evaluate.
Conclusion
Weight loss after the gastric bypass improved and normalized thyroid hormone levels. More studies are required to clarify the reason of decrease in serum TSH.

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EP1245

Correlation between serum nitrite (NO2) levels, TQ7 and GHQ12 questionnaire scores in treatment-naïve hypothyroid patients

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Introduction
Primary hypothyroidism, as a clinical syndrome caused by insufficiency or inefficacy of thyroid hormones, significantly influences on patients' quality of life (QoL). Accelerated atherosclerosis induces increased cardiovascular morbidity and mortality rates in hypothyroid patients. Serum NO2 levels, the stable NO metabolites, are among well-known markers for endothelial dysfunction and atherosclerosis in hypothyroidism. We examined the correlation between serum NO2 levels and QoL questionnaires scores (TQ7 and GHQ12) in treatment-naïve hypothyroid females.
Material and methods
Cross-sectional study involved 82 females, divided into three groups according to TSH and fT4 levels: latent (22) and overt (22) hypothyroid, and euthyroid (38) group, respectively. Initially, after informed consent was signed, serum NO2 levels were measured and TQ7 and GHQ12 questionnaires were fulfilled. Obtained data were analysed with appropriate statistical methods. Statistical significance was 0.05.
Results
Overall mean of NO2 level was 11.2 μmol/l (0.9–79.0 μmol/l) and didn't differ between groups. Mean overall TQ7 and GHQ12 scores were 14 (5–40) and 12 (1–32) respectively, and statistically differ between groups ($P < 0.01$). Correlation between serum NO2 levels and TQ7 and GHQ12 scores didn't significantly differ (ρNO2/TQ7 = −0.241, ρNO2/GHQ12 = −0.141; $P > 0.05$).
Conclusions
Decreased serum NO2 levels in hypothyroid groups pointed out to lowered NO bioavailability and therefore endothelial dysfunction. Otherwise, thyroid disease specific questionnaire score determined hypothyroid patients in moderately stressed cluster. A simultaneous use of NO2 levels and QoL scores can alleviate decision to introduce the l-thyroxin management in hypothyroid patients, presumably in latent ones.

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EP1246

Vitamin D levels in Graves' disease (GD) are lower than in general population but do not correlate with laboratory and clinical parameters in GD or SNPs associated with GD

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Introduction
The role of vitamin D in GD is poorly understood. The aim was to compare vitamin D levels in newly diagnosed patients with GD with the general population and to correlate vitamin D levels at diagnosis with laboratory and clinical parameters in GD. Moreover, we examined genetic variation in genes involved in the vitamin D metabolism and their association with GD.
Material and methods
Levels of vitamin D were compared in 292 patients with newly diagnosed GD and 2305 controls. Single nucleotide polymorphisms (SNPs) in the vitamin D receptor (VDR), vitamin D binding protein (DBP) and 1-alpha-hydroxylase (CYP27B1) were examined for association with GD and/or Graves' ophthalmopathy (GO) in 708 patients and 1178 controls.
Results
Patients with GD had significantly lower levels of vitamin D compared to general population (55.0±23.2 vs 87.2±27.6 nmol/l, $P<0.001$). In patients with GD ($n=219$), there was no association between the levels of vitamin D and the levels of free thyroxine (fT4), free triiodothyronine (fT4), thyrotropin receptor antibodies (TRAb), GO at diagnosis, or relapse after terminating treatment with anti-thyroid drugs. Two SNPs in VDR were associated with GD, rs10735810 (OR 1.36, 95% CI 1.02–1.36, $P=0.02$) and rs1544410 (OR 1.47, 95% CI 1.03–1.47, $P=0.02$). However, there was no difference in mean vitamin D levels between genotypes in either rs10735810 (AA 55.9 nmol/l, AG 56.1 nmol/l, GG 54.1 nmol/l, $P=$n.s.) or rs1544410 (AA 56.6 nmol/l, AG 57.5 nmol/l, GG 54.8 nmol/l, $P=$n.s.).
Conclusion
Patients with GD have lower vitamin D levels compared with general population; however, the levels of vitamin D do not affect the laboratory or clinical parameters of the disease. SNPs in the VDR influence the risk of GD through mechanisms other than reducing the vitamin D levels.

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EP1247

Action of several bioavailable antioxidants in orbital fibroblasts from patients with Graves' Orbitopathy (GO): a new frontier in GO treatment?

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Oxidative stress plays a crucial role in the pathogenesis of Graves' Orbitopathy (GO), supporting the use of antioxidants in GO patients. Selenium has a beneficial effect, but other antioxidants have not been investigated. Here we evaluated several antioxidants in primary cultures of orbital fibroblasts from GO patients and control subjects. The following substances were tested: Vitamin C (Vit-C), N-Acetyl-l-Cysteine (NAC), melatonin (Mel), retinol (Ret), beta-carotene (bCar), Vitamin E (Vit-E). Cells were treated with H_2O_2, which induced oxidative stress (increased glutathione disulfide). Pre-incubation with non cytotoxic concentrations of all substances in GO, and with Vit-C, NAC and Mel in control fibroblasts, prevented oxidative stress. H_2O_2 caused increased proliferation, which was reduced by Vit-C, NAC and bCar in GO, but not in control fibroblasts. H_2O_2 did not affect HA release, which was however reduced by NAC and melatonin in GO, and by all substances except for Vit-E in control fibroblasts. Our findings show an antioxidant actions of several compounds, especially NAC, in orbital fibroblasts. Some of the actions are exclusive to GO fibroblasts. These observation have important clinical implication, in that some of these antioxidants could be tested in patients with GO.

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EP1248

Intrathyroidal and peripheral venous blood lymphocyte subset patterns in patients with Graves disease

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Graves' disease (GD) is an autoimmune disease with genetic predisposition. The link with the major histocompatibility complex determines the complexity of the excess thyroid hormones molecular action on immune system that may cause the divergence of autoimmune process in GD, functioning not only in peripheral immune cells, but also in the thyroid. Objective: to study the phenotypic composition of T- and B-lymphocyte subset patterns in peripheral blood and thyroid tissue in patients with GD. Materials and methods. The study included 43 women with GD, mean age 39.95±14.38, who were performed the epifascial thyroidectomy. Phenotypic composition of T – and B-lymphocytes was investigated by flow cytometry. Analysis of stained cells was performed on a flow cytometer FC-500 (Beckman Coulter, USA). Each sample was analyzed at least 50,000 lymphocytes. Results. The median level of thyroid stimulating hormone (TSH), free thyroxine and autoantibodies to TSH receptor was respectively 1,9 (0,9; 2,9) umol/ml, 16,8 (13,2; 19,0) and 15,8 (9,4; 24,2) IU/ml. In peripheral blood of GD patients compared with healthy controls identified the increased in 9.2% the relative number of total T lymphocytes (CD3+, $P<0.001$) and in 5.8% relative level of T-helper cells (CD3+CD4+, $P=0.019$), but decreased content of T-regulatory cells (CD3+CD4+ CD127LowCD25High, $P=0.048$) and total activated T cells ($P<0.001$), T-helper cells (CD3+CD4+CD25+, $P=0.045$) and cytotoxic T-lymphocytes (CD3+CD8+CD25+, $P=0.041$). It is revealed that in the blood of GD patients increased in 35.9% the relative number of B2-lymphocytes (CD19+CD5+, $P=0.003$), while reducing the amount of activated total B cells (CD19+CD23+, $P<0.001$), B2 cells (CD19+CD5−, $P<0.001$), B2− simplet (CD19+CD5-CD27−, $P<0.001$) and B2-memory (CD19+CD5−CD27+, $P<0.001$) cells. In a comparative analysis of the phenotypic composition of T – and B-lymphocytes in peripheral blood and thyroid tissue revealed that in the tissues is 2.3 times higher relative content of total activated T cells (CD3+CD25+, $P=0.037$), in 5.1 times more of activated cytotoxic T-lymphocytes ($P=0.023$), 1.7 times increased the percentage of B2-memory (CD19+CD5−CD27+, $P=0.028$) cells. Conclusions. The reduction of activated T – and B-lymphocytes content in peripheral venous blood of patients with GD is determined by the migration of immune cells in thyroid tissue.

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EP1249

No impact of subclinical hypothyroidism on cognitive functions among the elderly

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Background
Most recent cross sectional and longitudinal studies have failed to find an association between cognitive dysfunction and subclinical hypothyroidism. A recent paper from our country however suggested a significant association.
Objectives
This study was undertaken to determine the prevelance of cognitive impairement among educated, elderly Indian patients (>60 years) with and without subclinical hypothyroidism.

Materials and methods
This study was conducted on educated, elderly patients admitted to the in-patient department of Christian Medical College, Ludhiana. One hundred patients with subclinical hypothyroidism an equal number of controls with normal thyroid functions were interviewed after taking informed consent. Subclinical hypothyroidism was defined as serum TSH level more than 4.0 mIU/L with serum fT3 and fT4 in the normal reference range. Cognitive function was assessed by Hindi/English Mini mental status examination (MMSE) and clock drawing test (CDT).
Results
The cases ($n=100$) had a mean age of 68.2 years, were 59% males and had a mean body mass index of 25.5 kg/m^2 compared to controls ($n=100$) who had a mean age of 69.9 years (P-0.09), were 64% male (P-0.5) and had a mean BMI of 25.3 kg/m^2.All other baseline variables including co-morbidities, family history of dementia, head injury, smoking, alcohol use, fruit and vegetable intake, daily newspaper reading, education and exercise regularity were comparable in both groups. The cases had mean MMSE of 26.1 and controls of 25.9 (P-0.68) respectively The cases had mean CDT of 2.19 and controls 2.18 (P-0.95).
Conclusions
There is no difference in cognitive function in elderly with subclinical hypothyroidism in comparison with elderly population having normal thyroid function.
Keywords: Subclinical, Hypothyroidism, Biochemical, Cognitive functions, Elderly

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EP1250

Prolonged iodine excess due to hysterosalpingography in a pregnant woman

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Introduction
Hysterosalphingography (HSG) is the radiographic examination of uterine cavity and fallopian tubes. It is generally used during evaluation of infertility and radioopaque contrast is injected through cervical duct during the procedure. Lipiodol which is the most commonly used contrast media in HSG is a fatsoluble iodinated contrast media. This iodine is progressively cleared from the body in a period ranging from a few weeks to a few months. Here, we present a 6 week pregnant woman who underwent HSG 9 months ago and has very high urinary iodine excretion.
Case
A 31 years old woman at the 6th week of pregnancy was consultated for high blood glucose. She was evaluated for infertility for 2 years, and HSG was performed 9 months before conception. There was no history of drug or nutritional supplement use that has high iodine content and that might affect iodine status. Iodine excretion was 10087 mcg/L (100–700 mcg/L) in random urine sample and >450 ug/L in 24 hour urine. Her serum TSH was 2.19 uIU/ml, fT4 was 1.32 ng/dl and fT3 was 1.32 pg/ml. Thyroid autoantibodies were negative and thyroid ultrasonography was normal.
Conclusion
The optimal time for normalization of body iodine stores after exposure of iodinated contrast media is not known exactly. Thyroid dysfunctions in the form of both hypothyroidism or thyrotoxicosis can develop in euthyroid subjects after use of iodinated contrast media during HSG. In our case, thyroid functions were normal but urinary iodine was very high even several months after HSG. This suggests that females at reproductive age who underwent HSG might have excess iodine concentration for a prolonged time and should be carefully evaluated for development of thyroid dysfunctions.
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EP1251

The challenge of diagnosing thyroid storm: a comparison of the Japanese Thyroid Association Criteria to de Burch Wartofsky Point Scale

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Thyroid storm (TS) is a rare and life threatening condition that requires a prompt recognition and treatment. The clinical features may overlap with other acute medical conditions. Currently both Akamizu Criteria (JTA) and Burch and Wartofsky Scale (BW) are helpful diagnostics tools.
Objective
To evaluate TS patients according to currently available criteria and to identify the clinical features and outcomes.
Methods
A single center retrospective study covering a 6 year period was performed.
Results
Fifteen cases were identified, resulting in four cases of TS per 10 000 admitted. Mean age 49.8 ± 17.3 years (range: 31–86). Male/Female: 3/12. Etiology: autoimmune ($n=8$), factitious ($n=3$), amiodarone-induced ($n=3$), undetermined ($n=1$). Manifestations at admission: cardiovascular ($n=8$), fever ($n=3$), delirium ($n=2$), diabetic ketoacidosis ($n=1$) and hypokalemic paralysis ($n=1$). Eleven had previous history of thyroid disease. Precipitating factors were found in 12 cases. Thyroid hormone levels did not correlate with the severity of thyrotoxicosis. Mortality rate was 6.6%: 1 patient died from sepsis. Late hospital discharge was found in 4 patients ($P=0.01$): 3 required antithyroid drugs withdrawal and the other received a heart transplant. The table resumes patients according to BW and JTA. JTA fails to detect 4 patients with impending TS (st0), one of which later on developed st1 (p8).
Conclusions
Ours results shows discrepancies between the two diagnostic systems. BW appears to select a higher percentage of patients for aggressive therapy than JTA. This presentation provides useful information for the management of TS, a rare and acute disease that requires high clinical suspicion in order to improve patient survival.

	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
BW	35	40	40	75	60	55	35	35	55	35	35	80	65	65	35
JTA	st0	st0	st2	st1	st1	st2	st1	st0	st1	st2	st2	st1	st1	st1	st0

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EP1252

The role of FNDC5 gene expression in irisin level changes accompanying thyroid pathologies

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Irisin is a recently reported, widely discussed new adipo-myokin secreted mainly by muscle tissue. It is a cleaved and secreted part of fibronectin type III domain containing 5, encoded by the *FNDC5* gene. Some of the previously published studies claim that alterations of irisin levels in patients affected by thyroid diseases may be connected mainly with accompanying myopathy. However, to date it has not been evaluated, whether the changes in expression of *FNDC5* may play a role in irisin level alterations. The aim of the presented study is to assess the expression of *FNDC5* gene in thyroid tissue of subjects with Graves' disease, multinodular benign goiter, toxic goiter and papillary thyroid cancer. The group of 80 patients with above mentioned thyroid pathologies were involved. All included subjects underwent total thyroidectomy for reasons unrelated to the study. Quantitative RT-PCR was used to analyze the *FNDC5* gene expression. As a result, the expression of *FNDC5* was noted in all analyzed samples. No statistical difference between *FNDC5* expression in benign and malignant

changes, as well as conditions associated with hyperthyroidism and euthyroid state were found. Statistically significant overexpression of *FNDC5* in patients with toxic goiter in comparison with tissues affected by Graves' disease, papillary thyroid cancer (tumor staged pT1 or pT2) and controls was observed. In conclusion, toxic goiter may be associated with *FNDC5* overexpression in thyroid tissue, in comparison with Graves' disease, papillary thyroid cancer staged pT1 or pT2 and controls. The *FNDC5* overexpression, on the other hand, is not directly associated with hyperthyroid state, as well as thyroid malignancy development. Hence, the changes in *FNDC5* expression probably do not play the role in irisin concentration changes associated with thyroid pathologies.

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EP1253

Long term effects of the less than total thyroidectomy: The experience of a tertiary care center

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Background and aims
Less than total thyroidectomy (lobectomy, partial or subtotal thyroidectomy) is used mainly to treat thyroid nodules, and/or hyperthyroidism. The aim of the study was to investigate the long term effects of less extensive surgical procedures. such as re-appearance of nodules and the need of thyroxin supplementation, or re-operation.
Material and methods
Retrospective study in a tertiary Academic medical center. The study population comprised initially 76 patients. Of whom 67 patients (age $\pm$ s.d.: 64.1 $\pm$ 13.3, 58 (86.5%) females) who underwent lobectomy, partial thyroidectomy or subtotal thyroidectomy with benign histology and a follow-up equal or longer to 5 years were included (9 excluded). None the patients appeared post-surgery permanent iatrogenic hypoparathyroidism or recurrent laryngeal nerve injury.
Results
Mean follow up was 22.1 $\pm$ 10.8 years. Patients who underwent lobectomy, partial thyroidectomy and subtotal thyroidectomy were 24 (35.8%), 9 (13.5%) and 34 (50.7%), respectively. Patients received thyroxin replacement were 62 (92.5%). Relapse as defined by re-appearance of nodules or recurrence of hyperthyroidism in total population was in 39 (58.2%) patients: 70.8% (17/24) in lobectomy group; 77.8% (7/9) in partial thyroidectomy, and 44.1% (15/34) in subtotal thyroidectomy group, respectively. Re-operation underwent 7 patients (10.4%) of total or 17.9% of the recurrence cases. Univariate analysis showed that the type of operation and the length of follow up were predictors for relapse (OR: 1.81, 95%CI: 1.03–3.19, $P=0.038$ and OR: 0.92, 95%CI: 0.87–0.97, $P=0.002$, respectively). Multivariate analysis showed that the length of follow up was superior independent factor predicting relapse (OR: 0.92, 95%CI: 0.87–0.98, $P=0.006$).
Conclusions
The majority of patients received thyroxin replacement. The length of follow-up and the type of operation have an impact on relapse, but mostly the length of follow up. Treatment with total thyroidectomy could eventually avoid a relapse and a possible need for re-operation.

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EP1254

Severe hyperthyroidism imposes large amounts of antithyroid compounds

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We present three cases of females with low body weight that needed large amounts of anti-thyroid drugs – 4–5 mg/kg Thiamazole and 50 mg/kg of Propylthiouracil. First patient, aged 32, weight 45 kg, had Graves's disease evolving for more than five years. She has been proposed surgery and needed 1200 mg/day of Propylthiouracil. She delayed surgery for 2 weeks, then the dosage required for euthyroidism was 1800 mg/day for three weeks. The goitre had 1.2 kg, from mandible angle to the supraclavicular region; she did not develop hypoparathyroidism or palsy of recurent laringeal nerve. Second patient, 47 years old,with Graves's disease, Addison disease, came with class III heart failure and severe asthma, She required 1800 mg of PTU before surgery and had persistent hypoparathroidism. Third patient, 60 years old had severe cardiomyopathy at the beginning, left ventricle ejection fraction 15%, atrial fibrillation that nedeed Cordarone both intravenously and orally. The dosage was progressivly increased from 60 to 180 mg/day Thyrozol until safely opperated. Patient did not tolerate Propylthiouracil due rash. Ejection fraction became 30% postopperatively and no complications occurred.

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EP1255

Postpartum thyrotoxicosis – a diagnosis, sometimes, postponed

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Postpartum thyroid dysfunction occurs in 5–10% of women in the general population within one year of delivery. The prevalence of postpartum Graves' disease is estimated at 0.54%. Postpartum thyroiditis is much more common. Differential diagnosis is essential for an adequate treatment. Radioactive iodine uptake can be useful to establish the etiologic diagnosis, but is contraindicated during lactation. Elevated titers of antithyrotropin receptor antibodies (TRAbs) are suggestive of Graves's disease but may be measurable in approximately 10% of patients with painless thyroiditis and their titers can be low in the early phase of Graves' disease. Therefore, the evolution of thyroid function and TRAbs' titers may be needed to distinguish both pathologies. We present the case of a 25-year-old Caucasian woman who presented to the Emergency Department, 4 months after giving birth and still breastfeeding, complaining of palpitations, anxiety, fatigue and insomnia with 1 week of duration and referring a 15 kg weight loss postpartum. She mentioned that her mother had Graves' disease. There was no ophthalmopathy; her heart rate was 140 bpm and the electrocardiogram confirmed sinus tachycardia. Thyroid examination showed a painless tender and slightly enlarged gland. Blood tests – TSH 0.011 uU/nl (0.3–4.2), FT3 > 20 pg/ml (2.3–4.2) and FT4 5.33 ng/dl (0.93–1.7). She was referred to the Endocrinology Department under treatment with methimazole and propranolol. Further testing revealed positive anti-thyroid peroxidase and thyroglobulin antibodies and TRAbs within 'grey zone'. Thyroid function was monitored with slowly tapering of methimazole dosage. Eight months postpartum, despite low methimazole dosage (2.5 mg id) she presented with asymptomatic hypothyroidism (TSH > 100 uU/ml). Anti-thyroid antibodies remained positive but TRAbs were negative. Methimazole was suspended and levothyroxine 25 mcg id initiated. At last follow-up, the patient remains asymptomatic and in euthyroidism. Diagnosis of postpartum thyroiditis was assumed. Monitoring thyroid function and TRAbs levels for several months might be necessary to allow the differential diagnosis.

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EP1256

Clinical characteristics of painless thyroiditis

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Background
There are a lot of painless thyroiditis cases without symptoms diagnosed on health check up or thyroid hormone screening, but there is a few data about it compared to much data about painful subacute thyroiditis. So, we collected data about diagnostic routes, laboratory and clinical characteristics of painless thyroiditis.
Method
Painless thyroiditis patients diagnosed between 2010 and 2016 were reviewed. We defined painless thyroiditis as disease with typical clinical courses of

thyrotoxicosis and sequential hypothyroid phase and decreased uptake on thyroid scan.
Result
Total 191 patients (139 female, 52 male) were involved. The diagnostic routes were classified under four entry. First, health check up: 47 patients, 24.6%. Second, patients evaluated with thyroid function test because of nonspecific other symptoms or routine check up of inpatient: 68 patients, 35.6%. Third, patients evaluated with thyroid function test because of thyrotoxic symptoms or signs (fatigue, palpitation, tremor, goiter etc): 59 patients, 30.9%. Fourth, patients associated with postpartum: 17 patients, 8.9%. Permanent hypothyroidism was not uncommon (7/191; 3.7%). Higher peak TSH level (P value below 0.001) was related with permanent hypothyroidism. 11.5% (22/191) experienced recurrence. Lower peak TSH (P value 0.018) and short duration of thyrotoxicosis phase (P value 0.001) was associated with recurrence.
Discussion
More than 50% of painless thyroiditis was diagnosed on health check up or accidental thyroid function test without typical thyrotoxic symptoms. Many patients with heterogenous parenchymal echogenecity on sonography finding without history of thyroid disease could be go for that cases. Higher peak TSH was related with permanent hypothyroidism. In contrast, lower peak TSH was associated with recurrence and short duration of thyrotoxicosis phase was also related with recurrence.

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EP1257

The effectiveness of parathyroidectomy in children with primary hyperparathyroidism

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Objective
To Evaluate the effectiveness of parathyroidectomy in children with primary hyperparathyroidism.
Materials and methods
Under our observation in the period 2014–2015, were 46 patients with primary hyperparathyroidism at the age of 11–16 years. To assess the effectiveness of parathyroidectomy a questionnaire was used and table PAS (Parathyreoidectomy Assessment of symptoms- table of symptoms in primary hyperparathyroidism to assess the effectiveness of parathyroidectomy).
The results of the study
Evaluation of the effectiveness of parathyroidectomy with regard to the elimination of most symptoms in primary hyperparathyroidism table PAS revealed a statistically significant reduction of symptoms and complaints. The amount of symptoms in the preoperative period was 445, a month after surgery decreased to 350, 3 months later 200, with certainty $P<0.01$. Indicators of the sum of symptoms after 1 year was 155, which represents a dramatic difference compared to the preoperative period. While decrypting the received data of the questionnaires, it became evident a significant reduction of complaints and symptoms of primary hyperparathyroidism which undoubtedly attests to the effectiveness of the operation.
Conclusions
Parathyroidectomy is undoubtedly the most effective treatment of primary hyperparathyroidism in children today. We recommend you to use the questionnaire on the table as PAS in the outpatient setting and in hospitals. This way complaints will allow you to suspect primary hyperparathyroidism in patients. Early detection of pathology of the parathyroid gland, and operative intervention are essential to early recovery of patients and their wellbeing.

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EP1258

Fluctuating thyroid hormones in Graves disease: a case series of brittle Graves

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Introduction
Brittle hypertyroidism is a term used for the clinical situation characterized by hypo-hyperthyroidism with antithyroid drugs, despite good compliance and follow-up. Here, we presented five patients suggested to have Brittle Graves.
Case-1
Thyrotoxicosis was observed in a 57-year-old female patient and Graves was diagnosed after laboratory and imaging examinations 25 months after initiation of propylthiouracil 50 mg/day, she developed hypothyroidism and the drug was discontinued. Thyrotoxicosis recurred in 3 months and the patient underwent thyroidectomy. The histopathological diagnosis was lymphocytic thyroiditis.
Case-2
Graves was diagnosed in a 22-year-old female patient with Down syndrome. After 15 days of propylthiouracil treatment, serum TSH was 100 IU/ml and hyper-hypothyroid periods recurred despite appropriate treatment and thyroidectomy was offered.
Case-3
Thyrotoxicosis was observed in a 48-year-old female patient with a history of levothyroxine use for 10 years. She had positive TSH receptor antibody and ophthalmopathy. Methimazole was started because thyrotoxic state persisted despite discontinuation of levothyroxine, but hypothyroidism developed in a short time and thyroidectomy was offered.
Case-4
A 67-year-old male patient with a diagnosis of Graves disease has used methimazol for 14 months and the drug was discontinued due to hypothyroidism. Recurrent periods of hyper-hypothyroidism developed in follow-up and BTT (bilateral total thyroidectomy) was performed.
Conclusion
Hyper-hypothyroid fluctuations can be observed in patients with Graves disease. This clinical manifestation overlap with hashitoxicosis. “Brittle Graves” seems to be a better definition for such cases.

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EP1259

The role of an ultra-sensitive fourth-generation TSH assay in the management of subclinical hyperthyroidism

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The management of endogenous subclinical hyperthyroidism is largely guided by perceived risk, including the presence of cardiovascular disease, atrial fibrillation or osteoporosis. We have utilised a fourth-generation TSH assay, providing a 10-fold increase in sensitivity compared to third-generation assays, to determine whether patients with subclinical hyperthyroidism can be differentiated from those with overt hyperthyroidism, based on their now measurable TSH levels. Two groups of patients were identified using thyroid function tests measured with a traditional third-generation assay (Roche). The first (Group 1) had normal free thyroid hormone levels and the second (Group 2) had elevated free thyroid hormone levels. Both had a suppressed TSH (<0.02). The samples were then re-analysed using a fourth-generation assay (Olympus AU3000i) and the values compared. All results are given as median and interquartile range. Group 1 ($n=23$, M:F 4:19), free T4 17.5 pmol/l (15.8–19.9), free T3 6.1 pmol/l (5.5–6.3); Group 2 ($n=54$, M:F 14:40) free T4 32.3 pmol/l (25.7–54.9), free T3 pmol/l 10.7 (7.9–13.0). Group 1 fourth-generation TSH 0.009 mU/l (0.007–0.014); Group 2 0.004 mU/l (0.003–0.008) ($P<0.001$, Mann–Whitney U). Whilst group 1 has a significantly greater fourth-generation TSH than group 2, comparison of the interquartile ranges confirms significant overlap. In group 1 12/23 patients had fourth-generation TSH values above the upper limit of the interquartile range of those with overt hyperthyroidism (group 2). Thus, the measured fourth-generation TSH may be of value in determining the need for treatment. Those in group 1 with TSH values falling within a comparable range to those with overt hyperthyroidism should be considered for treatment, whilst those with greater TSH values could be monitored for progression. Our data suggest that a fourth-generation TSH assay is of value in assessing which patients with subclinical hyperthyroidism should be treated and those who should be monitored.

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EP1260

Non-thyroidal illness syndrome in chronic renal failure and oxidative stress: preliminary data on triiodothyronine relationships with extracellular superoxide-dismutase

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Non-thyroidal-illness syndrome (NTIS) is present in chronic renal failure and considered an adaptive mechanism. However oxidative stress is linked to NTIS in a vicious circle, due to deiodinases alteration and negative effect on antioxidant levels or activity. One key antioxidant, protective toward ROS-mediated tissue damage, is extracellular superoxide-dismutase (ec-SOD), present in extracellular matrix and with a role in mediating nitric oxide-induced signaling. ec-SOD is specifically released from endothelium by heparin injection, allowing the determination of ec-SOD activity in vivo without affecting Cu,Zn-SOD or Mn-SOD. No data are reported on ec-SOD in renal failure and its relationship with thyroid function. Therefore we have studied 12 hemodialysis patients (9 males and 3 females, mean age 67 ys), evaluating thyroid hormones and ec-SOD activity after enoxaparin administration. Blood samples were obtained at the starting of hemodialytic session, 5 and 10 min after 1000–4000 U enoxaparin and at the end of the session. SOD activity was measured by a modified nitrite method. Superoxide generated by hypoxanthine and xanthine oxidase was changed by hydroxylamine to nitrite ion which was measured spectrophotometrically at 550 nm by the use of a chromogen. The amount of SOD required to inhibit 50% nitrite ion generation was defined as 1 U SOD activity. Six patients exhibited low fT3 values (1.8 ± 0.1 pg/ml); the others had normal fT3 (2.5 ± 0.2 pg/ml); fT4 and TSH values were normal. Basal eC-SOD did not differ between the two groups, but the percentual increase after heparin was significantly correlated with T3 levels ($r = 0.24$, $P < 0.05$). These preliminary data suggest that low T3 can negatively influence endothelial antioxidant defenses. The relationships of this datum with cardiovascular complications and prognostic usefulness remain to be established.

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EP1261

Therapeutic options in severe thyrotoxicosis with malabsorption

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Abstract
A 55-year-old woman was admitted to our hospital due to severe hyperthyreosis. She started to feel symptoms of hyper-metabolism four months prior to hospitalization. At that time she was admitted in regional hospital and had gastroenterological examination because of diarrhea. Crohn's disease was diagnosed and therapy started. At the same time, thyrosupressive therapy started. She had a history of hyperthyreosis thirteen years ago, duodenal hemorrhage ulcer, hypertension, cerebral vascular insult and myopericarditis. Despite maximal dose of thiamazole, on admission she was highly hyper-metabolic. Hormonal analysis revealed severe thyrotoxicosis (fT4 >100.0 pmol/l; T4> 320.0 nmol/l; TSH <0.005 mIU/l) with increased TRAb (13.9 IU/l), and negative TPOAb (<28.0 U/ml) and TgAb (<15.0 IU/ml). Stool analysis was positive for muscle fibers, fat and carbohydrates indicating maldigestion and malabsorption. Because of multiple comorbidities, we decided to prepare a patient for radioactive iodine treatment (RAI). We concluded that at this hyper-metabolic state, it could lead her in thyroid storm and that her thyroid hormones should be decreased at safer levels prior to RAI. After admission, we started with intrathyroidal dexamethasone injections with initial decreasing of thyroid hormones. The procedure wasn't continued because of gastric pain she started to feel (history of ulcer). We replaced thiamazole for PTU, and started with therapeutic plasma exchange (TPE). After TPE, we observed a significant decrease in fT4 (54.5 pmol/l), T4 (139.0 nmol/l) fT3 (8.5 pmol/l) T3 (2.27 nmol/l) levels. Clinical improvement was achieved. Patient underwent RAI treatment safely, and after two months, her thyroid hormones were in the normal referent range with TSH still suppressed (fT4 13.7 pmol/l; fT3 4.71 pmol/l; TSH 0.01 mIU/l). We concluded that severe thyrotoxicosis in our patient was due to malabsorption of thyrosupressive drugs caused by Crohn's disease and thyrotoxicosis itself. In such cases alternative therapy options should be considered.

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EP1262

Congenital disorders in children of the mothers with thyroid malfunctioning at pregnancy

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In the present study we hypothesized that maternal thyroid disorders may be associated with maternal and foetal morbidity and mortality. The present study included 136 pregnant women selected randomly in first trimester and observed throughout the pregnancy till birth. The assessment of thyroid hormones showed a total of 33.08% ($n = 45$) pregnant ladies were having thyroid disorders; 17.65% ($n = 24$) with hypothyroidism and 15.44% ($n = 21$) with hyperthyroidism. The mothers with hypothyroidism were significantly ($P < 0.05$) heavier than normal mothers while the mother with hyperthyroidism were significantly ($P < 0.05$) lighter than normal and those with hypothyroidism. The hyperthyroidism increased the odds (OR: 6.80; 95% CI: 1.65–28.09) of miscarriages significantly ($P < 0.05$). Maternal hypothyroidism increased the gestational period significantly ($P < 0.05$) and hyperthyroidism decreased the gestational age significantly ($P < 0.05$). Maternal hypothyroidism may lead to significantly ($P < 0.05$) increased birth weight and maternal hyperthyroidism may decreased the birth weight significantly ($P < 0.05$). The maternal hypothyroidism may lead to a statistically significant ($P < 0.05$) decrease in the size of skull and brain weight in neonates. Furthermore, the hypothyroidism and hyperthyroidism increased the odds of webbed neck neonates (OR: 5.87; 95% CI: 1.22–28.30 & OR: 11.73 95% CI: 2.64–52.06, respectively. The data exhibited that the maternal hyperthyroidism increased the odds (OR: 10.47; 95% CI: 1.78–61.78) of eyes defects in neonates. The maternal hypothyroidism increased the risk (OR: 18.00; 95% CI: 1.91–169.10) of neonatal congenital heart defects.

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EP1263

Psychometric evaluation of the newly developed hypoparathyroidism symptom diary

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Objective
The purpose of this study was to evaluate the psychometric properties of a novel, patient-reported outcome (PRO) measure, the Hypoparathyroidism (HPT) Symptom Diary (HPT-SD), using data collected during a cross-sectional, noninterventional, observational study. The HPT-SD, developed according to the US Food and Drug Administration PRO guidance, addresses the severity of key symptoms (muscle cramping, tingling and muscle spasms/twitching, fatigue, cognition, emotions) and impacts on sleep, ability to exercise, ability to work, and family relationships.
Methods
Individuals who self-reported HPT were recruited to participate in a paper-based survey collecting demographic and HPT-related clinical and treatment information, patient global impression of severity (PGIS), the HPT-SD, and three supporting measures: Functional Assessment in Cancer Therapy–Cognitive Function (FACT-Cog), Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-Fatigue), and the Hospital Anxiety and Depression Scale (HADS). Item- and scale-level internal consistency reliability, discriminating and construct validity were evaluated. A scoring algorithm was developed based on psychometric and qualitative results.
Results
Participants rated their HPT as moderate (34.6%) or severe (32.7%). Participants did not endorse the most severe response choices (e.g., 'Very severe') for 4

muscle-related symptom items. Inter-item correlations revealed a pattern of moderate to strong relationships among symptom ($r=0.3$–0.8) and impact items ($r=0.5$–0.7), providing evidence for two HPT-SD subscales: symptoms and impacts. Construct validity correlations supported a priori convergent validity hypotheses ($|r| > 0.5$) between HPT-SD subscales and the FACT-Cog, FACIT-Fatigue, and HADS. The HPT-SD demonstrated discriminating ability between patients who reported mild versus severe HPT on the PGIS ($P<0.05$ for 12 out of 13 items).

Conclusions

The HPT-SD is an appropriate measure of HPT-related symptoms and impacts. Severe muscle-related symptoms were reported during qualitative development; all HPT-SD response choices were retained to capture severe symptoms. Future studies should assess the HPT-SD measurement properties using longitudinal study designs.

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EP1264

Early diagnosis of primary biliary cirrhosis during follow-up for Graves' disease

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Introduction

Hepatic dysfunction in hyperthyroidism may occur due to high thyroid hormones, medications or associated autoimmune liver disease. Autoimmune hepatitis or primary biliary cirrhosis (PBC) has rarely been reported in Graves' disease. We report a patient presenting with pruritus and diagnosed as accompanying PBC and Graves' disease.

Case

A 50 years old female patient applied with progressive pruritus for at least 4 months. Laboratory investigations showed normal alanine aminotransferase and aspartate aminotransferase. Serum alkaline phosphatase (ALP) was 125 IU/l ($\leq$105 IU/l), gamma glutamyl transferase (GGT) was 132 IU/l ($\leq$42), and total serum bilirubin and conjugated bilirubin were within normal ranges. She had low TSH (<0.005 U/l) and high serum free T4 (4.6 ng/dl) and free T3 (14.71 pg/ml). Thyroid peroxidase antibody and thyroid stimulating hormone receptor antibody were also positive. She was afebrile and had regular pulse rate of 110/min and normal blood pressure. There was no exophthalmus, goiter, hepatomegaly or splenomegaly in physical examination. Ultrasonographically, the thyroid gland was enlarged with increased vascularity. Technetium-99m scintigraphy showed increased activity throughout the gland with cold nodules in an enlarged thyroid gland. She was started on methimazole and propranolol. After a week of treatment, her ALP and GGT levels raised to 160 and 151, respectively that we discontinued methimazol. Serology tests for viral hepatitis, human immunodeficiency virus and cytomegalovirus were negative; laboratory tests excluded copper, iron-related metabolic disorders and autoimmune liver diseases. Antimitochondrial antibody was found positive and PBC was diagnosed with clinical and laboratory findings. She was started on ursodeoxycholic acid and underwent bilateral total thyroidectomy.

Conclusion

PBC is often associated with other autoimmune diseases. When a cholestatic pattern of liver enzymes is observed during follow-up for Graves' disease, PBC should be considered in the differential diagnosis.

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EP1265

Survey on the management of hypothyroidism during pregnancy by general practitioners, endocrinologists and obstetricians in Australia and New Zealand

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Background

Optimal management of hypothyroidism prior to and after conception is associated with improved pregnancy outcomes. Compliance with existing management guidelines in Australia and New Zealand is unknown.

Methods

A validated electronic survey was distributed to endocrinologists, obstetricians and general practitioners via their specialty professional bodies and results were analysed.

Results

There were 394 survey respondents: 80.5% (317) from Australia and 19.5% (77) from New Zealand. They comprised 263 Obstetrics and Gynaecology doctors (OG), 69 Endocrinology doctors (E) and 58 General Practitioners (GP). Four respondents were excluded as they did not meet inclusion criteria. Over half of respondents (57.4%) had more than 10 years of specialty experience. 95.2% of respondents (375/394) completed the clinical questions as the remainder were not involved in managing hypothyroidism in pregnancy or in women of reproductive age. On confirmation of pregnancy, 68.3% of respondents ($n=233$) reported checking thyroid function tests (TFTs) before adjusting thyroxine dose. 27.7% of respondents reported increasing thyroxine dose by 30–50% or by 2 tablets per week as soon as pregnancy is confirmed as recommended by guidelines. 85.2% of respondents reported adjusting thyroxine dose during pregnancy to recommended TSH targets of TSH $<$ 2.5 mIU/l in the 1st trimester and $<$ 3 mIU/l in the 2nd and 3rd trimesters (46.7%=155/332) or to TSH and free T4 trimester specific ranges for their laboratory (38.5%=128/332). 75.9% of respondents would appropriately treat pregnant women with thyroxine if TSH was $>$ 2.5 mIU/l (36.0%=112/311) or above trimester specific ranges for their laboratory (39.9%=124/311).

Conclusions

Reported practice in management of hypothyroidism prior to and during pregnancy in Australia and New Zealand varies significantly from recommended guidelines. These findings have significant implications for pregnancy outcomes. Further education is needed for all medical practitioners involved in treating women of reproductive age.

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EP1266

Analysis of cardiovascular changes in Graves disease and their dynamic during the treatment

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Objectives

Estimate the prevalence of of cardiovascular symptoms, to identify the main changes in echocardiography at Graves disease (GD) and their dynamic during treatment.

Methods

Investigated 86 patients with GD. The functional class (FC) chronic heart failure (CHF) was determined according to the New York Heart Association (NYHA). All patients underwent echocardiography before treatment and after 3 months of euthyroid state.

Results

At baseline 32.6% patients had no symptoms of CHF, I FC had 19.7%, II FC – 34.9% and III FC – 12.8%. Tachycardia was presented in 87.2% patients, shortness of breath – 67.4%, arrithmias – 58.1%, pain in the chest – 26, 7%. Patients without CHF and with 1 FC showed no significant differences in the echocardiological parameters compared with the control. Patients with 2 FC observed a higher left ventricular ejection (LVE) ($P\leq0.05$), left ventricular posterior wall thickness (LVPWT) ($P\leq0.05$) and interventricular septum thickness (IVST) ($P\leq0.05$). Patients with 3 FC characterized by an increase of size of the left ($P\leq0.05$) and right atrials ($P\leq0.05$), end-diastolic dimension of left ventricle (EDD LV) ($P\leq0.05$), EDD of left ($r\leq0.05$) and right atrial ($P\leq0.05$). Clinically 3 months after reaching the euthyroid state at 48.8% were maintained complaints of palpitations, at 20.9%- shortness of breath. In patients with FC 2 maintained high LVE, LWPWT, IVST. Among patients with FC 3 also were signs oh heart cavities diliatation.

Conclusions

Cardiovascular symptoms frequently encountered in GD, and some may be stored on reaching euthyrosis. For patients with CHF FC 2 is characterized by left ventricular hypertrophy and myocardial hyperfunction that persist over time during treatment. At 3 FC showed signs of heart cavities diliatatation combined

systolic dysfunction, which are only partially reversible with normalization of thyroid function.

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EP1267

Prevalence of the thyroiditis in childbearing age women

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Background and aims
It has been demonstrated that the thyroid autoimmunity, during pregnancy, adversely affects the course of the pregnancy. The anomalies may be prior to the conception, hence the interest of studying the women during the genital activity period. Our objective was to determine the prevalence of the thyroiditis in childbearing age women.
Materials and methods
Prospective study, on 270 childbearing age women. Study protocol: clinical examination, thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid antibodies. Statistics tests: collection of data on EPI INFO 5.1.
Results
Data expressed as mean (270 women), age: 30.3 ± 0.4 years, weight: 65.9 ± 0.9 kg, body mass index: 24.7 ± 0.3 kg/m^2, TSH: 2.4 ± 0.2 mIU/l and FT4: 14.8 ± 0.2 pmol/l. The positivity of the antithyroperoxidase antibodies (TPO-ab) concerned 38/270 women (14.1%), the antithyroglobulin antibodies (Tg-ab) 42/270 women (15.6%) and one of the two antibodies (TPO-ab and / or Tg-ab) 54/270 women (20.0%). The mean TSH of the women with thyroiditis was 4.39 ± 4.93 mIU/l vs 1.89 ± 1.06 mIU/l for those without it ($P < 0.0001$). The mean FT4 of the women with thyroid autoimmunity was 14.38 ± 1.08 pmol/l vs 14.87 ± 2.05 pmol/l for those with negative antithyroid antibodies, NS. Of the 54 women with thyroiditis, 35/54 were in euthyroidism (64.81%) and 19/54 of them were in hypothyroidism (35.19%), 9/54 in subclinical hypothyroidism (16.67%) and 10/54 in overt hypothyroidism (18.52%).
Conclusion
In our study, 20.0% of the women had thyroiditis and their mean TSH was significantly higher vs those with negative antithyroid antibodies. In the subgroup of women with thyroiditis, 64.81% were in euthyroidism.

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EP1268

Prevalence and etiology of the hypothyroidy in childbearing age women

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Background and aims
The hypothyroidism may be prior to the conception, hence the interest of studying women during the genital activity period. Our objective was to determine the prevalence and the etiologies of the hypothyroidism in childbearing age women.
Materials and methods
Prospective study, on 270 childbearing age women. Study protocol: clinical examination, urinary iodine, thyroid stimulating hormone (TSH), free thyroxine (FT4) and thyroid antibodies. Statistics tests: collection of data on EPI INFO 5.1.
Results
Data expressed as mean (270 women), age: 30.3 ± 0.4 years, weight: 65.9 ± 0.9 kg, body mass index: 24.7 ± 0.3 kg/m^2, urinary iodine: 225.6 ± 5.8 µg/l, TSH: 2.4 ± 0.2 mIU/l and FT_4: 14.8 ± 0.2 pmol/l. The iodine deficiency was found in 19/270 women (7%). The hypothyroidism involved 31/270 women (11.5%), the subclinical form in 19/270 (7.1%) and the overt form in 12/270 (4.4%). Of the 31 hypothyroid women, the etiology of the hypothyroidism was related to the autoimmune thyroid disease in 19/31 women (61.3%) and to the iodine deficiency in only one case (3.23%).
Conclusion
In our study, 11.5% of women of childbearing age were in hypothyroidism (overt and subclinical forms). The etiology of the hypothyroidism was dominated by the thyroiditis.

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EP1269

Effectiveness of radioiodine treatment for autonomous toxic node

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Objective
The aim of this study was to evaluate the treatment outcomes in patients with autonomous toxic nodule (ATN) that received a radioiodine treatment (RAIT) and to determine the influence of age, gender, nodule size and iodine activity.
Methods
We performed a retrospective study of all RAIT done for hyperthyroidism ($n = 149$) in our hospital during 2014 and 2015. Patients with ATN submitted to RAIT were selected to analysis. We studied 58 patients (mean age 59.6 ± 13.98 years), a total of 59 treatments, corresponding to 39.6% of all RAIT. Treatment success was analysed according to demographic (age and gender) and clinical data (thyroid function tests 1 year after RAIT, iodine activity administered and nodule size). Activities of 5 or 10 mCi were the most used. Treatment success was defined as achieving euthyroidism or hypothyroidism 1 year after the last RAIT. For statistical data analyses was used a 95% confidence interval (sig < 0.05).
Results
The cure rate was 84.6%. Hypothyroidism was observed in 25.6% (10 patients). Only 6 patients remained in hyperthyroidism. Age and nodule size did not influence the outcome. Additionally, no correlation was found between gender and iodine activity in therapeutic effectiveness. Although not statistically significant, the cure rate was higher with 10 mCi (92.6%) comparing with 5 mCi (72.7%).
Conclusion
There is a trend for a higher effectiveness with 10 mCi than with 5 mCi. The cure rate with 10 mCi is similar to those described in the literature for 15 and 20 mCi, with a lower rate of hypothyroidism.

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EP1270

Endemic goiter in Xinjiang, Northwestern China

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Background
Endemic goiter occurs frequently in iodine deficient areas. Our past medical survey revealed that goiter was endemic in Xinjiang, Northwestern China, because, several elderly Uygur subjects had goiter. In the present study, several medical parameters were compared between subjects with and those without goiter.
Methods
Elderly Uygur (age, 65–70 years $n = 99$) and very old Uygur subjects (age, > 90 years $n = 111$) were hospitalized, requested to provide blood and urine samples, and underwent 24 h-ambulatoly blood pressure monitoring. Goiter was not identified in Hun and Kazakh participants.
Results
No subjects had any symptoms attributable to abnormal thyroid function. The goiters identified ranged in size from that of the walnuts to the fist. Body mass index of the subjects with goiter (GO+) was slightly but significantly lower than that of the subjects without goiter (GO−). There were no significant differences in blood pressure, heart rate, urinary catecholamine levels, insulin sensitivity, and serum levels of free thyroxin, thyroid stimulating hormone, triglycerides, or low-density lipoprotein and high-density lipoprotein cholesterol, between GO+ and GO− participants. The prevalence of goiter in women was 6 times that of men. The iodine content in the salt extracted from the study area was 0 parts per million (ppm) while in that obtained from the market was 29.1 ppm.
Conclusion
The results suggest that prevalence of goiter in Uygur might have been caused by intake of iodine-free salt. Individuals with goiter would live safely and come today. The higher prevalence of goiter among women suggests that hormones might play a role in the development of thyroid disease.

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EP1271

How does overt and subclinical hypothyroidism due to thyroiditis of Hashimoto affect lipid parameters

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Aim
The aim of this retrospective study is to assess the lipid disturbances in patients with autoimmune thyroiditis.
Methods
1380 patients with autoimmune thyroiditis, hospitalized in Endocrinology department of 'St. Marina' Hospital, Varna for the period of 2004–2015 year, participated in the study. After excluding conditions influencing lipid profile, 771 patients remained for analysis (36 men and 735 women, mean age 49.81 ± 13.98 years). They are divided in three groups according to TSH values - group A (0.4–4 mU/l), group B (4.01–10 mU/l), group C (TSH ≥ 10.01 mU/l). Group B is divided into two subgroups – B1 – patients with negative thyroperoxidase antibodies (TPO Ab) and B2 – patients with positive TPO Ab. We evaluated thyroid ultrasound data, laboratory tests of TSH, free T3 (FT_3), free T4 (FT_4), TPO-Ab, total cholesterol (TC), triglycerides (TG), LDL - and HDL-cholesterol levels.
Results
With the increase of TSH value, we observe elevation in serum triglycerides (group A-TG 1.34 mmol/l, group B-1, 44 mmol/l, group C-1, 69 mmol/l); as well as in LDL-c values (group A-3, 41 mmol/l; group B- 3, 53 mmol/l; group C-4, 19 mmol/l). The comparison of the two subgroups B1 and B2 find out increasing levels of TC, TG, LDL-c and a decreasing of HDL-c. A significant difference in TG between patients in group A and C is observed (P 0.001). Statistical significance in LDL-c level is achieved in group A and C (P 0.000), group B and C (P 0.000), in group B2 and C (P 0.001). 16.9% of the patients from group B and 17.1% from group C had already coronary heart disease and/or cerebrovascular disease.
Conclusions
Autoimmune thyroiditis as one of the main reasons for hypothyroidism is associated with lipid abnormalities and increased cardiovascular risk, which are more pronounced in overt than in subclinical hypothyroidism.

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EP1272

Primary hypothyreosis in cobalt intoxication

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Most common causes of primary hypothyreosis are destruction of thyroidal parenchyma by the autoimmune antibodies, interventions on the gland (surgery, radioiodine treatment) and external actinotherapy (hematologic and ENT malignancies). Drug induced thyroidal impairment is well-known too (amiodarone, lithium, interferon). Our case demostrates the primary hypothyreosis caused by cobalt. The source was Co-Cr hip prostehis after its rupture (PHACT). A 55 old man was reffered to endocrinologist in 2011 with enlargement of thyroid gland (volume 84 ml) and signs of primary hypothyreoidism (TSH 76 mU/l). No elevation of antibodies levels was present, family history of thyroid disease negativ. Thyroxin substitution treatment resulted in both normalisation of thyroid function and thyroid gland volume (TSH 1.3 mU/l, 18 ml).
Personal history
Hyperlipoproteinema, smoking. The man also underwent implantation of right hip prosthesis after an injury in 2002. The course was complicated by deep venous thrombosis of the right leg and massive pulmonary embolism requiring thrombolysis treatment. The prosthesis was damaged in 2010 because of necrosis and replaced with the Co–Cr type. Since 2010 the patient was examined by multidisciplinary specialists because of polymorhpic atypical complaints (arrhytmias – considered cardiomyopathy, atypical neuropathy, hypacusis). In 2014 patient was admitted to hospital with atypical back and pelvis pains. Following RDG imaging of the right trochanter and acetabulum a diagnosis was finally obtaned showing pathology - local osteal reaction. The puncture of the affected spot revealed dark fluid with high levels of cobalt and chromium. The defficient prosthesis was then removed. PHACT id.e prosthetic hip-associates cobalt toxicity. The symptoms are atypical – arrhytmias, different neurological symptoms, changes of thyroid gland functions, deafnes, eye disorders.

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EP1273

Evaluation of circulating irisin levels in patients with never treated overt hyperthyrodisim

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Aims
Because of an increased metabolic activity and thermogenesis in hyperthyroidism, we aimed to evaluate the association of serum irisin with thyroid hormones.
Methods
A total of 25 hyperthyroid patients and 24 age- and gender-matched healthy controls were enrolled. Serum irisin levels, thyroid hormones and body compositions were analyzed.
Results
Serum irisin levels were significantly higher in hyperthyroid group ($P < 0.001$). Distribution of fat free mass and muscle mass was similar between study groups. Serum irisin level has a negative correlation with TSH level ($P < 0.001$), %fat mass ($P = 0.021$) and positive correlation with TSH receptor antibody (TRAB) level ($P = 0.002$).
Conclusion
Our results showed that increased serum irisin levels in hyperthyroid patients might be associated with the effects of TSH.

Keywords: Hypertyroidism; irisin; TSH receptor antibody
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EP1274

Is there a correlation between serum selenium level and the severity of Graves' orbitopathy?

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Introduction
Selenium (Se) deficiency is a known risk factor for autoimmune thyroid diseases including Graves' orbitopathy (GO).
Objective
To determine the concentration of Se in serum and to determine the dependency of Se concentration on known markers of disease severity: the TRAB levels and the CAS (clinical activity score) in patients with GO.
Material
64 patients (50 women, 14 men; average age- 54.5 years) with active, moderate to severe GO who have not received prior selenium supplementation and were qualified to i.v. metylprednisolone treatment according to the EUGOGO scheme, at a single site in the years 2014–2016.
Method
Set average and median concentrations of Se, TRAB and CAS in the group of patients and determined the correlation coefficients between serum Se and TRAB and CAS.
Results
Selenium deficiency was found in 15 patients, in 27 the concentration was normal, in 22- the Se level was above the upper limit of normal. There was no correlation between Se and CAS or TRAB revealed.
Conclusions
1) The severity of OG expressed by well known indicators: CAS and TRAB were not dependent on the concentration of Se. 2) It seems that it should be recommended to measure the concentration of selenium before starting the supplementation of Se because of low frequency of Se deficiency in this group of patients.

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EP1275

Nicotinamide phosphoribosyltransferase expression in thyroid glands of patients with Graves' disease

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Abstract
Nicotinamide phosphoribosyltransferase (NAMPT) overexpression was reported in many autoimmune diseases. We have also found *NAMPT* overexpression in leukocytes of patients with Graves' orbitopathy. Therefore, we aimed to analyze *NAMPT* expression level in thyroid gland of patients with Graves' disease with orbitopathy and without orbitopathy, and in healthy thyroid gland. We have analyzed 80 thyroid tissue samples of patients who underwent thyroidectomy. Among these, there were 41 patients with Graves' disease (20 patients with orbitopathy and 21 patients without orbitopathy), and 39 samples of healthy thyroid tissue. *NAMPT* overexpression was found in thyroid glands of patients with Graves' orbitopathy ($P<0.000001$). NAMPT expression in patients with Graves' disease without orbitopathy was similar to healthy controls. Our results suggested that NAMPT might be involved in the inflammatory cascade in Graves' orbitopathy.

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EP1276

Associations between thyroid and kidney functions

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Two-way interactions between thyroid and kidney functions are known. Chronic kidney disease (CKD) is accompanied by changes in synthesis, secretion, metabolism, and elimination of thyroid hormones, increased risk of hypothyroidism, rarely subclinical hyperthyroidism, whereas thyroid dysfunction affects physiology of the kidney, renal blood flow, glomerular filtration rate (GFR), tubular function, metabolism of water and electrolytes, and kidney structure. The aim of the study was to examine associations between thyroid stimulating hormone (TSH) level and kidney function.
Methods
We analysed retrospective data of 781 adult patients, referred for routine simultaneous testing of TSH and serum creatinine in 2015 in Vilnius Antakalnio outpatient clinic. GFR was estimated by the simplified Modification of Diet in Renal Disease equation. Linear regression was used to evaluate the association between TSH and estimated GFR.
Results
Mean TSH concentration was 2.58 ± 4.19 mIU/l, mean serum creatinine 72.72 ± 22.32 µmol/l and mean estimated GFR 83.12 ± 24.91 ml/min/1.73 m^2. 45.3% of patients had stage 2 CKD, 16.0% – stage 3 CKD, 1% – stage 4 or end stage CKD. Patients with CKD of any stage were older than those with normal kidney function (mean age 66.98 ± 11.20 vs 50.96 ± 15.42 years, $P<0.0001$) and their TSH was higher (2.86 ± 5.07 vs 2.12 ± 1.93 mIU/l, $P=0.004$). 12.9% of patients had thyroid dysfunction: 7.9% had subclinical hypothyroidism (TSH 4.69–10 mIU/l), 1.3% overt clinical hypothyroidism (TSH >10 mIU/l) and 3.7% subclinical hyperthyroidism (TSH <0.465 mIU/l). 12.8% of patients with estimated GFR <60 ml/min/1.73 m^2 had subclinical hypothyroidism, 1.5% – overt clinical hypothyroidism. Lower estimated GFR was associated with higher TSH level ($B=-0.72$ (95% CI -1.13 – -0.30), $P=0.001$).
Conclusions
Thyroid dysfunction is relatively common among persons with CKD: 14.3% of patients with moderate, severe and established kidney failure have hypothyroidism. Reduction in estimated GFR is independently associated with increased TSH levels.

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EP1277

Hypothyroidism – once a week treatment option in young- and middle-aged adults

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Objective
To evaluate the effectiveness and compliance to L-thyroxine in the treatment of Hypothyroidism in a weekly dose of 7 times of normal dose as an alternative to daily dosing in young and middle aged adults.
Methods
A randomized prospective observational study on 180 patients (female:male) ratio of 5:1 aged between 18 and 55 years with an established diagnosis of Hypothyroidism were assigned a weekly dose of seven times of normal dose. The patients were randomized in 3 groups G1, G2 and G3. Group 1 (G1): 60 patients with established diagnosis of Hypothyroidism with TSH value of 4.2 or less, currently on daily dose. The subjects were assigned weekly dose of L-thyroxine which was 7-fold of normal dose. Group 2 (G2): 60 patients with established diagnoses of Hypothyroidism with TSH value of more than 4.2. The subjects were assigned weekly dose of L-thyroxine which was 7-fold of normal dose, the dose in this group was individualized as per the body weight and TSH value. Group 3 (G3): 60 patients newly established diagnoses of Hypothyroidism with TSH value of more than 4.2. The group was started with a weekly dose which was individualized as per the body weight and TSH value. All subjects in all the groups were screened for malabsorption and were not receiving any drugs which interfere with the absorption of L-thyroxine. The minimum to maximum dose used in this study was 175–1050 mcg.
Results or case presentation
We achieved complete restoration of euthyroidism in all 59 subjects in the group 1 (G1) at 12 weeks and it continued to 24 weeks. We had to withdraw it in a 55-year male patient because of hyperthyroid symptoms. In group 2 (G2), we achieved complete euthyroidism in 52 subjects at 12 weeks and it increased to 55 subjects with some dose adjustment at 24 weeks. We could not achieve euthyroidism in 5 subjects at 24 weeks. This may be attributed to other metabolic disorders like diabetes and obesity. In (G3) we achieved complete euthyroidism in 54 subjects at 12 weeks and it increased to 59 subjects with some dose adjustment at 24 weeks. 1 subject shifted to another city and so did not complete the study.
Conclusion
Once weekly dose of L-thyroxine as an alternative to daily dosing regimen was shown to be efficacious and safe for the treatment of hypothyroidism to treat non-compliant hypothyroid young- and middle-aged adults. The results show that it can be started in newly diagnosed hypothyroid patients. For patients who find it difficult to adhere to a rigorous treatment regime it is a valid therapeutic option and can also be considered as a first line therapy in young and middle aged working adults facing impaired absorption due to early breakfast (no need to wait 30–45 min for breakfast).

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EP1278

Effect of subclinical hypothyroidism and autoimmunity on adverse pregnancy and neonatal outcome in our population

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The effect of subclinical hypothyroidism (SH) and thyroid autoimmunity on adverse pregnancy and neonatal outcome, are still subject of interest and controversy. Nowadays, guidelines recommend establishing reference values of local thyroid hormones that allow definition of the SH in a specific population. The objective of this study was to assess the effect of SH and autoimmunity in early pregnancy on adverse pregnancy and neonatal outcome in our population. The reference range of thyrotropin (TSH) was 3,86 µUI/ml, in our Cádiz-San Fernando area, in Spain. 438 pregnant women with HS (defined according to our reference values) in the first trimester of gestation were recruited. Women were classified into two groups according to thyroid function and anti-TPO results. The mean age was $31,32\pm5,5$ years, BMI was 24.5 ± 5.3 kg/m^2. Twenty-four percent of the patients had a family history of Thyroid disease and 23% of miscarriage. The mean of levels of TSH at diagnosis were $5,1\pm1,3$ mUI/l with a final mean dose of levothyroxine 64.9 mcg/day and levels of TSH 2.5 ± 1.2 mIU/l at the end of pregnancy. Sixteen percent of the deliveries were by cesarean

section, and 20% had complications (premature rupture of membranes, preeclampsia, preterm delivery, small for gestational age). Thirteen percent had anti-TPO positive. Comparing anti-TPO positive/negative groups with obstetrics and perinatal outcomes, no statistically significant differences were found. We concluded that in our area, patients with HS, defined according to our local reference values, have a low rate of adverse pregnancy and neonatal outcome. Also, if we consider the presence of anti-TPO positive, there are no differences. Further studies will be needed to determine the relationships between HS and autoimmunity and adverse pregnancy and neonatal outcome.

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EP1279

Metastatic differentiated thyroid carcinoma: cumulative doses of adjunct 131i-iodide therapy

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Introduction
131I-iodide therapy (RIT) is an important treatment modality for patients with differentiated thyroid carcinoma (DTC). However, despite the overall excellent outcome, some DTC patients with poor prognosis may require multiple doses of radioactive iodine.
Aim
The purpose of our study was to evaluate the efficacy of cumulative doses (CDs) of RIT in metastatic DTC patients.
Material and methods
A retrospective study was conducted on a cohort of 84 metastatic DTC patients (mean age 46.6 ± 17.4 years) who received a CDs $\geq$300 mCi of RIT, between January 1956 and December 2016. A disease-free status was established as: undetectable TSH-suppressed Thyroglobulin levels, whole body imaging scan without local-regional uptake or distant metastases and negative cervical ultrasound or thoracic CT scan.
Results
Eighty-four patients, 58 females and 26 males, who completed more than one RIT with a CD $\geq$300 mCi, were followed up for 15.0 ± 8.8 years. At the time of diagnosis 62 (73.8%) patients had local cervical metastases and 22 (26.2%) had distant metastases. Papillary carcinoma sub-type was present in 75 (89.3%) of patients. Seventeen out of 84 patients (20.2%) achieved a disease-free status. No patient with CDs higher of 450mCi has reached a disease-free status. Patients with evidence of brain or bone metastases (7 out of 94) did not achieve the disease-free status, regardless of the CDs received.
Conclusion
Twenty percent of patients who received a CDs $\geq$300 mCi of RIT achieved a disease-free status. Quality of life and the disease progression rate are important aspects that were not addressed in our study. The decision of further treatment with RIT should be carefully evaluated and made on a case-by-case basis. Furthermore, this study seems to indicate that brain or bone metastases may not respond to higher CDs.

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EP1280

Autoimmune thyroid disease may affect prognosis of breast cancer

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Aim and objective
The aims of this study were to determine the incidence of breast cancer molecular subgroups, to investigate the relationship between autoimmune thyroid disease and prognostic and predictive factors in patients who were diagnosed with breast cancer.
Materials and methods
One hundred one patients who were followed up with the diagnosis of breast cancer at our Endocrinology and Medical Oncology Departments were included. Patients are divided into subgroups based on the molecular classification. Patients with high serum levels of thyroid peroxidase antibody (anti-TPO) were considered as autoimmune thyroid disease. Prognostic and predictive parameters such as tumor size, axillary involvement, histological grade, lymphovascular invasion, hormone receptor status, HER2 overexpression were collected. The relationships between autoimmune thyroid disease and tumor's prognostic and predictive factors were studied.
Results
The prevalence of thyroid autoimmunity was 23.8% ($n=24$) among with our study group. Patients with autoimmune thyroid disease had a significant lower rate of axillary involvement (37.5% vs 61% [$P=0.043$], respectively). Other parameters did not differ between patients with and without autoimmune thyroid disease.
Conclusions
We found a favorable association between autoimmune thyroid disease and axillary involvement which is crucial and strongly prognostic parameter of breast cancer prognoses. This supports the idea of thyroid autoimmunity being a favorable prognostic parameter in breast cancer. Further studies are necessary to investigate the reasons of protective or predictive effect of high anti thyroid peroxidase levels in breast cancer patients.

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EP1281

Subacute Thyroiditis with an atypical clinical course and thyroid ^{99m}Tc uptake

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Background
Subacute thyroiditis (SAT) is a transient inflammatory, probably viral disease of the thyroid gland. It is clinically characterized by pain, fever, increased erythrocyte sedimentation rate (ESR) or other markers of inflammation, transient thyrotoxicosis, and has a tendency to recur. In most cases, in addition to the clinical features, scintigraphy and ultrasound may support the diagnosis of SAT. However, in the present case, SAT with an atypical thyroid ^{99m}Tc uptake and a nodule formation in ultrasound lead to diagnosis difficulties.
Case presentation
A 31-year-old woman with the clinical suspicion of SAT was observed. Thyrotoxicosis was present and the tests for anti-thyroid peroxidase, anti-thyroglobulin and TSH receptor antibodies were negative. Thyroid scintigraphy with ^{99m}Tc demonstrated decreased uptake in the right but a normal uptake in the left lobe. Four weeks after clinical and laboratory remission she developed a painful palpable nodule of the left thyroid lobe. Increased erythrocyte sedimentation rate above 100 mm/h and elevated C reactive protein were present. Ultrasonographic examination showed an enlarged left lobe and area of low echogenicity with shaded margins and microcalcifications. The lesion showed a contrast uptake in contrast-enhanced magnetic resonance imaging (MRI). The second scintigraphy demonstrated a bilateral, heterogeneous uptake with a suspected hipoactive nodular image of the left thyroid lobe. Fine-needle aspiration biopsy from the nodule revealed multinuclear giant cells consistent with SAT.
Conclusion
In most cases, the diagnosis of SAT can be made based on the physical and laboratory findings of the patient and the clinical course of the disease. Findings of thyroid scintigraphy and ultrasound that are not consistent with subacute thyroiditis do not exclude the diagnosis of SAT. For definitive diagnosis of an atypical SAT and exclusion of thyroid malignancies, fine-needle aspiration biopsy may be required.

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EP1282

Weak numeracy is common problem in patients with thyroid diseases

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Introduction
In modern medicine, we expect from patients numeracy skills. Starting with the correct dosage of drugs up to understand the principles of risk assessment of alternative treatments. These skills, however, are probably rarely checked. Just as the skills of reading, where we entrust signature 'read and understood'. That is why we want to introduce our observation.
Method
Subsequent patient, outpatient endocrinological clinic, we have proposed making two tests to assess numeracy: Schwartz test (max. 3 points) and Berlin Numeracy Test (max. 4 points).
Results
We investigated 112 patients (101 women) in age 17 to 85 years (average 55 ± 15). No one person became maximal possible results, and 11 (10%) had not answered any question. The results of other patients indicate significant problems with simple counting. 2 person rejected Schwartz test, and 1 person rejected BNT test. From others 36 person became 0 points in Schwartz test, 43 patients 1 point, 23 patients 2 points and only 8 maximally possible 3 points. Similar or even worse are the results in BNT 29 person became 0 points, 56 1 point, 22 2 points, only 3 3 point and no one maximal possible 4 points. We did not find significant correlations between the results of the tests, and the sex, age and TSH.
Conclusion
Weak numeracy is a common problem in patients with thyroid diseases.

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EP1283

A case of levothyroxine tablet malabsorption associated with gastric neuroendocrine tumour corrected with gel capsule formulation

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Multiple dose adjustments can sometimes be inefficient in reaching eumetabolic state in patients with hypothyroidism treated by levothyroxine sodium tablets. We report a case of 44-year-old female who has been on levothyroxine sodium tablet replacement therapy since 2004 without ever reaching eumetabolic state, presented as outpatient one year ago. As sellar MRI ruled out pituitary adenoma, investigation targeting malabsorption was initiated. Antibodies to gliadin and transglutaminase were in normal range. Absorption test with 300 mcg levothyroxine was positive in aspect of presence of selective levothyroxine malabsorption. Initial endoscopies revealed chronic atrophic gastritis without excluding possibility for tumor presence. Serum CgA level was 521 mcg/l. The final third endoscopy was successful in detecting the gastric submucosal change, confirmed by endoscopic ultrasound as submucosal lesion no larger than 12 mm located in the upper part of anterior gastric wall. Histological analysis of biopsy specimen confirmed lesion to be neuroendocrine tumor grade 1. Further imaging excluded its metastatic spreading, so the indication for surgical removal was established. Patient could not undergo surgery with TSH levels exceeding 100 mmU/l and free T4 lower than 5 pmol/l despite being on 300mcg of levothyroxine daily substitution regimen. Changing to a gel capsule formulation taken once a day at dose of 100 mcg lead to a rapid TSH decreasement and thyroid hormones normalization, so the patient was surgically treated as eumetabolic. On reviews thereafter she remained euthyroid, without complaints of previously reported fatigue and loss of appetite. This case suggests that gastric chronic inflammatory processes and neuroendocrine tumors as well may affect levothyroxine absorption where gelatine capsules appear to be effective treatment option.

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EP1284

Percutaneous ablation of benign thyroid nodules: specific simulators for practicing enolization and laser procedures

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Ethanol and laser ablation of benign thyroid nodules is bursting rapidly in clinical practice because of its efficacy, safety and economy. However, these techniques require some manual operator training. In order to facilitate this hands-on training, we propose two homemade, cheap and specific simulators to practice these clinical procedures.
Material and methods
Two models were optimized: *Gel-Phantom Coruna VR16* (gelatine and plantago-ovata with inlays of different objects simulating pure and mixed cysts) and *Proteon-Phantom Coruna VR17* (pork loin with inlays of different objects simulating solid nodules (homogeneous, heterogeneous and with microcalcifications). For enolization, pure ethanol and a 2-way device (*Device Coruna VR15*, poster 94, 58th Congress Malaga, Spain, SEEN 2016) were used for sequential ethanol-NSS instillation (to reduce irritation of the capsule upon withdrawal of the needle). For laser ablation, a 1064 nm Nd-YAG laser through a thin optic fiber of 300um obtained from an EchoLaser generator (Elesta, Florencia-Italy) was used. Monitoring was performed with the Acusson 2000 Hellix ultrasound platform (Siemens, Forchheim-Germany). The assessment was performed among different operators ($n = 12$), especially those attending the Coruna Workshop on Laser Ablation.
Results
For cystic nodules simulation and practicing ethanol sclerosis, the most valued simulators were: fluid on a knotted glove (pure cyst), grapes or dwarfish tomatoes (mixed cyst), piece of wet sponge wrapped in knotted kitchen plastic ('sponge' cyst) and anchovy stuffed olive (hyperechoic nodule with hypoechoic center). For solid-state nodules simulation and practicing laser ablation, the most valued were: beef liver wrapped in knotted plastic (solid isoechoic nodule), cooked yolk wrapped in knotted plastic (hyperechoic solid nodule), raisins and water wrapped in knotted plastic (heterogeneous nodule), and raisins, water and eggshells (heterogeneous nodule with 'microcalcifications').
Conclusion
In summary *Gel-Phantom Coruna VR16* and *Proteon-Phantom Coruna VR17* simulators were surprisingly useful for practicing percutaneous ethanol and laser ablation procedures. In addition, we highlight their low cost and easy preparation.

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EP1285

Improved diagnostics with increased treatment of hypothyroidism during pregnancy – a 10 year study of Finnish pregnant women

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Thyroid diseases affect up to 4% of all pregnancies. Several evidence-based recommendations have been created to observe and treat thyroid diseases in pregnant women. We studied whether the diagnostics and treatment of hypothyroidism among pregnant women have improved in the course of time. Data consisted of all singleton pregnancies ($N = 571785$) during 2004–2013 in Finland, collected from the Finnish Medical Birth Register (MBR). Data on maternal thyroid diseases were obtained from the MBR and the Hospital Discharge Register, and combined with the Special Refund Entitlement Register and the Register on Reimbursed Drug Purchases consisting data on medication purchases during the index pregnancy. Women with thyroid diseases other than hypothyroidism were excluded ($N = 4561$), rendering a final study population of 567 224 singleton pregnancies. Pregnancies were divided into four categories: mothers with diagnosed hypothyroidism treated with levothyroxine ($N = 8893$), mothers treated with levothyroxine without a recorded hypothyroidism diagnosis ($N = 6788$) (mostly treated in the primary care), mothers with diagnosed hypothyroidism but without levothyroxine treatment ($N = 683$) and mothers without thyroid diseases or thyroid medication ($N = 550\,860$). In 2004

approximately 1% of pregnant women had diagnosed hypothyroidism and were treated with levothyroxine. By 2013 this prevalence had more than doubled up to 2.4%. The prevalence of women receiving levothyroxine treatment without recorded hypothyroidism diagnosis was 0.2% in 2004 but 12-fold higher (2.5%) in 2013. The increase in prevalence of diagnosed hypothyroidism and levothyroxine treatment has been steady over time. Surprisingly, the prevalence of pregnant women with hypothyroidism and no recorded levothyroxine treatment has been constant between 0.1 and 0.2%. Our study shows that the diagnoses of hypothyroidism and use of levothyroxine treatment among pregnant women have increased markedly during the past 10 years. This suggests that clinical recommendations have improved the awareness on the risks of hypothyroidism on pregnancy and the threshold to treat hypothyroidism during pregnancy seems declining.

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EP1286

Radiofrequency ablation for benign thyroid nodules: 450 patients - three years follow-up

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Purpose
The objective of this study was to evaluate the efficacy and safety of ultrasound (US)-guided radiofrequency ablation (RFA) for treating of benign thyroid nodules.
Material and methods
The retrospective analysis included the results of treatment of 450 patients with benign tumors of the thyroid gland in the Samara Oncology Center. 91 (20.2%) patients had autonomously functioning thyroid nodules and 359 (79.8%) had symptomatic ones. The mean volume of nodule was 33.5 (4.1–179.5).
Results
RFA reduced nodular volume by 70% after 6 months, 84% after 36 months and it was an effective method for treating nodule-related clinical problems and hot nodules. 47 (10.4%) patients with big nodule volume underwent 2–6 sessions of RFA. Cosmetic results were excellent in 96% of patients in the RFA group. No serious complications such as thyroiditis, voice change, and hematomas were observed in RFA patients.
Conclusion
RFA was effective and safe for treating benign thyroid nodules. RFA might be recommended for treating benign thyroid nodules as the first-line treatment.

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EP1287

Coexistence of Graves' disease and unilateral benign struma ovarii: A case report

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Introduction
Struma ovarii (SO) is a rare ovarian teratoma composed predominantly (more than 50%) or entirely of thyroid tissue. It constitutes 2% to 4% of ovarian teratomas. This tumor is often asymptomatic and discovered incidentally. Only 8% of patients present clinical hyperthyroidism.
Case report
A 42-year-old woman presented palpitations, anxiety, sweating, emotional lability and weight loss for several months. Physical examination revealed goitre, tachycardia and slight tremor. Laboratory tests confirmed hyperthyroidism: thyrotropin (TSH) 0.01 mcU/ml (0.3–5), serum-free thyroxine 5.21 ng/dL (FT4) (0.9–2.1), serum-free triiodothyronine (FT3) 22.5 pg/ml (2.57–4.43) and thyrotropin receptor antibody (TRAb) 21.78 U/l (positive >2). Thyroid ultrasound identified a multinodular goitre with a dominant nodule of 14 mm in left lobe. Technetium thyroid scan showed diffuse uptake. She was diagnosed as having Graves' disease (GD) and started on thiamazole and propranolol. Several months later, she remained hyperthyroid and appeared proptosis, lid retraction and ocular chemosis. Magnetic resonance of the orbits demonstrated bilateral mild swelling of extraocular muscles. She was diagnosed with Graves' ophthalmopathy too. After that, it was decided thyroidectomy. In addition, oligoamenorrhea appeared and ultrasound and magnetic resonance of the abdomen and pelvis detected an $11\times11\times9$ cm solid-cystic mass in right ovarian. The patient underwent right salpingo-oophorectomy. Histology revealed a benign SO. Immediately, ocular disease and hyperthyroidism improved. Subsequently, total thyroidectomy was performed, which showed GD and benign thyroid nodules.
Conclusions
The diagnosis of functioning SO in presence of GD may be a challenge and it may be difficult to determine the precise cause of hyperthyroidism. When a patient has increased thyroid uptake of technetium in the scan, an ectopic hormone production is not suspected. When SO is surgically removed and subsequently the hyperthyroidism and ocular disease improve considerably, the diagnosis of functioning SO is quite likely.

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EP1288

Clinical characteristics and outcomes of patients with myxedema coma: a 15-years experience of a tertiary care center in Thailand

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Background
Myxedema coma is an uncommon but life-threatening condition of severe and decompensated hypothyroidism requiring early recognition and prompt treatment. The aim of this study is to describe the clinical features and identify factors associated with mortality of our patients diagnosed myxedema coma over the past 15 years.
Materials and methods
Retrospective chart review of patients diagnosed and treated at King Chulalongkorn Memorial Hospital for myxedema coma during 2002–2016 was performed. Their demographic data, clinical features, precipitating factors and treatment outcomes were analyzed. We also compared different scoring systems including Glasgow Coma Scale (GCS), Acute Physiology and Chronic Health Evaluation II (APACHE II) score, Sequential Organ Failure Assessment (SOFA) score and Wartofsky myxedema coma score to predict the outcomes.
Results
A total of 13 cases, 9 females and median age of 79 years ranged between 60-94 years, were recruited. All of them had primary hypothyroidism. Seven patients (54%) were newly diagnosed hypothyroidism at the time of presentation of myxedema coma. Six patients (46%) died and sepsis was the major cause of death. Lower FT_4 level was only parameter significantly different between the patients who survived and those who died ($P=0.04$). On analyzing the various scoring systems, they did not demonstrate a significant difference between survivors and non-survivors; however, a Wartofsky myxedema score below 90 was associated with a better outcome.
Conclusions
Myxedema coma still carries a high mortality rate even with the appropriate diagnosis and treatment. With a high proportion of undiagnosed hypothyroid patients in our study, it should be alert clinicians to beware of this preventable condition in an appropriate clinical context. Thyroid hormone levels and Wartofsky myxedema score may be applied as clinical prognostic parameters.

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EP1289

Evaluation of interrelationships between thyroid function, autoimmunity, insulin resistance and lipid profile in Graves' disease

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Background
Thyroid hormones modulate the lipoprotein and glucose metabolisms. In hyperthyroidism, insulin resistance is a frequent finding.
Aim
To assess interrelationships between thyroid function, autoimmunity, lipid profile, glucose metabolism and other cardiovascular risk factors in patients with Graves' disease.
Methods
We recorded free T3 (FT3), free T4 (FT4), TSH, TSH receptor antibodies (TRAB), parameters of the lipid profile, glucose metabolism [including insulin resistance marker Homeostasis Model Assessment for Insulin Resistance (HOMA-IR)], C reactive protein (CRP) and homocysteine in 126 patients with Graves' disease in the first cycle of treatment with methimazole (93% females, mean age 44.8 ± 15.2 years). Patients were divided in subgroups according to: TRAB (positive ($n=57$) or negative ($n=69$)) and thyroid function (normal ($n=74$), subclinical ($n=29$) or clinical hyperthyroidism ($n=22$)). Spearman correlations, *T*-tests and Mann–Whitney tests were performed for statistical analysis.
Results
Comparing TRAB- and TRAB+ groups, significantly lower apolipoprotein B (80.3(73.2–87.4) vs 89.7(83.5–95.8)mg/dl, $P=0.047$) and TSH (0.180(0.002–1.080) vs 1.020(0.235–2.055)μUI/ml, $P<0.001$) were found in the TRAB+ group. Comparing with the normal thyroid function group, patients in the clinical hyperthyroid group presented significantly lower apolipoprotein B (70.9(57.2–84.6) vs 89.7(83.7–95.8)mg/dl, $P=0.007$) and higher fasting glucose (96.0(83.0–109.0) vs 86.4(83.8–89.0)mg/dl, $P=0.019$), insulin (10.4(6.2–15.8) vs 7.5(4.8–9.7)μUI/ml, $P=0.021$), HOMA-IR (2.09(1.29–4.53) vs 1.55(0.95–2.13), $P=0.023$) and CRP (0.57(0.20–0.93) vs 0.20(0.07–0.38)mg/l, $P=0.005$). No significant differences were found between the subclinical hyperthyroid group and the remaining groups. There was a negative correlation between TSH and TRAB ($r=-0.386$, $P<0.001$). Apolipoprotein B was positively correlated with TSH ($r=0.236$, $P=0.016$), and negatively with TRAB ($r=-0.211$, $P=0.030$). Both FT3 and FT4 were positively correlated with fasting insulin ($r=0.268$, $P=0.008$ and $r=0.226$, $P=0.025$, respectively) and HOMA-IR ($r=0.258$, $P=0.010$ and $r=0.259$, $P=0.010$, respectively). FT4 was also positively correlated with fasting glucose ($r=0.269$, $P=0.008$).
Conclusion
In patients with Graves' disease, the interrelationships between thyroid function, autoimmunity, insulin resistance and lipid profile may contribute to the increased cardiovascular risk.

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EP1290

Successful radioiodine treatment of Graves disease for a patient with a history of «iodide allergy»

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Introduction
Graves's disease is the most common cause of hyperthyroidism. There are three current therapeutic options: anti-thyroid medication, surgery, and radioactive iodine (I 131). There are few data in the literature regarding the effects of radioiodine therapy.
Case report
We describe a 47-year-old patient who had Grave's disease resistant to anti thyroid medication. Radioactive iodine was indicated. The patient was reluctant because she had a history of anaphylactic reaction to computed tomography (CT) contrast agent. We explicated to the patient that the implication of iodine has never been demonstrated during allergic hypersensitivity reactions due to iodinated drugs. She successfully underwent treatment with 12 mCi (444 MBq) radioactive iodine.
Conclusion
Asking a patient if he/she is 'allergic to iodine' is a question that should be avoided because its significance is null. A diagnosis of drug allergy, essentially relying on clinical symptoms, biological tests and cutaneous tests, is required to take adequate preventive measures.

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EP1291

Trans-axillary endoscopic thyroidectomy – technique

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Introduction
Trans-axillary surgery is an emerging technique for cervical approach with fantastic cosmetic result. With more than 50 cases treated by our group, we developed our technique with specific safe methodologies.
Aims
To present step-by-step technique of trans-axillary endoscopic thyroidectomy.
Material and methods
This is a video surgery that uses three trocars and a harmonic scalpel for dissection and ligation. Incisions are made in the armpit and areolar border.
Results
Technique is described in 10 steps: (i) trocars and patient position; (ii) dissection; (iii) landmarks (sternal notch, ECM anterior border, thyroid cartilage); (iv) omo-hyoid muscle dissection; (v) split strap muscles; (vi) upper pole dissection and ligation; (vii) ligation of the middle thyroid vein and recurrent laryngeal nerve (RLN) visualization; (viii) inferior pole ligation; (ix) lobectomy; (x) specimen removal and haemostasis; Three auxiliary techniques are used to increase safe and to reduce complications:
1. Intra-operative ultrasound
2. Neuromonitoring of the RLN
3. Indocyanine green (ICG) fluorescence for parathyroid vascular assessment

Conclusions
Cervical scar-less surgery is very appealing for the patient. For the surgeon with advanced laparoscopic skills this is a feasible and reproducible technique, with excellent results. Security techniques can have great value in more demanding cases.

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EP1292

Trans-axillary endoscopic thyroidectomy – scarless surgery of the neck: our experience

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Introduction
Endoscopic techniques are uprising in the cervical field mainly because of the exceptional cosmetic results. These surgeries are frequent in the far east Asia but still rare in Europe. We started these approach on November 2014. This paper is a review of our experience.
Aims
To present a series of trans-axillary endoscopic thyroidectomy.
Material and methods
This is a cohort study of 50 consecutive patients treated by trans-axillary endoscopic thyroidectomy. Patients are selected using the following indications: benign or suspicious nodules until 35 mm, micro papillary cancer, lobes until 65 mm. Interventions are video recorded and time, recurrent laryngeal nerve identification and parathyroid identification are registered. Laryngoscopy is performed at the end of the procedure. Morbidity data are collected during surgery, on the day after, 2 weeks, 2 months and one year after the operation. All the pathological reports are reviewed.
Results
Among the series, 78% were women with an average of 48 year old. All patients had normal thyroid function at the time of the operation and 95% were low-risk anaesthetic candidates (ASA1 or 2). Half complained of goitre. All but 2 were submitted to lobectomy. There was no conversion to open surgery. No dead was registered. There were 5 cases of morbidity: 2 seromas, 2 skin burn and 1 transient recurrent laryngeal nerve palsy. All cases of lobectomy were discharged home on post-operative day 1.
Conclusions
Endoscopic cervical approach is difficult to implement among surgeons without advanced laparoscopic skills.The technique revealed to be safe and reproducible with potential to enlarge indications. The use of neuromonitoring, ICG fluorescence and intra-operative ultrasound are tools already tested by the group with a benefit in safety.

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EP1293

TSH oscillations in young patients with type 1 diabetes may be due to glycemic variability

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A link between thyroid dysfunction and diabetes mellitus exist. Uncertainties on the role of glycemic variability on thyroid hormones and TSH concentrations still persist. We want to evaluate the influence of glycemic variability on thyroid hormones and TSH concentrations in patients with type 1 diabetes (T1DM). 77 patients with T1DM on insulin therapy without thyroid dysfunction and 100 healthy controls were evaluated for basal glucose concentrations, HbA1c, thyroid hormones and TSH levels. Glucose variability was investigated through the standard deviation of blood glucose (BGSD) readings and through the mean amplitude of glycemic excursions (MAGE) and continuous overlapping net glycemic action (CONGA), the low (LBGI) and high (HBGI) blood glucose indices. The links between TSH, thyroid hormones, glycemia and HbA1c were studied in patients and in controls, whereas those between TSH, thyroid hormones and indices of glucose variability only in patients. All subjects had TSH, thyroid hormones and thyroid antibodies in the normal range. No correlations were found in T1DM patients between free thyroid hormones and glycemic values, HbA1c and indices of glucose variability, while an inverse correlation was observed between TSH levels and glycemic values ($r=-0.4$; $P=0.02$), CONGA index ($r=-0.3$; $P=0.04$) and HBGI ($r=-0.3$; $P=0.05$) but not with HbA1c ($r=-0.1$; $P=0.47$). No significant correlations of TSH and thyroid hormones with glycemia and HbA1c were observed in controls. In T1DM patients was found an inverse correlation between TSH and glycemic variability with direct action of glycemic excursions on TSH secretion disengaged from variations of thyroid hormone concentrations. The study of thyroid function (TSH concentrations) in these patients should be made by multiple samples on patients in euglycemic state to avoid underestimation or overestimation of thyroid dysfunction due to a misdiagnosis of euthyroidism or dysthyroidism with consequent inappropriate therapy.

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EP1294

May erythrovirus (parvovirus) B19 trigger autoimmune thyroid diseases?

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Erythrovirus (EVB19) can recognize auto-antigens by using molecular mimicry mechanisms. EVB 19 is accused in the pathogenesis of many autoimmune diseases. Especially EVB19 is very important in the pathogenesis of autoimmune thyroid diseases. Thus in some case presentations; it was shown that EVB19 might be related with Hashimoto's thyroiditis. Although etiopathogenesis of Graves' disease and Hashimoto's thyroiditis is not known exactly; they are thought to occur as a result of interaction of genetic and environmental factors. Infections are one of the environmental factors, which were alleged to be involved in the pathogenesis, but this was not proved. Parvovirus B19 (EVB19) is an unproven viral agent, which was thought to play a role in pathogenesis. In this study; the prevalence of EVB19 was studied in autoimmune thyroid patients. This study was conducted on patients who were followed-up in the Endocrinology and Internal Medicine Polyclinics and who agreed to participate in the study. Total 90 individuals were counted in this study including 30 patients with Hashimoto's thyroiditis, 30 patients with Graves' disease and 30 control individuals who were compatible in terms of age. EVB19 IgG-IgM was studied manually using immunological ELISA method and values were read in spectrophotometer. According to results of this study; there was no significant difference for Parvovirus B19 IgG-M levels between patients with autoimmune thyroid disease and the control group.

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EP1295

Treatment of toxic multinodular goiter with 131 radioactive iodine – effects in volume reduction, thyroid function and autoimmunity

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Abstract
Radioiodine is a definite treatment option for toxic goiter. We have evaluated volume reduction, function and autoimmunity outcomes with a 15 mCi fixed regimen. Patients with at least one US evaluation before and after Iodine-131 therapy and with at least one year of follow-up were included. TSH, free-T4, antibodies and goiter volume before and yearly after Iodine-131 treatment were analysed for the length of the entire follow-up. The total 151 patients, 72.6% females, had a mean follow-up of 6.2 (1–12) years. At the time of treatment, the mean age was 68.8 years and the initial goiter volume 48.9 (8–255.7) ml, with no statistical difference between sexes. Increased volume was observed in 96.5% females and 91.7% males and there were 10.6% in hyperthyroidism and 89.4% in subclinical hyperthyroidism. The mean percentage volume reduction in the first year was 29.8% which represents 14.7 ml with a Pearson coefficient of correlation with initial volume of 0.058. During the following years mean reductions of 19.7, 15.8, 9.7, 5.8 and 1.4% were observed. Absolute volume reductions were maximal at the 3rd and 4th years representing mean reductions of 50 and 52%. Initial volume, TSH and age could not produce an explicative model for the percentage of reduced volume. Euthyroidism was achieved in 60.9% patients, subclinical hyperthyroidism in 8.6% and hypothyroidism in 26.5% of which 23.8% were subclinical. Hypothyroidism was related significantly with initial volume ($P<0.001$) and maximal percentage of reduction ($P=0.012$). The development of new detectable anti-thyroid antibodies was identified in 5 patients (6.9%), the result being above cut-off in none of them. New anti-TSH-receptor antibodies developed in 4 (5.5%) patients 1–3 years post-treatment. With 15 mCi, all patients experienced volume reduction in the first years after treatment, achieving means above 50% at the 3rd year, most were rendered euthyroid and developed no auto-immunity.

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EP1296

Four out of five patients with acute kidney injury have thyroid dysfunction

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Objectives
This study was undertaken to ascertain the prevalence of thyroid dysfunction(TD) in patients with Acute Kidney Injury(AKI) and assess the prognostic implications of TD in AKI patients.
Materials and methods
Consecutive adult patients (>18 years) admitted with AKI to the departments of Nephrology & Medicine were recruited if they met AKIN classification criteria for AKI after 48 h of admission (1). Patients were screened for thyroid dysfunction with serum sampling of Thyroid stimulating hormone, Free T3 and Free T4 after taking informed consent. Prognosis of TD in AKI patients was assessed in terms of: 1) Duration of hospital stay, 2) Need for Renal Replacement Therapy (RRT), 3) In-hospital mortality.
Results
147 patients with AKI (93M:54F) with a mean age of 57.8 years were recruited and TD was noted in 114 patients(77.5%). Of these, 74(64.91%) patients had Non-thyroidal illness (NTI), 10(8.77%) had primary hypothyroidism, 17(14.91%) had subclinical hypothyroidism, 4(3.51%) had primary hyperthyroidism, 7(6.14%) had subclinical hyperthyroidism and 2(1.75%) had central hyperthyroidism. A trend to longer duration of hospitalisation for AKI patients (>7 days) was seen in 65(75.58%) patients with TD compared to 17(62.96%) patients without TD ($P=0.09$). RRT requirements (56.36 vs 59.38%) ($P=0.84$) and in-hospital mortality (31.58 vs 33.33%) ($P=0.84$)of AKI patients with and without TD were similar. However, a trend of increasing mortality was seen in AKI patients with NTI ($P=0.059$).
Conclusions
Four out of five patients with AKI had some form of thyroid dysfunction, of which majority of them had NTI. However, presence of TD did not significantly affect prognosis of these patients.

Reference
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EP1297

The assessment of influence vitamin D deficiency on the Hashimoto's thyroiditis activity

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The observed increase in the incidence of Hashimoto's thyroiditis (HT) requires research on factors that may affect its development. One of them may be vitamin D deficiency which is an epidemiological problem all over the world.
Aim
The assessment of influence vitamin D deficiency on the HT activity.
Material and methods
310 people were enrolled in the study: 155 patients with HT (a-TPO and/or a-TG positivity)-144 women (93%), 11 men (7%) and 155 healthy volunteers-139 (90%) women and 16 men (10%); mean age: 49 ± 18, 58 ± 17, 49 ± 17 and 56 ± 16 years respectively. For analysis purposes the HT group was divided into two subgroups: without (E) and with l-thyroxine treated hypothyroidism (H): 45 patients aged 50 ± 14 and 110 patients aged 50 ± 17 respectively. Serum 25OHD3, TSH, a-TPO, a-TG, 25OHD3 levels were measured in all subjects. Vitamin D deficiency was defined as 25OHD3 < 30 ng/ml.
Results
In HT patients 25OHD3 level was lower than in the control group: 23.2 ng/ml (Q_1-Q_3: 18.6–29.0) vs 25.6 ng/ml (Q_1-Q_3: 21.0–31.4; $P = 0.006$). There is no difference between 25OHD3 concentration in subgroup E and control group (28.7 vs 25.6 ng/ml; $P = 0.4$) but 25OHD3 level was significantly lower in subgroup H than in subgroup E (21.5 ng/ml; Q_1-Q_3: 17.8–27.3 vs 28.7 ng/ml; Q_1-Q_3: 21.4-33.2; $P < 0.001$). The study showed higher 25OHD3 level in a-TPO negative than in a-TPO positive patients (32 ng/ml; Q_1-Q_3: 25.6-37.7 vs 22.1 ng/ml; Q_1-Q_3: 18.1–28.4; $P < 0.001$); the same was observed in a-TG negative and a-TG positive subjects (28.7 ng/ml; Q_1-Q_3: 23.2–32.7 vs 20.2 ng/ml; Q_1-Q_3: 15.4–23.6; $P < 0.001$). In subgroup E 25OHD3 level was similar independently of a-TPO or a-TG positivity.
Conclusions
Evidence of a link between increased level of antithyroid antibodies in hypothyroid patients with HT and 25OHD3 deficiency may suggest that this group is particularly prone to the vitamin D deficiency and can benefit from its alignment.

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EP1298

The role of 99mTc-sestamibi in amiodarone-induced thyrotoxicosis – Case report

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Introduction
Amiodarone is an antiarrhythmic iodine-rich drug, known to induce thyroid dysfunction both due to its high iodine content and through amiodarone-induced thyrotoxicosis (AIT), being this latter process classified into three different types. Type 1 is associated with increased thyroid hormone synthesis; type 2 is a destructive process with thyroid hormone release and type 3 is thought to be a mixture of the former two. Since treatment options are different, there has been a growing need for a diagnostic method that could accurately distinguish these types and therefore allow targeted therapy. 99mTc-sestamibi scintigraphy has been gaining a specific role in this matter: with recognized increased uptake by epithelial cells that show high mitochondrial concentration, it allows the physician to visually differentiate between necrotic or destroyed tissue (which shows absent or very low uptake of the radiopharmaceutical) from hypermetabolic cells (with increased uptake).
Case report
A 72-year-old male with atrial fibrillation treated with amiodarone for 10 years was sent to our Endocrinology outpatient clinic for new-onset asymptomatic subclinical hyperthyroidism (FT3 2.56 pg/ml (2.00 4.40); TT3 85 ng/dl (80–200); FT4 1.59 ng/dl (0.93–1.70); TT4 10.0 (5.1–14.1); TSH 0.03 mU/l (0.27–4.20)). He had a history of euthyroid benign nodular disease. We admitted AIT type 2, but considering the mild thyroid dysfunction, we chose to pursue further evaluation with 99mTc sestamibi scintigraphy, in order to initiate targeted therapy. Scintigraphic images showed initial uptake by the thyroid gland with rapid washout, a pattern described in literature as corresponding to AIT type 3. The patient's thyroid hormones normalized before starting any medication and he is currently on follow-up.
Conclusion
This case report is illustrative of the possible role of 99mTc sestamibi scintigraphy in diagnosis and management of thyroid disfunction induced by amiodarone. However, more expertise is further needed.

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EP1299

Effect of vitamin D supplementation on patients with Graves disease

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Multiple factors contribute to the etiology of Graves disease(GD), including genetic and environmental factors.vitamin D is well known in calcium metabolism and has also been shown to be a modulator in innate and adaptive immunity. There is a well-established link between vitamin D deficiency and various autoimmune diseases. The prevalence of vitamin D deficiency was reported to be common in patients with GD. Whether vitamin D deficiency has a causal relationship with GD remains controversial.Aim:to evaluate the effect of vitamin D supplementation in patients with GD with and without opthalmopathy methods: A randomized prospective study was conducted on 60 adult patients with GD.
Group 1
20 patients with GD receiving 30 mg of methimazole daily.
Group 2
40 patients with GD receiving same dose of methimazole and vit. D3 200 000 IU/month. Patients were followed up for 3 months.
Results
40% of patients in group 1 and 72.5% in Group 2 were vit. D deficient,Vit. D was significantly correlated with thyroid volume and degree of exophthalmos. Gp 2 had significant lower thyroid volume and better effect on degree of exopthalomos.
Conclusion
Vit. D suuplementation for GD has a favourable effect on thyroid volume and degree of exophthalmos.

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EP1300

Primary hyperparathyroidism coexisting with Graves' disease in a patient with vitamin D deficiency

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Primary hyperparathyroidism is known to coexist with thyroid cancer and breast cancer. However, primary hyperparathyroidism coexisting with Graves' disease is extremely rare. The aim was to describe the case of a patient with Graves' disease causing severe hyperthyroidism who in the course of the disease developed vitamin D deficiency and primary hyperparathyroidism. A patient, female, aged 49 years, presented with severe hyperthyroidism causing tachycardia, palpitations and weight loss. TSH receptor antibodies were positive in the context of Graves' disease. She was treated with methimazole and

propranolol and the disease went into remission. A year later treatment with methimazole was discontinued and 4 months later the patient had a relapse of hyperthyroidism. Laboratory tests revealed hyperthyroidism along with vitamin D deficiency and elevated PTH levels. Vitamin D was administered along with methimazole and propranolol. During follow up, despite normal vitamin D levels, PTH levels remained extremely elevated and blood calcium levels in the upper normal range. Ultrasound of the thyroid and parathyroid glands revealed a parathyroid adenoma adjacent to the left thyroid lobe. The adenoma was visible in a scan with ^{99m}Tc-sestamibi. The patient is being followed up and prepared for surgical treatment of both hyperthyroidism and primary hyperparathyroidism. The extremely rare case of a patient with concurrent Graves' disease causing severe hyperthyroidism and primary hyperparathyroidism along with vitamin D deficiency is presented. This case further illustrates that primary hyperparathyroidism may be diagnosed in the context of severe vitamin D deficiency, being aggravated by vitamin D administration and that primary hyperparathyroidism may coexist with thyroid disorders.

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EP1301

Primary underdosed hypothyroidism – parodontal implications in adults

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Introduction
Dento-maxillary system changes associated to thyroid disorders are constantly present. Differentiated impairment, depending on the period of evolution of the disease, explains the high percentage of over 60% of cases with parodonthopathy.
Aim of the study
Evaluating the oro-maxillo-facial changes in patients with underdose treated hypothyroidism.
Methods
The study group comprised 154 patients with hypothyroidism, 132 women and 22 men. The examination included the assessment of oral cavity under parodontal status, the quality of dentition, changes of dento-maxillary dynamics.
Results
Facial and lip changes were present in 28.4% of cases; macroglossia 13%; mucoid infiltration of lingual mucosa and oral submucosa −76%; gingivitis and chronic marginal periodontitis −98%; pathological tooth mobility – grade 1(73%) and grade 2 (15%); 12 patients (9.16%) required periodontal abscess drainage – 2 cases of upper premolars (14%) – 10 cases of lower molars (36,5%). Modification of occlusion by changing maximum pressure points – 72 patients (52%). A total of 61 patients (46.5%) presented vestibular pockets – 23 periodontal (17.5%), 25 palatal (19%) and 13 with lingual localization (10%). The average time of evolution of hypothyroidism with subdosed treatment was 4.3 ± 1.2 months. Dental cavities were present in 77% of patients; partial edentation – in 89.3%; total edentation – 9.16%.
Atrophied prosthetic field
Four cases (3%); 8 cases (6%): osteophitic hyperostosis. The average time of evolution of hyperthyroidism: 7.4 ± 1.5 months. The specific dento-parodontal and prosthetic treatment previously assumes the control of the thyroid hormone deficiency.
Conclusions
Periodontal changes are almost constantly found in hypothyroidism. The extent of the disease without a normal substitution is directly proportional to the severity and a high incidence of complications.

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EP1302

Assessment of the degree of depression in patients with chronic autoimmune thyroiditis depending on the serum autoantibodies and thyroid hormone levels

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Introduction
The incidence of depressive type psychoaffective disorders is significantly increased in patients with chronic autoimmune thyroiditis.
Objectives
The study of thyroid autoimmunity correlated with serum levels of TSH, FT4 and depression degree.
Methods
The study comprised 70 patients (64 women and 6 men), aged between 18 and 66 years, divided in 4 groups. All study groups were analyzed according to the degree of depression and serum TSH, FT4, thyroid peroxidase antibody(TPOAb) ,thyroglobulin antibody(TGAb). There were calculated the average values, standard deviation, incidence and statistical significance of p value <0.01. Beck depression test was used to determine the level and severity of depression.
Results
Absence of depression was associated with elevated TSH (6.49 ± 3) and low FT4(10 ± 6); TPOAb values (199 ± 12) and TGAb values (358 ± 8). Minimum depression was correlated with elevated TSH (6.6 ± 3) and normal FT4 (14.8 ± 9.8); TPOAb values (247 ± 18) and TGAb values (385 ± 22). Moderate depression has been associated with normal TSH (4.2 ± 2) and normal FT4 (18.5 ± 15); TPOAb values (253 ± 26) and TGAb values (422 ± 16). Severe depression was accompanied by slightly elevated TSH (4.3 ± 3) and normal FT4(15.5 ± 8.7); TPOAb values (336 ± 18) and TGAb (425 ± 22).
Conclusions
It was revealed a high incidence of depressive disorders among the pacients with chronic autoimmune thyroiditis with a distribution of medium and severe forms of depression predominantly in women without any evidence of thyroid hormonal level involvement.The study shows a heterogeneity of thyroid autoimmunity regarding the effect of antithyroid antibodies in generating psycho-emotional processes commonly found in these patients.

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EP1303

Frequency and prognostic factors of non-diagnostic cytology in ultrasound guided thyroid fine needle aspiration biopsy: a 2-year single centre experience

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Aim
Ultrasound-guided Fine Needle Aspiration Biopsy (USg-FNAB) is the most accurate modality for distinguishing malignant or possibly malignant from benign thyroid nodules. However, a certain amount of specimens turn out to be non-diagnostic or inadequate. Several factors contribute to this outcome such as the examiner's experience, characteristics of the nodule and patient's compliance. Understanding these factors could contribute to reduction of non-diagnostic results.
Methods
All nodules examined by USg-FNAB between Jan 2014 and Nov 2015 at the thyroid clinic of our department were reviewed ($n=682$ patients with 987 nodules). Patient demographic characteristics (sex and age), nodule characteristics (size, location, previous FNAB) and the experience of the examiner were recorded.
Results
The only factor that exhibited a significant positive association with non-diagnostic cytology on USg-FNA was the age of the patient ($P < 0.01$). Nodule size was marginally negatively associated ($P=0.054$). No other factor emerged as a predictor of non-diagnostic cytology.
Conclusions
The present study indicates that patient age is a prognostic factor for non-diagnostic cytology on USg-FNA. This might be attributed to the fact that older patients usually present with nodules baring morphologic characteristics such as cystic composition and peripheral calcifications that are associated with non-diagnostic cytology. On the other hand, the marginally negative association with nodule size, seems justified by the fact that small nodules are technically more difficult to biopsy. It is of note that the examiner's experience has not emerged as a prognostic factor, possibly due to the fact that nodules which are not easily accessible are usually biopsied by more experienced staff.

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EP1304

Juvenile hypothyroidism-particularities in the development of the dento-maxilary system

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Introduction
Juvenile hypothyiroidism shows various complications depending on the correctitude of substitutive treatment.
Aims of the study
To identify the massive facial changes with occlusive disorders, dental malpositions, altered chronology of dental eruption, periodontal changes in terms of absence of thyroid replacement therapy or drug sub-dosing.
Methods
The study group comprised 24 children, 15 girls and 8 boys; 4 cases of congenital myxedema;19 cases of earned hypothyroidism and the mean age was 9 ± 2.4 years- that presented in their evolution periods of underdosed substitutive thyroxine treatment.
Results
Facial changes: infiltrated facial skin and lips; widened transverse diameter of the skull; microretrognathia – 12 cases (52%). pale and infiltrated lingual and jugal mucosa, 14 children (60.8%) – lingual fungal detritus; 8 children (34.7%) – 'geographic' tongue. Occlusive disorders: frontal malocclusion in the sagittal plane – 19 children (80%); front reverse occlusion – 8 cases (34.7%); open bite – 4 cases (17.4%); lower *proalveolodentition* with interdental spacing – 17 children (68%). Dental malpositions:reverse overlap – 11 cases (47.8%), eruption of central upper incisors in vestibular position – 1 case (4.3%); bilateral ectopic canine – 1 case (4.3%); dentoalveolar incongruence – 1 case (4.3%). The chronology of dental eruption: late eruption – 19 patients (78.2%); prolonged mixed dentition – 14 patients (60.8%); taurodontism – upper molars–1 case (4.3%); accelerating the teeth eruption when introducing thyroxine therapy between 6 and 8 months. Periodontal changes: pathological dental mobility, pathological diastemas, gingival recession, real periodontal pockets – 8 cases (34.7%).
Conclusions
In hypothyroid child prevail the disorders of occlusion and chronology of eruption. Early diagnosis and a well conducted thyroxine treatment requires the prophylaxy of dento-maxillary complications in children.

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EP1305

Thyrotoxic periodic paralysis

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Thyrotoxic periodic paralysis (TPP) is due to a fall in potassium levels and threat life if it effects respiratory muscles. Men are more effected than women, and lower extremeties are more prone to involvement. Serum potassium in hyperthroidism is usually normal, but Na^+/K^+ ATP'ase sensitivity is increased and extracellular potassium rapidly passes to the intracellular space. Beta blockers, small dose potassium replacement and hyperthyroidism treatment blocks this shift and TPP can be treated. Achieving euthyroidism is essential for the cure of TPP. Although hyperthyroidism effects mainly females, TPP is seen more in males especially in the second and fourth decades. Periodic paralysis is seen only in 2% of thyrotoxic patients which is characterized by hypokalemia, proximal muscle weakness and acute onset. We present four cases of male patients aged between 28 and 36 years old. Their complaints were, fatique, weakness and difficuilty in walking. Two patients had known Graves' disease and two patients were diagnosed as new onset Graves' disease. They did not have predisposing factors such as alcohol intake, using diuretics or laxatives. On phsical examination, they all had proximal muscle weakness and diminished lower extremity deep tendon reflexes. Their potassium levels were 2.7-2.3-2.1-1.9 mEq/l respectively. Their thyroid antibodies were positive, TSH levels were supressed and free thyroid hormones were elevated. Patients were treated with potassium replacement and antithyroid drugs and lower extremity weakness and paralysis were disappeared. HPP is a genetic disorder but rarely it can be due to thyrotoxicosis. Although TTP is more commonly seen in Graves disease, it is free of disease duration and severity.

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EP1306

Audit of utility of radio-isotope scan in the investigation of thyrotoxicosis or subclinical hyperthyroidism and timing of anti-thyroid medication

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Thyrotoxicosis is one of the most common clinical problems in patients referred to endocrine clinic. TRAb is specific for graves disease (GD) and radioisotope scan (RIS) is useful diagnostic test in the investigation of thyrotoxicosis. RIS is commonly used when TRAb is borderline or negative to exclude thyroiditis.
Aims and methods
To look at the use of RIS in the investigation of thyrotoxicosis and sub-clinical hyperthyroidism (SCH), and use of anti-thyroid medication (ATM) in these conditions. Retrospective audit, data collected from electronic pathology and radiology system, and clinic letters over 11months (Jan 15 to Nov 15).
Results
$n=66$, of which 63 (95.5%) were sub-clinical hyperthyroidism or thyrotoxicosis. Female=52(82.5%). Mean age: 54.07 years. 60 (95%) patients had TRAb checked and 3 (5%) patients not. ($n=1$ SCH, planned for radio iodine, $n=1$ on carbimazole and planned for radioiodine, $n=1$ TRAb requested but not processed). All patient with TRAb −ve and 5 patients with TRAb +ve had RIS. 23 (36.5%) were diagnosed with graves disease. 3 patients with negative TRAb who were later diagnosed with GD on RIS were commenced on carbimazole before diagnosis. 17 (27%) were diagnosed with thyroiditis, of which 4 (23.5%) were commenced on carbimazole before diagnosis.
Conclusion
This audit shows appropriate use of RIS in all patients in the investigation of thyrotoxicosis and SCH. 5 patients with positive TRAb had RIS as TRAb was borderline and history was not typical of graves disease. 7 patients were commenced on ATM before diagnosis of GD. All these patients had mild to moderate thyrotoxicosis. These patients could have been started on β-blockers rather than ATM as they are associated with side effects of agranulocytosis which can risk life threatening infections.

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EP1307

Thyroid autoimmunity and frequency of malignant or suspicious for malignancy thyroid nodule cytology

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Introduction
Thyroid autoimmunity has been associated with the diagnosis of differentiated thyroid (DTC) cancer in surgical series. However, this finding has not been consistent in Fine Needle Aspiration Biopsy (FNAB) cytology series.
Aim
We aimed to investigate the association between thyroid autoimmunity and DTC in patients who underwent ultrasound-guided FNAB.
Methods
A retrospective analysis of patients who had undergone ultrasound-guided FNAB between Jan 2014 and Nov 2015 was performed. Patients were classified into two groups, according to the presence of thyroid auto-antibodies (ATA): ATA negative (ATA −) and ATA positive (ATA+) patients. In ATA+ patients, either one or both antibody types (anti-thyroid peroxidase abs or anti-thyroglobulin abs) were positive. Patient demographic characteristics, the presence of risk factors for thyroid cancer and nodule size were recorded. Cytology reports were classified, according to the Royal College of Pathologists guidance, as negative for malignancy (Thy2), possible neoplasm (Thy3), suspicious for malignancy (Thy4) and malignant (Thy5). Non-diagnostic cytology reports (Thy1) were excluded. The frequency of possible neoplasm, suspicious or malignant (Thy3, Thy4, Thy5) was estimated in the two patient groups (ATA−, ATA+).
Results
During the study period 673 nodules of 466 patients were biopsied. Thyroid autoimmunity was present in 41.8% of patients. The frequency of suspicious or malignant (Thy3, Thy4, Thy5) cytology reports was comparable in the two patient groups (5.8% in ATA+ patients vs. 4% in ATA− patients; $P=0.303$).
Conclusion
In the present study, no association between the presence of thyroid autoimmunity and suspicious or malignant findings in thyroid nodule cytology was found.

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EP1308

Clinical experience with glucocorticoid therapy in patients with endocrine ophthalmopathy

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Objective
To evaluate the efficacy, safety and to determine the criteria for the glucocorticoid therapy scheme: intravenous pulse therapy followed by tablet form in prolonged regime in the treatment of active phase of endocrine ophthalmopathy (EOP).
Materials and methods
28 patients of both sexes (52 eyes) with endocrine ophthalmopathy in the active phase were included in the study. The average age – 43.4 ± 10.6 years. The duration of the disease ranged from 3 to 12 months. The activity of disease was evaluated according to a scale of clinical activity of EOP – Clinical Activity Score (CAS), and thickening of the extraocular muscles based on MSCT of the orbits.
Results
One month after the start of pulse therapy there was a significant reduction of EOP activity and severity in all patients, which was confirmed by an increase in vision, a decrease in the level of intraocular pressure, reduction in the amount exophthalmus at 0.8 ± 0.02 mm ($P < 0.05$) and the frequency of diplopia. 3 months after the start of glucocorticoid therapy in 100% of cases a transition to the inactive phase of the disease was determined. Reoccurrence of the disease after 12 months was diagnosed in 3 patients (10.7%).
Conclusions:
i) Intravenous pulse therapy with high doses of methylprednisolon followed by oral administration in prolonged regime is effective and safe; it contributes to the rapid achievement of clinical effect and stable remission of the disease. ii) A thickening of the extraocular muscles is the criteria for the start of glucocorticoid therapy.

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EP1309

Thyroid storm presenting in the context of recent influenza vaccination and untreated Graves disease

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Introduction
Thyroid Storm is a life-threatening but rare (incidence 0.2 per 100 000) disease state which presents as an extreme form of thyrotoxicosis. A hyper-metabolic state resulting from excessive thyroid hormone release which can be precipitated by both thyroidal and non-thyroidal illness.
Case
In this case we discuss a 72 year old female with previously treated Graves disease who presented in thyroid storm one week after annual flu vaccination. On initial presentation, she was in overt heart failure with bilateral pleural effusions and a community acquired pneumonia, atrial fibrillation at a rate of 170 beats per minute and acute confusion with significant agitation. The decision to treat initially with beta blockers was complicated by her being in heart failure with significant pulmonary oedema and a rapid ventricular rate precipitating a peri-arrest state. The guidance of the cardiologists to give amiodarone to chemically cardiovert conflicted with her thyrotoxic state. Relevant Data includes a Thyroid stimulating hormone of < 0.05 mIU/l and a T4 of 96.5 pmol/l. A biochemically euthyroid state was eventually achieved using propathyaurocil, intravenous hydrocortisone, Lugols Iodine and Bile salts. Beta blockers and amiodarone were used with caution in the context of heart failure/suspected thyrotoxic cardiomyopathy and a thyrotoxic state respectively. Further investigation showed the patient had previously been treated for Graves and this was a late presentation recurrence seven years after completing block and replace therapy.
Discussion
We present this case because it highlights a rare case of thyroid storm presenting seven years following initial block and replace therapy had discontinued. The temporal relationship between presentation and the administration of the flu vaccination mean this must be considered as a potential non-thyroidal precipitant. The presentation in fast atrial fibrillation is also significant as the treatment of choice was amiodarone and this could have potentially exacerbated her underlying thyrotoxicosis.

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EP1310

Relapsing Graves' hyperthyroidism in a male patient with central hypothyroidism after surgery of craniopharyngioma: case report

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Introduction
Graves' disease is an autoimmune thyroiditis, less common in men but with relapse of hyperthyroidism significantly more frequent in men than in women after anti-thyroid medications' withdrawal. Craniopharyngioma is a rare brain tumor which arises in the pituitary stalk and project into the hypothalamus. The distribution by age is bimodal with a slight male predominance and a poor survival rate for older than 65 years. The association of these pathologies is extremely rare.
Observation
We report the case of a 67 years-old patient who presented a severe thyrotoxicosis due to a relapse of a Graves' disease in remission since 2009. At the moment of presentation the patient was in treatment with levothyroxine for a central hypothyroidism secondary of a craniopharingyoma surgery. Clinically he presented tachycardia, weight loss, confusion, anorexia and biologically he had low TSH value and very high FT4 (100 pmol/l) and FT3 (50 pmol/l) values which were increasing 5 days after stopping the levothyroxine. TSH receptor antibodies were positives (2.8 U/l) and the I-123 scintigraphy found an intense and uniform fixation confirming the relapse of Graves' disease. A treatment with carbimazole 60 mg per day was started with a strictly surveillance of hepatic enzymes. There was a decrease of thyroid hormones and hepatic enzymes and also symptoms in 2 weeks. A thyroidectomy is to discuss, because of the relapse and the severity of the symptoms, after achieving the euthyroid status.
Conclusion
We described here, for the first time, an association of a relapsing Graves' disease in patient with hormonal supplementation for central hypothyroidism after surgery of craniopharyngioma, with a favorable evolution after treatment with anti-thyroid medications.

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EP1311

TSH normalization and negative anti-TSH receptor antibodies – Predictive value for remission in Graves' disease

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Graves' disease is the most common cause of hyperthyroidism in non-endemic areas and antithyroid drugs are the preferred first-line therapy in many centers. The aim of this retrospective investigation was to verify the association of remission with the achievement of normal TSH and free-T4 during the first 18 months of treatment and to compare it with negative anti-TSH-receptor antibodies at 18 months, a marker with known prognostic value. All patients diagnosed with Graves' disease from 2008 to 2015 were selected. Those with more than 2 years of follow-up and with synchronous determination of TSH, free-T4 (fT4), free-T3 and anti-TSH-receptor antibodies (TRAb) performed at our clinic were included. We compared TRAb titer, TRAb positivity, TSH and fT4, between the group that achieved remission and the one that did not, for the length of treatment and follow up. We obtained 71 patients with mean age of 47 years of which 76% were females. The mean follow-up after remission was 2 years. Remission was achieved in 28% patients after 18 months of treatment. There were no significant differences in sex or age among the 2 groups. No association was found between the development of hypothyroidism during therapy and remission. Negative TRAbs at 18 months associated with remission significantly ($P < 0.001$) with a strength of association of 0.86. A non-supressed TSH accompanied by normal fT4 levels achieved during therapy was associated significantly with remission ($P < 0.001$) with a strength of association of 0.74. Logistic regression with this parameter could explain 59.8% of remissions after initial therapy with $P < 0.001$. This profile of thyroid function was associated with negative TRAbs significantly ($P < 0.001$). Achieving a non-suppressed TSH in the presence of normal fT4, during the first 18 months of therapy, associates with TRAb negativization and could predict remission in approximately 60% of patients.

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EP1312

Treatment choice and patient satisfaction in thyrotoxicosis

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Background
Thyrotoxicosis may be associated with considerable patient morbidity. Graves' disease (GD) and toxic multinodular goitre (TMNG) are the most common causes of thyrotoxicosis. Therapeutic options include anti-thyroid medication or definitive treatment by radioiodine or surgery. Efficacy, quality of life and cost-effectiveness are among the outcomes that have been compared between these two therapies. However, there is still no clear consensus as to which treatment option offers a better outcome.
Aims
The aim of this study was to assess quality of life amongst patients who received anti-thyroid medication, radioiodine or surgery and to assess patient satisfaction with the treatment modality selected.
Method
Participants in a prospective study with new onset thyrotoxicosis were invited to participate. Those who agreed to be involved completed a questionnaire detailing factors involved in treatment choice, quality of life (ThyPRO) and satisfaction with their treatment.
Results
Of those eligible for the study 146 patients completed the questionnaires, representing a return rate of 73%. GD was the cause of the thyrotoxicosis in 84% and TMNG in 16%. Fifty-eight percent of patients had received anti-thyroid medication, 19% radioiodine, and 22% thyroid surgery, the latter two groups usually following a period of medical therapy. The impact of treatment on recovery time, activities of daily living, possibility of depression or anxiety, and doctor's recommendations were identified as the most important factors in choosing a treatment. Satisfaction levels were high across all three treatment types. There was no difference in quality of life between the treatment types apart from a higher score for cosmetic concerns in the surgical group.
Conclusions
These results indicate that overall patient satisfaction with treatment and quality of life are comparable across all three treatment options. Therefore, factors such as patient preference and resource availability may be more important than treatment type.

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EP1313

Management of relapsing Graves: a clinical survey among endocrinologists in Israel

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Background
The management of relapsing Graves' disease is controversial. Previous surveys from different regions in the world demonstrated variations in the clinical practices of patients with Graves' disease relapse.
Methods
To determine management pattern among endocrinologists in Israel an electronic questionnaire was e-mailed to all members of the Israeli Endocrine Society. Questionnaires included demographic data and clinical scenarios with questions regarding the treatment and follow up of patients with relapsing Graves' disease.
Results
We received 98 responses from Israeli endocrinologists. 42 (43%) males and 56 (57%) females. 41.8% had board certificate for more than 10 years. 72.4% responders work in hospital environment and 26.5% work in community clinics. 61.2% see more than 10 thyroid patients in clinic per week. When managing Graves' relapse following ATD treatment in a young male, 68% would restart ATD (98% mercaptizol) and 32% would refer to RAI treatment. Interestingly, endocrinologist who treat more thyroid patients (more than 10/week) tend to choose ATD over RAI ($P=0.04$). In case of recurrent Graves' and ophtalmopaty 50% would continue ATD, 22.4% would recommend RAI treatment and 27.6% surgery. Most endocrinologists (56%) would continue ATD for 12–24 months. 75% would monitor CBC and liver function (39% for the first month and 36% for 6 months). 44% would recommend routine neck US, and 19.3% would recommend routine DEXA. In a case of thyrotoxicosis due to 3 cm toxic nodule tirads 4a most endocrinologists (70%) would refer to RAI ablation, 46.4% without FNA and 23.7% with FNA. No significant difference was found in correlation with gender, years of board certificate, or work environment.

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EP1314

Case report: identification and characterization of interference by IgM anti-streptavidin antibody in a patient with spurious thyroid function tests

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Introduction
Falsely high FT4 and FT3 with concurrent falsely low TSH have been reported in patients taking biotin and in a few case reports of patients with IgG anti-streptavidin antibody. However, other isotypes and effects on other immunoassays have not been reported.
Case
A 77 year female presented with worsening fatigue with a background of hyperthyroidism on carbimazole. Clinically she appeared hypothyroid. Her results on Roche Cobas platform were: TSH 0.75 mIU/l (R.I. 0.27–4.2), FT4 12 pmol/l (12–22) and FT3 8.1 pmol/l (3.9–6.8). However, tests repeated on Siemens Centaur platform were: TSH 37 mIU/l (0.3–4.0), FT4 7 pmol/l (10–20) and FT3 3.0 pmol/l (3.0–6.5), suggesting Cobas results were falsely low for TSH and falsely high for FT4 and FT3. To identify the cause of interference a second sample from the patient was preincubated with streptavidin microparticles. After incubation TSH on Cobas platform increased from 0.2 to 0.7 mIU/l, while FT4 reduced from 28 to 16 pmol/l, and FT3 from 9.0 to 4.7 pmol/l. Siemens results were unchanged. Elution of streptavidin microparticles with 0.1M citric acid identified a 75 kDa band on reducing SDS–PAGE. Purification and sequencing of peptide fragments by LC-MSMS of this band identified this protein as IgM heavy chain. This demonstrates IgM anti-streptavidin antibody as the cause of interference. The patient's hypothyroid symptoms resolved when carbizamole was stopped. The effect of preincubation with streptavidin microparticles was also tested on Roche Cobas immunoassays for FSH, LH, oestradiol and testosterone in this patient's serum. Sandwich immunoassays were falsely low and competitive immunoassays were falsely high. Oestradiol exhibited the largest difference, at 240 pmol/l initially but becoming undetectable following incubation.
Conclusions
This is the first case describing IgM anti-streptavidin antibody as the cause of interference on thyroid function tests and also shows its effects on other immunoassays.

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EP1315

Severe Grave's dermopathy and acropachy discording with moderate ophtalmopathy: (a case report)

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Introduction
Pretibial Myxedema(PM) and acropachy(AP) are rare extrathyroidal manifestations of Graves' disease observed only in 0.5–4% of all cases. These extrathyroidal manifestations are generally associated to severe ophtalmopathy.

Only few cases of severe thyroid dermopathy and achropachy occurring with moderate ophtalmopathy were reported.
Observation
We present a 60years old female patient who developed grave's disease on a pre-existing goiter associated to extrathyroidal manifestations. Physical examination revealed; some signs of hyperthyroidism, moderate exophthalmos measured by hertel's exophtalmometer at 20 for right eye and 19 for Left eye, bilateral severe PM manifested by elephantiasis, severe AP manifested by clubbing and finger deformations, compressive goiter with 3 palpated nodules (a 5 and 4 cm nodules occupying the totality of the right and left lobe respectively, and a 2 cm left lobo-isthmic nodule) which were confirmed by ultrasound of the neck that showed hypervascularization of the normal parenchyma. Thyroid function tests before treatment showed FT3 predominating hyperthyroidism: TSHus <0.005, FT4 $=$ 4.11 ng/dl (N:0.7–1.4), FT3 >30 pmol/l (N:3.0–8.3 pmol/l). Anti-thyroid peroxidase antibodies were positive 149.6 UI/ml (N: <12 UI/ml). Total thyroidectomy was performed after normalization of thyroid function under 60 mg of neomercazol, and this goiter was benignant on pathology. PM was stabilized after surgery and management of hypothyroidime by levothyroxine.
Conclusion
PM and AP are very rare. They reflect the severity of autoimmunity and long duration of hyperthyroidism. These signs are often observed in severe hyperthyroidism and are constantly associated to ophtalmopathy which is generally severe. Infiltration corresponds to the accumulation of GAG in the 3 conditions. Moderate ophtalmopathy occurring with severe PM(elephantiasis) and AP(clubbing and deformations) is not habitually reported.

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EP1316

The importance of the study of several immunoregulatory cytokines in the manifest hypothyroidism

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The research goal was to study serum concentration of immunoregulatory cytokines (IL-1ß, IL-6ß, IL-8ß, IL-10ß) in 80 patients with manifest hypothyroidism at the age of 21–50. 48 patients suffering from chronic autoimmune hypothyroidism and 32 patients with postoperative hypothyroidism were examined. It was revealed that autoimmune hypothyroidism effects balance disturbance of cytokine-producing activity Th1 and Th2 types, this plays an important role in development of autoimmune state, chronization and disease progress. The research goal was to study kidneys' function in conditions of thyroid hormone deficit. Estimation of kidneys' function included study of daily microalbuminuria; serum concentration of creatinine and rate calculation of glomerular filtration with MDRD formula; examination of urea level; potassium and natrium in blood serum; urinary excretion of chemokines: monocyte chemoattractant protein-1 (MCP-1) and Regulated on Activation, Normal T-cell Expressed and Secreted. In both groups of patients with hypothyroidism is established a significant decrease of glomerular filtration rate, tubular reabsorption, and increase sodium excretion in the urine, indicating a violation of tubular functions in form of decrease sodium reabsorption in the proximal tubule, and was accompanied by a decrease in median serum sodium levels below the normal range. Level of proinflammatory cytokines IL-1ß, IL-6ß, IL-8ß and anti-inflammatory cytokine IL-10ß; vascular endothelial growth factor in blood serum of 80 patients with clinical hypothyroidism and 50 healthy persons were studied. Our data are the evidence of increase in patients with autoimmune hypothyroidism of IL-6 level of blood serum and urea excretion level of anti-inflammatory cytokine MCP-1, decrease of IL-10 production in patients with clinical hypothyroidism in their second age period. Healthy persons aged over 35 demonstrate increase of level of anti-inflammatory cytokine IL-10 on a background of gently cut cue of proinflammatory cytokines IL-1ß, IL-8ß.

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EP1317

The position of immunoglobuline G4 positive in Hashimoto's thyroiditis

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Aim
There are studies showing that Hashimoto's thyroiditis (HT) progresses more rapidly, thyroid echogenicity is lower and thyroid autoantibodies are higher titer positive in immunoglobulin G4 (IGg4) positive patients.But a small number of studies that do not support this data have also been published.We planned this study to evaluate the findings of IgG4 (+) Hashimoto's thyroiditis cases.
Materials and methods
New diagnosis without treatment of thyroid 92 patients with HT and 60 healthy volunteers were included fort he study between October 2015 and October 2016. After 8 hours of fasting, basal thyroid function tests and serum IgG4 level were analyzed in the whole of the individual and thyroid ultrasonography was performed all of them.HT patients were divided into subgroups with IGG4 (group 1) and without IgG4 (group 2).
Findings
Mean IgG4 levels were similar between patient group and healthy volunteers.There were 22 patients in group 1 and 70 patients in group 2. Mean age values of two groups were similar.Statistically men patients were more in group 1 ($P=0.009$). There was no statistically significant difference was detected between two groups in terms of mean thyroid stimulant hormone (TSH), free T4, free T3, anti-TPO and anti-Tg antibodies, thyroid volume, thyroid nodule quantity and thyroid parenchyma echogenicity.
Results
There are publications in the literature that, IgG4 positive HT is more often detected in younger age and men patients, it is related lower echogenity ultrasonographically and higher titre thyroid autoantibodies. However in our study, among IgG4 positive HT patients, statistically meaning difference was not detected in terms of parameters examined, except more men numbers. We have thought that, these results arised because of the premise of working and IgG4 positive case number scarcity.

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EP1318

TRAB positive thyroid dysfunction associated with Alemtuzumab treatment for MS: A case series

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Alemtuzumab is a monoclonal antibody directed against CD52 licenced for the treatment of relapsing remitting multiple sclerosis (MS). Thyroid dysfunction occurs in one third of patients, likely secondary to lymphocyte reconstitution.
Case 1
A 36 year old female, treated with alemtuzumab 15 months prior, presented to antenatal clinic at 12 weeks gestation with symptoms of thyrotoxicosis. fT4 was 83.7 pmol/l (RR 12-22), TSH suppressed, TRAB positive. She was treated with carbimazole and remains on antithyroid medication at 30 weeks gestation; TRAB titer has risen to >40 IU/l (RR 0–1.5).
Case 2
A 36 year old male, treated with alemtuzumab 18 months prior, was admitted for investigation of weight loss and functional decline. fT4 was 37.9 pmol/l, TSH was suppressed and he had a large smooth goiter. TRAB was 18.9 IU/l. He was treated with carbimazole and is undergoing rehabilitation.
Case 3
A 39 year old female, treated with alemtuzumab 2 months prior, was referred to the endocrine clinic with fT4 of 60.2, suppressed TSH and TRAB 24 IU/l. She was asymptomatic and became hypothyroid four weeks later (fT4 <5.2 pmol/l, TSH 58 mU/l). Twelve months on, she is euthryoid on L-thyroxine 100 µg daily. In this case series we demonstrate three cases of alemtuzumab induced thyroid disease, occurring 2–18 months post treatment, all of which are TRAB positive. Case 1 highlights that women of child-bearing age treated with alemtuzumab should be counseled regarding the risk of thyroid dysfunction in future pregnancy. TRAB should be monitored in each trimester and close monitoring for foetal thyrotoxicosis is required. Case 3 highlights that TRAB positivity is not specific for Graves disease and in this case is associated with overt hypothyroidism. This case series illustrate the unpredictable clinical course of thyroid dysfunction in patients treated with alemtuzumab; long-term monitoring of thyroid function is recommended.

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EP1319

Serum levels of insulin-like growth factor 1 in patients with hyperthyroidism or euthyroidism

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Background
Insulin-like growth factor 1 (IGF1) has molecular structure similar to insulin. As an important mediator of growth hormone, IGF-1 plays roles in growth of children and anabolic effects of adults. We evaluate serum levels of IGF-1 in patients with hyperthyroidism or euthyroidism.
Subjects and methods
In this study, 30 patients with hyperthyroidism (HY group) and 30 euthyroid individuals (EU group) were recruited. The patients of HY group were treated with anti-thyroid regimens as clinically indicated, whereas no medication was given to EU group. The demographic characteristics, anthropometric and laboratory data of both groups at baseline and at the 6th month were compared. Associations between levels of IGF1 and free thyroxine (fT4), TSH, or log transformation of TSH (logTSH) were analyzed.
Results
At baseline, the HY group had significantly higher serum IGF1 levels than the EU group (median (Q1, Q3): 305.4 (257.4, 368.1) vs 236.7 (184.6, 318.8) ng/ml, $P<0.01$). The serum IGF-1 levels of the HY group decreased after anti-thyroid regimens, but still were higher than that of the EU group at the 6th month (299.5 (249.9, 397.9) vs 222.1 (190.2, 305.4) ng/ml, $P<0.01$). At the baseline, the serum levels of IGF1 in all patients were positively associated with fT4 ($\beta=29.02$, $P<0.01$) and negatively associated with TSH ($\beta=-31.46$, $P=0.04$). The associations between serum levels of IGF1 with fT4 or TSH became insignificant at the 6th month. However, the serum IGF1 levels were persistently negatively associated with logTSH both at baseline ($\beta=-29.04$, $P<0.01$) and at the 6th month ($\beta=-26.65$, $P=0.02$).
Conclusions
In comparison to EU group, patients with hyperthyroidism had higher serum IGF1 levels, which decreased after anti-thyroid regimens. The serum IGF1 concentrations were negatively associated with logTSH in patients with hyperthyroidism or euthyroidism.

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EP1320

Evaluation of oxidative stres by means of thiol-disulphide homeostasis in patients with euthyroid Hashimoto's thyroiditis

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Aim
In this study we aimed to evaluate the oxidative stress via evaluating changes in dynamic thiol-disulphide status in euthyroid patients with Hashimoto's thyroiditis (HT).
Methods
Fifty euthyroid patients with HT and 50 healthy individuals were enrolled in this study. Thyroid function tests (free triiodothyronine (fT3), free thyroxine (fT4), thyrotropin (TSH)), acute phase reactants (C-reactive protein (CRP), high sensitive CRP (hs-CRP)) and thiol-disulphide parameters were evaluated. Native thiol (-SH), total thiol (-SH+-S-S-), disulphide (-S-S-) levels, calculated disulphide/native thiol (-S-S-/-SH), disulphide /total thiol (-S-S-/-SH+-S-S-), native thiol/total thiol (-SH/-SH+-S-S-) ratios were compared between groups.
Results
Mean age was 38.3 ± 10.4 years in the patient group and 37.2 ± 10.1 years in the control group. There were 43 (86%) females and 7 (14%) males in the patient group while there were 39 (78%) females and 11(22%) males in the control group. Median TSH level was significantly higher in the patient group compared to controls ($P=0.04$). However, fT3 levels were similar statistically between groups ($P=0.347$), free T4 was significantly lower in the patient group ($P=0.01$). Mean native thiol and total thiol levels were significantly higher in the patient group compared to the control group ($P=0.04$ and $P=0.036$, respectively). There were not any statistically significant differences between groups regarding calculated disulphide/native thiol (-S-S-/-SH), disulphide /total thiol (-S-S-/-SH+-S-S-), native thiol/total thiol (-SH/-SH+-S-S-) ratios. The association between acute phase reactants and thiol-disulphide parameters were evaluated and no significant correlation was found. Similarly, there was no significant correlation between antibody positivity and thiol-disulphide parameters.
Conclusion
To our knowledge, our study is the first one that evaluated the association between HT and thiol-disulphide status according to Erel and Neselioglu method. In conclusion native and total thiol levels were detected to be increased in euthyroid HT patients, these results were not consisted with the literature data using different methods.

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EP1321

Hashimoto Encephalopathy with polymorphic neuropsychiatric signs: a case report

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Hashimoto encephalopathy (HE) is a rare and steroid responsive encephalopathy associated with autoimmune thyroiditis (1). Patients with Hashimoto encephalopathy may present with a variety of neuropsychiatric signs (2). 68-year old woman was admitted to the Neurology Department, of Hospital of Lithuanian University of Health Sciences, Kauno klinikos (HLUHS KK), due to disorder of consciousness of uncertain aetiology in August 2016. The signs of motor dysfunction, generalized rigidity, and disorientation, with several episodes of loss of and recurrent episodes of psychosis with hallucinations were observed since 2011. She had hospitalisations in neurology units of several hospitals and was discharged with different diagnoses and modes of treatment. She developed cerebral oedema with abundant myoclonic seizures in extremities in August 2016. The possibility of ischemic, neurodegenerative or neuro-inflammatory disease was ruled out in LUHS KC. Irregular activity of slow range waves was observed in EEG. Brain CT showed no signs of ischemia. High protein concentration was found in lumbar aspirate. Brain MRI SI T2W revealed changes characteristic of HE. Laboratory tests: FT4 6.7 pmol/l (normal 9–21), TSH 17.71 mU/l (0.4–3.6), antiTPO 270 kU/l (0–2), and signs of chronic thyroiditis in thyroid ultrasound made possible to diagnose autoimmune thyroiditis with hypothyroidism and HE. The treatment with L-thyroxine 50 μg/d, and 3-day bolus therapy of Methylprednisolone 1 g/d was started with rapid regression of clinical neurological signs. Prednisolone per os followed, with gradually reduced dose. The patient's condition improved significantly and she was discharged. During follow-up appointment after 3 months, her neurological state and psychiatric condition were deemed stable, thyroid hormones in normal range on L-thyroxine 50 μg/d. MRI HE changes have regressed. Patients with unexplained encephalopathy, progressive cognitive impairment, polymorphic neuropsychiatric should be considered to rule out HE, MRI and test of antiTPO levels should be performed.

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EP1322

Cardiothyreosis: prevalence and risk factors

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Background
Cardiothyreosis (CT) or thyrotoxic heart is associated with higher morbidity and mortality than the other forms of hyperthyroidism. Its risk factors have been investigated in a limited number of studies. The aim of our study was to identify risk factors of CT in patients with hyperthyroidism.
Methods
We identified 538 patients with a hospital discharge diagnosis of hyperthyroidism from January 2000 to December 2015. Thirty five patients were diagnosed with CT. Their demographic, clinical and biological characteristics were retrospectively studied and compared with those of 72 controls randomly selected, using univariate and multivariate analysis.
Results
The prevalence of CT in patients hospitalized for hyperthyroidism was 6.5%. The cardiac complications were atrial fibrillation (AF) in 33 cases (6.1%) and cardiac heart failure (CHF) in 11 cases (2%). The risk factors of CT were age greater than 50 years (OR = 13.1 (95% CI, 4.9–34.4)), low socioeconomic status (OR = 2.8 (95% CI, 1.2–6.7)), low educational level (OR = 3.1 (95% CI, 1.2–8.3)), history of hypertension (OR = 3.5 (95% CI, 1.1–11.2)) and a multinodular toxic goiter as the etiology of hyperthyroidism (OR = 4.6 (95% CI, 1.6–13.9)). After multivariate analysis, age greater than 50 years was the only independent risk factor of CT (adjusted OR = 11.6 (95% CI, 2.7–49.5)). Severe biological hyperthyroidism (FT4 > 3 times normal) was associated with a lower risk of CT (adjusted OR = 0.2 (95% CI, 0.1–0.9)).
Conclusions
The prevalence of CT in patients with hyperthyroidism was 6.5%. The two types of cardiac disease observed were CHF and AF with a clear predominance of the latter. Advanced age was the only independent risk factor of CT.

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EP1323

Takotsubo cardiomyopathy associated with thyrotoxicosis

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Background
Takotsubo cardiomyopathy is a rare, acute, nonischemic cardiomyopathy causing transient systolic disfunction of the apical and/or mid segments of left ventricle and is commonly associated with emotional and physical stress. Thyrotoxicosis is a rare cause of this condition, resulting from direct and indirect action of thyroid hormones on the cardiovascular system.
Case presentation
A 43-year-old woman presented at emergency room with chest pain, shortness of breath, palpitations, nausea, anxiety, slurred speech and myalgia. Two months earlier she had been admitted in another hospital with chest pain and a diagnosed Takotsubo cardiomyopathy, based on normal cardiac catheterization and compatible echocardiographic changes. At admission, diagnosis of recurrent Takotsubo cardiomyopathy in the context of thyrotoxicosis was assumed (TSH < 0.05 µm/l, fT4 65 µg/dl). Further evaluation confirmed Graves' disease. Recomended treatment was started and follow-up at 5 weeks revealed improvement of cardiac function and near normalization of thyroid hormone levels.
Conclusions
Takotsubo cardiomyopathy could be the presenting manifestation of thyroid storm. Awareness of this possible association is important in establishing the diagnosis and institution proper management.

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EP1324

Therapeutic and evolutionary characteristics of subclinical hypothyroidism

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Subclinical hypothyroidism (SCH) is a common disorder and indications of treatment are still being debated. The aim of our study was to describe the therapeutic and evolutionary characteristics of SCH.
Methods
We undertook a longitudinal retrospective study in 110 patients with SCH biologically defined by increased serum thyroid-stimulating hormone (TSH) levels (>4 mIU/l) and normal FT4. Pregnancy, age less than 18 years, personal history of partial thyroidectomy or radioactive iodine therapy were exclusion criteria.
Results
Sixty-one (55.5%) patients were put under L-thyroxine therapy. The TSH level of treated subjects was significantly higher than that of untreated subjects (8.1 mIU/l vs 5.9 mIU/l, $P<0.001$). Thyroid peroxidase antibodies were more frequently positive in treated subjects (93% vs 7%, $P<0.001$). The dose of L-thyroxine which allowed the normalization of the TSH level was on average 63.9 µg ± 39.4 µg/day. There was no significant difference between the results of the metabolic parameters (weight, blood pressure, fasting glucose, total cholesterol, triglycerides and HDL cholesterol) before and after normalization of TSH level. In untreated patients, spontaneous TSH normalization occurred in 27% of cases after an average time of 3.5 ± 3.1 months.
Conclusion
L-thyroxine replacement in patients with SCH concerned almost half of our patients. Higher TSH level and positive thyroid peroxidase antibodies were more frequently associated with L-thyroxine requirement. Spontaneous TSH normalization was relatively frequent (one quarter of untreated patients); hence repeating measurement of FT4 and TSH is necessary before starting L-thyroxine therapy.

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EP1325

The manner of performing the thyroid ultrasound examination and the reliability of assessment of the thyroid size in school-aged children

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Goitre incidence in school-aged children evaluated by the use of ultrasonography (US), apart from reflecting urine iodine concentration and percentage of households consuming iodized salt, is an essential indicator for assessing iodine intake in a given area. The position in which the US examination is being performed can also be an important problem in terms of its result interpretation. The aim of the study was to examine what is the difference between the thyroid volume measured in the supine and sitting position and to determine the coefficients of variation between measurements performed by the same observer (intra-observer variation), between two (2) observers (inter-observer variation) and between two different positions (inter-position variation). The survey included 87 children (56 girls and 31 boys, aged 7–13 years). The US tests were carried out by two (2) examiners (AZ and ZA). Thyroid volume measured in a sitting position was significantly lower than in the supine position. The intra-observer variations equalled 9.7% (CI – 8.1–11.13) for ZA and 9.56% (CI – 7.66–11.45) for AZ. The inter-observer variations amounted to 34.53% (CI – 31.9–37.1) and 35.7% (CI – 32.5–38.9) for measurements performed in the supine and the sitting position, respectively. We have concluded that the size of the thyroid gland depends on the position in which it is examined. The manner the US evaluation is being performed is important for the analysis of the results. It is crucial to aim at the smallest value of inter-observer variation, which can be achieved by strictly defining the methods of measurement of the thyroid and comparing one's measuring techniques with the reference technique. Conclusions: The use of standards in US evaluation performed in the supine position, as well as those without a strict determination of the study method, including body position during examination, can lead to erroneous conclusions.

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EP1326

Which cytologic or architectural characteristics are associated with malignancy in AUS/FLUS cytologies according to subgroups?

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Aim
Atypia/follicular lesion of undetermined significance(AUS/FLUS) is a category of thyroid cytology with features that are neither definitely benign or malignant. We aimed to determine whether specific cytologic or architectural features are associated with malignancy in AUS/FLUS category of Bethesda system according to subgroups.
Methods
The specimens of patients who underwent surgery with preoperative thyroid fine neeedle aspiration (FNA) biopsies of Bethesda Category III (AUS/FLUS) were reanalyzed**.** An experienced cytopathologist who blinded to original cytology and final histopathology was reevaluated the specimens and numerated the cytology from 1 to 7 according to Bethesda system as follows; Group 1: cells producing microfollicles, Group 2: containing predominantly Hurthle cells with rare cells and colloid, Group 3: difficulty in evaluation of atypia due to smear artifacts, Group 4: cellular smears containing benign Hurthle cells, Group 5: focal cells with nuclear changes like papillary carcinoma but generally benign appearance, Group 6: cells with atypic features but generally benign appearance, Group 7: rare follicular cells with nuclear enlargement and frequently apparent nucleoli.
Results
Specimens of one hundred and ninety five patients (153 females, 42 males) with a mean age of 47.87 ± 12.18 years were included to the study. Of these 195 patients, 148 had AUS and 47 had FLUS cytology. Nuclear groove formations are found as higher in malignant group in overall study population and in also AUS subgroup ($P=0.005$ and $P=0.023$, respectively), but not in FLUS subgroup ($P=0.164$). Nuclear enlargement, overlapping, elongation, inclusions, and papilleroid features were similar between malignant and benign groups in all patients, AUS and FLUS subgroups. Furthermore cytologic groups distributions are similar between benign and malignant groups in all patients, and in AUS and FLUS subgroups ($P>0.05$, for all).
Conclusion
Patients in Bethesda Category III particularly in AUS subgroup with cytologic interpretation of nuclear grooves are at higher risk of malignancy and should undergo surgery.

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EP1327

Relationship between thyroid volume and baseline vitamin D levels in new-onset graves disease

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Introduction
Serum 25(OH) vitamin D levels are shown to be significantly lower and associated with lower remission rates in Graves disease. In this study we aimed to investigate the impact of baseline vitamin D levels on thyroid volume in patients with new-onset Graves disease.
Materials and methods
This is a monocenter cross sectional study with a total of 61 new-onset Graves disease patients (n:61, F: 40, M:21) who were divided into two groups according to baseline serum vitamin D levels, as Group-1 (D vit <20; n:42) and Group-2 (D vit ≥ 20; n:19). Plasma fT4, fT3, TRAb, TPOAb and PTH levels were analysed and thyroid volume (ml), isthmus thickness (mm) were measured by the same physician with thyroid ultrasonography at the time of diagnosis for each patient. The results were compared between the two groups. Categorical variables were processed with the chi-square test. Pearson and spearman correlation analysis were performed for normally and non-normally distributed data, respectively.
Results
There was an inverse correlation between baseline serum vitamin D levels and thyroid volume, TRAb, fT3 and PTH levels ($P=0.02$, $r=-0.31$; $P=0.005$, $r=-0.36$; $P=0.04$, $r=-0.26$; $P=0.02$, $r=-0.32$; respectively). Thyroid volume was also correlated with serum fT4, fT3, TRAb and TPOAb ($P=0.001$, $r=0.426$; $P=0.001$, $r=0.50$; $P=0.04$, $r=0.26$; $P=0.001$, $r=0.42$; respectively). Low vitamin D and high TgAb levels were independently associated with thyroid volume in logistic regression analysis ($P=0.03$, OR:18.7, CI 95% 1.34–260.91 and $P=0.04$, OR: 16.6, CI 95% 1.07–255.64; respectively).
Conclusion
Baseline serum vitamin D levels are inversely related with thyroid volumes, fT3 and TRAb levels in new-onset Graves disease. In addition to several advantages, optimization of vitamin D levels would also be beneficial in the surveillance of these patients. However larger scale studies are required in order to make further suggestions.

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EP1328

A novel mutation in thyroid hormone receptor-beta gene causing resitance to thyroid hormone in a tunisian female

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Introduction
The syndrome of resistance to thyroid hormone is a rare inherited disorder characterized by elevated circulating thyroid hormones, failure to suppress pituitary thyroid stimulating hormone (TSH) and variable tissue target hyposensitivity to thyroid hormone action. We reported the case of a RTH syndrome with a novel mutation.
Case report
A 15-year-old girl was investigated for visual hallucinations and behavior disorders. Her medical history was unremarkable except for a learning disability and a hyperactivity disorder in childhood. There was no family history of thyroid diseases and she was not taking any regular medication. She was found to have abnormal thyroid function tests with increased plasma free T_3, free T_4 of 2.51 ng/dl (reference range: 0.71–1.85 ng/dl) with non-suppressed TSH of 7.7 μUI/ml (reference range: 0.12–3.4 μUI/ml). On examination, weight was 48 kg, height was 141 cm, blood pressure was normal and pulse rate was 92 beats/min. She had clinical symptoms of thyroid hormone excess: moist skin, insomnia and agitation. She had no goiter or dysthyroid eye disease. Repeated thyroid function tests confirmed previous findings. Thyroid antibodies (anti-peroxydase and anti-TSH receptor) were negative. The level of TSH α-subunit was normal 0.54 μUI/ml (range: 0.05–0.9) and the ratio TSH α-subunit/TSH was less than 1. TSH-secreting tumor was ruled out by normal pituitary magnetic resonance imaging (MRI). Genetic analysis yielded a novel mutation in the THRβ gene, c.1369 G > A in exon 10, due to a base pair substitution of glutamic acid by lysine in position 457.
Discussion
We reported a novel mutation in the THRβ gene that has not been previously described and discussed the clinical presentation of the thyroid hormone resistance syndrome according to the different mutations.

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EP1329

Succesfull treatment of hyperthyroidism with plasmapheresis

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Introduction
Hyperthyroidism is the condition that occurs due to excessive release of thyroid hormone by the thyroid gland. Anti-thyroid drugs are usually the first choice of

the treatment but surgery and radioactive iodine can also be used in treatment of hyperthyroidism. Plasmapheresis is a rapid and effective treatment option in cases where immediate euthyroidism is needed to be obtained due to complications of thyrotoxicosis and major side effects of antithyroid drugs.
Material and method
Between January 2012 and December 2016, we evaluated patients who received plasmapheresis to provide immediate euthyroidism due to severe hyperthyroidism or side effects of anti-thyroid drugs or urgent non-thyroid surgery were included to the study.
Results
Eighteen patients were included the study, of whom 11 were female and seven were male. The mean age was 52.44 years. Seven patients had TDG (%38.9), two patients had TDMNG (%11.1), two patients had TA (%11.1), four patients had TMNG (%22.2) and one patient had amiodarona induced thyrotoxikosis (%5.6). Additionally, plasmapheresis was performed to achieve euthyrodism before non-thyroid surgery in two patients (11.1%). The mean plasmapheresis sessions was 5.22. The mean sessions was 3.62 for patients with TDG and TDMNG, whereas it was 6.43 for patients with TA and TMNG (P:0.029). The decrease of mean fT_4 and fT_3 were 48% and 65%, respectively ($P<0.0001$). Anaphylaxis was seen only in one patient due to fresh frozen plasma. So treatment was changed to albumin.
Conclusions
Although plasmapheresis is not commonly used for the treatment of the hypertyroidism, it is a reliable and effective treatment option for patients who can not use antithyroid drugs or hyperthyroidism can not resolve with these drugs before total thyroidectomy, RAI or non thyroid emergency surgery.

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EP1330

Measurement of anti-thyroglobulin antibodies, a matter of equipment?

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Introduction
The presence of anti-thyroglobulin antibodies (ATG) can induce falsely lower thyroglobulin (Tg) values. The methods characteristics used for ATG measurement vary according to the equipment/reagent used. ATG at our centre is measured by Unicap.
Objective
To assess if patients with negative ATG by Unicap® have different results with other equipment.
Methods
A cross-sectional retrospective study was conducted in February-March of 2016, in which blood samples from patients followed at our Centre, with negative ATG, were selected and separated into three groups: 1) differentiated thyroid carcinoma (DTC), total thyroidectomy, Tg <0.2 ng/ml; 2) without DTC and positive TPO; 3) without DTC and negative TPO. ATGs were measured by Immulite®, Cobas®, Architect® and Advia®. ATG's classification was based on the cut-off of each manufacturer. Q-Chrocan test was used to calculate the p-values ($P<0.05$ were considered statistically significant).
Results
A total of 141 samples were analysed. The results are described in the table below: high significant differences were found between the various methods in all groups. The Architect and the Immulite had the highest and lowest rate of ATG positives, respectively, compared to Unicap.
Discussion
ATG results depend on the equipment used. This can influence the follow-up strategy of patients with DTC. These results also raise the question of which method is more reliable for ATG detection and how a result of 'ATG positive' actually influences the Tg measurement.

Table 1

		Positive ATG					Q test	
Group	N	Unicap	Immulite	Cobas	Architect	Advia	χ^2	P
(A) DTC+/Tg<0.2	88	0	1 (1%)	3 (3%)	23 (26%)	6 (7%)	70.0	<0.001
(B) DTC−/TPO+	28	0	2 (7%)	8 (29%)	26 (93%)	11 (39%)	67.2	<0.001
(C) DTC−/TPO−	25	0	0	1 (4%)	6 (24%)	2 (8%)	17.7	0.001
Total	141	0	3 (2%)	12 (9%)	55 (39%)	19 (14%)	152.7	<0.001

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EP1331

Reference range determination of TSH during the first trimester of pregnancy and the impact of its future implantation in the South area of Seville

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Objectives
Different scientific societies recommend performing screening for clinical primary hypothyroidism during the first trimester of pregnancy using local normality ranges of TSH and just in the lack of these, should the American population reference levels be used. Our objective is to determinate the reference range of TSH during the 1st trimester of pregnancy in our healthcare area and the impact of its implantation.
Material and methods
Prospective study where women selected had no history of thyroid pathology nor where taking any drugs that may disrupt thyroid function. TSH, FT4 and anti-thyroid antibodies (TPOab, TGab, TRab) were determined between week 9 and 11. TSH >5 μU/ml, positive thyroid autoimmunity or any condition that may interfere were excluded (final $n=282$). Reference levels were defined by calculating the confidence interval between p2.5 and p97.5 of the distribution. Tests for hypothyroidism screening in the last two years were reviewed and variations on the diagnosis of hypothyroidism depending on the TSH reference level used was analysed.
Results
New local reference level for the 1st trimester: TSH 0.17–4.39 μU/ml; T4L 0.97–1.88 ng/dl. Screening tests in the last 2 years (1/12/2014 to 30/11/2016) $n=6032$. Diagnosis of hypothyroidism using American standard reference levels (TSH$>$ 2.5 μU/ml): 35.8% (2181 women). Diagnosis of hypothyroidism with our reference levels (TSH >4.39 μU/ml): 8,6% (524 women). Total number of TSH $\geq$ 10 μU/ml: 0.6% (37 women).
Conclusions
Reference levels for TSH in our study are similar to others in different Spanish areas and differ significantly from the American reference range, those standard ranges imply an unacceptable rate of diagnosis of hypothyroidism (one out of three women), even more if a universal screening strategy is carried out. Determination and implementation of locally assessed reference levels would avoid overdiagnosis, unnecessary treatment and follow-up.

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EP1332

Iodine content of iodized salt in Spain

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Introduction
Optimization of iodine intake aims to prevent the irreversible damage that iodine deficiency (ID) can cause in the central nervous system during its development, as well as thyroid disorders that can be induced by both ID and excessive micronutrient intake. The Spanish legal regulation stipulates that iodized salt (IS) must contain 60 mg of iodine per kg of salt (60 ppm), allowing a tolerance of $\pm$15%. The aim of this study is to address the iodine content of different commercially available IS in Spain.
Methods
162 different IS lots from 51 different product presentations were collected from Spanish food stores in Andalusia, Aragon, Asturias, Balearic Islands, Catalonia, Madrid and Basque Country between 2014 and 2016. Iodine concentration in these samples was assessed by HDL-chromatography (HPLC).
Results
The mean (S.D.) and median (P25–P75) iodine concentration for these 162 samples was 61.2 (19.7) and 59 (50–70) µg I/g salt, respectively. Iodine concentration dispersion was mainly attributable to iodide-fortified IS ($n=67$). The analysis of these fortified IS revealed that 67.2% of them had iodine levels out of the legal threshold (51–69 µg I/g salt), whereas only 43.2% of the iodate-fortified IS ($n=95$) were outside this limit ($P<0.05$).
Conclusions
IS, having an average 60 µg I/g salt, is an important alimentary source of iodine in Spain. The use of iodate instead of iodide for the fortification of the salt allows a greater proportion of IS with iodine concentration within the legal limits. Public Health and Consumer Affairs authorities should closely monitor IS production processes and eventually check IS sale points in order to homogenize the iodine content of commercially available IS packages and thereby optimize their intake by the population.

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EP1333

Low DHEAS levels predict rheumatism in primary hypothyroidism: preliminary data from tertiary hospital

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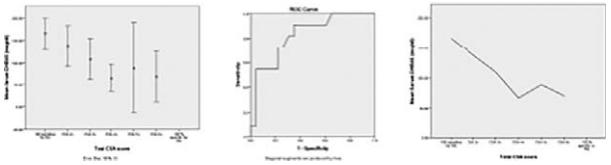
Introduction
DHEAS is weak androgen with specific role in human physiology illdefined. Various studies have implicated role of DHEAS in autoimmune arthritis including SLE and RA. Recently EULAR consensus statement has approved CSA (clinically significant arthralgia) for incipient RA.
Methods and material
34 follow up patients of primary hypothyroidism rated their symptom score on CSA (clinically suspect arthralgia) as given by EULAR(1) Their DHEAS levels were divided into quartiles while CSA was graded from 100 sensitivity (when one component is positive) to 100 specificity (when all seven component are positive). Kendal tau test of correlation was run using SPSS 21. ROC curve for DHEAS to predict at least one symptom of CSA was run. SPSS version 20 used for analysis.
Results
Anti TPO Ab were available for 19 subjects, out of which 16 were Anti TPO Ab+. 25(OH) vitamin D levels were available for only seven patients hence excluded from analysis. Kendal's tau correlation test yieldedstrong negative correlation between DHEAS levels at the time of presentation and CSA score.{$P<0.01$; r −0.512}.
Discussion
This the first study evaluating role of DHEAS in rheumatism of primary hypothyroidism. Musculoskeletal abnormalities arecommon in primary autoimmune thyroid disease (AITD); 2) AITD is also associated with rheumatoid arthritis (RA); 3) There has been recent acknowledgement of role of local androgen in molecular pathogenesis of autoimmune arthritis; 4) We found inverse correlation between serum DHEAS and rheumatism. The serum DHEAS levels seemed to predict grade of rheumatism in these patients. The finding and strength of association is significant and opens further avenues for research regarding role of DHEAS in musculoskeletal manifestations of AITD. DHEAS supplementation has been evaluated in SLE (4) but not in hypothyroidism. Although association between Rheumatoid arthritis (RA) and DHEAS is not well defined, improvement in RA is associated with increase in DHEAS levels (5) Does DHEAS supplementation early in RA or pre –RA alters its natural history, in background of hypothyroidism? Well designed studies are needed.
Conclusion
Rheumatism as evaluated by CSA criteria bears strong inverse correlation with DHEAS. Further trials examining role of DHEAS in such group of patients can be explored.



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EP1334

A thyroid storm in a context of diabetic ketoacidosis: case report

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Introduction
The association of a thyroid storm and diabetes ketoacidosis is relatively rare. We report two cases.
Observations
The first one is a 20 years old woman, with no history of diabetes, who came with ketoacidosis, a history of non medicated thyrotoxicosis, and she was complaining about fever, a thyrotoxicosis syndrome, a vascular goiter, and exophtalmos. Her general condition had improved significantly after the treatment in emergency and under maintenance therapy. The second one is a 54 years old female, with a case of diabetes mellitus, who presented a ketoacidosis. But despite the control of this situation, the patient's consciousness level became disturbed and she presented hyperthermia. The thyroid function tests revealed hyperthyroidism. Thus, thyroid storm was evocated and managed. The patient finally passed away despite the prompt medical care.
Discussion
In these two cases, a thyroid storm, associated with Graves' disease covered by diabetic ketoacidosis was the final diagnostic. Thereby, for patients having diabetic ketoacidosis one should seek an eventual thyroid storm, and *vice versa*: in fact, there are some symptoms in common. But there are scores to help systematize the diagnosis. The management is controlled, acutely based on antithyroid drugs in high doses, betablockers and corticosteroids. We should not disregard the search for and treatment of precipitating factors: ketoacidosis in our cases. And identify the thyroid underlying disease: most commonly Graves' disease.

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EP1335

Hyalinizing trabecular adenoma of the thyroid

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Introduction
Hyalinizing trabecular adenomas (HTA) of the thyroid gland is a rare neoplasm of follicular cell origin. HTA can be present as a thyroid nodule or incidental finding in a thyroidectomy specimen. HTA is generally accepted to be a benign tumor,

but their cytological features can be similar to those of papillary thyroid carcinoma (PTC).
Case report
A 59 year old woman, who had cholangiocellular carcinoma, admitted to our institution with a solitary thyroid nodule and cervical lymphadenopathy. Fine needle aspiration biopsy of the cervical lymphadenopathy revealed suspicious for carcinoma metastasis. Her serum free thyroxine (fT_4), free triiodothyronine (fT_3) and TSH levels are 1.42 ng/dl, 2.82 pg/ml, and 0.486 mIU/ml. Ultrasonography of the thyroid gland showed a 1.4 cm sized, regularly marginated, hypoechoic, calcified thyroid nodule. Fine needle aspiration biopsy of the thyroid nodule revealed suspicious for PTC. Total thyroidectomy were perfomed. The final pathology was 1.0-cm sized hyalinizing trabecular adenoma. Histologically, the tumor showed tumor cells arranged in trabeculae and a prominent hyaline stroma. The neoplastic cells were focally immunoreactive for thyroglobulin and negative for calcitonin and chromogranin. After surgery L-thyroxine replacement therapy was started. Cervical metastasis was thought to be associated with cholangiocellular carcinoma. The patient referred to the Oncology department for the treatment of metastatic cholangiocellular carcinoma.
Conclusion
Ultrasonografic features of HTA similar to malign thyroid lesions and frequently misdiagnosed as papillary carcinoma on fine-niddle aspiration cytology. The most recent and controversial debate surrounding HTA concerns its potentially malignant behavior and the possible relationship to PTC. Although cases of malignant HTA have been recorded, HTA should be considered a benign neoplasm or, at most, a neoplasm of extremely low malignant potential. In this report we present and discuss an unusual case of a patient who had a hyalinizing trabecular adenoma and cholangiocellular carcinoma.

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EP1336

Amiodaron induced hyperthyreosis and recurrent ventricular tachycardia

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52 years old man medicated with amiodaron 12 months, with laboratory confirmed hyperthyroidism, in us-examination 45 ml Basedow goiter, TRAb positive; ventricular tachycardia 180/min intermittent with sinusal tachycardia 120/min, thiamasol 120 mg i.v./daily, hydrocortisone 400 i.v. daily, crystalloids, beta blockers, diazepam, albumin. J131 scintigraphy – no iodine uptake. natriumperchlorate 1500 mg daily initially, continued next month 900 mg coused iodine uptake 17%. Finally -radioiodine 20 mCi, followed with thiamazole and steroids. After 4 weeks – euthyroid. 32 years old woman after many hospitalizations because of ventricular tachycardia. Clinical, ultrasound and laboratory parameters of Basedow disease. Medication: thiamasole, cortisone and Irenat prepared to the radioiodine therapy. After three times of 20 mCi I131 hypothyroid, 100 μg thyroxin. 48 years old man with hypertrophic cardiomiopathy, after over 6 months use of amiodaron lack of effect and recidive of ventricular tachycardia. Lab. – thyreotoxicosis, in ultrasound left lobe tumor 27 ml, biopsy benign. Initially cured with thiamazole 60 mg, followed with irenat 900 mg daily and after iodine uptake recurrence -20mCi radioiodine 131, euthyreosis after 3 months.
Cases demonstrate problematic situation of amiodaron cured patients, thyroid dysfunction may occur during amiodaron therapy and in some patients is dangerous. Hyperthyroidism is difficult to cure if caused by amiodaron but in this patients should be radical, it is necessary to have available perchlorat for this cases and rodioiodine therapy.

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EP1337

Autoimmune thyroiditis in patients with latent autoimmune diabetes of adults (LADA)

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Introduction
Latent autoimmune diabetes in adults (LADA) is an endocrine disorder characterized by a progressive destruction of pancreatic beta cells by an autoimmune mechanism leading to absolute insulin deficiency. In patients with an autoimmune endocrine disease, there is a high risk of development of another autoimmune endocrine disorder. The purpose of our work is to assess the prevalence of thyroid autoimmunity among our LADA patients.
Patients and methods
Our study has included 17 patients followed for LADA. Thyroid status and thyroid autoimmunity were ordered in all patients.
Results
The mean age of patients was 46.7 years and the mean age of discovery was 40.5 years. The sex ratio was 1.4 with a female predominance. The average BMI was 24.5 kg/m^2. The TPO antibodies were positive in five of our patients (29.4% of cases), including four women. The rate of anti-GAD antibodies was higher in the LADA group with positive anti TPO antibody compared to the group with negative anti TPO (345.6 mUI/l vs. 250.4 mUI/l).
Discussion
The prevalence of thyroid antibodies in patients with LADA varies between 20 and 30%. The association has been explained by the sharing of a common genetic material, but also by a deficit in the immune regulation or a poor ability to develop tolerance to auto antigens.
Conclusion
Thyroid autoimmunity is frequently observed in LADA diabetes, identifying a particular phenotype of patients with higher titer of anti GAD antibodies, and eventually, a poor glycemic control where the interest of its systematic screening.

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EP1338

Thyroid and metabolic disorders in patient with kidney injury undergoing renal biopsy

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There are a several known interactions between kidney functions, thyroid and metabolic balance. Hypothyroidism is associated with reduced GFR and hyperthyroidism results in increased GFR and increased RAA activation. Chronic kidney disease is characterized by low T3 syndrome, increased primary hypothyroidism and subclinical hypothyroidism. The hyperthyroidism increases CKD progression while hypothyroid state lowers it. Proteinuria, especially in nephrotic syndrome, often results in urinary loss of thyroid hormones bound to the various binding proteins which results in reduction in the serum total thyroid hormone levels. Isolated cases of hyperthyroidism have been associated with tubulointerstitial nephritis. Thyroid dysfunction is also associated with glomerulonephritis by a common autoimmune etiology. There are known several mechanisms like the presence of circulating immune complex among patients with thyroid disease, the association of Hashimoto's thyroiditis and membranous nephropathy with immune complex deposition in the glomerular as well as thyroid epithelial basement membrane. There is also common occurrence of thyroid and renal disease in association with other autoimmune diseases such as type 1 diabetes mellitus. We retrospectively analyzed the data (thyroid function, metabolic syndrome occurrence, type of diabetes) of 126 patient hospitalized in our clinic from 2013 to 2016 who underwent renal biopsy (52 women, 62 men and 6 children). The most common indications for renal biopsy were nephrotic syndrome in 47 patients (37.3%), non-nephrotic proteinuria in 31 patients (24.6%), worsening renal function in 22 patients (17.5%), coexistence of proteinuria with hematuria in 16 patients (12.7%), nephritic syndrome in 9 patients (7.1%) as well as an isolated hematuria in 1 patient (0.8%). Membranous glomerulonephritis was the most common histological diagnosis observed in biopsies, and was diagnosed in 19 patients (15.1%). Our analysis proved higher occurrence of hypothyroidism (8.7%), hyperthyroidism (2.38%) and goiter (3.17%) in comparison to general population. Interestingly there was no higher occurrence of obesity and overweight (40.4%) and type 1 and 2 diabetes, but many patient had steroid-induced diabetes (16%). It is important to monitor every patient with renal dysfunction due to higher prevalence of thyroid pathology.

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EP1339

Reversible thyrotoxic pulmonary hypertension with heart failure: 2 cases

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Introduction
Heart failure is a complication of thyrotoxicosis. We present 2 unusual cases presenting with pulmonary hypertension with isolated right heart failure that reversed after treatment.
Case description
***Case 1*:** A 55-year-old man presented with weight loss, dyspnoea and leg swelling. HR: atrial fibrillation 51/min. He had a raised JVP, tricuspid regurgitation and severe pitting oedema. Pro-BNP: 4995 pg/ml, TSH: 0.06 mU/l, FT4: 54.1 pmol/l, FT3:10.5 pmol/l. TSH receptor antibodies (TRAb) were positive. CTPA: no pulmonary embolism. Echo: PAP 45 mmHg, LVEF preserved. Carbimazole, diuretics, ACE inhibitors and Apixaban were commenced. Right heart catheterization showed non-obstructive coronary artery disease and pulmonary hypertension. Repeat ECHO 7 months later revealed normal right heart pressure and size when euthyroid. Tricuspid regurgitation and Pulmonary Hypertension were resolved.
***Case 2*:** A 34-year-old male presented with oedema, elevated JVP, tricuspid regurgitation and atrial fibrillation. Pro-BNP: 2064 pg/ml TSH: 0.05 mU/l, Free T4: 72.6 pmol/l, TRAb positive. CTPA negative for PE. ECHO: PAP 60 mmHg. Right cardiac catheterisation when euthyroid demonstrated a RVSP of 32 mm Hg, pulmonary artery systolic pressure of 27 mmHg and a wedge pressure of 14 mmHg indicating a resolution of his RHF.
Learning point
Selective right heart failure may occur in thyrotoxicosis perhaps due to altered metabolism of pulmonary vasodilators resulting in raised pulmonary vascular resistance.

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EP1340

Peripheral neuropathy in hypothyroidism - about a clinical case

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Introduction
Hypothyroidism can affect the nervous system, commonly causing mono and polyneuropathies which show a variable frequency and pattern. Its mechanisms are not fully understood. Symptoms usually correlate better with the duration of the dysfunction rather than with its severity and typically improve significantly after medical therapy.
Case report
A 58-year-old woman was admitted at our hospital with a one-year history of progressive weakness of both lower extremities, more evident on her left limb. The patient reported a 20-year history of hypothyroidism medicated with levothyroxine 25mcg id and type 2 diabetes medicated with metformin 1000mg bid, without proper follow-up. She denied other relevant long-term medication or addictions. Fifteen days prior to admission, she was paraparetic and had lost her ability to walk. No other relevant personal or familial medical history was found. Neurological examination showed painless sensorimotor polyneuropathy and lower muscular strength on both legs. Laboratory results revealed hypothyroidism: TSH 37.1mU/L and FT4 0.5ng/dl. Serologic studies were negative and B12-deficiency was excluded, as well as other common causes of peripheral neuropathy. Lumbar MRI did not show spinal cord compression and cerebrospinal fluid analysis was inconclusive. Bilateral carpal tunnel syndrome and sensorimotor polyneuropathy, without criteria of Guillain-Barré syndrome, were found on electromyography (EMG). Furthermore, myopathic aspects compatible with muscular necrosis were detected, despite normal creatine kinase levels. Few weeks after progressively increasing levothyroxine dose, laboratory studies showed: TSH 10.2mU/L, FT4 1.27ng/dl, Anti-TPO 66U/mL. Unsatisfactorily controlled hyperglycemia persisted (HbA1c 10.2%). Paraparesis significantly improved and sensorimotor dysfunction subsided.
Conclusion
In general, sensorimotor peripheral neuropathy is common in diabetes and occasional in hypothyroidism. In the described case, it is difficult to ascertain the relative contribution of each nosological entity. Nevertheless, the clinical presentation, the EMG and the prompt response to levothyroxine, favor hypothyroidism as the main cause.

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EP1341

Is Levothyroxine requirement the same for tablet and soft gel formulation in postsurgical hypothyroidism?

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Background
In a previous publication we identified the major predictive factors of levothyroxine (LT_4) requirement and proposed an efficient nomogram to calculate LT_4 substitutive starting dose after total thyroidectomy for benign disease. The aim of this study was to assess whether the LT_4 requirement differs between the tablet and the soft gel capsules formulations.
Methods
One hundred and three consecutive patients submitted to total thyroidectomy for benign disease and were receiving substitutive therapy with LT_4 were enrolled. All patients received the LT_4 tablet formulation. The specific substitutive starting dose was calculated using the previously described nomogram and was aimed at achieving normal TSH levels (0.4–2.5 mU/L). Exclusion criteria were: malignancy at histological examination, symptoms or signs of malabsorption, assumption of drugs or habits interfering with LT_4 absorption, impaired renal function, pregnancy, poor compliance with drug administration. TSH, FT_4, and FT_3 were assessed three months after the switch from tablet to soft gel capsule formulation at the same dose of LT_4. Mean and standard deviation (SD) were used for quantitative variables. The paired t-test was applied in order to compare the thyroid function tests with different formulations of LT_4.
Results
Serum TSH was significantly lower during treatment with soft gel capsules [1.3 mU/L (SD 0.9) and 1.8 mU/L (SD 1.2) respectively, $P = 0.02$]. There were no statistically significant differences for FT_3 and FT_4.
Conclusions
Levothyroxine substitutive dose is not significantly different between soft gel capsules and tablets in patients without malabsorption but TSH is significantly lower with the first one. This datum must be considered in clinical practice, particularly for patients with TSH at limits of the therapeutic range or if a strict therapeutic goal is needed.

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EP1342

Immune reaction to food antigens in Graves'disease (GD) patients: role of gliadin and other food antigens

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As known, an imbalance of the gut microbiota is associated with a higher risk for autoimmune diseases. Moreover the increased rates of autoimmunity reported in urban residential areas worldwide suggest a possible influence of diet. We report

on the antibody response to food antigens in GD patients. Since 10% of celiac patients develop an autoimmune thyreopathy we focused on gliadin (DGP), transglutaminases (tTG) and 40 other food antigens (FA). Commercially available ELISA assays were performed according to the manufacturer's instructions. 105 and 108 sera from 5 European endocrine centres have been tested for IgG and IgA to tTG and DGP. Results have been compared to epidemiological data. 71 sera have also been tested for IgG to FA and compared to 25 healthy controls. 6 out of 105 sera (5.7%) showed positive tTG; 16 and 7 out of 108 (15 and 6.5%) positive DGP-IgA and IgG, respectively; a higher prevalence compared to the worldwide prevalence of celiac disease (1%) (chi-squared test; p-value < 0.001). Prevalence of smokers and ocular involvement was not higher in patients with positive sera compared to negative. 23 out of 71 (32.3%) GD sera showed sensitivity against a food antigens, compared to 25% (6 out of 24) positive results among healthy controls (chi-squared test; P-value = 0.4). Interestingly, some antigens (cow's milk, egg white, wheat, yeast) are more frequently positive than others. The distribution of antibodies against TSH receptor (TRAb) values was not different in positive or negative sera. In conclusion, the prevalence of positive tTG antibodies is higher in GD patients than worldwide. Even though autoantibodies to DGP and tTG were equally distributed between all 5 centres we observed the highest percentage of positive responses to other food antigens in Cardiff, suggesting that diet may contribute to the increased sensitivity. More studies are needed to confirm these data.

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EP1343

Neutrophil/lymphocyte (N/L) ratio should not be used as an indicator of inflammation in hyperthyroid patients

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Introduction
Neutrophil/lymphocyte (N/L) ratio is considered as a sign of systemic inflammation in recent years. In our study, we aimed to investigate N/L ratio in hyperthyroid patients and healthy control group.
Material & methods
A total of 121 hyperthyroid patients (71 patients with Graves' disease and 50 patients with other causes of hyperthyroidism) and 40 healthy volunteers were enrolled. Complete blood count was obtained from both group and thyroid function tests were obtained from hyperthyroid patients.
Results
There was no significant difference between hyperthyroid patients and control group in terms of gender, leukocyte and lymphocyte count. There was a statistically significant difference between groups in terms of neutrophil count and N/L ratio ($P = 0.003$ and $P < 0.001$). Surprisingly, neutrophil count and N/L ratio were significantly lower in Graves' patients. We also find a significant negative correlation between serum free T3 levels and neutrophil count ($r = -0.28$, $P = 0.01$).
Conclusion
N/L ratio was lower in Graves' patients than in the control group. Slowing of granulopoiesis, shortening of the life span of circulating neutrophils, and the development of anti-neutrophilic antibodies in autoimmune thyroid diseases may be responsible for this condition. N/L ratio should not be used as an indicator of inflammation in hyperthyroid patients.

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EP1344

Quality of life in patients with hyperthyreosis and hypothyreosis in slovak republic

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Objectives
The prevalence of thyreoid diseases eg hyperthyreosis and hypothyreosis in Slovak Republic is about 240 000 patients. The objective of this study was to find out the level of quality of life (QoL) in patients and other relevant characteristics of diseaseas.
Methods
The primary method used for the analysis of QoL was the own orginal combined questionnaire. Statistical methods from Excel 2010 were used in results evaluation.
Results
There were 214 patients in the examined group: 34 patients with hyperthyreosis (10 men, 24 women) – group A, and 180 patients with hyperthyreosis (25 men, 155 women) – group B. QoL was evaluated on numeric scales from 0 – the worst to 10 – the best. Present level of QoL was 6.4 vs 7.25, when in the time of diagnosis it was 4.6 vs 6.0, in the time without disease – 7.6 vs 8.3 and in the time excellent health – 8.0 vs 9.2. The average duration of disease was 6.5 vs 11.30 years and the duration of symptoms before diagnosis was 0.74 vs 0.99 years. Patients were very satisfied with the level of information about their disease: 4.6 vs 4.3, with medical care – 4.8 vs 4.7 and with nursing care4.8 vs 4.7 (1- the worst, 5- the best). Disability of work was 0.8 vs 4.9 days in employed patients (19 in group a and 79 in group B) per year. Patients visited endocrinologic outpatients department 5.1 vs 2.2 times per year. Willingness to pay was 55 vs 48 € per month.
Conclusions
Hyperthyreosis and hypothyreosis had a significant impact on patients's QoL mostly hyperthyreosis. There are a significant differences in duration of disease and symptoms, disability of work and professional visits – hyperthyreosis had greater impact. Information about the disease, evaluation of medical and nursing care and willingness to pay had no statistical differences.

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EP1345

Broken heart by thyroid? A rare case of Graves' disease associated to Takotsubo cardiomiopathy

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Introduction
Takotsubo disease is a non-ischemic, reversible form of cardiomyopathy, triggered by intense emotional or physical stress. Characterized by normal coronaries and a particular ventricular contraction, it is also known as 'apical ballooning syndrome'. Thyrotoxicosis, especially Graves' disease, has been associated with Takotsubo cardiomyopathy.
Case report
We report the coexistence of Takotsubo cardiomyopathy in a 37 year old female patient presenting with thyroid storm secondary to untreated Graves' disease. Addressed to the emergency unit with suspicion of acute coronary syndrome, signs of lateral inferior apical ST-segment elevation were noticed on the ECG. At clinical examination: pale wet teguments, tachycardia, visible goiter and bilateral exophtalmia. According to the Burch Wartofsky criteria for thyrotoxicosis the patient had a score of 70, highly suggestive for thyreotoxic crisis, sustained by the biological data (high free T4 5.27 ng/dl and free T3 7.47 pg/ml levels with inhibited TSH 0.008 uUI/ml). She also associated anemia, inflammatory syndrome and important hepatocytolisis. Echocardiographic she presented a severely impaired left ventricular systolic function (ejection fraction 15%) with apical ballooning and elevated left ventricular end diastolic pressure. Coronary angiography revealed non-obstructive coronary atheroma. The final diagnosis of Takotsubo cardiomyopathy was made on the basis of cardiac computer tomography. At the 7 weeks follow up, under antithyroid drugs there was an improvement of thyroid hormone levels. Moreover, consistent with Takotsubo cardiomyopathy, at re-evaluation there was a cardiac function recovery with normal ejection fraction (66%).
Conclusions
Thyrotoxicosis is associated with multiple implications in cardiovascular system. Pathologically high levels of thyroid hormones cause exaggerated chronotropic and inotropic response to cathecolaminee. One possible explanation could be the upregulation of beta adrenergic receptors by thyroid hormones in many tissues, including cardiac.

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EP1346

The association of gene polymorphisms with the clinical outcome of Graves' disease

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The aim
Of this study was to investigate the association between two common CTLA-4 gene SNPs (49A/G in exon 1 and CT60 A/G in 3'UTR) and Graves' disease outcome in Lithuanian population.
Methods
This case-control study was performed in the Hospital of Lithuanian University of Health Sciences. Graves' disease patients ($n=105$) were divided into remission and failed treatment groups according to the final outcome of the disease. The remission group ($n=49$) – patients with euthyroid status minimum 1 year after antithyroid drugs (ATD) withdrawal. The failed treatment group ($n=56$) – patients submitted radioiodine therapy or surgery due to poor response to ATD therapy. Genomic DNA was extracted from the peripheral blood leukocytes with kit Qiagen GmbH, Hilden, Germany.
Results
The patients in failed treatment group had significantly higher frequency of GG genotype and a lower frequency of AA genotype than patients in remission group. Patients with GG homozygous genotype had more than four-fold (OR 4.94, 95% CI 1.38–17.65) and more than sixteen-fold (OR 16.91, 95% CI 1.83–156.62) increase in risk of ATD treatment failure compared to patients with homozygous genotype AA for 49A/G SNP and for CT60 SNP, respectively. When association of 49A/G and CT60 genotypes on the outcome of Graves' disease was analyzed separately it provided significant prognostic information but after multiple logistic regression analysis these genetic markers were not independent of other factors. Only TRAb levels before treatment was independently associated with elevated odds of failure (OR 1.05, 95% CI 1.02–1.08).
Conclusion
the data shows significant association of two polymorphisms (A/G at position 49 and CT60 in 3'UTR) in the CTLA-4 gene with Graves' disease in Lithuania and suggest that these genetic markers may provide important information in predicting high risk patients for failure to ATD therapy.

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EP1347

The impact of levothyroxine sodium treatment on dynamic thiol/disulphide homeostasis in overt hypothyroidism

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Objective
Thiols are organic compounds that contain sulphydryl group (-SH) and have important role in preventing oxidative stress especially in cells. The aim of our study is to investigate the relationship between hypothyroidism due to HT and the thiol disulfide homeostasis, the effect of treatment on this homeostasis and to demonstrate the utility of thiol/disulphide homestasis as a marker for assessing the damage to functional group of proteins and the oxidative balance in this group of patients.
Design, patients and measurements
Thirty-five patients with a new diagnosis of hypothyroidism due to HT who were not yet under treatment is enrolled in the study. Serum samples were taken prior to the treatment and 6 months after initiation of levothyroxine sodium treatment to compare clinical and laboratory parameters of patients. Thiol/disulfide homeostasis is evaluated by Erel & Neselioglu method.
Results
After 6 months of treatment the native thiol and total thiol levels were significantly increased ($P=0.001$ and $P=0.001$). The disulphide level, the disulphide/native thiol and the disulphide/total thiol ratios showed a significant decline ($P=0.001$, $P=0.001$, $P=0.001$ respectively).
Conclusion
Decrease in the disulfide/thiol ratio after levothyroxine sodium treatment in hypothyroidism may suggests that treatment plays a role in reducing both oxidative stress and free radical mediated damage to the functional groups of proteins. Thus, it may be possible to avoid the complications caused by oxidative stress. As a result disulfide/thiol ratio may contribute to the management of treatment in hypothyroid patients.

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EP1348

The role of vitamin D receptor gene FokI (rs2228570) polymorphism in the pathogenesis of thyroid associated orbitopathy

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Introduction
Vitamin D, known mainly as a calcium-phosphorus homeostasis regulator, turned out to play also a significant role in the immune system modulation. Vitamin D deficiency has been reported in some autoimmune disorders. It is also suspected that polymorphisms of vitamin D-related genes comprise a risk factor for different autoimmune diseases. Therefore the aim of our study was to assess vitamin D receptor (VDR) gene FokI polymorphism in thyroid associated orbitopathy (TAO) in comparison to the controls among the Caucasian-Polish population.
Patients
The group studied consisted of 100 subjects diagnosed with TAO (mean age 53.8) and 142 healthy age and sex matched controls. TAO was diagnosed by clinical examination, TRAb assessment and orbit MRI or CT. TAO group was further divided into: A- orbitopathy from the onset of Grave's disease, B- later development of TAO. In the control group both TAO and autoimmune thyroid diseases were excluded by clinical examination and thyroid ultrasound.
Methods
FokI polymorphism of the VDR was studied by PCR-RFLP analysis, randomly selected patients were additionally analyzed by direct sequencing. The statistical significance of differences between the allele and genotype frequencies in TAO vs controls, as well as in subgroups of TAO were evaluated by $\chi 2$ or Fisher's exact test. A P-value of <0.05 was considered significant.
Results
Observed allele frequencies were in Hardy-Weinberg equilibrium. C allele and CC genotype were more frequent in TAO compared to the controls (59.50 vs 55.28% and 34.00 vs 31.69%, respectively), although differences were not statistically significant ($P=0.36$ and $P=0.50$). CC+CT genotypes (dominant inheritance model) were more frequent in the subgroup A compared to B (89.70% vs 75.00%), $P=0.07$.
Conclusions
There is no statistically significant difference in allele or genotypes distribution of VDR FokI polymorphisms between TAO and the control group among the Caucasian-Polish population.

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EP1349

Lymphoid hyperplasia in Graves' disease: about 2 cases

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Introduction
Graves' disease GD is an autoimmune disease, which can manifest with a variety of extrathyroidal clinical syndromes. Though quite rare, this disease can also manifest with lymphoid hyperplasia.

Case report
Two cases are reported in the department of endocrinology and diabetology of Hedi Chaker hospital in Sfax-Tunisia from 2006 to 2016 associated GD with lymphoid hyperplasia reaction. The first case was a 32 years old male with history of GD 6 years back treated with propylthiouracil and beta blockers. He was admitted with follow complaints: dyspnea and edema of the lower limbs. The diagnosis of cardiothyrosis with dilated cardiomyopathy has been confirmed by echocardiography. Neck-chest computerized tomography (CT) has been made to explore swallowing disorder wich showed the presence of no compressed heterogeneous goiter with mediastinal polyadenopathy and bilateral suspect lung nodules. The body scan revealed the same results with other deep localization of lymph nodes. The infectious and inflammatory etiological investigations were negatives. A total thyroidectomy with biopsy of mediastinal lymph node under mediastoscopy confirmed histologically the presence of lymphocytic thyroiditis with a lymphoid hyperplasia. The second case was a 47 years postmenopausal female followed for Graves's disease complicated with cardiothyreosis. We have discovered incidentally deep lymph nodes (mediastinal, coeliomesenteric, aortocave) with lung nodules. The biopsy of the lung was not conclusive. The stability of these lesions for 10 years argues for a reactive lymphoid hyperplasia.
Conclusion
Reactive lymphocyte proliferation remains a histological diagnosis. It is necessary to complete with exhaustive etiology investigation in front of this clinical presentation.

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EP1350

Effects of hypothyroidism on nutritional status: which impact?

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Introduction
Hypothyroidism is a common disease in Morocco because of the iodine deficiency frequency. The metabolic and nutritional effects of hypothyroidism are known in the literature. The hypothyroidism is classically described among the causes of secondary obesity. The aim of the study is to evaluate the nutritional status and anthropometric parameters in patients having hypothyroidism.
Patients and methods
Patients were recruited from the out-patients clinics. All the patients with the diagnosis of hypothyroidism and not receiving yet the L-thyroxin were included. All the patients were examined by the dietitian and the clinical and laboratory evaluation were carried on in all patients.
Results:
A total of …. were included. The mean age was 41 years. The sex ratio is 6/1. Weight gain was found in 67% of patients with a mean gain of 8kg. The mean weight was 80 kg for men and 68 kg for women for an average ideal weight of 64 and 54 kg respectively. The BMI was normal in 43, 30% of cases, 26.60% were overweight and 23.20% were obese. Waist circumference was pathological in 92% of women and 80% of men. The body fat percentage was high in 60% of female patients and 80% of male patients. The average daily caloric intake for women was 2138.77 Cal while the caloric intake was 1856.6 Cal in men. High intake in macronutrients was found in all patients.
Conclusion
Hypothyroidism is responsible for an important increase in body fat leading to overweight and obesity. The hormonal replacement is an efficient way to overcome these nutritional and metabolic changes. The nutritional evaluation is critical for any patient consulting for hypothyroidism.

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EP1351

Outcome of radioiodine therapy in patients with hyperthyroidism

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Introduction
Radioiodine treatment (RAIT) is an effective definitive treatment for Graves' Disease (GD) and Toxic Nodular Goiter (TNG). The aim of this study was to analyze demographic and clinical factors affecting the outcome of RAIT in patients with hyperthyroidism.
Methods
Retrospective review of patients treated with RAIT for hyperthyroidism. A fixed dose of 10 mCi was administered to patients with GD and 15 mCi to patients with TNG. Treatment success was defined as euthyroidism or hypothyroidism (subclinical/overt hypothyroidism) 12 months after RAIT.
Results
217 patients were included; 122 with GD and 95 with TNG (52 patients with toxic multinodular goiter and 43 with Toxic Adenoma). RAIT was more effective in TNG than in GD (94.7% vs 71.3%, $P<0.05$). Gender, previous thyroid function and thyroid volume were significantly as-sociated with an effective outcome in patients with GD ($P<0.05$). No clinical or demographic factors affected the outcome in patients with TNG, although a higher Tc99 uptake on scintigraphy was associated with persistent hyperthyroidism. Hypothyroidism was more common in GD (62.3% vs 41.1%, $P=0.001$). Hypothyroidism was significantly more frequent in smaller nodules (26 ± 8 mm vs 32 ± 11 mm, $P<0.05$) and in lower thyroid volumes (24.3 ± 14 ml vs 37.7 ± 19 ml, $P<0.05$).
Conclusion
Thyroid volume seems to have a significant influence on the development of hypothyroidism after the treatment and, in patients with GD, the efficacy of RAIT. In GD, larger goiters may need a greater dose and beneficiate from a calculated dose of radioiodine instead of a fixed predefined dose. In TNG, a fixed dose of 15 mCi successfully cured hyperthyroidism in almost all patients although in selective patients with smaller thyroid nodules or smaller goiters a lesser RAIT dose may restore euthyroidism.

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EP1352

An unusual case of subacute thyroiditis after alemtuzumab treatment

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Introduction
Alemtuzumab, a humanized monoclonal antibody against CD52, is effective in the treatment of early relapsing-remitting multiple sclerosis (MS). Thyroid side-effects such as Graves' disease have been already described. We describe one case of unusual subacute thyroiditis after alemtuzumab treatment.
Clinical case
A 38 year-old-female was treated by alemtuzumab for 2 years. She was referred for hyperthyroidism with 10 kg weight loss, diarrhea and palpitations. Clinical examination found cervical pain and fever. Thyroid function tests revealed low TSH at 0.0170 mUI/l (N 0.270–4.20), increased fT4: 71.4 pmol/l (N 12–23) and fT3: 18.2 pmol/l (N: 3.84–7.07). Thiamazol (20 mg bid) and propranolol (20 mg tid) were started with daily neutrophil evaluation. First hypothesis was Graves' disease, since it is currently described with alemtuzumab. Blood tests revealed increased CRP: 156 mg/l ($N<4$ mg/l) without increased leukocytes. Ceftriaxone was started in front of a urinary infection suspicion. Finally, bacteriological analyses (blood and urine) were negative and ceftriaxone was discontinued. After 3 days under thiamazol treatment, fT4 increased up to 100 pmol/l and fT3 up to 26.5 pmol/l without clinical improvement. Thyroid ultrasonography showed isolated heterogeneous parenchyma. Technetium scintigraphy showed no uptake; allow us to make the diagnosis of subacute thyroiditis. Finally, anti TSH receptor, thyroglobulin and thyroperoxidase antibodies results came back negative. Thiamazol was resumed, prednisolone (1 mg/kg per day) started. After 1 week, neck pain and fever disappeared and fT3, like CRP, were normalized. After 2 weeks, fT3 and fT4 were in the normal ranges.
Discussion
Although subacute thyroiditis is not known as an auto-immune disease, an increase of its incidence rate is found after alemtuzumab or INF-alpha treatment suggesting an immune participation. Moreover, this rise is not found after alemtuzumab therapy for chronic B cell leukemia (suggesting a specific background in MS patient). We describe here the case of unusual severe subacute thyroiditis after alemtuzumab treatment.

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EP1353

Pattern of amiodarone-induced thyrotoxicoxis before and after universal salt iodization

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Background
Prevalence and type of amiodarone-induced thyroid dysfunction in a population depend on geographical iodine intake.
Aims
To assess differences in amiodarone-induced thyrotoxicosis pattern before and after iodine supplementation.
Patients and methods
84 patients (41M/43F) with amiodarone-induced thyrotoxicosis, aged 60.1 ± 11.9 years, were retrospectively reviewed. 28 patients were resident in former iodine-deficient areas. TSH, FT_4 and total T_3 were measured by chemiluminescence; 2 h and 24 h radioiodine (^{131}I) uptake and color flow Doppler were performed.
Results
Type 1 amiodarone-induced thyrotoxicosis (AIT) was diagnosed in 21 cases (25%), type 2 in 26 cases (30.9%) and mixed type in 37 cases (44%). Before universal salt iodization were diagnosed 38 cases (type 1 AIT in 12 cases – 31.6%, type 2 in 14 cases – 36.8% and mixed type in 12 cases – 31.6%); after universal salt iodization were diagnosed 46 cases (type 1 AIT in 9 cases – 19.6%, type 2 in 12 cases – 26% and mixed type in 25 cases – 54.3%); Patients with type 1 AIT were significantly younger (62.5 ± 9.6 years vs 56.1 ± 12.8 years, $P = 0.05$), with significantly higher radioiodine uptake at 24 h (median 7% vs median 1%, $P = 0.022$) and had higher thyroid volume (29.9 ± 14.8 ml vs 19.9 ± 8.6 ml, $P = 0.015$) than patients with type 2 AIT. Patients with type 1 AIT had higher total T_3 levels than patients with type 2 AIT (340.9 ± 157.4 vs 246.7 ± 135.9 ng/dl, $P = 0.06$) and type 3 AIT (216.4 ± 111.8 ng/dl, $P = 0.003$, respectively). There were no statistically significant differences in body mass index, amiodarone treatment duration, amiodarone cumulative dose, FT_4 levels between AIT type 1, 2 and mixed type.
Conclusion
After universal salt iodization, AIT type 2 and mixed type prevailed in our geographical area.

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EP1354

They think it's all ovar(ii)

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A 37 year old woman was referred to the endocrinology clinic from the gynaecologists. She was awaiting an 8 cm left ovarian cyst removal and found to be hyperthyroid (fT3 7.8 pmol/l, fT4 of 19.0 pmol/l, TSH < 0.01 mU/l). She described 4 months of palpitations, change in bowel habit and menstrual irregularity. She had no tremor or tachycardia. She had no palpable goitre or eye signs. She had a past medical history of asthma on inhalers. There was no family history of thyroid disease. Repeat bloods confirmed T3 toxicosis, negative TPO and TSH receptor antibodies. She was commenced on carbimazole 10 mg od. She underwent a successful left salpingo-ooperectomy. Histology showed a multi-loculated cyst containing hyperplastic thyroid tissue and no evidence of malignancy. Following surgery she reported resolution of symptoms and had normalisation of thyroid function. Her carbimazole was reduced. At recent clinic review she is clinically and biochemically euthyroid off carbimazole. Struma Ovarii is a rare finding of ectopic thyroid tissue in an ovarian teratoma. This case illustrates the importance of checking thyroid function prior to gynaecological surgery and to consider rarer causes of thyrotoxicosis.

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EP1355

Perinatal outcome in graves-basedow disease during pregnancy

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The purpose of this study is to assess the treatment outcome of pregnant patients with Graves-Basedow disease. In the period of 20 years 59 pregnancies in hyperthyroid patients were registered with Graves-Basedow disease in the Department of Nuclear Medicine in Clinical Hospital Bitola. Thyrostatic therapy was applied in 29 (56.5%) pregnant patients divided into 2 groups. The first group were patients who used methimazole therapy (MMT) or 50–400 mg propiltiuracil (PTU). Of this group, 19 were born healthy infants (74.3%), 2 (5.12) with low birth weight, 5 (12.8) were premature but with no fetal malformations. The second group were patients who were not regularly controlled and treated. Of them all three babies were born with malformations (two newborns died shortly after birth and one newborn died six months after birth).
Conclusion
Our study suggests that patients treated with Graves-Basedow disease during pregnancy with a low dose of thyrostatic therapy, provides a significant reduction of fetal complications. Our study also indicated no significant difference in the effects of both drugs - PTU and MMT in these doses although preferably PTU because of reduced transplancental passage compared to MMT. In our study observed complications and mortality in newborns of mothers with uncontrolled or inadequate and irregular treated hyperthyroidism.

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EP1356

TSH receptor stimulating immunoglobulins – performance of an automated immunoassay

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Introduction
Graves' disease (GD) hyperthyroidism is caused by autoantibodies against TSH receptor (TRAb). Three varieties of TRAb are now recognized: stimulating (TSI), blocking and neutral antibodies. Current TRAb immunoassays detect and quantify serum immunoglobulins that interact with the TSH receptor but without discriminating their function. An automated immunoassay for the detection and quantification of TSI is available.
Objective
Our study objective was to determine the performance of TSI assay in patients with thyroid autoimmune disease, nodular disease, and healthy individuals.
Methods
59 subjects were enrolled in the study: 37 samples of consecutive individuals referred to the endocrinology consultation with thyroid pathology and 22 healthy subjects. The Immulite® 2000 TSI (Siemens) was used to measure TSI.
Results
Of the 37 patients, 30 (81,1%) were female and 7 (18,91%) were male, with a mean age of 58 (±14) years. 18 patients were diagnosed with autoimmune thyroid diseases (10 with untreated GD and 8 with Hashimoto thyroiditis (HT)) and 19 with nodular thyroid disease (12 with non-toxic goiter and 7 with toxic adenoma). Healthy subjects and those with nodular thyroid disease had a negative TSI assay but one patient with HT had a positive TSI assay (specificity 98%). Of the ten patients with diagnosis of Graves' disease 10 had positive TSI assay (sensitivity of 100%) with a median value of 3.6 IU/L (maximum of 90.1, minimum of 1.2). There was a positive correlation between the value of TSI assay and the amount of the free fractions of thyroid hormones.
Conclusion
This easy to perform assay method of TSI revealed high sensitivity and specificity in the diagnosis of Graves' disease.

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EP1357

Genetic variation in NFE2L2 and SEPS1S associated with increased risk of Hashimoto's thyroiditis

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Hashimoto's thyroiditis (HT) is the most common chronic autoimmune thyroid disease, which is characterized by alteration of the thyroid function. HT is a multifactorial disorder and several candidate genetic loci have been identified as contributing to HT. The transcription factor Nrf2, encoded by the NFE2L2 gene, is an important regulator of the cellular protection against oxidative stress. The relevance of selenoproteins in follicular thyroid cell physiology and in molecular physiology have pointed to a putative role of the interaction of Nrf2 with selenoproteins in the pathogenesis of autoimmune thyroid diseases. In order to evaluate the role of a promoter variation in *NRF2 and SEPS1* in the risk for developing Hashimoto's thyroiditis (HT), we performed a case-control study comprising 997 individuals (HT patients and unrelated controls). Genetic variants were discriminated by real-time PCR using TaqMan SNP genotyping assays. Three polymorphisms (– 653A/G: rs35652124; – 651G/A: rs6706649 and – 617C/A: rs6721961 SNPs) in the NRF2 gene promoter were studied and no significant difference were found between HT patients and controls with regard to genotypic or allelic frequencies of the three NFE2L2 SNPs ($P > 0.05$). The joint effect of genetic polymorphisms in NFE2L2 and SEPS1 was assessed considering the high-risk genotypes of *NF2L2 and SEPS1*. Our findings suggest that the risk to develop Hashimoto's thyroiditis is not associate to a single NFE2L2 polymorphisms but increases with the combined effect of the number of risk alleles in *NFE2L2* and *SEPS1*. Individuals carrying two high-risk genotypes present a significant increased risk for HT.

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EP1358

Safety and efficacy of cholestyramine in the adjuvant management of Graves thyrotoxicosis

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Introduction
Graves's disease is an autoimmune condition both cell and antibody-mediated, which is associated with thyrotoxicosis and extra thyroid features.
Case report
A 35-year-old female presented with symptomatic hyperthyroidism due to graves thyrotoxicosis. She developed adverse reactions, including severe dermatitis and hepatotoxicity, to two of the thionamide drugs (carbimazole and propylthiouracil). Eventually we decided for definitive treatment in the form of a total thyroidectomy, as it appeared to be the only option in a mother of a young child, which precludes radioiodine therapy. Unfortunately, we were unable to treat her with a beta-blocker due to her history of severe Raynaud's disease. We arranged for her to undergo rapid thyroid blockade 10 days prior to her surgery with Lugol's iodine. After she had Lugol's iodine, she exhibited a paradoxical increase in her thyroid hormone levels, which was unusual and necessitated cancellation of her surgery. It appears she did not go through the Wolff-Chaikoff effect but instead showed Jod-Basedow effect, resulting in a significant rise in free T_4. We have agreed to commence her on cholestyramine 2 g three times a day and prednisolone 40 mg once a day in order to improve her thyrotoxicosis. Eventually she became euthyroid after a few weeks of starting the treatment and then underwent total thyroidectomy.
Comments
Thionamides are widely used as anti-thyroid drugs in the management of hyperthyroidism but unfortunately they are also associated with serious adverse effects which was exhibited by this patient. In our case we have successfully used adjunct treatment including steroids and cholestyramine to achieve euthyroid state and making patient ready to undergo thyroidectomy. Although steroids are not used as a mode of achieving euthyroid status with hyperthyroidism, though it is often used in thyroid crisis.

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EP1359

A slow but continuous growth: Case study of a thyroid nodule

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Thyroid nodules are a common clinical finding, with an estimated prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in men. The clinical importance of thyroid nodules rests with the need to exclude thyroid cancer. The prevalence of malignancy reported for palpable thyroid lesions ranges from 5.0% to 6.5%. Patients with benign thyroid nodules are unlikely to suffer morbidity or mortality due to thyroid cancer. A 53 aged man presented with a 20-year history of a slow-growing nontender neck mass. *He denied* any *compressive symptoms, such as* dysphagia, dyspnea or hoarseness. On physical examination of the thyroid, the patient had a right-sided soft, elastic nodule larger than 10 cm of diameter. TSH, T4l were within normal range and thyroid antibodies were negative. CT scan of the neck indicated a solitary dominant nodule of the *right* thyroid *lobe* measuring 140×78×84 mm without invasion of adjacent structures. A minor compression and tracheal deviation to the left was also reported. Thyroid ultrasound indicated a large, heterogeneous nodule, solid with some cystic component and well-defined contours, occupying the entire right lobe of the thyroid gland. Left lobe also had a 1.4 cm solid nodule. FNAB of both nodules were benign. The patient remained asymptomatic throughout. Natural growth behaviour of thyroid nodules is controversially discussed. In our clinical case, the slow progression and the absence of compressive signs was suggestive of a benign lesion. However, the large dimensions and the progressive growth of the nodule might also be indicative of malignancy. There are few studies about long-term prognosis of thyroid nodules, including their malignant transformation. Although well established that approximately 90% of non-functioning thyroid nodules are benign, even in slow growth big nodules with benign FNAB, surgery is crucial to the final diagnosis.

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EP1360

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Introduction
Many causes of malabsorbtion of levothyroxine (LT_4) in patients with hypothyroidism have been thoroughly described in literature. Pseudomalabsorption, poor compliance of the patient is most common cause of failure of LT4 and/or liothyronine (LT_3) treatment.
Case report
27 years old woman, normopondeal, presented from the age of 11 years for short stature. Further investigations found pluritrope pituitary insufficiency (somatotrophic, gonadotroph, corticotroph and tireotroph) and substitutive treatment was started (GH-treated off 17 years, actual height 168 cm, cortisol, esoprogestative and thyroid hormones). MRI described a small pituitary. Despite of increasing dose of LT_4, ulterior in association with LT_3, and vitamic C for better absorption, THS remained high (13 μUI/ml, reference 0.4–4 mU/L) with constantly low fT_4. Celiac disease, pernicious anemia, gastrointestinal, liver, pancreatic, heart disease or pregnancy were excluded by laboratory and imagistic investigations, also were

excluded drugs and dietary interactions; To evaluate the hypothesis of pseudomalabsorption, the patent was submitted to rapid LT_4 absorption test. After an overnight fasting, it was administreted 1000 μg LT_4; We measured fT4 at 30′, 2, 4, 6 h.Immediately fT4 serum increase, with the maximum serum level after 2 h (basal $fT_4 = 0.56$ ng/dl, 2 h = 1.72 ng/dl, peak $fT_4 > 2.5$). The test showed a normal absorption of LT_4 and malabsorption was excluded.
Conclussion
Our case showed an inadequate thyroid hormone supplementation (3.3 μg/kg); the literature suggested that after excluding organic cause or drug interaction, is useful to make a malabsorption test, which confirms the diagnostic pseudomalabsorption; based on his historical attempts to stop the treatment, a psychological counseling may be necessary. Once weekly oral thyroxine treatment, supervised, can be a safe, well-tolerated, and effective therapy for patients with non-compliance.

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EP1361

Oxidative profiles in patients with autoimmune thyroid diseases

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Introduction
Autoimmune thyroid diseases are known to be associated with oxidative stress.
Objectives
We studied the oxidative profiles in plasma and thyroid tissue of 82 patients having Graves' disease (GD) or Hashimoto thyroiditis (HT) or hashitoxicosis (HTX) vs 65 healthy controls in order to evaluate the antioxidant enzymes' activity and the lipid peroxidation.
Results
The lipid peroxidation was objected with a significant higher level of Malondialdehyde (MDA) in the plasma of our patients vs healthy controls ($P < 0.01$ for HT, $P < 0.001$ for GD and HTX). A very low antioxidative activity of Glutathione peroxidase (GPx) was found in our patients vs healthy controls ($P < 0.001$ for HT and HTX, $P < 0.01$ for GD). The Selenium which is GPx-cofactor and the Catalase were found to be reduced as well. For the proteins oxidation, we found a higher level in Carbonyl-group, MDA and a lower level of thiol-group in our patients vs healthy controls. Similar results were found in the thyroid tissue samples.
Conclusion
This study shows clearly the presence of an oxidative stress in both plasma and thyroid tissue in patients with autoimmune thyroid diseases.

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EP1362

Levothyroxine absorption test in the management of a patient with persistent hypothyroidism

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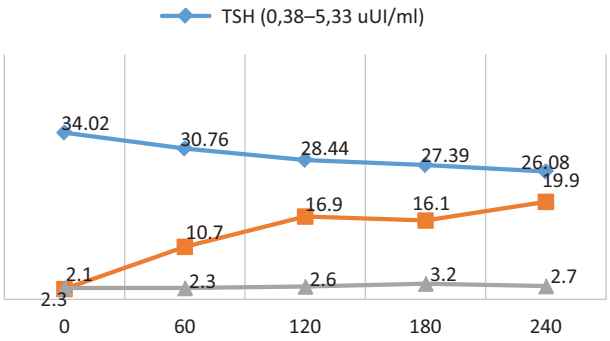
Nonadherence to levothyroxine therapy is one cause of persistent hypothyroidism. To distinguish nonadherence from malabsorption, a levothyroxine absorption test (LAT) is sometimes required. The authors report a case of a 60-year-old female patient suffering from hypothyroidism resistant to oral levothyroxine (LT_4) substitution after radioiodine therapy for Graves' disease. Despite the continuous increases of LT_4, over 10 years, to a maximum of 1 mg/day, she remained with high thyrotropin (TSH) and low free thyroxine (FT_4). Extensive investigation excluded disease of the small bowel, liver and pancreas as well us drugs interactions. After careful consideration was decided to conduct a LAT. Serum levels of TSH, FT_4 and free triiodothyronine (FT_3) were drawn at 0, 60, 120, 180 e 240 min after 1mg of LT_4. The results are presented in the graphic below. The patient remained with normal heart rate and normotensive along LAT. The results showed a normal absorption of LT_4, so pseudo-malabsorption was proven. Based on this diagnosis was prescribed 1 mg of LT_4 weekly to improve therapeutic compliance. Nowadays, patient present normal TSH and FT_4 serum levels. In conclusion, pseudo-malabsorption is an important differential diagnosis in persistent hypothyroidism to achieve therapeutic success and LAT is a simple, secure and useful tool in this cases.



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EP1363

Serum irisin level in different thyroid dysfunction states and its relation to markers of muscle dysfunction

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Introduction
Irisin is a myokin secreted by myocytes responsible for transmission of signals from muscles to other body tissues. It improves systemic metabolism by increasing energy expenditure and has a significant influence on the body metabolism and thermogenesis. Thyroid disorders are characterized by a disrupted thermo-metabolic state and muscular damage, and the underlying mechanisms still not clear.
Aim
To evaluate serum Irisin levels in patient with hypothyroid and hyperthyroid disease and its relation to creatinine kinase (CK) a marker of muscle damage.
Method
90 subjects participated in the study. They were divided into three groups: Group 1: 30 hyperthyroid patients, Group 2: 30 hypothyroid patients, Group 3: 30 normal persons. They were submitted to history, medical examination (Weight, Height and BMI) and measurement of fasting serum Irisin, TSH, Free T_3, Free T_4, CK.
Results
Irisin hormone level was lower in hypothyroid patients (16.60 ± 4.07) Pg/ml than hyperthyroid patients (26.83 ± 7.95) Pg/ml and controls (25.70 ± 5.29) Pg/ml ($P < 0.01$). However, it was higher in hyperthyroid than ($P > 0.05$). Creatine kinase (CK) level decreased in hyperthyroid patients (33.80 ± 1.49) μ/l than hypothyroid patients (196.26 ± 4.53) μ/l and controls (62.86 ± 1.63) μ/l ($P < 0.01$). However, creatine kinase increased in hypothyroid patients (196.26 ± 4.53) μ/l in comparison with control (62.86 ± 1.63) μ/l ($P < 0.01$). There is a negative correlation between Irisin, TSH, Weight, BMI and CK ($P < 0.01$), and a positive correlation with freeT_3 and free T4 ($P < 0.01$) in hyperthyroid patients.
Conclusion
Lower Irisin hormone level was found in patients with hypothyroidism which might be explained by muscles destruction demonstrated with high CK levels, however the higher level of Irisin in hyperthyroidism might explained by hypermetabolic state.

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EP1364

Iodine deficiency is still prevalent in pregnant women from Romania after universal salt iodization

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Introduction
Even mild to moderate maternal iodine deficiency during pregnancy is associated with impaired child cognition. Iodine deficiency is especially problematic in pregnant women, who have a higher iodine requirement (250 μg/day) than non-pregnant women (150 μg/day).
Objective
To assess iodine status (median urinary iodine concentration, UIC) in pregnant women from multiple endemic or non-endemic areas in Romania, 13 years after implementation of the Universal Salt Iodization (25–40 mg iodine/kg salt).
Subjects and methods
Median UIC in the morning urine was evaluated by spectro-photometry in 409 pregnant women in the third trimester from seven geographical regions in Romania (age range 16–44 years, median age 29 years, none treated with thyroxine, 80% from endemic regions, 59% from urban regions). Data regarding iodized salt intake, bread intake (usually containing 6–9 μg iodine/slice) and iodine supplements were assessed. The study was approved by the local Ethics Committee.
Results
Iodized salt was consumed by 87% of women, iodine supplements during pregnancy by 48% of women. Median UIC in the study group was 131 μg/l, reflecting iodine deficiency during pregnancy (normal values $\geq$150 μg/l). Lower median UIC (μg/l) were recorded in the endemic regions of Transilvania (92), Oltenia (114), Moldova (129) and Muntenia (149) as compared to Bucharest area (206) and other non-endemic regions (206.6), except Timis (140); 55.7% of women had values below 150 μg/l, 13% below 50 μg/l, 1.7% had values over 500 μg/l. Higher median UIC was recorded in women with a daily intake of $\geq$5 slices of bread, 166 vs 111 μg/l, $P<0.01$. Similar UIC were found in women taking prenatal vitamins containing iodine and in those with no supplements. In Transilvania region there is a discrepancy between schoolchildren (normal median UIC) and pregnant women (low median UIC). Urinary iodine/creatinine ratio was not significantly different from urinary iodine levels.
Conclusions
Mild iodine deficiency is still prevalent in Romanian pregnant women from historical endemic regions after 13 years of universal salt iodization. Iodine supplementation during pregnancy should be encouraged in these regions.

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EP1365

The potential of smartphone applications in management and compliance to recommended lifestyle in Hashimoto's patients

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Background
Hashimoto's thyroiditis (HT), a chronic autoimmune disease caused by an interaction between genetic factors and the environmental is treated by thyroid supplementation as the first line of treatment. However, many of the symptoms are unrelated to the failing thyroid function, but seem to be connected to the autoimmune disease, remain. Literature has reported on many of the environmental triggers of autoimmune response, however patients do not have a unified way to record, document, measure and understand their experiences and share them with their healthcare practitioners.
Objective
We aim to build a mobile phone application that would allow patients to record and overview their symptoms as well as their compliance to medication.
Design
The app is build on a combination of thus far biomedical knowledge of symptoms related to Hashimoto's as well as information gathered from interviewing individuals diagnosed with Hashimoto's. It enables individuals to record their experience on daily-weekly and monthly basis. No data are collected, the system is decentralized, and the recorded data are stored only on patient's phones.
Results
Patient's needs could be easily served through a mobile phone app, according to the first results. It could help the patients implement lifestyle changes that would serve as a first line of defence against non-thyroid related Hashimoto's symptoms.
Conclusion
Smart phone apps have a great value and potential in collecting a large pool of worldwide data, however they need to be co-developed with biomedical scientists and healthcare professionals in order to fully serve to patients, medical healthcare professionals as well as the research.

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EP1366

Dynamic risk stratification for predicting recurrence in patients with differentiated thyroid cancer treated without radioactive iodine remnant ablation therapy

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Background
Increased incidence of small differentiated thyroid cancer (DTC) has emphasized the need for risk stratification and individualized disease management for these low risk DTCs. The aim was to validate a new dynamic risk stratification (DRS) system for prediction of structural recurrent/persistent disease in patients with DTC treated without radioactive iodine (RAI) remnant ablation therapy.
Methods
This historical cohort study included 357 patients with DTC treated with lobectomy or total thyroidectomy without RAI therapy. We stratified patient response to initial treatment as excellent, indeterminate, biochemical incomplete, and structural incomplete according to the DRS system.
Results
During a median 8.6 year of follow-up, 3.6% patients had structural recurrent DTC. The response was excellent in 71.7% patients, indeterminate in 18.5%, biochemical incomplete in 8.4%, and structural incomplete in 1.4%. There were significant differences in disease-free survival among the DRS groups ($P<0.001$). The hazard ratio (HR) of recurrent/persistent disease was significantly higher in biochemical incomplete group (HR $=20.8$, $P<0.001$) and structural incomplete group (HR $=243.3$, $P<0.001$) compared with the excellent group. However, the tumor node metastasis (TNM) staging system and the American Thyroid Association (ATA) initial risk classification did not effectively predict recurrence of DTC.
Conclusions
The new DRS system was effective for predicting risk of recurrent/persistent disease in patients with DTC who underwent lobectomy or total thyroidectomy without RAI remnant ablation.

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EP1367

Association between lymph node metastasis and patients' age in papillary thyroid microcarcinoma

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Background
Recent studies presented that younger patients with papillary thyroid microcarcinoma (PTMC) had poorer clinical outcomes compared to older PTMC patients. The aim of this study is to investigate the impact of patient's age on the lymph node metastasis (LNM) status of PTMC, a risk factor for recurrence and poor clinical outcome of PTMC.
Methods
The study evaluated 2068 PTMC patients who underwent thyroid operation with lymph node (LN) dissection from 2001 to 2009. All patients were allocated into five groups by age; Group A ($\leq$35 years), Group B (35 $<$age$\leq$45), Group C (45 $<$age$\leq$55), Group D (55 $<$age$\leq$65), and Group E (65 $<$age). LNM status was divided into three groups by the number of metastatic LNs: no LNM, low volume LNM ($\leq$5 metastatic LNs), high volume LNM ($>$5 metastatic LNs). We evaluated the correlation between patient's age and high volume LNM in this study.
Results
High volume LNM was found in 199 (8.9%) patients among whole study subjects and was the most frequently found in the young age group (A 17.3%, B 8.4%, C 7.2%, D 8.4%, and E 7.1%, respectively). Young age (Group A), male gender, larger primary tumor ($>$0.5 cm), multifocality, and extrathyroidal extensions were significant risk factors for high volume LNM in univariate and multivariate analysis. In multivariate analysis, odd ratio (OR) of Group A for high volume LNM was 3.49 (95% CI, 1.67–8.06; *P*-value 0.002) compared to the Group E. When analyzed only in women, young age (Group A) was also a significant risk factor for high volume LNM (OR 6.00, 95% CI 2.73–20.76, *P* value 0.001). But when analyzed in men, there was no significant difference in the incidence of high volume LNM by different age groups (A 25%, B 18.1%, C 20.2%, D 22.0%, and E 22.7%, respectively).
Conclusion
High volume LNM was more frequently found in young aged female and male patients. For patients under 35 years or male patients, immediate diagnosis and surgical treatment for PTMC might be needed.

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EP1368

Breast cancer and family history for breast cancer in patients with differentiated thyroid carcinoma

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Background and aim
The risk for breast cancer in patients with thyroid cancer has been investigated in previous studies, and has been found to be increased. In this study we, therefore present retrospective analysis of the patients with differentiated thyroid carcinoma in respect to breast cancer and family history for breast cancer.
Methods
We conducted a retrospective study involving 455 patients with a diagnosis of differentiated thyroid carcinoma between January 2009 and March 2016.
Results
The majority of them were female (403, 88.6%). Mean age at diagnosis was 45.5$\pm$12.8 (range 10–81) years. We detected that 0.7% patients with thyroid cancer had breast cancer and 13.4% patients had a family history of breast cancer within three generations of the proband. There was no significantly differences between family history of breast cancer and gender, age at diagnosis, pathologic types, and RAI therapy.
Conclusion
In the literature, there are many clinical, epidemiological, and experimental studies that show an association between thyroid cancer and breast cancer. Our study is the first report showing history for breast cancer and family history for breast cancer is 0.7 and 13.4% this particular group of Turkish differentiated thyroid cancer patients.

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EP1369

Differential diagnosis between Anaplastic Thyroid Cancer and Primitive Lymphoma of the Thyroid gland: A 66-cases study

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A rapidly growing neoplastic mass of the neck can either be caused by an anaplastic thyroid cancer (ATC) or a primitive lymphoma of the thyroid gland (PLT). These two malignancies share the same clinical features but vary widely in their treatment and outcome. Only histologic criteria through biopsy can provide a definitive diagnosis. The aim of this study was to assess biological and radiological differences between ATC and PLT in order to hasten differential diagnosis. Sixty-six patients were included, 33 ATC and 33 PLT, diagnosed between January 2000 and February 2016. Biological status (blood count, TSH, antithyroid peroxidase antibodies, CRP, β2 microglobulin and LDH) and imaging evaluation (Ultrasound (US) and computed tomography (CT) scanning) were compared. ATC patients were all from Lille University Hospital. PLT being less common, 16 patients were included from Lille and 17 from other hospitals in France. ATC was associated with higher leucocytes and neutrophils counts: over 10000/ml and 7500/ml with positive predictive values (PPV) of 77.3 and 75%, respectively. Neutrophils-to-lymphocytes ratio over 3,8 was noted in 77 and 48% of ATC and PLT patients, respectively. Thyroid tumor macrocalcifications and jugular vein thrombosis were found more frequently in ATC patients than in PLT patients with PPV for ATC of 93 and 77.8% respectively, regardless of the imaging technique (US or CT scan). PLT was associated with a thyroiditis history and/or high antithyroid peroxidase antibodies (PPV for PLT of 83 and 76.5% respectively). We conclude that blood count, antithyroid peroxidase antibodies measurement, search for tumor calcifications and jugular vein thrombosis provide basic and relevant information in the initial work-up of thyroid mass to distinguish between ATC from PLT.

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EP1370

The role of preoperative serum thyroglobulin values in the diagnosis of differentiated thyroid cancer

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Introduction
Thyroglobulin (TG) is the most important protein produced by the thyroid. TG is considered a reliable marker of recurrent disease in patient with differentiated thyroid carcinoma (DTC). Before surgery, high serum TG values may be due to an abnormally large thyroid, excessive thyroid stimulation, or physical damage to thyroid etc.
Methods
We evaluated in the retrospective study 20 patients (mean age 49.6$\pm$12 S.D., range from 25–73 years old), with a histological diagnosis of DTC. Clinical diagnosis before surgery was: 20% (4) solitary nodule; 10% (2) hyperthyroidism; 5% (1) thyroid cancer with lytic bone metastasis; 65%(13) non toxic multinodular goiter.
Results
Histological diagnosis: 85% (17) papillary thyroid cancer, and 15% (3) cases with follicular thyroid carcinoma. 25% (5) cases with micro DTC and 75% (15) of cases with DTC more than 1 cm. We excluded from study one case with large lytic bone metastasis because the serum TG value was very high 11096 ng/ml. Mean TSH values were 1.4$\pm$0.9 IU/ml and mean TG values was 88.1$\pm$67 ng/ml (range 16.7–255 ng/ml). In 20% (4) of cases with DTC less than 1 cm TG values it were in the normal range. In 14 patients with DTC bigger than 1 cm: 42% (6) of cases had TG values more than 2 fold of normal range, 28% (4) of cases had TG values in the normal range and 28% (4) of cases had TG values between normal and two fold normal range.
Conclusions
In our study TG are more sensitive to detect DTC macro carcinoma, but we need to evaluate more cases, to compare TG values in cases with negative biopsy and to evaluate even the TG antibodies.

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EP1371

Is there an impact of the concurrent presence of chronic autoimmune thyroiditis in differentiated thyroid cancer patients?

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Background
The association between differentiated thyroid carcinoma (DTC) and autoimmune thyroiditis (AT) has been reported in numerous studies, yet the impact of the concurrent presence of AT and DTC remains controversial.
Methods
We retrospectively analysed the files of 493 patients submitted to thyroidectomy in our surgery department between January 2012 and September 2015.
Results
A total of 86 patients with DTC were enrolled, mean age 53.99 ± 13.91 years, 83.7% females. 25 (29%) patients, all women, associated biochemical and/or histopathological AT. We found no significant differences between patients with DTC and AT compared to patients without AT regarding the ultrasound characteristics of the thyroid nodules: nodule diameter ($P=0.330$), echogenicity ($P=0.572$), halo presence ($P=0.528$), microcalcifications ($P=0.347$), vascularization ($P=0.199$) and lymph nodes involvement ($P=0.418$), nor the histopathological characteristics of the DTC: tumor subtype ($P=0.100$), tumor diameter ($P=0.726$), the presence of multifocality ($P=0.829$), TNM staging ($P=0.672$), vascular invasion ($P=0.149$), capsular invasion ($P=0.617$), extracapsular extension ($P=0.713$) or the presence of local lymph nodes metastasis ($P=0.888$).
Conclusions
Although our data showed a high prevalence of AT in patients with DTC, we found no significant differences regarding the ultrasound and histopathological characteristics of DTC in patients that concurrently had AT compared to patients without AT.

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EP1372

20,000 euros for diagnosis of one thyroid cancer case: It is not too much?

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Introduction
Thyroid cancer is a major public health problem, and fine-needle biopsy is an established method of its early detection. However, there are still some controversy about the indication for BACC depending on the clinical data and the results of diagnostic imaging. An important role is also played by economic criteria, including socially acceptable, so-called equitable cost of obtaining additional year of life, which in our country is determined to three times the average national income per capita.
Results
We analyzed the results of fine needle biopsy of thyroid nodules taken in the years 2008–2016 in ambulatory patients. In most cases, these people were targeted due to changes in the ultrasound detected by examination performed for other indications, the so-called incidentalomas. The most common indication was evaluating the patency of the carotid arteries. We have performed total of 5347 biopsy of thyroid focal lesions which led to the diagnosis of eight cases of thyroid cancer. Average cost detection of a single cancer case amounted to approximately 20 000 Euro.
Conclusion
This cost does not exceed three times the annual GDP per capita, but is high. Therefore, it seems reasonable to discuss the criteria for performing the BACC in case of incidental thyroid focal changes, particularly in regions with a lower incidence of thyroid cancer.

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EP1373

Unilateral Graves' disease with papillary carcinoma of the hyperfunctioning lobe

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Background
Graves' disease (GD) typically manifests as an autoimmune hyperfunction of both thyroid lobes. Less than 10 cases of unilateral GD have been described, and the pathophysiology of unilateral GD remains unknown. Co-existence of malignancy has never been reported. We report a case of GD of the left lobe with simultaneous discovery of a papillary carcinoma within the hyperfunctioning lobe.
Case description
A 49-year-old patient of Middle-Eastern origin was referred to our clinic in November 2016, one year after the diagnosis of symptomatic thyreotoxicosis, treated by carbimazole for the first 6 months. Subclinical hyperthyroidism recurred after treatment withdrawal. Thyroid isotope scanning with ^{99}Tc in September 2016 showed diffusely increased uptake of the left lobe (with the exception of a low uptake zone) and minimal uptake of the right lobe. In November 2016, the patient was asymptomatic and had subclinical hyperthyroidism. Thyroid gland ultrasonography (US) showed a slightly enlarged and heterogeneous left lobe with clearly increased vascularity. The right lobe was smaller, homogeneous, with normal vascularity confined to its periphery. Based on the imaging results and positive thyrotropin receptor antibodies, unilateral GD was diagnosed. The low uptake zone in the left lobe corresponded to a hypoechoic nodule with suspicious US features (central calcification, possible infiltration of the thyroid capsule). Fine-needle biopsy of this lesion revealed papillary carcinoma (Bethesda class VI). Total thyroidectomy will soon be performed.
Conclusion and perspectives
GD can rarely present with an asymmetric involvement of the thyroid lobes. Our patient is the first case associating unilateral GD and thyroid malignancy in the ipsilateral lobe. Given that total thyroidectomy is indicated, complete histological, biochemical and genetic evaluation of both lobes will allow us to test current hypotheses on the pathophysiology of unilateral GD.

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EP1374

Trends in the clinicopathological features and clinical outcomes of medullary thyroid carcinoma – an Israeli multicenter study

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Background
The massive use of neck sonography has led to a dramatic increase in the incidence of thyroid cancer detection, predominantly small papillary carcinomas. However, changes in the presentation and course of medullary thyroid carcinoma (MTC) over time remain unclear.
Objective
To evaluate trends in the presentation and outcomes of MTC.
Methods
Patients treated for MTC at four medical centers in Israel were divided into two groups by year of diagnosis, 1963–2005 (period A) and 2006–2016 (period B), and compared for clinicopathological variables.

Results
The cohort included 189 patients (55% female) of mean age 48.9±18.6 years followed for 10.1±9.4 years. Of these, 104 patients (55%) were diagnosed in period A, and 85 (45%) in period B. No significant between-group differences were found in primary tumor size at diagnosis (26.2±18.5 and 23.7±17.6 mm, respectively), proportion of micro-MTCs (<1 cm) (18/74, 24.3% and 19/75, 25.3%, respectively), or TNM staging. Period A was characterized by a higher rate of familial MTC (28/98, 28.6% vs 6/73, 8.2%; $P=0.001$) and lower age at diagnosis (45.2±18.6 years vs 53.7±17.7 years; $P=0.002$). Cervical lymph node dissection was more commonly performed in period B (58/81, 71.6% vs 68/80, 85%; $P=0.05$), but no concomitant increase in the rate of metastatic lymph node excision (46/64, 71.9% and 45/70, 64.3% respectively, $P=0.36$). There was no significant difference between groups A and B in disease-free-survival (DFS) at one year after diagnosis (34/87, 39.1% and 35/70, 50%, respectively $P=0.2$) or at last follow-up, comparing patients with similar surveillance periods (11/28, 39.3% and 36/75, 48%, $P=0.5$).
Conclusions
Unlike differentiated thyroid cancer, most presenting features of MTC have not changed in recent years. The most significant temporal change is a decreased rate of familial MTC. Despite the use of more extensive surgical procedures and new treatment modalities, there has not been significant improvement in disease-related outcomes.

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EP1375

Association of preoperative neutrophil lymphocyte ratio and platelet lymphocyte ratio with clinical features of differentiated thyroid cancer

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Introduction
Platelets and neutrophils take part in proliferation of cancer cells, angiogenesis, and metastasis. Studies on various cancer types showed relation between prognosis and absolute numbers of neutrophils, lymphocytes, and the ratio in-between (NLR) and platelet/lymphocyte ratio (PLR). We aimed to evaluate NLR and PLR and their relation with features of differentiated thyroid carcinoma (DTC).
Materials and methods
Electronic data of 330 patient with pathologic diagnosis of thyroid carcinoma were evaluated retrospectively. Two hundred and fifty five patients with other chronic diseases and medullary thyroid carcinoma and whose pathology reports and preoperative CBC data were unavailable were excluded. Clinical and laboratory features of 75 patients (63 female, 12 male) were analysed.
Results
The most common subtype was conventional type papillary thyroid cancer ($n=46$). Mean age was 46±12 years. 50 tumours were unifocal, 25 multifocal. Forty-two patients had tumour less than 1 cm in size, 33 had 1 cm or larger. Forty patients underwent radioactive iodine therapy or remnant ablation (RAI dose: 92±32 mCi). Preoperative and postoperative NLR and PLR were not different according to age (younger than or older than 45 years, focality (uni/multi focal), RAI history (absence/presence), tumour size (less than 1 cm or larger), invasion ($n=11$). When 2.5 was chosen as cut-off value for NLR, preoperative and postoperative PLR was significantly ($P=0.0001$ and $P=0.046$) different; age at diagnosis was also significantly different ($P=0.002$). There was a positive relation between preoperative and postoperative PLR ($r=0.575$, $P=0.0001$) and NLR values ($r=0.431$, $P=0.004$). NLR was also positively correlated with PLR both in pre- and postoperative period. Postoperative thyroglobulin data were available in 55 patients. It was negatively correlated with preoperative NLR ($r=-0.354$, $P=0.008$). Age was positively correlated with NLR ($r=0.245$, $P=0.345$). Tumour size was negatively correlated with postoperative PLR ($r=-0.102$, $P=0.048$).
Conclusion
Preoperative NLR and PLR does not predict clinical features of DTC. Association between pre- and postoperative PLR and NLR may be due to a continuum instead of causal relation. Unlike high NLR associated poor prognosis in other cancer types, higher NLR was observed in cases with lower thyroglobulin levels. CBC has no effect on thyroid cancer with indolent nature.

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EP1376

Differentiated thyroid cancer in patients taking lithium for bipolar affective disorder: a case series

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Aim
Lithium bicarbonate is a drug used in the initial treatment of bipolar disorders. Lithium is an element of alcali metal group and besides being a causative agent for goiter and hypothyroidism primarily, it has also some antithyroid effects. Rarely, lithium may cause hyperthyroidism secondary to thyroiditis or probably autoimmune mechanisms. The association between lithium and thyroid cancer is very little known subject. In this case series, we presented differentiated thyroid cancer in five patients using lithium for the treatment of bipolar affective disorder
Cases
Three of patients were female and two were male. Three patients had hypothyroidism and were using levothyroxine and two patients were euthyroid. There was a solitary thyroid nodule in two, while multiple nodules were present in others. Preoperatively, thyroid fine needle aspiration biopsy was performed in all patients and cytological results were suspicious for malignancy in three, atypical cells in one and atypia of undetermined significance in one subject. Histopathologically, one patient had minimal invasive follicular carcinoma, two had papillary thyroid carcinoma, and two had concomitant papillary thyroid carcinoma and papillary thyroid microcarcinoma. All patients were given radioactive iodine ablation treatment postoperatively.
Conclusion
Thyroid dysfunctions can be observed in patients using lithium due to various mechanisms. Among these, thyroid cancers are the least known and patients with nodular goiter on lithium therapy should be evaluated carefully for the risk of development of thyroid cancer.

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Predictive value of CHAID Algorithm in the diagnosis of malignancy in thyroid nodules with Bethesda III (AUS/FLUS) cytology

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Introduction
'Artificial intelligence' is an information-processing technology developed and inspired by the information processing technique of human brain. Artificial intelligence applications are used with an increasing ratio in medicine; particularly in the fields of breast cancer, radiology, cardiology, health management and drug effects analysis. There is not any study concerning thyroid diseases and artificial intelligence applications in the literature. In this study, we aimed to use an artificial intelligence application - CHAID (Chi-Squaered Automatic Interaction Detection) algorithm- to predict malignancy risk in thyroid nodules with Bethesda III –atypia of undetermined significance/follicular lesion of undetermined significance (AUS/FLUS)- cytology.
Methods
Data of 3300 patients (6863 nodules) evaluated by our multidisciplinary council and operated between 2005–2016 were analysed retrospectively. There were 364 patients with 385 nodules with AUS/FLUS cytology in. 65 parameters including clinical, laboratory, ultrasonographical, cytological and histopathological features of each nodule were evaluated. The diagnostic value of CHAID algorithm was determined considering histopathological diagnosis as the reference method.
Results
There were 75 male (20.6%) and 289 female (79.4%) patients. Histopathological diagnosis was benign in 282 (73.2%) and malignant in 103 (26.8%) nodules. Analysis with CHAID algorithm revealed that presence of thyroiditis/chronic

thyroiditis ultrasonographically, and presence of nuclear groove and intranuclear inclusions cytologically were predictive for malignancy. This algorithm had a sensitivity of 49.5%, specifity of 96.8%, positive predictive value of 85%, negative predictive value of 16% and accuracy of 84.15%.
Conclusion
The main issue in thyroid nodules is to differentiate benign and malignant lesions. While doing this, clinician should try to avoid unnecessary ultrasonography examinations, fine needle aspiration biopsy and surgical approach. Superfluous interventions cause increased economical burden for both the patient and the country. Use of artificial intelligence applications in clinical practice might help to reduce unnecessary diagnostic procedures and surgical interventions in thyroid nodules with AUS/FLUS. cytology.

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Thyroid autoimmunity and risk of incidental thyroid microcarcinoma in non-toxic nodular thyroid diseases

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Aim
Thyroid cancer comprises the most common endocrine malignancy and a variety of studies have investigated the role of thyroid autoimmunity as an independent risk factor for the manifestation of differentiated thyroid cancer in otherwise benign thyroid disorders. Objective of the current retrospective study is the assessment of any possible correlation between thyroid autoimmunity, in terms of elevated thyroid autoantibodies, and incidental thyroid microcarcinoma (ITC) in non-toxic nodular thyroid diseases, subjected to total thyroidectomy (TT).
Patients and methods
In First Surgical Department between 1 January 2005 and 01 March 2010 a total of 186 patients (146 females/40 males) underwent TT after referral for benign non-toxic nodular thyroid diseases. Surgical specimens were evaluated in University Pathology Department and the diagnosis of ITC was recorded. Elevated thyroid autoantibody titers were assessed in patients without (group A) and those with (group B) thyroid cancer. The results were also compared regarding preoperative diagnosis.
Results
32 patients (17.2%) were diagnosed with microcarcinoma (females/males: 2.2/1), while 154 patients (82.8%) were free of malignancy. 9/34 patients with solitary thyroid nodule (STN) and 33/152 subjects with multinodular goiter (MNG) had biochemical signs of thyroid autoimmunity. 9/32 (28.1%) cancer patients had elevated thyroid autoantibodies preoperatively. The prevalence of thyroid autoimmunity was higher (non-statistically significant) in the cancer-group compared to the non-cancer cohort (28.1% vs 21.4% respectively; $P=0.41$). Furthermore, the prevalence of thyroid microcarcinoma was also higher (non-statistically significant) in the autoimmunity subgroup compared to the non-autoimmunity subgroup (21.4% vs 16%; $P=0.41$). These differences were manifested solely in the MNG group.
Conclusions
Thyroid autoimmunity does not seem to feature an independent risk factor associated with thyroid microcarcinoma in non-toxic nodular thyroid diseases. However, a non-significant higher correlation is recognized in the subgroup of euthyroid multinodular goiter. Further studies are required to investigate the potential association between thyroid autoimmunity and carcinoma, as a helpful indication for surgical referral.

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EP1379

Effects of combination of metformin and pioglitazone on AMPK/mTOR signal pathway, p53 and apoptosis in human anaplastic thyroid cancer cells

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Thyroid cancer is the most common malignant tumor of the human endocrine system. Recently, its incidence has increased significantly. Anaplastic cancer constitutes 2–4% of thyroid cancers and remains aggressive. The life expectancy is 2–6 months. It is often beyond the surgical margin. External radiation therapy or chemotherapy are the treatment options. Therefore, new therapeutic approaches are needed. Peroxisome proliferator-activated receptor (PPAR) gamma is a DNA-binding nuclear hormone receptor and regulates transcription effects in cell energy metabolism. PPAR gamma agonists may inhibit tumor growth through terminal cell differentiation induction, cell cycle arrest, apoptosis induction and angiogenesis inhibition. PPAR gamma agonists show significant antitumor activities against various cancers both *in vitro* and in vivo. Metformin (1,1-Dimethylbiguanide) is the most widely used drug in treatment of type 2 diabetes patients. Preclinical data show its anticancer effects. The molecular mechanisms of metformin in cancer cells is still unknown. In our study, we plan to evaluate effects of combination of metformin and pioglitazone on AMPK/mTOR signal pathway, p53 and apoptosis in human anaplastic thyroid cancer cells. In C643 and SW1736 cell lines, IC50 doses of metformin and pioglitazone were found as 17.69 and 11.64 mM, and 27.12 and 23.17 μM respectively. The combination of metformin and pioglitazone was determined as additive with isobologram analyses. Both of the compounds induce apoptosis separate or in combination. Consequently, we have evaluated the down regulation of the expression levels of oncogenic AKT3, CHUK, CDC42, EIF4E, HIF1A, IKBKB, ILK, PIK3CA, PIK3CG, PLD1, PRKCA, RICTOR genes in MET and PIO combination treated cells. Moreover, expression levels of tumor suppressor DDIT4, DDIT4L, EIF4EBP1, EIF4EBP2, FKBP1A, FKBP8, GSK3B, MTOR, MYO1C, PTEN, ULK1, ULK2 genes were found to increase functionality. The results show that these agents can be used in the treatment of thyroid cancer as novel therapeutic agents.

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EP1380

Vitamin D status and MPV changes in differentiated thyroid cancer

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Thyroid cancer is the most common cancer in the endocrine system. Thyroid follicular epithelial-derived cancers are papillary, follicular, and anaplastic cancer. Risk factors for differentiated cancers are radiation exposure, and family history. Possible risk factors like occupational and environmental exposures, increased parity, late age at first pregnancy, and hepatitis C-related chronic hepatitis are potential but not proven risk factors. In order to evaluate other potential risk factors have we investigated the vitamin D status and MPV (mean platelet volume) in thyroid cancer patients and in other benign thyroid disorders. 25-OH vitamin D3 levels were low and MPV

Table 1 MPV values and 25-OH vitamin D3 levels in benign and malign thyroid disorders

	Thyroid cancer ($n=47$)	Hashimoto thyroiditis ($n=30$)	Graves disease ($n=30$)	Healthy controls ($n=30$)	P
Age (years)	45.96 (21–84)	41.43 (17−59)	42.37 (18–75)	45,37 (19−69)	–
Gender (male/female)	4/43	4/26	14/16	6/24	–
WBC ($\times 10^9$/l)	7.42±2.19	7.34±1.42	7.92±1.91	7.39±2.16	0.174
Hb (g/dl)	13.11 (9.3–16.8)	13.47 (11.1−15.3)	13.98 (10.9–17)	13.55 (8.50−16.80)	0.035*
Platelets ($\times 10^9$/l)	279.14±81.98	293.43±66.27	272.8±67.90	266.57±61.10	0.145
MPV (femtoliters,fl)	8.22 (6–10.7)	8.41 (6.9−10.6)	8.38 (6.5–11.2)	8.56 (6.40−10.90)	0.001*
25-OH Vitamin D3	13.82±8.01	19.94±11.68	20.05±12.63	18.94±11.70	0.006

values have been found to be low. Low vitamin D may be a risk factor for thyroid cancer. Decreased MPV values may be used as a predictor of thyroid cancer.

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EP1381

BRAFV600E status and Stimulated Thyroglobulin at ablation time increase prognostic value of American Thyroid Association (ATA) classification systems for persistent disease in Differentiated Thyroid Carcinoma (DTC)

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Background
Stimulated Thyroglobulin levels measured at the time of remnant ablation (Htg-A) and BRAFV600E mutation were shown to have prognostic value in predicting persistent disease in DTC. The aim of this study was to evaluate the prognostic role of Htg-A combined with BRAFV600E status in association with revised American Thyroid Association (ATA) risk stratification.
Patients and methods
620 patients treated for a DTC were included in this study with median follow-up duration of 6.1 year. All patients were submitted to a total thyroidectomy, followed by radioiodine ablation. Patients with positive antibodies anti-Tg were excluded. The predictive value of Htg-A was calculated by receiver operating characteristic curve analysis. Cox proportional hazard regression modeling, including BRAF status, Htg-A and ATA classification system, was assessed to evaluate existing persistent disease risk.
Results
BRAF status and Htg-A levels together improve ATA risk classification in all categories. In particular in Low risk ATA only BRAFV600E + Htg-A > 8.9 ng/ml was associated with persistent disease ($P = 0.001$ HR 60.2 CI 95% 5.28–687. In Intermediate ATA risk BRAFwt + Htg-A > 8.9 ng/ml was associated with persistent disease ($P = 0.029$ HR 2.71 CI 95% 1.106–6.670) and BRAFV600E + Htg > 8.9 ng/ml was associated with persistent disease ($P = 0.000$ HR 5.001 CI 95% 2.318–10.790). In High risk ATA BRAFV600E + Htg-A < 8.9 ng/ml was associated with persistent disease ($P = 0.042$ HR 5.963 CI 95% 1.069–33.255) and BRAFV600E + Htg-A > 8.9 ng/ml was associated with persistent disease ($P = 0.002$ HR 11.564 CI 95% 2.543–52.576).
Conclusion
BRAF status and Stimulated Thyroglobulin levels at ablation time improve the ATA risk stratification, so also Htg-A could be included in ATA risk classification.

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EP1382

High sensitivity of BRAF detection method does not alter response to therapy of papillary thyroid cancer of known BRAF status

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Background
A dynamic risk stratification with modified initial estimated risk based on response to therapy and disease course is one of the crucial changes adopted recently by the American Thyroid Association (ATA). The analysis of *BRAF* status is not routinely recommended by ATA, although this finding may be advantageous to individualized risk-adapted approach in papillary thyroid cancer (PTC). The methods used to detect the *BRAF* V600E are known of variation in the sensitivities, variable susceptibilities for DNA degradation, and possible equivocal results with direct DNA Sanger sequencing (Seq), particularly. The aim of this study was to examine the relation between the *BRAF* status of PTC detected applying three methods and ATA response-to-therapy categories (excellent, indeterminate, biochemical/structural incomplete), and recurrence identified after no evidence of disease (NED) or persistence disease.
Methods
Unselected 723 PTC cases with known *BRAF* status diagnosed 2000–2013, actively monitored at single institution, and reviewed retrospectively up to December 31, 2015. Genotyping of *BRAF* was implemented using the algorithm: Seq, followed by more sensitive allele-specific polymerase chain reaction (PCR), and real-time PCR (quantitative PCR; qPCR). Considering various limitations of particular methods 639 specimens were available for the analysis by Seq, 638 by ASA-PCR, and 705 by qPCR.
Results
BRAF V600E was found in 51.6%, 67.7%, and 67% PTCs detected by Seq, PCR, and qPCR, respectively. The indeterminate response was significantly more frequent in *BRAF*-positive PTCs identified by SDefault ($P = 0.03$), but not by ASA-PCR ($P = 0.07$), and qPCR ($P = 0.06$). There was no significant relation between *BRAF*-positive cases and other not-excellent response-to-therapy categories, recurrences and persistent disease regardless of the method used.
Conclusions
The *BRAF* V600E mutation identified by high sensitive methods (ASA-PCR, qPCR) did not significantly alter a response-to-therapy category and out-come of PTC. However, an indeterminate response was more frequent in *BRAF*-mutated PTC detected by direct sequencing.

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EP1383

Thyroid nodules ultrasound classification and the importance of the endocrinologist clinical feeling

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Background and aim of the study
Several ultrasound (US) classifications for estimating thyroid nodules risk have been proposed. Since most of them are hardly applicable in clinical practice, we created a local tool, named Modena classification (MC), considering US characteristics and clinician subjective impression. The aim is to verify the diagnostic accuracy of MC and to compare it to US classifications of American Thyroid Association(ATA) (1) and British Thyroid Association(BTA) (2).
Methods
We prospectively enrolled 111 patients (33M, 78F; age 19–75; total 457 nodules) with an indeterminate, suspicious for malignancy or malignant cytology. All the patients underwent neck US before surgery and a score risk was assigned, according to MC: low (not certainly nodular or not suspect); intermediate (indeterminate); high (suspect or very suspect). Then, we retrospectively classified nodules according to ATA and BTA. The US pattern was related to hystology.
Results
All the classifications had low sensitivity and positive predictive value (PPV), and high specificity and negative predictive value (NPV) for low risk categories. For the intermediate risk category, BTA had the highest accuracy (68%). For higher risk categories, MC had good sensitivity (62%), high specificity (89%) and accuracy (81%); ATA had high sensitivity (83%), low specificity (48%), accuracy 58%; BTA had high sensitivity (88%), low specificity (44%), accuracy 57%.

Conclusions
A classification that considers the subjective impression of the clinician, in addition to the known US characteristics, has highest accuracy and specificity compared to guidelines classifications, particularly if the nodule has suspect US features.
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EP1384

Five-year follow-up of thyroid cold nodules with somatic oncogene mutations in Hungarian patients

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Cold nodules are one of the most common findings on scintiscans and ultrasound examinations of the thyroid gland. About 5-10% of these nodules turn out to be histologically malignant. Our aim was to examine the predictive value of somatogenetic alterations associated with thyroid cancer in FNA samples of thyroid cold nodules being citologically benign at the beginning of the study. These alterations included single nucleotide mutations (BRAF, HRAS, NRAS, KRAS) and genetic translocations (RET/PTC1, RET/PTC3, PAX8ex7/PPARgamma, PAX8ex9/PPARgamma). The SNPs were tested by real-time PCR with fluorescence melting curve analysis and the rearrangements were detected by Taqman probe-based quantitative real-time PCR. We have analyzed 779 consecutive FNA samples and followed the patients up for 5 years. We identified 39 BRAF, 23 NRAS, 9 HRAS, 1 KRAS mutations and 1 RET/PTC3 rearrangement. No PAX8/PPARgamma rearrangements were demonstrated in the nodules. During the five-year follow-up, 57 cases (7.3%) were classified as malignant by histology, from which we indentified genetic alterations in 27 (47.4%). The statistical performance of our genetic panel showed a specificity of 93.6%, sensitivity of 47.4%, a negative predictive value of 95.8% and a positive predictive value of 37.0%. In summary, our test approach may be used for the prediction of malignant transformation of thyroid cold nodules, however, its sensitivity requires improvement.

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Usefulness of preoperative ultrasonography and computed tomography for evaluation of recurrent laryngeal nerve invasion by Papillary Thyroid microcarcinoma

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Background
Papillary thyroid microcarcinoma (PTMC) has low malignant potential and an extremely good prognosis. However, surgical findings of asymptomatic PTC, can occasionally reveal tumor invasion into the recurrent laryngeal nerve (RLN). The present study assessed the feasibility of evaluating tumor invasion into the RLN using ultrasonography (US) and computed tomography(CT).
Materials and methods
Of 7,916 patients with a PTC who underwent surgery at our hospital, 35 with preoperative tumors that were $\leq$10 mm, without distal metastasis or lymph node metastasis, and with surgical findings of RLN invasion were included. The location of the tumor and the degree of contact with the thyroid capsule (DCTC) were examined by US and CT.
Results
Ten of the 35 patients were treated by combined resection of the RLN, and 25 patients were treated by shaving the RLN. US revealed that the tumor was located at the dorsal side of the thyroid in 31 patients (88.5%). In all patients who were treated by combined resection of the RLN, the tumor was located at the dorsal side of the thyroid. Among these patients, the DCTC determined by US was $\geq$25% in nine patients and $<$25% in one. Among those who were treated by RLN shaving, the DCTC was $\geq$25 and $<$25% in nine and 16 patients, respectively ($P=0.003$). The DCTC was $\geq$25% in all patients who were treated combined resection and in 15 of the 25 patients who treated by RLN shaving ($\geq=0.018$) according to CT imaging. The tumor was located 1–1.5 cm from the cricoid cartilage in most patients who were treated by combined resection.
Conclusions
When a PTC is located at the dorsal side of the thyroid with $\geq$25% DCTC, surgery should be selected for RLN invasion. Our results showed that the accuracy of predicting recurrent laryngeal nerve invasion can be improved by combining US with neck CT.

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EP1386

Solitary metastasis of papillary thyroid cancer in the sellar region and cavernous sinus

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The commonest site of metastasis from papillary carcinoma is regional lymph nodes. Distant metastases are rare, most presenting synchronously. Brain metastases in papillary carcinoma are rare, reported with a frequency of 0.1–5% and cavernous sinus metastasis is extremely rare.
Case report
A 62-year-old woman presented with a history of non-secretory pituitary macroadenoma present with symptoms of hypopituitarism. MRI of the brain revealed a $4.5\times3.1\times3$ cm, extension into the cavernous sinuse. The tumorwas not rescable, she Underwent a simple biopsy in view of the haemorrhagic nature of the tumor. Histopathology revealed a tumor with diffuse papillary architecture. On immunohistochemistry: positive for TTF1, PAX8, thyroglobulin, TPO;Ki67 (10–15%) and negative for GH, LH, FSH, ACTH, TSH. A diagnosis of metastatic papillary carcinoma was made. Thyroid ultrasound revealed two hypoechoic nodules. After thyroidectomy the histopathology was papillary micro- carcinoma thyroid-follicular variant of 05 mm. She received radioiodine therapy.
Discussion
The incidence of distant metastases from papillary carcinomas is reported to be 6–23%, the majority occurring within 5 years of the initial diagnosis. There have been case reports of papillary carcinoma with metastasis at unusual sites like the breast and cavernous sinus. All these cases were associated with a missed diagnosis of thyroid carcinoma, like our case, should be considered exceptional. There have been five reports of papillary carcinoma with metastasis to the skull base.
Conclusion
There is no consensus for the treatment of papillary thyroid carcinoma with cavernous sinus metastasis. Thus, that solitary distant metastasis from thyroidcarcinoma though rare, is a possibility, a difficult diagnosis to be made on radiology.

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EP1387

Calcitonin: clinical and laboratory evaluation in a tertiary hospital

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Background
Calcitonin is a hormone secreted by thyroid C cells, and is considered an excellent marker for medullary thyroid carcinoma (MTC). However, the use of calcitonin to screen patients with nodular thyroid disease (NTD) remains controversial.
Objective
Defining the frequency of hypercalcitoninemia among NTD patients followed at a tertiary referral hospital.
Methods
Retrospective analysis of basal calcitonin measurements and corresponding patients' records between January 2011-December 2015. The method used was immunochemiluminescent assay. Hypercalcitoninemia was defined as $>$ 10 pg/ml.
Results
In five years, there was a total of 6551 calcitonin measurements requested, by different physicians from different services, to 5149 patients: median age 57 years, 80.6% female. Calcitonin measurements were divided into 3 groups according to their levels: GI $\leq$10 pg/ml; GII 10–100 pg/ml; GIII $\geq$100 pg/ml. Excluding patients with no clinical information, there were 3097, with the following distribution: GI 2913, GII 158, GIII 26. Among these, calcitonin was requested in NTD context to 1504 patients: 69 patients had hypercalcitoninemia (GII and GIII). Of these, 21 underwent surgery (GI 12, GIII 9); a histological diagnosis of MTC was established in 12 (GII 3/25%, GIII 9/100%). Surgery was decided based, solely, on calcitonin levels in 7 cases, since only 5 had a positive cytology.
Conclusions
NTD was the reason for calcitonin measurement in less than 50% of total measurements. Hypercalcitoninemia was found in 4.6% of NTD patients. Calcitonin levels $\geq$100 were associated to a greater CMT risk, comparative to values between 10 and 100 and reinforcing results from other groups. A cost-effective approach includes avoid unnecessary requests, adequate interpretation of results as well as appropriate selection of patients to surgery.

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EP1388

Neuroendocrine progression of medullary thyroid cancer – case report

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Thyroid cancers represent approximately 1% of new cancer diagnoses. Thyroid malignancies are divided into papillary carcinomas (80%), follicular carcinomas (10%), medullary carcinomas (5–10%), anaplastic carcinomas (1–2%) other rare tumours (primary thyroid lymphomas, primary thyroid sarcomas). The main therapeutic options are surgery (mainly total thyreoidectomy), radioiodine treatment (depending on the type and stage of the tumour), levothyroxine therapy (thyroidea stimulating hormon – TSH suppression dose), others (external beam irradiation, chemotherapy, thyrosine kinase receptor inhibitors). Thyroid aspiration cytology was performed due to a rapidly growing neck mass of a 41 years old male patient, revealed a suspicion of neuroendocrine tumor. After the total removal of the thyroid gland and paratrecheal and upper mediastinal lymph node dissection histology showed medullary thyroid cancer and metastases in the lymph nodes. Somatostatin receptor scintigraphy (SRS) was negative. PET-CT showed suspicion of mediastinal metastases, at this time external beam radiotherapy was performed. During the follow up calcitonin and chromogranin A levels decreased presenting a stable disease, imaging investigations showed small remnant of the tumour without any progression or metastases. After three years of the operation the patient had weight loss and diarrhea, CT scan showed cervical and mediastinal lymph node enlargement, hepatic and pancreas metastases, bone scintigraphy showed multiple bone metastases. SRS was positive in these areas, somatostatin analogue (SSA) treatment was started. Histological verification of the metastases are in progress. In our case a medullary thyroid cancer after three years of stable diasease showed a neuroendocrine progression with multiple metastases. SSA treatment was started and we plan to perform peptid receptor radionuclide therapy (PRRT).

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EP1389

Cytohistologic correlation of thyroid nodules

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Background
The discovery of a thyroid nodule exposes the problem of the possibility of thyroid cancer. The difficulty of management of this situation is the fact that only the histopathological examination can confirm or refute the malignancy. Fine-needle aspiration (FNA) is used as a diagnostic tool to assess thyroid nodules. The purpose of our study is to correlate the clinical, ultasonographic, the FNA results and final pathology to determine the predictors of malignancy of thyroid nodules.
Patients and Methods
We conducted a retrospective study on 33 patients with thyroid nodule. Data were obtained for FNA diagnosis, demographics, findings on ultrasound, and histologic findings.
Results
The average age of our patients was 41.7years$\pm$15.6 SD with a female predominance (100%). Ultrasound findings were as follows: singles nodules, multinodular goiter (MNG), and multiple nodules in respectively 48.5, 39.4 and 12,1% of cases. Thyroid function tests prior to surgery were normal in all patients. Among the 33 patients, 7 (21.2%)have malignant tumors in histological findings: Two patients had signs of locoregional compression. A case of fixed nodule was noted and one patient had cervical lymphadenopathy. On ultrasonogrqphy: the average size of the nodules was 34.0$\pm$14.5 mm, three nodules were hypoechogenic, and 1 case of mixed vascularity was diagnosed. The FNA was benign in 90.9% of cases (n=30), and indeterminate in 9.1% (n=3). Of the 30 patients with a benign FNA result, 7 were found to have carcinoma on final pathology for 23.3% false negative rate and sensitivity of 76.7%. 1 patient were found to have incidental microcarcinoma which was located in the palpated lesion.
Conclusion
FNA biopsy is essential in the assessment and management of thyroid nodules. However, we report a high rate of malignancy among FNA diagnosed as benign lesions. This high rate of malignancy is the basis for our recommendation for a surgical approach for benign lesions.

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EP1390

Importance of central compartment neck metastasis in the differentiated thyroid microcarcinomas

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Elective central compartment neck dissection in the treatment of differentiated thyroid carcinomas (CDT) remains controversial. In a series of 1500 patients undergoing thyroid surgery, the authors evaluated the prognosis related to central compartment neck metastasis in differentiated microcarcinomas.

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EP1391

The impact of age and gender on the presentation and prognosis of medullary thyroid cancer – an Israeli multicenter study

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Background
Data regarding the effect of gender and age on medullary thyroid cancer (MTC) presentation and prognosis is limited. Although older age and male sex were found to correlate with poorer prognosis in some studies, this correlation may reflect differences in MTC presentation between sex and age groups, or a mixture of hereditary and sporadic MTC forms.
Objective
To evaluate the impact of age and sex on the presentation and outcomes of MTC.
Methods
Epidemiological and clinical data of MTC patients was extracted from a joint registry of four medical centers in Israel.
Results
The study included 193 MTC patients (106 females, age 48.9 ± 18.6, median 51), who were followed for 10.1 ± 9.4 years. Female gender was associated with smaller tumor diameter (22.3 vs 28.7 mm, $P=0.032$), lower rate of lymph nodes involvement (42/70, 60% vs 49/64, 76.6%, $P=0.044$) and lower rate of distant metastases (11/87, 12.6% vs 23/75, 30.7%, $P=0.007$). Although females achieved higher cure rates (47/97, 48.5% vs 20/72, 27.8%, $P=0.007$), disease related mortality and all cause mortality did not differ between the genders. Patients aged <45 year at diagnosis had higher rates of hereditary familial forms of MTC (32/74, 43.2% vs 3/114, 2.6% .4%, $P<0.0001$). Analysis of the sporadic MTC cases ($n=137$) revealed that younger age at presentation was associated with higher number of metastatic lymph nodes (19.7 ± 23.5 vs 10.2 ± 9.3, $P=0.05$) and more therapeutic interventions during the follow-up (62.9% vs 33.7%, $P=0.04$). However, cure rate and disease related mortality were similar between the age groups.
Conclusions
In concert with previous literature, female MTC patients present with milder disease and achieve higher cure rates than males. However, younger age in the sporadic MTC form is associated with more advanced disease at presentation. Neither age nor gender affected disease related mortality.

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EP1392

Is post-treatment whole body scan useful in differentiated thyroid cancer after thyroid ablation?

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Background
The short-term follow-up of patients with differentiated thyroid cancer (DTC) after the initial treatment is based on the measurement of stimulated thyroglobulin (s-Tg) and the use of diagnostic whole body scan (WBS).
Objective
To evaluate the clinical utility of WBS performed at 6–12 months after thyroidectomy. Examine the correlation between s-Tg and results of WBS.
Methods
We retrospectively evaluated all patients who were diagnosed with DTC ($n=213$) at a tertiary hospital center in Cordoba (Spain), between January 2000 and December 2013. The patients who had positive anti-thyroglobulin antibodies microcarcinomas (Tumors < 1 cm) were excluded from the study. Patients were classified according to the new ATA- guideline.
Results
169 patients were included. Mean age: 40.05 ± 6.20 years; ♀: 76.3%; Papillary subtype: 89.3%.The great majority were classified as Stage I-II (81.1%). At the end of the follow-up, 72.2% had achieved a complete remission. 6 to 12 months after thyroid ablation, s-Tg was negative in 111 patients and WBS control showed negative uptake in 98 of these patients. In 13 patients (13/111), uptake remained in the thyroid bed but no evidence of disease was found. In 4/111 subjects, persistence of disease was detected by ultrasound scan, all of them with negative WBS. Of 58 patients with detectable s-Tg (>0.3 ng/ml), only 22 showed pathological uptake in the thyroid bed ($n=16$) or in the distance ($n=6$). In 36 patients with evidence of disease (62.1%) uptake was not observed. In 43 of these 58 patients disease-free status has not been reached. This facts reflect a low correlation between s-Tg level and results of the WBS (I.Kappa = 0.226; $P=0.001$). The diagnostic accuracy of WBS was founded to be low ((Sensitivity = 0.36; 95% CI: 0.22–0.49) (Specificity = 0.85; 95% CI: 0.79–0.91)).
Conclusions
WBS performed at 6–12 months after initial treatment is out of clinical utility, especially in the presence of a s-Tg <0.3 ng/ml. WBS does not correlate with results of s-Tg determination and its accuracy has turned out to be low.

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EP1393

Evolution in the management of thyroid cancer: an observational study in two Belgian referral centres

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Background
Thyroid cancer incidence is increasing, especially the cancers ≤1 cm (T1a). Previous evidence suggests underuse of FNA. Several international guidelines for the management of thyroid cancer have been published. Especially the year 2006 was a hallmark, with the publication of both the ETA consensus and ATA guidelines.
Aim
Compare thyroid cancer subtypes and management before and after 2006.
Methodology
Retrospective observational study of non-medullary thyroid cancer patients diagnosed after total thyroidectomy in two Belgian referral centres (University Hospital Leuven, General Hospital StJan Bruges), comparing pre/per/postoperative parameters of patient cohort1 (diagnosis 2004–2005, $n=69$) and cohort2 (diagnosis 2011, $n=60$).
Results
The histology and tumor dimensions were comparable, with papillary thyroid cancer (PTC) as main histologic subtype (86% of cohort1, 82% of cohort2) and T1a as most frequent dimension subtype (respectively 30 and 38%). In cohort2 a comparable low proportion first presented following incidental finding at imaging (21 vs 17% in cohort 1). Pre-surgical FNA was performed in 91% in cohort1 and 86% in cohort2. The indications for thyroidectomy were comparable, with Bethesda 5-6 as most frequent indication (44% in cohort1 and 53% in cohort2). The execution of a simultaneous lymph node dissection in the PTC subgroup was not different, neither the frequency of postoperative hypoparathyroidism and recurrent nerve paresis after 1 year. However, radioiodine ablation was less frequently given in cohort2 (58 vs 76% in cohort1, $P=0.03$) and neck ultrasonography at 1 year was performed in a higher proportion of >T1a patients (73 vs 49% in cohort1, $P=0.02$).
Conclusion
In two Belgian referral centres the use of FNA is high and established, and the proportion of T1a cancers is stable and low compared to the national data. A clear change in the postoperative management of thyroid cancer patients is observed towards more restrictive use of radioiodine ablation and increased use of neck ultrasound.

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EP1394

Retrospective analysis of unusual thyroid tumours with clear cell features: morphology and differential diagnosis

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Background
In accordance with the WHO Classification of tumours of endocrine organs (Lyon, 2004) clear cell thyroid lesions have not been separated in one category as they are occurred quite rare, characterized by various cellular origin, heterogeneous morphological type, and malignant potential. Difficulties of morphological diagnosis of clear cell thyroid lesions are also obvious.
Aim
Retrospective morphological study of clear cell thyroid tumours has been performed by pathologists of two research centres (MRRC and ERC) for the period of 10 years (2007–2016) to analyse difficulties of diagnosis related with different histotype, and tumour grade.
Materials and Methods
Histological sections of paraffin blocks from 14 cases of clear cell tumours in 5 male and 9 female aged from 15 to 78 years have been stained with H&E, and immunohistochemistry (IHC) for Thyroglobulin (Tg), Thyroid Transcription Factor 1 (TTF1), Calcitonin (Cal), Chromogranin A (Chr A), Parathyroid Hormone (PTH), CD10, and Ki-67.
Results
Retrospective review of H&E and IHC stained sections allows to make diagnosis of 3 benign follicular thyroid adenomas (FTA), 2 follicular thyroid carcinomas (FTC), 3 papillary thyroid carcinomas (PTC), 1 medullary thyroid carcinoma (MTC), 2 poorly differentiated thyroid carcinomas (PDTC) with clear cell features, 2 intrathyroid parathyroid carcinomas (ITPTC), and 1 renal cell metastasis into thyroid (RCC metastasis). Tumour cells of FTA (2 pure clear cell and 1 signet ring cell), FTC, PTC, and PDTC are Tg-, and TTF1-positive, in comparison with negative Cal-, Chr A-, PTH-, CD10-staining. Ki-67 is expressed by nucleus of more than 30% PDTC tumour cells in comparison with low expression rate (less than 1%) of highly differentiated tumours. Tumour cells of MTC are Tg-, PTH-, and CD10-negative, but positive for TTF1-, Cal-, and Chr A-staining. Cells of ITPTC are Tg-, TTF1-, Cal-, CD10-negative, but Chr A-, and PTH-positive. Cells of RCC metastasis are positive for CD10, but negative for Tg-, TTF1-, Cal-, Chr A-, and PTH.
Conclusions
Clear cell thyroid tumours are rare and should be distinguished in accordance with their different cellular origin and histotype, as well as various tumour grade and prognosis.

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EP1395

Stimulated calcitonin levels as a predictor of medullary thyroid cancer

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Abstract
Medullary thyroid cancer (MTC) is a highly aggressive neuroendocrine tumour originating in the thyroid parafollicular cells. Calcitonin measurement and RET gene ascertainment have been used as markers for early diagnosis of MTC. Since pentagastrin is not available, calcium stimulation test helps to preclude 'gray zone' values of basal calcitonin, diagnose minimal residual disease and help the early diagnosis of C cell hyperplasia.
Aim
To establish a gender specific threshold for positive calcium stimulation test as well as indication for thyroidectomy and therefore prevention of MTC through early diagnosis.
Materials and methods
We conducted the calcium stimulation test on a series of patients with either nodular goiter, single nodule, RET positive or history of MTC associated with elevation of basal calcitonin values. Calcium gluconate 25 mg/kg adapted on the ideal BMI was administered over 3 min under ECG monitoring. Blood was collected before, at 2; 5 and 10 min after calcium infusion. Calcitonin was measured using LIAISON XL assay.
Results
The ongoing test has been performed on 17 patients, aged (23–67), 11 M, 6 F. Mean calcitonin values were: basal = 19.98 pg/ml (normal range: 1–11.8 pg/ml); at 2 min = 209.159 pg/ml; at 5 min = 143.619 pg/ml, at 10 min = 100.557 pg/ml; 10 subjects had a significant 2 min stimulated calcitonin (> 100 pg/ml) and were operated, 3 subjects had an intermediate response (53.31–81.7 pg/ml) and 4 patients had low stimulated values(< 54 pg/ml) therefore they are to be followed up. C cell hyperplasia (CCH) and MTC was confirmed histologically in 4 out of 10 patients (2 CCH and 2 MTC); 2 subjects had benign nodular goiter and 2 papillary thyroid microcarcinomas. More results are expected.
Conclusions
Stimulated calcitonin may be useful in the early diagnosis and follow-up of MTC and could reduce false negative rate of basal calcitonin measurement.

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EP1396

The relationship between extrathyroidal extension and BRAFV600E mutation in papillary thyroid cancer

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Aim
BRAF is one of the serine threonin kinases that activates mitogen activated protein kinase (MAPK) signal pathway.The aim of this study is to evaluatethe relationship between extrathyroidal extension (ETE) and BRAFV600E mutation in the subjects with papillary thyroid cancer.
Materials and methods
Clinical and laboratory data of 455 patients, who had been followed-up in our clinic between the years 2010 and 2015 for PTC, were evaluated. The relationship between extrathyroidal extension and BRAFV600E mutation was examined in the subjects enrolled in the study.
Results
Among 455 patients, 382 (83.9%) were female and 73 (16.1%) were males. The mean age of the participants was 49 ± 11.8 years. While 368 (80.9%) of the patients had no extrathyroidal extension, 87 (19.1%) of the patients had extrathyroidal extension. 362 (79.6%) of the patients were BRAFV600E mutation (−) and 93 (20.4%) patients were BRAFV600E mutation (+). 320 patients were negative for both BRAFV600E mutation and extrathyroidal extension. The prevalence of PTC larger than 1 cm was significantly more common among BRAFV600E mutation and ETE (+) cases (*P*:0.004). The prevalence of capsular, lymphovascular and perineural invasion, lymph node metastasis and ultrasonographically detected pathologic lymphadenopathy was significantly higher among BRAFV600E mutation (+) and ETE(+) subjects (*P*:0.004, $P < 0.05$, $P < 0.05$, *P*:0.05, *P*:0.01).
Conclusion
In this study, BRAFV600E mutation and ETE positivity were found to be poor prognostic parameters in the patients with PTC. However, the evaluation of long term follow-up data is required to more clearly understand prognostic effect and especially to determine the effect of this situation on mortality.

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EP1397

Insulin resistance and BRAFV600E mutation in the patients with differentiated thyroid carcinoma

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Aim
The incidence of nodular thyroid disease is high among patients with insulin resistance. The aim of this study is to evaluate the relationship between BRAFV600E mutation and insulin resistance in the patients with papillary thyroid cancer.
Materials and methods
We examined clinical and laboratory data of 103 patients who had been followed up by our department between the years 2010 and 2015. The diagnosis of insulin resistance (IR) was made when the homeostasis model assesment of insulin resistance (HOMA-IR) index was higher than 2.5.
Results
90 (87.4%) of 103 patients were female, while 13 (12.6%) of them were male. HOMA-IR was $\geq$ 2.5 in 58 (56.3%) patients and $<$2.5 in 45 (43.7%) patients. 19 of the patients were BRAFV600E mutation (+), while BRAFV600E mutation was (−) in 84 cases. Among 58 patients with insulin resistance, 46 (79.3%) patients were BRAFV600E mutation (−) and 12 (19.7%) patientswere BRAFV600E mutation (−). There was no statistically significant relationship between BRAFV600E mutation and HOMA-IR in terms of demographic data, clinical and histopathologic results.
Conclusion
In this study, no statistically significant relationship was detected between insulin resistance and BRAFV600E mutation among the patients with PTC.

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EP1398

Beware a rapidly enlarging Thyroid mass- a case of Thyroid Lymphoma

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Primary Thyroid Lymphoma is rare comprising less than 5% among all thyroid malignancies. It is historically associated with Hashimotos thyroiditis. It typically presents as a rapidly enlarging, painless goitre resulting in compression symptoms. Thyroid ultrasound and FNA cytology, using flow cytometry and immunohistochemistry, remain the primary modalities to confirm the presence of lymphoma. Treatment depends on the immunohistology. The prognosis is subtype depended and is generally good. A 53 years old female was seen in the Endocrine clinic with a right sided neck lump. On examination a smooth enlarged right thyroid lobe was noted. Her history suggested Hashimoto's thyroiditis but she has an enlarged right thyroid lobe. Biochemically her TSH was 11.87 with a FT4 being low/normal at 13. She had positive TPO antibodies. She was referred for a Fine needle aspiration of the right lobe demonstrated lymphoid cells consistent with lymphocytic thyroiditis and was started on Levothyroxine 50mcg as she was symptomatic and an interval scan was recommended in 3 months' time. She was seen in a 4 months' time with her scan results and her right sided thyroid swelling appeared to have increased in size. A repeat ultrasound scan confirmed an increase in size compared to previous scans with level 6 and 4 lymph nodes. A core biopsy showed features consistent with an Extranodal marginal zone lymphoma (MALT-type). A staging CT showed stage 2E with FDH avid right thyroid lobe and 4 cervical lymph nodes of 10mm. A bone marrow aspiration showed no lymhomatous infiltrate. She underwent a radical radiotherapy with 24 Gy in 12 fractions with good effect. A repeat PET CT scan showed no residual disease. This case demonstrates that a rapidly enlarging thyroid lump should be investigated urgently to facilitate early diagnosis of the underlying cause, Thyroid lymphoma being one of them.

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EP1399

Complementary thyroidectomy in papillary thyroid cancer

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Aim
ATA guideline recommends complementary thyroidectomy after thyroid lobectomy in case of tumor diameter$>$1 cm, in the presence of metastatic tumor, invasion, history of radiation therapy, familial history of thyroid cancer, multifocal or agressive variant tumor. In this study, we aimed to evaluate the relationship between the necessity of complementary thyroidectomy and post-surgery clinical, radiologic and histopathologic results in the patients who underwent complementary thyroidectomy for papillary thyroid cancer (PTC).
Method
We retrospectively evaluated the data of 110 patients who had undergone complementary thyroidectomy following lobectomy and been followed-up by our department between January 2010 and January 2017. 67 of these patients had unifocal and 43 had multifocal PTC. The relationship between demographic data, histopathologic results, BRAF mutation status and complementary thyroidectomy was evaluated.
Results
Among 110 patients, 85 (77.2%) were female and 25 (22.8%) were male. The mean age of the subjects was 47.8$\pm$12.3 years. Following complementary surgery, 70 (63.6%) of the patients were found to have benign pathology and 40 (36.4%) were found to have PTC on controlateral lobe. Parameters such as gender, age, hormonal status, presence of Hashimoto disease, tumoral variant, lymphocytic thyroiditis, tumor localisation, tumoral focality, number of tumoral foci, perineural invasion, capsular invasion, lymphovascular invasion, extra-thyroidal extension, lymph node metastasis and BRAFV600E mutation status were found to be insignificant for complementray thyroidectomy.
Conclusion
We suggest that unifocality or multifocality of single lobe tumor is not determinative for complementary surgery during initial operation. However, long-term follow-up data is required to determine the effect complementary thyroidectomy on prognosis and mortality.

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EP1400

A case report: co-occurence of medullary thyroid carcinoma and papillary thyroid carcinoma

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Introduction
Co-occurence of medullary thyroid carcinoma and papillary thyroid carcinoma in the same patient is unusual. We report a case with this rare event.
Case
A 39 year old woman was presented with cough and shortness of breath. She had no prior history of radiation exposure, cigarette or alcohol consumption and no family history of thyroid cancer. On physical examination, a 3x5 cm thyroid nodule was palpated in the middle portion of thyroid gland, which could be noticed after neck extention. Laboratory examination revealed calcitonin 348 pg/ml(n:0-10), CEA 12,39 mg/L (*n*: $<$ 3,8 mg/L), FT3: 3,6 pg/mL (*n*: 1,71-3,81), FT4: 1,41 ng/dl (n:0,7-1,48), TSH:0,53 mlU/ml (n:0,35-4,94). Thyroid ultrasonografy examination demonstrated a hypoechogen 3*3*5 cm sized nodule invading thyroid gland. I131 thyroid uptake scintigraphy was negative and autoantibodies were also found to be negative. Cytologic examination of fine needle aspiration biopsy was suspicious for follicular neoplasia. Therefore, she underwent total tyroidectomy. Pathologic examination of the specimen revealed both medullary and papillary thyroid carcinoma. 3.5 cm sized classic variant

papillary tyroid carcinoma was reactive for thyroglobulin and tumor stage was reported as pT3pNxpMx; 5*3*3 cm sized medullary thyroid carcinoma was reactive for calcitonin. Investigation for multiple endocrine neoplasia (MEN) detected RET protooncogen mutation. She underwent 100 mCi radioactive I131 treatment. Since CEA and calcitonin levels were high during follow-up period, neck ultrasonography was performed, which revealed no pathologic lymphadenopathy. PET/CT examination detected metastasis in the upper lobe of the right lung, mediastinal lymph nodes and liver. The patient was given vandatanib chemotherapy by medical oncology department. In conclusion, co-occurence of medullary and papillary thyroid carcinoma in the same gland has rarely been reported. Occurence of medullary and papillary tyroid carcinoma are independent; however, common points of pathogenic events can not be ruled out in their carcinogenesis.

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EP1401

Thyroid papillary carcinoma in the patients with resistance to thyroid hormone

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Resistance to thyroid hormone (RTH) is a genetic disease characterized by a reduced target tissue responsiveness to thyroid hormones and increased or normal TSH level despite elevated levels of thyroid hormones. This condition is mainly caused by mutations of thyroid hormone receptor beta (THRB) gene. The role of THRB mutation in carcinogenesis is still unclear. In here, we report a case of papillary thyroid carcinoma (PTC) with RTH, with a past medical history of subtotal thyroidectomy due to diffuse goiter. A 61-year-old woman was referred to our hospital with recurrence of goiter and displayed elevated serum thyroid hormones and unsuppressed TSH levels. Genetic analysis of THRB identified a missense mutation, (Exon 7, rs3752874, c.735C>T) leading to diagnosis of RTH. The neck ultrasonography showed an isoechoic $9\times11\times11$ mm sized nodule, a cystic $13\times13\times15$ mm sized nodule with microcalcification in the right lobe, a $7\times9\times9$ mm sized nodule with thin hypoechoic ring around in the right isthmus, a $9\times12\times14$ mm sized, iso-hypoechoic,uniformly restricted nodule with cystic component in the left isthmus and a $17\times25\times29$ mm sized hypoechoic nodule in the left lobe. Ultrasound-guided fine-needle aspiration biopsy was performed for microcalcific nodule in the right lobe. Cytologic examination of fine needle aspiration biopsy specimen was suspicious for follicular neoplasm. Total thyroidectomy was performed. Pathologic examination of thyroid tissue revealed capsulated oncocytic variant papillary thyroid cancer in 32 mm sized nodule in the left lobe and 7 and 2 mm sized nodules in the right lobe. The patient was scheduled for radioactive I-131 treatment. There is no consensus on the management of thyroid carcinoma in patients with RTH. The main concerns are the relationship between differentiated thyroid cancer and thyroid hormone resistance, whether it is a coincidence, how to suppress TSH levels, which treatment regimen should be chosen and which parameters should be considered in the follow-up of these patients. Further studies are required to find scientific answers to these questions.

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EP1402

A rare case: papillary thyroid carcinoma in the ectopic thyroid

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Ectopic thyroid tissue is the localization of thyroid tissue at any place other than the normal localization of the thyroid during the migration of embryonic period. Concurrent normal thyroid tissue may accompany. It usually is seen in women and in the midline. Very rarely thyroid carcinoma can develop. Treatment is like normal thyroid carcinomas, suggesting simultaneous thyroidectomy if accompanied by normal thyroid tissue. A 42-year-old female patient presented with complaints of swelling on the right side of the neck for 3 months. There was no chronic disease or drug use in her story. On physical examination, a painless, moving 30×30 mm mass lesion was detected in the middle cervical region. Imaging revealed a mass lesion in the lower right cervical region near the right lobe of the thyroid gland, $36\times25\times35$ mm heterogeneous signal density same as the thyroid gland. Histopathological examination of the excised mass revealed TTF1 positive, galectin positive, CK19 positive, HBME1 positive and 36×30 mm encapsulated follicular variant papillary carcinoma considered as thyroid carcinoma and lymphoid tissue has not been observed. Thyroid function tests and laboratory findings were normal. Thyroid ultrasonography revealed bilateral hypoechoic and isoechoic nodules maximal 1 cm in diameter and malignant lymphadenopathy 2 cm in the left cervical area. As a result of total thyroidectomy + neck dissection, 8 and 9 mm diameter papillary thyroid carcinoma encapsulated follicular variant was detected in the right lobe and thyroid carcinoma metastasis were observed in 3 of 10 lymph nodes removed in the left cervical area. This was evaluated as high-risk thyroid carcinoma and treated with radioactive iodine (RAI-131) at 150 mCi. At post-RAI whole body scan screening, 2 local foci were observed in the thyroid location and were followed up. The patient was followed for 6 months with asymptomatic levothione suppression therapy. We aimed to present a rare case of ectopic thyroid carcinoma.

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EP1403

Co-occurrence of papillary and follicular thyroid carcinoma in a patient

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Occurance of papiller carcinoma with foliculer thyroid carcinoma is a rare situation. We report a 49-year-old male with asymptomatic goiter. The first biopsy from the right tyroid lobe from a $6\times6\times4$ cm iso-hypoechogen heterogeneous nodule showed bening, hurthe cell and thyrocyte rich cytology. Two months later the patient went through right lobectomy which patology defined as 4.3 cm minimal invasive follicular carcinoma. Two months after right thyroidectomy, a second operation was performed on the left thyroid to complete the process of total thyroidectomy. The speciment was sent to patology which bore the following result: Papillary microcarcinoma with follicular variant. This was evaluated as high-risk thyroid carcinoma and treated with radioactive iodine(RAI-131) at 100 mCi. At post-RAI whole body scan screening, 2 local foci were observed in the thyroid location and were followed up. This work shows two different

carcinomas that belong to different lineages existing in two different lobes of the thyroid with no coheisive malignity triggering factors.

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EP1404

A rare cause of respiratory failure: Anaplastic carcinoma

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Anaplastic thyroid carcinoma (ATC) is one of the most aggressive and lethal human malignancies. The median survival time following diagnosis is typically six months or less. Rapidly growing tumors may cause respiratory failure by compressing trachea. A 71-year-old woman presented with 1-month history of dyspnea, cyanosis and rapidly enlarging neck mass for the past 2 weeks. She had been suffering from multinodular goiter disease. Physical examination revealed a large, fixed and mildy tender thyroid mass and cyanotic extremities. Breath sounds were bilaterally decreased on auscultation. Arterial blood gas analysis showed hypoxia. Chest X-ray imaging revealed bilateral multiple nodular opacities, which were found to be bilateral metastatik nodular lesions involving all segments on thoracic tomography. In addition, a 35×20 mm sized lingular metastatic lesion invading 5th rib was present in the left lung. Thyroid gland was slightly larger than normal with heterogeneous parenchyma and there were multiple, heterogeneous and hypoechoic nodules, the biggest one was being $30\times32\times30$ mm in size in the right thyroid lobe. In addition, 2 cm sized multiple necrotic lymph nodes were visible. Laryngoscopic examination demonstrated externally compressed trachea. Tru-cut biopsy of left thyroid lobe detected anaplastic carcinoma with rhabdoid giant cell formation. Despite oxygen supplementation, hypoxic state worsened and the patient was referred to intensive care unit following emergent tracheostomy. In conclusion, although it is rare, anaplastic carcinoma should be considered in the patients presenting with respiratory failure. Anaplastic thyroid carcinoma should should be considered in patients presenting with rapidly growing neck mass and respiratory failure.

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EP1405

Our experience of strain elastography in the evaluation of thyroid nodules

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Introduction
Thyroid nodule is a common finding in neck ultrasonography performed in adult age group. Appropriate management of patients with thyroid nodules accuretly is very difficult process. Fine needle aspiration biopsy (FNAB), is the traditional invasive method used to identify nodules. Investigations are continuing for noninvasive techniques. Elastography is the imaging new technic,to evaluate the nodules. Aim of this study to evaluate the results of FNAB and elastography performed in patients with thyroid nodules.
Methods
173 thyroid nodules were examined by Elastography and fine needle aspiration biopsy. Strain elastography was performed with Siemens Acuson s1000 14L5 lineer transducer. Elastography findings were evaluated together with b-mode ultrasonography. The susceptible nodules with an S/R ratio of over 2,6 were accepted as malignant nodules.
Results
Results of 155 (89%) FNAB were benign, 18 (10.4%) were malignant. The elastographic appearance was categorized at the time of the examination, 154 (89%) of them were categorised as benign and 19 (10.9%) of them were categorized as malignant. The sensitivity of Elastography for malignancy was 90.0%, specificity was 22%, PPV was 21%, NPV was 90% and accuracy was 83.2%.
Conclusion
Elastography seems to require more experimentation in this regard with hope being a technique. Our study strongly suggests, biopsy is still the most reliable method for the evaluation of nodules.

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EP1406

Association of TIMP-3 expression and BRAF V600E mutation status in papillary thyroid cancer

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Background
The aim of this study was to assess the association between tissue inhibitor of metalloproteinase-3 (TIMP-3) gene expression and B-Raf Proto-Oncogene (BRAF) V600E mutation in marginal and tumoral tissues of papillary thyroid carcinoma (PTC) patients.
Methods
Sixty fresh frozen tissues of PTC including 55.3% women were collected during thyroidectomy surgery. All clinicopathologic features of subjects were collected which confirmed by a pathologist. The exon 15 of BRAF gene was genotyped by sequencing, TIMP-3 gene expression was assessed using SYBR-Green Real-Time PCR, and the protein level of TIMP-3 was measured using ELISA.
Results
The mean age in men and women was 39.6 ± 15.6 and 37.5 ± 11.6 years, respectively. BRAF mutant was found in 24 (31.6%) of PTC samples. The mean of TIMP-3 mRNA level was higher in marginal tissue compare to tumoral ones ($P>0.05$). However, the mean of protein level of TIMP-3 was significantly higher in marginal tissue compare to tumoral ($P=0.001$). Moreover, in subjects with BRAF positive mutation, the mean of TIMP-3 gene expression was higher in marginal compare to tumoral tissues ($P=0.066$). On the other hand, in subjects without BRAF mutation, the mean of TIMP-3 protein level was significantly lower in tumoral tissues compare to marginal tissue ($P=0.003$). However, this difference was not significant in subjects with negative BRAF mutation ($P=0.084$).
Conclusion
This study showed that although the gene expression of TIMP-3 was marginally different in two BRAF positive and negative mutation groups, it was significantly different in protein levels.

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EP1407

Histologically-proven Hashimoto's thyroiditis significantly decreases the risk of structural recurrence in patients with low risk intra-thyroidal papillary thyroid cancer

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Introduction
Due to the absence of randomized controlled trials, management of low risk papillary thyroid cancer (PTC), which represents the most commonly diagnosed form of thyroid malignancy, remains controversial. Hashimoto's thyroiditis (HT) is significantly more frequent in patients with PTC, as compared with subjects carrying benign lesions as well as different tumour histotypes. Despite still controversial, HT is considered a protective factor in PTC being associated with favourable tumour features and better outcome. Nevertheless, all studies dealing with this issue included all PTC stages. We aimed to assess prognostic value of histologically-proven HT in a large cohort of consecutive low-risk intra-thyroidal PTC.
Patients and methods
Multicenter retrospective study including pT1/2 PTC without any evidence of extra-thyroidal disease, who were subjected to surgery and follow-up within the involved centers. Pathological review of all specimens was performed. Co-existing HT was defined by the presence of diffuse/focal lymphoplasmacytic infiltrate, oxyphilic cells, lymphoid follicles with germinal centers, and atrophic changes involving normal thyroid tissue, whereas isolated peri- and intra-tumoral lymphocytic infiltration was not considered as HT. Study endpoint was recurrent structural disease.
Results
Two-hundred eighty-four patients (156 without and 128 without HT) were included. Mean follow-up was 75 ± 61 months (6.3 years). Concomitant HT was related to significantly lower rate of recurrent structural disease ($P = 0.018$, OR 0.33 95% CI 0.13–0.86). This finding was confirmed by survival analysis, where PTC with HT showed significantly higher recurrence-free time. After adjustment for other variables affecting prognosis at univariate analysis (age at diagnosis, tumour size, multifocality, and post-surgery radiometabolic treatment), concomitant HT retained its protective effect ($P = 0.036$, OR 0.34 95% CI 0.12–0.93).
Conclusions
In our series of low risk intra-thyroidal PTC, concomitant HT independently predicted recurrent structural disease and may therefore represent a useful tool for the decision-making process of these patients.

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EP1408

Evaluation of disease outcome in patients affected with differentiated thyroid carcinoma treated with total thyroidectomy or lobectomy

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Abstract
An individualized risk-based approach to the treatment of thyroid cancer is being extensively discussed in the recent literature, but controversies remain about the ideal surgical approach. In particular, if some data showed that properly selected thyroid cancer patients can be treated with lobectomy (LT) with excellent clinical outcomes, other results demonstrated an increased incidence of persistent recurrent disease in patients submitted to LT with respect to those treated with total thyroidectomy (TT). This study was aimed to describe clinical outcomes in a retrospective large series of low and intermediate risk thyroid cancer patients treated with LT or TT.
Methods
We evaluated retrospectively 336 patients affected with differentiated thyroid cancers (DTC); 292 of them were treated with TT and 44 with LT. The initial surgical treatment was not chosen based on the risk class. The median age was 48 yrs, 274 were females and 62 males. Remission or persistent/recurrent disease was defined on the basis of biochemical and/or structural evidence of disease after a median follow-up period of 65 months.
Results
Only 1/292 patients treated with TT needed additional therapy (surgery for malignant lymph node metastases), and none of them was submitted to radioiodine ablation. On the other hand, 15/44 patients treated with lobectomy were submitted to following treatment (completion thyroidectomy alone in 3, associated with lymphadenectomy and radioiodine treatment in 12 cases). As far as the outcome concerns, remission was documented in 281/292 cases (96.2%) and 30/44 cases (68.2%) in the TT and LT groups, respectively ($P < 0.0001$).
Conclusions
Our data suggest that lobectomy should be performed only in patients with a very low risk at diagnosis, in order to avoid the need for a second treatment. Moreover, since virtually all patients treated with TT were cured after surgery, our data support the selective use of radioiodine ablation treatment.

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EP1409

Does the delayed risk stratification system help to evaluate the risk of unfavorable clinical outcome in pT1aN0/Nx stage patients with differentiated thyroid cancer treated without radioactive iodine?

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Introduction
In ATA recommendations (2016) a delayed risk stratification (DRS) system proposed by D.P. Momesso et al. was accepted as a diagnostic tool for the risk stratification of unfavorable clinical outcome and for monitoring the clinical outcome in differentiated thyroid cancer (DTC) patients treated without radioactive iodine (RAI).
The aim of the study
To evaluate the DRS system in patients with low clinical stage (pT1aN0/Nx).
Material
304 patients after total thyroidectomy ($n = 202$) or lobectomy ($n = 102$) without adjuvant RAI therapy, with a follow-up period of at least 24 months, treated at a single center were enrolled to the study. The median age was 50.5 years, 91.1% were women, 100% at baseline had a low risk according to ATA, the median follow-up was 4 years (2–24).
Methods
DRS of the treatment response was conducted, based on the medical records, according to the criteria by Momesso *et al*. The course of the disease was evaluated (recurrence, death) as well as the status on 31.12.2016, which is the end of the follow-up (remission, persistent disease). The relationship between unfavorable outcome and the DRS system was evaluated.
Results
The response to initial therapy was excellent in 272 patients (89.5%), intermediate in 31 patients (10.2%) and biochemically incomplete in 1 patient (0.3%) (increased concentration of TgAb). There was a recurrence in 2 patients from the excellent response group at 6 and 7 years of follow-up (after lobectomy). No patients with intermediate and biochemically incomplete response were diagnosed with the structural disease and none of the patients died during the follow-up.
Conclusions
The DRS system did not prove useful in predicting the risk of unfavorable clinical outcome and cannot be used to personalize the monitoring method of the disease in patients at pT1aN0/Nx, not treated with RAI.

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EP1410

The impact of post-radioiodine therapy SPECT/CT on risk stratification in differentiated thyroid cancer; a bi-institutional study

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Objective
SPECT/CT has numerous advantages over planar and traditional SPECT images. The aim of this study was to evaluate the role of post-radioiodine therapy SPECT/CT of patients with differentiated thyroid cancer (DTC) in early risk classification and in prediction of late prognosis.
Patients and Methods
323 consecutive patients, 181 at the University of Pecs and 142 at the University of Debrecen, were investigated after their first radioiodine treatment (1100–3700 MBq). Both SPECT/CT and planar camera images of the head, neck, chest and abdomen regions were taken four days after radioiodine therapy. Patients were re-evaluated 9–12 months later as well as at the end of follow-up (median 37 months).
Results
Post-radioiodine therapy SPECT/CT showed metastases in 22% of patients. Lymph node, lung and bone metastases were detected in 61, 13 and 5 patients, respectively, resulting in early reclassification of 115 cases (36%). No evidence of disease was found in 251 cases at 9-12 months after radioiodine treatment and 269 patients at the end of follow-up. To predict residual disease at the end of follow-up, the sensitivities, specificities and diagnostic accuracies of the current risk classification systems and SPECT/CT were: ATA: 77%, 47% and 53%; ETA: 70, 62 and 64%; SPECT/CT: 61, 88 and 83%, respectively. There was no difference between cohorts of the two institutions when data were analyzed separately.
Conclusions
Based on our bi-institutional experience, the accuracy of post-radioiodine SPECT/CT outweighs that of the currently used ATA and ETA risk classification systems in the prediction of long-term outcome of DTC.

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EP1411

Clinical features of medullary thyroid carcinoma (MTC) in simultaneous occurrence with differentiated thyroid cancer (DTC)

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Objective
Simultaneous occurrence of MTC and DTC is frequently found. It is unclear whether there is a common pathogenic mechanism. Aim of our study was to characterize clinical features of MTC when coexisting with DTC.
Methods
Of 273 MTC patients followed-up in our department 39 (14.3%) had MTC simultaneously with DTC. They were divided in 4 subgroups according to size. Clinical histopathological data were recorded.
Results
The patients were followed for 1–35 yrs (median:5). Median age at diagnosis was 45 yrs (4–81 yrs). Simultaneous occurrence of distinct MTC-DTC was observed more frequently in patients diagnosed after 2001 compared to earlier (16.7 vs 6.3%, $P=0.036$). Sex and history of familial disease did not differ. In familial forms of MTC, DTC occurrence was higher in carriers of RET exon 8 (G533C) mutation compared to other RET mutations (17.6 vs 1.8%, $P=0.004$). Patients with concomitant MTC-DTC had less frequently lymph node infiltration from MTC compared to those with MTC alone (26.3 vs 47.8%, $P=0.015$), marginally smaller MTC size (median (IQR) 0.9 (1.5) vs 1.2 (1.4) cm, $P=0.058$) and more often c-cell hyperplasia (58.6 vs 31.5%, $P=0.006$). No differences were found regarding capsular and soft tissue invasion, multifocality, distant metastases at diagnosis. Stage at diagnosis differed between groups (MTC-DTC vs MTC alone: Stage I+II:71.8 vs 49.8%, III:20.5 vs 27.6%, IV:7.7 vs 22.7%, $P=0.007$) with the difference remaining significant in both sporadic ($P=0.022$) and familial MTC ($P=0.035$). MTC-DTC group had marginally better disease prognosis compared to MTC alone (remission: 67.6 vs 48.7%, stable: 16.2 vs 25.2%, progression: 16.2 vs 26.1%, $P=0.05$). The 10-year probability of lack of progression of disease did not differ between the two groups. Size of DTC did not seem to affect the clinical course of MTC-DTC.
Conclusions
Simultaneous occurrence of MTC-DTC is occasionally diagnosed. Even though stage at diagnosis is better in MTC-DTC patients, there is no difference in 10-year probability of lack of progression of disease. We report for the first time an increased incidence of DTC in RET exon 8 (G533C) carriers. Whether this mutation-quite common in Greek MTC patients-might participate in shared pathogenic mechanisms needs further investigation.

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EP1412

Concomitant thyroid inflammatory myofibroblastic and follicular tumors

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Abstract
We present a rare clinical case. Inflammatory myofibroblastic tumors (IMT) are extremely rare neoplasms of unknown etiology and most commonly found in lungs and gastrointestinal tract. A rare clinical case of the thyroid IMT occurred in a 50-year-old lithuanian female patient with clinical manifestation of breathlessness, dry cough, hemoptysis, neck mass, arrhythmia and loss of consciousness. Because of elevated D dimers values, pulmonary artery thromboembolism was suspected and CT scan was performed. CT showed no pulmonary embolism, but revealed a large tumor in the neck. After patient was investigated in cardiology department to exclude sick sinus syndrome, fine needle aspiration cytology of thyroid nodus was done with non-diagnostic results. Thyroid scintigraphy showed cold node suggesting maligancy. All symptoms and findings indicated the need of surgical treatment. The patient underwent total thyroidectomy. Histopathology analysis revealed two separative tumors: follicular carcinoma and thyroid inflammatory myofibroblastic tumor. Because of folicular carcinoma the patient was treated with radioiodine. She was comfortable after treatment with thyroid hormone replacement therapy. We managed to find only 20 cases of this type of tumor located in thyroid reported in the literature. And we did not find reports with two concomitant thyroid tumors including IMT.

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EP1413

Is thyroid imaging reporting and data system useful in prediction of malignancy in thyroid nodules with persistent nondiagnostic cytology?

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Introduction
Although malignancy rate is low in thyroid nodules with nondiagnostic (ND) cytology, it is reported as higher in persistent ND nodules. We aimed to determine the role of ultrasonography (US) features and Thyroid Imaging Reporting and Data System (TIRADS) in the prediction of malignancy in patients with persistent ND cytology.
Methods
246 patients who underwent thyroidectomy with an indication of at least two ND cytologies were included in this study. Suspicious US features (solid component,

hypoechogenicity, irregular margin, microcalcification, and taller-than-wide shape) and TIRADS categories (TIRADS category 3, 4a, 4b, 4c and 5) of each nodule were obtained from medical records.
Results
Of the 246 patients, 218 (88.6%) had benign and 28 (11.4%) had malignant final histopathology. Of these 28 patients with malignant histopathology, 25 (89.3%) were evaluated as papillary thyroid carcinoma, 1 (3.6%) as follicular thyroid carcinoma, 1 (3.6%) as medullary thyroid carcinoma, and 1 (3.6%) as undifferentiated thyroid carcinoma. Frequencies of taller-than-wide shape, solidity, hypoechogenicity, microcalcifications, and irregular margins were similar in benign and malignant groups ($P > 0.05$, all). TIRADS categories of 246 nodules with ND cytology were as follows; 12 (4.9%) TIRADS 3, 53 (21.5%) TIRADS 4a, 104 (42.3%) TIRADS 4b and 77 (31.3%) TIRADS 4c. There was not any nodule with TIRADS 5 category. Malignancy rates of categories 3, 4a, 4b, and 4c nodules were 0, 13.2, 9.6 and 14.3%, respectively. No significant differences were found in TIRADS categories between benign and malignant nodules ($P > 0.05$, all).
Conclusion
In the present study, malignancy rate was found as 11.4% in nodules with persistent ND cytology. There was not any suspicious US feature that was predictive for malignancy in ND nodules. Thyroid nodules in TIRADS 4a, 4b and 4c categories had higher malignancy rates than estimated risk of malignancy reported by the Bethesda system in ND cytology.

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EP1414

Significant difference between the prevalence of C cell hyperplasia (CCH) in benign thyroid nodules without histological thyroiditis (HT) and in papillary/follicular thyroid cancers (PTC/FTC) at histology

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Background
CCH and serum hypercalcitoninemia (iperCT) can be found in benign thyroid diseases such as thyroiditis and in some cases of papillary (PTC) or follicular (FTC) thyroid microcarcinomas. The question of whether the association with these latter is related to the malignancy of the nodule is still unclear.
Aim of the study
To evaluate the difference in the CCH prevalence, at histology, in a series of benign (BTN) and malignant (PTC/FTC) thyroid nodules. The correlation with the serum CT was also analysed.
Materials and methods
We selected 315 consecutive cases surgically treated between 2012 and 2016 in our Hospital: 137/315(43.5%) resulted to be BTN and 178/315(56.5%) to be PTC/FTC. In 27/315(8.5%) cases there was a serum iperCT (Immulite 2000, Siemens). The definition of CCH was based on the presence of more than 50 C-cells at least in one microscope field, in a thyroid cross section.
Results
At a first analysis no differences were observed in the prevalence of CCH between BTN and PTC/FTC. When we excluded from the analysis the cases with reported HT, both benign and malignant, the prevalence of CCH was statistically significant more frequent and bilateral in PTC/FTC (32.6%) than in BTN (19.5%) ($P < 0.05$). The cases with iperCT were exclusively in the PTC/FTC group and among them those case with iperCT showed the highest prevalence of CCH ($P < 0.001$). In PTC/FTC with serum iperCT we observed that 11/21(52.4%) were follicular variant PTC(FVPTC) while this variant was present in only 30/84(35.7%) PTC/FTC without iperCT ($P < 0.05$). The cases with iperCT were also more often multifocal ($P < 0.005$).
Conclusions
CCH is more frequent in PTC/FTC than in BTN when the cases with HT were excluded; the serum iperCT was found exclusively in the PTC/FTC group and these cases showed the highest prevalence of CCH; a higher prevalence of FVPTC and multifocal cases were observed in the PTC/FTC group associated with CCH.

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EP1415

Primary thyroid lymphoma: a differential diagnosis to be considered

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Introduction
Primary lymphoma of the thyroid, although rare, should be considered in the differential diagnosis of patients with thyroid nodules or goiter, because its prognosis and treatment differ substantially from that of the other disorders. Thyroid lymphomas are nearly always of the non-Hodking type (70–80% B cell lineage). There is a 4:1 female predominance and the mean and median ages at diagnosis are between 65 and 75 years. Hashimoto's thyroiditis is the only known risk factor.
Case report
A 70 years old woman with a rapidly enlarging goiter without local symptoms or signs. The patient presented a history of hypothyroidism on treatment with thyroxine. Her tiroglobulin antibodies were positives but not TPO. An ultrasound scan of the thyroid showed a 7-cm mass in the left lobe and istm. The fine needle biopsy was nondiagnostic but suggestive of Hashimoto's thyroiditis. The excisional biopsy confirmed the diagnosis of a diffuse large B-cell lymphoma. Imaging studies demonstrated cervical and mediastinal lymph nodes and bilateral pulmonary metastases.
Discussion
Thyroid lymphoma represents no more than 2% of all malignant thyroid tumors. The vast majority are of the non-Hodking type, the most frequent the B-cell lineage. The typical presentation is a rapidly enlarging goiter with symptoms or signs of tracheal, esophageal or neck vein compression. In 10–20% there is a known goiter often with hypothyroidism. Up to 10% have systemic ('B') symptoms of lymphoma (fever, night sweats, weight loss). Diagnosis is established by cytologic examination; when the fine needle biopsy is nondiagnostic the excisional biopsy is required. The treatment includes Radiaton and Chemotherapy. Definitive surgery is not usally performed. Our patient was treated with six cycles of CHOP followed by radiation.
Conclusions
Thyroid lymphoma is a rare cancer but must be considered in the differential diagnosis of patients with thyroid nodules or goiter specially if a Hashimoto's thyroiditis is present. The risk of Thyroid lymphoma is at least 60 times higher than in patients without thyroiditis. The treatment is not the surgery like in the others thyroid pathologies and the prognosis depends on the type and tumour extension.

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EP1416

Relation between TSH levels and the aggressiveness of differentiated thyroid carcinomas

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Aim
Differentiated thyroid carcinomas (DTC) composes 95% of all thyroid malignancies originating from thyroid follicular epithelial cells. DTC expresses TSH receptors so long time TSH stimulation may cause cancer occurrence or malignancy progression. So we aimed to assess the role of TSH levels in predicting thyroid cancer stage or aggressiveness.
Methods
We retsopectively searched thyroid cancer patients fort he last 10 years in our instution. Totally 329 patients record were eligible for the study. TSH levels and disease stage, age and sex were evaluated.
Results
322 (97.9%) were papillary thyroid carcinomas and 7 (2.1%) were follicular carcinomas 261 79.3(%) were females, 68 (20.7%) were males. Median age was 45 (17–76) years old. Among the patients; 273 (83.0%) had stage 1 disease, 22 (6.7%) had stage 2 disease, 11 had (3,3%) stage 3 disease and 23 (7.0%) had stage 4 disease. Median TSH level was 1.34 (0.01–9.97) mIU/ml. Serum TSH levels were different when compared stage 1 and 4 patients ($P = 0.004$). But there was no significant difference between other stages. Additionally, subjects with lymph node at diagnosis had higher TSH levels according to patients who had not ($P = 0.0001$).

Conclusion
Higher TSH levels were observed in patients with lymph node metastasis at the diagnosis and there was statistically higher TSH levels in stage 4 patients compared to stage 1 patients. But this relation was not seen in other stages. Further studies with larger number of patients could show the relation with TSH levels and thyroid cancer aggressiveness.

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EP1417

Ultrasonographic features of thyroid nodules with suspicious or malignant cytology

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Introduction
Thyroid sonography has become the first line diagnostic procedure for thyroid nodules. The characterization of specific sonografic patterns associated with high risk of malignancy has enabled physicians to determine which nodules are more likely to be malignant and thus merit further evaluation.
Aim
We investigated whether the ultrasonographic nodule characteristics proposed in the literature were able to predict cytology findings after ultrasound-guided fine needle aspiration biopsy (USg-FNAB), in our centre.
Materials and methods
A retrospective analysis of patients who had undergone USg-FNAB between Jan 2014 and Nov 2015 was performed. Nodules were classified according to the following sonographic characteristics a) size, b) solid hypoechoic nodule, c) presence of microcalcifications, d) irregular borders, e) vertical growth ('taller-than-wide' orientation), and, f) increased vascularity. Cytology reports were classified, according to the Royal College of Pathologists guidance, as non-diagnostic for cytological diagnosis (Thy 1), negative for malignancy (Thy2), neoplasm possible (Thy3), suspicious for malignancy (Thy4) and malignant (Thy5). Category Thy1 nodules were excluded from the analysis. The association of suspicious ultrasound characteristics with the composite cytology outcome of possible neoplasm, suspicious or malignant (Thy3, Thy4, Thy5) was investigated.
Results
During the study period, 736 nodules in 571 patients were biopsied. The most common ultrasonographic feature was low echogenicity (175/736, 23.8%), whereas the most rear was the vertical nodule growth ('taller-than-wide' appearance, (28/736, 3.8%)). In a logistic regression model, where patient age was entered along with the ultrasonographic features, all variables emerged as predictors of the composite category Thy3, Thy4, Thy5 cytology, except vertical nodule growth and increased vascularity.
Conclusion
Sonographic nodule characteristics proved to be accurate predictors of cytology in the present patient series. Thyroid ultrasonography is a useful tool in determining which nodules should be biopsied.

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EP1418

Development of papillary thyroid carcinoma in a patient with multiple solid cell nests of the thyroid

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Introduction
Solid cell nests (SCNs) of the thyroid are considered embryological remnants of the ultimobranchial bodies and the thyroid diverticulum. They are frequently (61–89%) detected in the thyroid gland, but their biological significance remains disputable. According to the fetal cell thyroid carcinogenesis hypothesis SCNs may act as a source for specific thyroid cancer stem cells generating distinct thyroid cancer phenotypes. We report a case of a patient with concurrent SCNs and papillary thyroid carcinoma (PTC).
Case report
A 46-yr-old man presented to the emergency department with a painful mass on the anterior side of his neck. Laboratory tests revealed leukocytosis, while thyroid functions tests, calcitonin, carcinoembryonic antigen and calcium levels were in the normal limits. Neck ultrasound revealed an enlarged thyroid gland with a 2.5 cm dominant nodule on the right thyroid lobe. Fine-needle aspiration cytology showed 'atypia of undetermined significance' (AUS). The patient underwent total thyroidectomy. Histological examination revealed a papillary carcinoma 1.4 cm in diameter with central fibrosis, degenerative necrosis and the presence of foam histiocytes. It also showed multiple solid cell nests, nodular hyperplasia and rare lymphoid aggregates in the rest area of the thyroid.
Discussion
Rare cases of concurrent PTC up to 1 cm and SCNs have been described in the literature. SCNs may harbour multipotent stem cells which after a combination of mutations affecting their differentiation and unlimited growth potential may generate cancer stem cells predisposing to thyroid cancer. Immunohistochemical and molecular studies of neoplastic SCN lesions are needed to better understand the complexity of stem cells and their malignant counterparts, advancing our knowledge on thyroid pathophysiology, carcinogenesis, and treatment.

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EP1419

Statistical analyses on thyroid cancer in Romania

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For over 50 years the casuistic of patients with thyroid cancer registered in the Nuclear Medicine Department of the National Institute of Endocrinology in Bucharest, Romania, has over 12 000 cases. In the last 6 years, a total of 2580 new cases have been added. They are organized in a 'classic file' format. As a necessity and the first step in order to build a digital national database, we developed the BIOMAT-ENDO software as a Windows Forms application that stores all the main data regarding the patient hospitalized in the department, starting with the first hospitalization, continuing with all the periods of radioiodine therapy and the follow up. The patient-monitoring MODULE contains: clinical parameters, surgery details, *in vivo* and *in vitro* investigations, therapy information. Correlations can be done between any input data. We present preliminary results on 2000 cases of patients with thyroid cancer digitalized during one year in this database. We used the Structured Query Language in order to verify the functionality of the system, the correctness of the existing data and for some preliminary statistics. Results shows the following distributions: *onset disease age*: $<$ 18 year: 3%; 19–45 year: 37%; 46–65 year:42%; $>$66 year:18%; *genders:* F:84%; M:16% M, *area distribution*: urban:74%; rural:26%, *personal history*: multi nodular & nodular goitre: 81%, Graves's 1%, Hashimoto: 1%; no history:16%, *risk factors*: endemic area:70%; non-endemic area:30%, *histopathology*: papillary/follicular:30%; papillary: 28%; follicular: 17%; micro-carcinoma: 20%; others: 5%. Preliminary results on a target group with the *onset disease age* $<$*18 years* (n=58) show the following distribution on: *TNM*: T1:7%; T2:14%; T3:19%; T4:5%; unclassified: 9% and on *disease stage*: STD1:57%; STD2:4%; STD3:23%; STD4a:10% and STD 4b:6%.

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EP1420

Prognostic value of preoperative serum calcitonin concentration on primary surgery outcomes in medullary thyroid cancer

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Calcitonin assessment in thyroid diseases is recommended when medullary thyroid cancer (MTC) is suspected in fine needle biopsy, as well as in 'suspicious for a follicular neoplasm' class, especially oxyphilic type, in patients with germinal RET proto-oncogene mutation and in nondiagnostic biopsy when no surgical treatment is planned. This assessment is also suggested before any planned thyroid surgery to exclude MTC. Beyond diagnosis confirmation it is also suggested to take the concentration into account planning the extent of neck lymph node resection, although the threshold values are not precisely established. The aim of this work was to assess the prognostic impact of preoperative serum calcitonin concentration on primary surgery outcomes in medullary thyroid cancer. Among 1575 MTC patients followed-up in single clinical centre 248 patients were identified in whom serum calcitonin concentration before primary thyroid surgery was available (63 men and 185 women). Its mean concentration was 3647.8 ± 18862.7 pg/ml (median – 612 pg/ml, max. 286 643, min. 2 pg/ml). All patients underwent total thyroidectomy, and in 233 at least central and unilateral neck lymph node resection. In postoperative assessment in 145 patients serum calcitonin was undetectable and in 187 remained within normal ranges for healthy population (<10 pg/ml; in 11 of them in the follow-up calcitonin increased). In 217 patients after surgery no macroscopic cancer foci were visible in the imaging, and in further follow-up in 11 metastases or recurrence were found. Maximal preoperative concentration in patients who had no nodal metastases and normal calcitonin after surgery was 2513.8 pg/ml. Maximal preoperative concentration in patients in whom postoperative calcitonin was normal and were free from relapse in further follow-up was 15302.0 pg/ml. The minimal preoperative calcitonin in patients with histologiacally confirmed neck nodal metastases was 23 pg/ml. Conclusions: High preoperative serum calcitonin concentration up to a value of almost 12 000 pg/ml does not exclude the possibility of radical surgical treatment in MTC patients. Neck nodal MTC metastases can be found when serum calcitonin is as low as 23 pg/ml.

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EP1421

Standardized mortality of thyroid cancer in Korea between 1985 and 2015: analysis of Korean national data

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Background
The prevalence of thyroid cancer has increased very rapidly in Korea. However, there is no data focusing on thyroid cancer mortality in Korea. In this study, we aimed to evaluate standardized thyroid cancer mortality using national data from Statistics Korea.
Methods
Population and mortality data from 1985 to 2015 were obtained from Statistics Korea. Age-standardized mortality rates (ASMR) of thyroid cancer per 100 000 were calculated according to the standard population of Korea, as well as World Health Organization (WHO) standard population and International Cancer Survival Standard (ICSS) population weights.
Results
The ASMRs of thyroid cancer was increased from 0.19 to 0.87 between 1985 and 2004. And the ASMRs were decreased from 2005 until 0.43 in 2015. The estimated annual percent change (APC) from 1985 to 2004 was 7.64 and corresponding value from 2004 to 2015 was -4.28. These changes in the ASMRs were similar patterns in males (APC 8.23, 1985–2003 and APC -4.33, 2003–2015) and females (APC 7.33, 1985–2004 and APC -4.63, 2004–2015). These patterns of the change of ASMR were also observed in elderly subgroup (≥ 55 years). When ASMRs were calculated based on the WHO standard population and ICSS population weights, those was similarly increased until 2004, and decreased from 2004.
Conclusion
Thyroid cancer mortality in Korea was increased until 2004 and started to decrease after then. The increase in early diagnosis of thyroid cancer might be associated with decrease of thyroid cancer mortality in Korea.

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EP1422

Incidental thyroid uptake detected by ^{68}Ga-DOTANOC positron Emission Tomography: is it clinical significant?

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Background
The detection of thyroid incidental uptake of radiopharmaceuticals has been increasing. Those detected by ^{18}F-fluorodeoxyglucose positron emission tomography (PET) have been associated with a significant risk of malignancy (8–64%). Gallium-68 (Ga-68) labelled peptides are now the standard imaging modality for staging neuroendocrine tumours (NET). Its high sensitivity has increased the discovery of incidental findings. The aim of this study was to evaluate the frequency and clinical significance of incidental thyroid uptake as detected by ^{68}Ga- DOTANOC PET in patients without a history of thyroid cancer.
Methods
A retrospective analysis was conducted over 49 patients who underwent ^{68}Ga-DOTANOC PET as part of a work-up for non-thyroid cancer. The uptake in the thyroid gland (focal/physiologic) was evaluated and compared with the uptake in the liver.
Results
24 (49%) of the 49 patients were female with a median age of 64 years (p25 53 and p75 74). Thyroid nodules were known in 14 patients with a median size of 9.1 ± 8.4 mm. The reasons for ^{68}Ga-DOTANOC PET staging were: intestinal NET in 29 (59.2%), bronchial NET in 10 (20.4%), pancreatic NET in 5 (10.2%), paraganglioma in 2 (4.1%), an ectopic ACTH in one (2%), ectopic GH in 1 (2%) and meningioma in 1 (2%). Eight patients (16%) had ^{68}Ga-DOTANOC thyroid uptake: one (2%) had anomalous focal uptake, and 7 (14%) had physiologic uptake. The patient with focal uptake, had thyroid nodules on the corresponding side, as detected by anatomic imaging with a final diagnosis of a benign nodule. Of the seven patients with physiologic uptake, 3 (47%) had a corresponding nodule on ultrasonography and 1 (14%) had a papillary thyroid carcinoma. Ten patients with known nodules did not have ^{68}Ga-DOTANOC uptake, including a follicular tumour.
Conclusions
In contrast to the published research of ^{68}Ga-DOTANOC uptake in patients with known thyroid cancer, in our short series, the incidental uptake in thyroid gland does not seem to be related.

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EP1423

An association between breast cancer and the development of thyroid cancer

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Introduction
Women with breast cancer (BC) have an increased risk of developing thyroid cancer (TC), specifically papillary and follicular thyroid carcinomas at a median of 5 years. The aim of the present retrospective study is to describe the clinical characteristics of women who present this association.
Results
A total of 260 patients with an authenticated TC who were the median age at diagnosis is 41 years old (36–65). All our patients live in areas of moderate iodine deficiency. The frequency of the association of BC-TC $=6/260$ (4.3%). The median duration between the two diagnoses $=24$ months (12–84). The BC has always preceded theTC. The histopathological aspects are respectively for the BC: invasive ductal carcinoma ($n=4$) invasive lobular carcinoma ($n=2$) and TC: pure vesicular ($n=2$); Papillary ($n=4$). All these women underwent chemotherapy, hormone therapy and radiotherapy for BC and total thyroidectomy and an irradiation (100 mCI 131) for TC.

Discussion
The coexistence BC and TC is not fortuitous but the related pathophysiological mechanisms remain poorly elucidated Exposure to estrogens and to thyroid-stimulating hormones may play a role in the development of breast cancer or thyroid cancer. Radiation exposure is also a well-known risk factor for the development of TC, so a germline mutation could be responsible for the connection between breast and thyroid cancers.
Conclusion
The association of these two pathologies is not incidental and should lead otherwise to the systematic screening of the thyroid cancer in women with breast cancer.

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EP1424

Lung metastases from differentiated thyroid carcinoma: long term outcome and its prognostic factors related to progression free survival

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Background
Distant metastasis rarely occurs in differentiated thyroid carcinoma (DTC), but represents most common cause of death in patients with DTC. Lung and bone are the most frequent sites of distant metastases. This study investigated long term outcomes of lung metastasis in DTC patients and its prognostic factors influencing disease progression and cancer specific survival (CSS).
Methods
A total of 134 DTC patients presenting with lung metastasis from 1994 to 2012 were retrospectively analysed. Factors predictive of the outcome were determined by Cox-proportional model.
Results
With a median follow up of 81 months after surgery, the 5- and 1-year CSSs were 80 and 66%, respectively. The predictors of disease progression were older age ($\geq$45 years), ^{131}I non-avidity and co-existing bone metastases other than lung. Similarly, older age ($\geq$45 years), ^{131}I non-avidity, co-existing bone metastases and follicular pathology was associated with CSS. Cox proportional hazard ratio for progression-free survival and disease-free survival showed that older age was the only independent predictive factor for poor prognosis.
Conclusions
Older age, additional bone metastases, ^{131}I non-avidity and follicular histology were found to be significantly associated with poor clinical outcome. Therefore, strict surveillance should be tried in these patients.

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EP1425

Is Hashimoto's thyroiditis a risk factor for papillary thyroid cancer?

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Aim
Hashimoto's thyroiditis (HT) is the commonest autoimmune thyroid disease. Papillary thyroid cancer (PTC) is the most often thyroid cancer and its incidence is increasing yearly. It is not clear that HT is a predisposing factor for PTC. We studied PTC's frequency among HT patients went to total thyroidectomy.
Materials and methods
Five hundred and thirty four patients done total thyroidectomy by general surgery were evaluated retrospectively from July 2015 to July 2016. Preoperative thyroid function tests, anti-thyroid antibodies, thyroid ultrasonography findings, fine needle aspiration biopsies of nodules and pathology results of total thyroidectomy were examined. According to pathology results, HT was detected in 139 patients. Patients with PTC and HT (group 1) and PTC without HT (group 2) were compared in terms of demographic characteristics, tumor size, focus number of tumor, invasion, extrathyroidal spread and lymphatic metastasis presence.
Findings
PTC was detected in 70 (%50.4) patients in group 1 and 156 (%39.5) patients in group 2 ($P=0.026$). There was no statistically significant difference between them in point of gender, age, tumor size, microcarcinoma-macrocarcinoma distribution, focus number of tumor, invasion, extrathyroidal spread and lymphatic metastasis. The number of patients with PTC who had at least 1 kind of high anti-thyroid antibody was greater in group 1 then group 2 ($P<0.001$).
Results
In our study,we determined more PTC among HT patients but we find no difference according to age, gender, tumor size, invasion and metastasis. By the way anti-thyroid antibody positiveness was higher in cancer patients of group 1. Long term follow-up studies are necessary for detecting the effect of HT to PTC prognosis.

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EP1426

A new strategy to estimate levothyroxine requirement after total thyroidectomy and radioiodine remnant ablation for 'intermediate' and 'high' risk differentiated thyroid cancer

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Introduction
The approach for initial thyroid hormone suppression in patients who undergo surgery for differentiated thyroid cancer (DTC), is based upon the risk of disease recurrence. In particular, recent American Thyroid Association guidelines suggest to maintain TSH levels between 0.1 and 0.5 mU/l and less than 0.1 mU/l for patients with 'intermediate' and 'high' risk respectively. The aim of the study is to identify the major predictive factors of LT4 requirement to obtain semisuppressed or suppressed TSH levels and to elaborate a new method that could improve the accuracy of the LT4 therapeutic starting dose in intermediate and high risk DTC patients.
Methods
Two hundred and nineteen patients who underwent total thyroidectomy and radio-remnant ablation for DTC have been retrospectively evaluated. One hundred and forty nine were on TSH suppressive therapy (TSH $<$ 0.1 mU/l) and 70 on TSH semisuppressive therapy (TSH: 0.1–0.4 mU/l). The results obtained by this retrospective analysis were used to formulate a nomogram for the calculation of the LT4 dose.
Results
For both groups (suppressive and semisuppressive LT4 therapy) the best parameters to predict the optimal LT4 starting dose are body mass index (BMI) and age. On the basis of the nomogram, the LT4 dose in μg/kg to obtain suppressed and semisuppressed TSH levels ranged from 1.6 to 2.1 μg/kg per day and from 1.5 to 1.9 μg/kg per day respectively. The dose is higher in younger patients with lower BMI.
Conclusion
In our study BMI and age represent important parameters to predict LT4 dose in intermediate and high risk DTC patients. LT4 requirement decrease with the increase in age and BMI, probably due to the relative decrease of lean body mass. Based on these data, a user-friendly nomogram, representing an efficient method to calculate LT4 starting dose in patients who underwent thyroidectomy for differentiated thyroid cancer, has been created.

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EP1427

Follicular thyroid carcinoma in a patient with graves' disease

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Introduction
Follicular cancer has a low incidence in Graves' disease when compared to papillary thyroid cancer. Some studies have not reported any follicular cancer in patients with Graves' disease. We describe a rare occurrence of follicular cancer in a patient with Graves' disease.
Observation
A 37-year-old female patient presented to our institute with symptoms of thyrotoxicosis. She had no family history of thyroid cancer or of radiation exposure in the neck area. She presented with typical clinical and biochemical features of Graves' disease. Tc-99m scintigraphy of the thyroid showed diffusely increased uptake with hypo functioning (cold) nodule. She underwent uneventful surgery after achieving an euthyroid state. A total thyroidectomy was performed with resection of an enlarged lymph node detected on intra-operatively. A follicular thyroid carcinoma was diagnosed on the cold nodule with metastatic lymph node. Patient was given an ablative dose of I131. Post-therapeutic scintigraphy revealed a significant residual thyroid tissue/residual tumor in the neck. The TSH-stimulated serum Thyroglobulin level measured by radio-immunoassay was 13 ng/ml. Being sensitive to iodine, patient will continue to receive I-131cures to complete remission.
Conclusion
Surgical treatment should be indicated if graves disease is associated to suspected nodule.

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EP1428

Papillary thyroid carcinoma in children: report of 15 cases

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Papillary thyroid carcinoma is rare in young patients and have a good prognosis, although it is often diagnosed at the stage of lung metastases. Our multicenter study included 15 children aged between 5 and 18 years with female predominance, followed for differentiated thyroid cancer with lung metastases. All these patients underwent a whole body scan with I-131, serum thyroglobulin, chest radiography and/or cervico-thoracic CT. Scintigraphy had shown pulmonary miliary among all patients. Iodine treatment was successful in all patients, which proves the high sensitivity of these metastases to iodine treatment. The differentiated thyroid cancer is characterized by local aggressiveness and a high frequency of distant metastases. Prognosis does not seem to be influenced by histology alone, but by its association with other prognostic factors: age, metastases and surgery.

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EP1429

Evaluation of differentiated thyroid cancer patients according to different scoring systems: a single center experience

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Introduction
True risk evaluation is important in the management of thyroid cancer. We aimed to evaluate patients with differentiated thyroid cancer (DTC) according to the different staging systems.
Method
Data of patients diagnosed with DTC between 2007 and 2014 at our institution were analysed retrospectively. TNM, MACIS, EORTC, AMES, De Groot, ETA, LATS, and ATA staging systems were applied to patients according to their original description. In ATA ***risk*** classification ***system, we*** classified patients into four categories considering inappropriate postoperative thyroglobulin levels.
Results
There were 983 patients (218 male and 765 female) with a mean age of 49.4 ± 12.5 and a mean follow-up of 42.6 ± 24.3 months. Distribution of patients according to the staging systems were as follows; TNM: 81.1%, 4.7%, 12.7%, 1%, 0.3%, 0.2% of patients in stage I, II, III, IVA, IVB, IVC respectively; MACIS: 91%, 5.9%, 2.2%, 0.8% of patients in group 1–4 respectively; EORTC: 39.4%, 36.7%, 19.8%, 4%, 0.1% of patients in group 1–5 respectively; AMES: 82.2% of patients in low risk and 17.8% in high-risk group; De Groot: 81.6%, 4.7%, 13.3%, 0.4% of patients in stages 1–4 respectively; ETA: 35.5%, 25.9%, 12.4%, 26.1% of patients in very low, low, high and undetermined risk groups respectively; LATS: 35.5%, 26.7%, 17.7%, 20.1% of patients in very low, low, high and undetermined risk groups respectively. According to ATA, distribution of patients in low, intermediate, high and undetermined risk groups were respectively 26.4, 8.7, 40.8 and 23.6% in category 1, 39.7, 12.9, 23.8 and 23.6% in category 2, 46.7, 15.2, 14.5 and 23.6% in category 3, and 3.9, 19.2, 3.3 and 23.6% in category 4.
Conclusion
Variable scoring systems with variable risk assessments were suggested for DTC in the literature. A standardized categorization is required to overcome confusion and help clinicians during management of these patients.

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EP1430

A rare association of thyroid micro carcinoma and thyroid tuberculosis

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Introduction
Thyroid tuberculosis is a rare disease, its frequency is 0.15–0.2% of autopsic data. We report a case of micro papillary carcinoma of thyroid revealed by thyroid tuberculosis.
Observation
Mrs. K.J aged 54 years presented a multinodular goiter without ultrasound signs of malignancy. The patient underwent total thyroidectomy. Histological examination revealed a granulomatous and giganto cellular inflammation which is in favor of a tuberculosis. The left lobe of the thyroid contained a 4 mm papillary microcarcinoma. No metastatic adenopathy was found. The tumor was classified pT1aN0Mx. The patient was addressed to department of nuclear medicine for supplementation of radioactive iodine treatment. In addition, the patient had benefited of anti-tuberculosis treatment for 7 months.
Conclusion
Thyroid tuberculosis is a rare entity. In the absence of other tuberculous sites, diagnosis is often difficult. It is based on bacteriological and / or thyroid anatomopathological evidence. The association with a microcarcinoma is also rare and has to be carefully investigated by the anatomopathologist

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EP1431

GA/GG Heterozygosity of ARG280HIS polymorphism in XRCC1 GENE: Genetic susceptibility genotype in differentiated thyroid cancer?

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Background
Thyroid carcinomas are the most frequent endocrine malignancies of which more than nighty percent are differentiated thyroid carcinomas (DTC). It's known that

genetic variation plays 75% role in the development of papillary thyroid carcinoma (PTC).
Material and methods
In a case control setting subjects between January 2005 and December 2015 were evaluated for inclusion in the study. We aimed to compare the genotype frequency distributions of three common X-ray repair cross-complementing group 1 (XRCC1) SNPs in those with differentiated thyroid carcinoma (n: 228) and cancer-free patirents with benign nodular goiter (n:100) and the healthy controls (n:98) with regard to some predefined risk factors like existence of Hashimoto's thyroiditis, smoking, obesity, family history of thyroid cancer, and radiation exposure. In the present study we tried to assess the genotype frequency distributions of three common XRCC1 SNPs. Genomic DNA was extracted from peripheral lymphocytes using phenol–chloro form extraction. XRCC1 Arg194Trp, Arg280His and Arg399Gln polymorphisms were detected by amplification with real-time PCR followed by melting-curve analysis with fluorescence-labeled hybridisation probes in a LightCycler.
Results
Heterozygous GA/GG genotype frequency of the Arg280His polymorphism in DTC cases was significantly higher than in those with benign nodular goiter and in those in the healthy control group (64.5 and 3%, respectively; $P<0.001$). The frequency of homozygous AA genotype of Arg280His polymorphism was lowest in the DTC group (35.5%). The difference was statistically significant ($P<0.001$). Presence of family history of thyroid cancer was 7.9% in DTC group and 1% in benign nodular group. The difference was statistically significant ($P=0.014$).
Discussion
In conclusion, our study demonstrates that Arg280His GA/GG genotype of XRCC1 gene polymorphism is more frequently encountered in DTC than in cancer-free controls. GA genotype frequency is highest in those DTC cases with a family history of thyroid cancer.

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EP1432

Expression analyses of HABP2 in neoplastic and normal thyroid tissues: could this gene play a role in the pathogenesis of familial non medullary thyroid cancer?

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Recently, the G534E variant of the HABP2 gene was reported as the underlying genetic defect in large kindred with non-syndromic familial non medullary thyroid cancer (FNMTC), but these data were not confirmed in additional cohorts. Consistently, we found in our wide series of FNMTC that the HABP2G534E variant is frequent, but does not segregate with the disease. Nevertheless, a possible role for this gene in the pathogenesis of FNMTC cannot definitely ruled out also because contrasting but interesting expression data are available in other human tumors. To get more insights into the expression of this gene in thyroid tumor and normal tissues, HABP2 expression levels were determined by non-quantitative or quantitative Real-time PCR of RNA extracted from nine neoplastic and matched normal thyroid tissues: seven sporadic papillary thyroid cancer (PTC) cases not carrying HABP2G534E, 1 FNMTC from a member carrying HABP2G534E and 1 FNMTC from a member not carrying the variant. Immunohistochemistry for HABP2 was performed in 6 neoplastic and matched normal thyroid tissues: 2 sporadic PTC cases, 2 FNMTC from members carrying the HABP2G534E variant and 2 FNMTC from members not carrying the variant. HABP2 mRNA had a very variable expression in tissues from FNMTC, sporadic PTCs or contralateral normal tissues. In almost all cases, the gene appeared down- or up-regulated in tumors with respect to the corresponding normal tissue. At immunohistochemistry, HABP2 was expressed in both tumor and matched control tissues, without differences between sporadic and familial cases. In conclusion, our data confirm the apparent lack of co-segregation of the HABP2G534E variant with FNMTC. Nevertheless, the dysregulation of HABP2 expression found in either sporadic or familial PTCs or normal thyroid tissues, suggests potential post-transcriptional and post-translational alterations, and is consistent with similar findings in other malignancies, possibly indicating a role of this gene also in thyroid cancer.

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EP1433

Abstract withdrawn.

EP1434

Mutation analysis of papillary thyroid cancers using a newly developed targeted multi-gene panel in Hungarian population

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Thyroid cancer is the most common malignancy of endocrine organs and its incidence is steadily growing worldwide. Approximately 80% of differentiated thyroid tumors are papillary carcinomas. Next-generation sequencing (NGS) allows for high-throughput sequencing analysis of large number of samples at a time in a cost effective manner. We have developed a targeted sequencing parallel testing panel for multiple mutations in genes involved in thyroid cancer pathology. A custom-made AmpliSeq hot spot panel was designed to target 23 cancer genes (NRAS, MET, CTNNB1, PIK3CA, DICER1, VHL, BRAF, PTEN, LPAR4, EIF1AX, HRAS, RET, GAS8-AS1, KRAS, TSHR, AKT1, GNAS, TERT, TP53, AXIN1, APC, IDH1, SMAD4) which containes 357 known mutational hot spot areas with COSMIC IDs. Semiconductor sequencing was performed to analyze DNA from 56 papillary thyroid carcinomas with matched normal fresh frozen samples. The average coverage was 400X. BRAF, TSHR, APC, RET, LPAR4, TP53, AXIN1 and SMAD4 genes were the most mutated genes in our papillary thyroid cancer samples. Altogether, mutations, with at least 5% variant coverage and less than 1% minor allele frequency in general population, could be shown in all of the samples, while mutation could be seen in seven control samples. The distribution of genetic alterations was similar to the published data. The sensitivity and the specificity of the method were 100% and 90%, respectively with a positive predictive value of 87%. Our multi-gene panel testing approach allows parallel analysis for multiple mutations with high accuracy and sensitivity, and short turnaround times.

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EP1435

K1 cell line *in vitro*: the impact of diagnostic absorbed doses from ^{131}I

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Background
Diagnostic whole-body scan is a standard procedure in patients with thyroid cancer prior to the application of therapeutic dose of ^{131}I. Unfortunately, administration of radioisotope in diagnostic dose may decrease further radio-iodine uptake – the phenomenon called 'thyroid stunning'. We estimated radiation absorbed dose-dependent changes in genetic material, in particular in sodium iodide symporter (NIS) gene promoter, and NIS protein level in K1 cell line.

Materials and methods
We used the K1 cell line derived from the metastasis of human papillary thyroid carcinoma exposed to ^{131}I in culture. The different ^{131}I activities applied were calculated to result in absorbed doses of 5, 10, and 20 Gy.
Results
Radioiodine did not affect the expression of *NIS* gene at the mRNA level, however, we observed significant changes of the NIS protein level in K1 cells. The decrease of NIS protein level, observed in the cells subjected to the lowest absorbed dose, was paralleled by significant increase in 8-oxo-dG concentrations ($P < 0.01$) and followed by late activation of the DNA repair pathways.
Conclusions
Our findings show that the impact of radiation on living cells, in the range compared to doses absorbed during diagnostic procedures in patients, does not show the linear dose-effect.

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EP1436

Massive thyroid gland metastasis from nonsmall cell lung cancer

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Despite that the thyroid gland is one of the most vascular organs of the body but thyroid gland is an uncommon site for metastasis [1]. It represents less than 4% of thyroid malignancy in clinical and surgical studies [2, 3]. 58-year-old male, a prior smoker, was diagnosed with nonsmall cell lung cancer T4N3M1 St IV, histopathological findings - infiltrative adenocarcinoma, G1. About eight months he was treated with chemotherapy. At the beginning of the disease, the patient was examined by the endocrinologist and diagnosed a nodule thyroid. A fine needle aspiration (FNA) revealed a cystic degeneration. It was intended to repeat the FNA after three – 6 months. After 2 months, a patient presented to Endocrinology department of Hospital of Lithuanian University of Health Sciences Kauno klinikos because of increasing volume of the neck, shortness of breath, changes in voice and swallowing disorder. Thyroid ultrasound examination showed an enlarged thyroid gland, its structure was hypoechogenous and non-homogenous. Because of rapid tumor growth, we differentiated between lymphoma, anaplastic and hypopharyngeal cancer, lastly metastatic lesion. Metastasis from primary lung cancer was confirmed by thyroid fine-needle aspiration, cervical lymph nodes and laryngeal biopsies. After 1 week complications progressed. Thyroid was dramatically enlarged, acute respiratory failure evolved and the patient was unsuccessfully treated at Intensive Care Unit. In conclusion, a diagnosis of metastatic disease should be considered when new thyroid lesion is identified in any patient with a known history of malignancy until such a diagnosis can be ruled out. Because detection of metastasis to the thyroid gland often indicates a poor prognosis, aggressive treatment in time may be sufficient.

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EP1437

Papillary thyroid cancer and chronic lymphocytic thyroiditis presenting with diffuse microcalcifications without focal mass on ultrasound

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The detection and characterization of PTC are based on the evaluation of specific ultrasonographic features of thyroid nodes. However, there is limited data regarding diagnostics without typical malignant-appearing nodules. We report a very rare case of PTC in underlying chronic lymphocytic thyroiditis ultrasonographically manifested with diffuse microcalcification without focal mass. A 22-year-old woman visited our institution complaining of weight loss, general weakness, and headache. A physical examination revealed a painless, firm thyroid without a palpable mass. In an ultrasonography of the neck, the pathology was not assessed. The thyroid hormones concentration, TPOAb (Thyroperoxidase Antibodies) were within normal ranges. Thus, we did not find any evidence of thyroid disease. Two years later, the woman made an appointment at our clinic complaining of exercise – associated dyspnea. Her thyroid-stimulating hormone (9.96 mU/l; normal, 0.4–3.6 mU/l) and TPOAb (685 kU/l; normal, 0–78 kU/l) were increased. The ultrasonography showed marked bilateral low parenchymal echogenicity, inhomogeneous thyroid. In the left thyroid lobe, there were diffuse microcalcifications without focal mass. Sonographically, the thyroid lesions were indicative of chronic lymphocytic thyroiditis. A subsequent fine needle aspiration biopsy was performed. The cytologic examination assessed a suspicion of malignancy with chronic lymphocytic thyroiditis. The patient underwent the total thyroidectomy with lymph node dissection. Histopathologically, a chronic lymphocytic thyroiditis and 0.7 cm size papillary microcarcinoma in the left lobe were detected. Numerous stromal psammoma bodies, lymphatic intralobular spread with lymph node metastasis were revealed. We have demonstrated a very rare case of PTC with chronic lymphocytic thyroiditis ultrasonographically presenting with diffuse microcalcification without thyroid nodes. In our case, an atypical sonographic appearance of papillary microcarcinoma was associated with lymphatic intralobular spread and numerous stromal psammoma bodies in the thyroid. We conclude, in a case of ultrasonographically detected diffuse microcalcification without focal lesions, a careful examination for thyroid malignancy should be proposed.

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EP1438

Columnar cell variant of papillary thyroid carcinoma

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Columnar cell variant is rare variant of papillary thyroid carcinoma. It occurs in both genders with the most common occurence in the middle age of life. It differs from common PTC both in morphology and especially in biological behavior. The cancer cells also commonly harbor BRAF mutation. We describe a case of young women, who came for the examination of the thyroid gland before *in vitro* fertilization. We found normal thyroid function tests, negative antibodies. A small cystic lesion in the middle line of her neck under hyoid bone was seen at ultrasound. The small primary tumor in pyramid lobe of thyroid gland was found and cystic lesion was identified as the metastatic lymphonode. We scrutinized the genetic background of this more aggresive PTC variant and BRAF mutation was found. We mentioned the necessity of the differential diagnosis of cystic lesion of the neck. This case has happy end untill now thanks to early diagnosis.

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EP1439

A higher frequency of papillary thyroid carcinoma in myotonic dystrophy

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Background and purpose
Type 1 myotonic dystrophy (MD), associates neuromuscular, cardiac, respiratory and endocrine disorders. The aim of this study was to determine the prevalence of thyroid disorders and of any causal factors.
Methods
A retrospective single centre study was conducted, between 2000 and 2016, in 127 MD patients, diagnosed by familial genetic screening after informed consent. Clinical examination, TSH assay, 120-min glucose and insulin levels post-OGTT, number of CTG repeats and ultrasound thyroid exam were performed. Eleven patients refused the assessment. The 116 remaining were divided into 2 groups according to the presence of a goiter defined as an ultrasound volume $<$ (usNG) or $>$ (usG) 18 ml, whatever the presence of nodules.
Results
The whole population (61.2% female) was aged 45.1 ± 12.2 years; the BMI was 26.2 ± 6.5 kg/m^2; at least one palpable nodule or a goiter was present in 33.6%, and hypothyroidism in 8.6%. The percentage of usG was 38.8%. Age (46.6 ± 9.6

vs 44.1 ± 13.6 years), BMI (28.1 ± 7.1 vs 24.9 ± 5.9 kg/m^2), and frequency of papillary thyroid carcinoma (PTC) (17.8% vs 1.4%) were significantly higher in usG than in usNG. UsG was associated with BMI increase (P 0.017, IC 95% (−5.609 to −0.556), and hyperinsulinism (trend: P = 0.069), but not with CTG repeats. 11 (24.4%) of the 45 usG patients had a total thyroidectomy. Six micro (whose one had a capsule rupture) and 3 macro-PTC (with a high-risk level for 2 of them (pT2N1aM0, pT3N0M0) were diagnosed. 80% of these 9 PTC were associated with a palpable thyroid anomaly.
Conclusion
A third of these 116 MD patients had a palpable thyroid anomaly and 7.7% a PTC vs respectively 10% and 0.1% of the general population. The risk of usG was more related to a high BMI than to CTG repeats. Clinicians should be aware of this high prevalence of PTC in MD.

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EP1440

Management of treatment-related toxicity caused by multi kinase inhibitors administered due to advanced thyroid carcinoma

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Multi kinase inhibitors (MKIs) constitute a new therapeutic option in advanced RAI-refractory differentiated thyroid cancer (DTC) and medullary thyroid carcinoma (MTC). To date four different MKIs demonstrated a beneficial effect on progression free survival in DTC (sorafenib, lenvatinib) and MTC (vandetanib and cabozantinib). However, the treatment related toxicity, which potentially may limit their clinical use and lead to a negative impact on the quality of life, have been widely discussed recently.
Material and methods
The study group involved 81 patients with advanced thyroid cancer, who received different MKIs: 24 patents – lenvatinib, 20-vandetanib, 22-sorafenib, 4-cabozantinib, 4-motesanib and 3-axitinib. All side effects were classified according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Median treatment duration was 21.3 months (range 0.7–100.0 months).
Results
Among the most common adverse effects were hypertension (73%), skin reactions (70.3%), diarrhea (54.1%), weight loss (54.1%) and stomatitis (43.2%). The majority of side effects fulfilled G1 (mild) and G2 (moderate) criteria except of hypertension mainly classified as G3 (the necessity of the administration of at least 2 antihypertensive drugs). The management of treatment related side effects was based mainly on cautious follow-up (wide panel of laboratory examinations, regular ECG monitoring, echocardiography and other examinations, if necessary), non-pharmacological methods (sun blockers, moisture creams), concomitant pharmacotherapy (antihypertensive drugs, loperamide and other depending on different side effects) and dose modifications: 52.7% of patients needed dose reduction. Multidisciplinary team involving oncologists, internists, dermatologists, cardiologists, nurses and psychologists was also an important part of our successful patients care. Only 14.5% of patients required drug withdrawn due to its poor tolerability.
Conclusion
The proper management of MKI-related side effects is essential to keep patients on therapy as long as the treatment is beneficial without an unfavorable impact on their quality of life.

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EP1441

Cooperation between an endocrine nurse, psychologist and physician and their mediating role in the care of depression in patients treated with multi kinase inhibitors due thyroid cancer

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The treatment with multi kinase inhibitors (MKI) under clinical trials due to advanced thyroid cancer (TC) may postpone moving on the patients with advanced disease to the palliative care stage. However, chronic and escalating somatic symptoms during the treatment may promote the appearance of depressive reactions. It can be expected that a cognitive image of the disease, as a collection of subjective beliefs concerning patient's own illness and treatment, will be an important determinant of mental functioning. The aim of the study was to define a mutual dependence between the intensity of somatic problems, self-image of the illness and depression in patients receiving an experimental treatment of TC.
Material and methods
The study included 32 patients treated with MKI due to TC for at least one year. The study was cross-sectional and it based on different questionnaires: List of Somatic Problems, Beck's Depression Inventory and Short Questionnaire of Diseases Perception (B-IPQ).
Results
Nineteen patients showed severe somatic symptoms (HSS; High Somatic Symptoms), whereas 13 patiens demonstrated none or mild physical symptoms (LSS; Low Somatic Symptoms). The depression intensity was higher in HSS patients than in LSS group. In HSS group a mediating role of self-image relationship to disease somatic symptoms and depression was noticed. The direct effect of somatic symptoms on depression severity was insignificant. While, the belief about a negative impact of physical symptoms on the daily functioning was an important mediator of relations between somatic symptoms and depression in the study group.
Conclusions
The inclusion of interaction aimed at changing the perception of a negative impact of the disease and its treatment on daily life in TC patients can reduce the risk of deterioration in depressive symptoms. The role of a nurse in psychologist-physician-nurse team is crucial for better patients care and quality of life.

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EP1442

Malignancy risk stratification in thyroid nodules according to the Bethesda system for reporting thyroid cytopathology

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Introduction
Fine needle aspiration biopsy (FNAB) plays a crucial role in the diagnosis of thyroid nodules. The choice of further therapeutic strategy depends largely on its result. Knowledge of the risk of malignancy in each diagnosis class in the population is necessary. The aim of the research was to analyse the risk of malignancy in thyroid nodules in each diagnosis class according to Bethesda system.
Materials and methods
Retrospective research included 1001 patients with thyroid nodules diagnosed and treated surgically between 2002 and 2015 in one department. Women accounted for 86% of the research group. The median age was 52 years. The results of the guided FNAB performed before the introduction of the Bethesda scale (621) were re-evaluated and qualified to the appropriate group according to the new criteria.
Result
The preoperative FNAB results presented as follows: non-diagnostic material (class I) – 6 (0.6%); benign (class II) – 522 (52.1%); follicular lesion of undetermined significance (class III, FLUS) – 62 (6.2%); suspicious for a follicular neoplasm (class IV, SFN) – 138 (13.8%); suspicious for malignancy (class V) – 74 (7.4%), malignant (class VI) –199 (19.9%). The postoperative histology follow-up in the research group were spread as follows: benign – 708 (70.7%); malignant – 292 (29.3%). Malignancy risk for each class according to Bethesda system amounted to respectively: I – 33%, II – 4.21%, III – 11.2%, IV – 13.04%, V – 59.46%, VI – 100%.
Conclusions
The present study shows that the risk of malignancy in class III and IV is low. The diagnosis of FLUS or SFN in the absence of clinical indications is not a basis for surgical treatment.

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EP1443

The sensitivity and positive predictive value (PPV) of 131I-post-therapy whole body scan is higher than serum Tg values in detecting metastases in early stage of differentiated thyroid cancer patients

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The work-up of Differentiated Thyroid Cancer (DTC) patients includes thyroid surgery, thyroid remnant ablation (TRA) with 131-radioiodine and long life follow-up. 131I-post therapy whole body scan (pT-WBS) and thyroglobulin (Tg) are used in identifying metastatic patients. Some authors suggested to use post-surgical Tg (ps-Tg) values in deciding for or against TRA. The aim of our study was to verify the sensitivity and PPV of 131I-pT-WBS compared to serum Tg levels in detecting metastases in early stage of DTC patients.

Material and method

We retrospectively reviewed the records of 570 patients affected by pT1-pT3 DTC (F=450, M=120, mean age 48.5±13.2; F/M ratio=3.7:1) referred to our Nuclear Medicine Unit in the last five years. None of our patients had: 1) loco-regional or distant metastases at the time of recruitment; 2) age ≤16 years; 3) positive thyroglobulin-antibody (Tg-Ab); 4) pT_4 stage, 5) poorly-differentiated thyroid cancer. The majority of patients (98.2%) were affected by papillary carcinoma. Before TRA, all patients underwent neck-ultrasonography, laboratory test and, if treated in hypothyroid state (321/570, 56%), radioiodine thyroid uptake. Both ps-Tg and Tg values obtained at TRA were matched with 131I pT-WBS results.

Results

131I pT-WBS discovered metastases in 82 out of 570 (14.4%) patients. Seventy-three out of these patients (90.2%) showed ps-Tg levels ≤1 ng/ml. At TRA, forty of them (54%) maintained Tg levels ≤1 ng/ml. The majority of these patients (38/40, 95%) showed lymph-node metastases at 131I-pT-WBS while three had lung metastases (one of them showed lymph-node metastasis). The metastases were confirmed by targeted morphological studies.

Conclusion

ps-Tg cannot be used to decide for or against TRA. In early stage of DTC, 131I-pT-WBS is an accurate method in detecting metastases also in patients with stimulate Tg values ≤1 ng/ml, showing sensitivity and PPV significantly higher than Tg (100% vs 29.3% for both).

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EP1444

Evaluation of clinicopathological factors in papillary thyroid cancer with cervical lymph node metastasis

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Introduction and purpose

More than 90% of differentiated thyroid cancers are papillary thyroid cancer (PTC). Lymph node metastasis is common in PTC and has been reported to have no effect on prognosis. The risk of cervical metastasis is high in the presence of clinicopathologic factors including extrathyroidal extension, multifocality and lymphovascular invasion. In this study, it was aimed to evaluate the clinicopathological features of lymph node metastasis development.

Materials and methods

Patients with papillary thyroid carcinoma diagnosed between 1995 and 2016 were retrospectively reviewed. Patients who previously had another cancer story were excluded from the study. The demographic characteristics and pathology findings (histopathology, tumor size, lymph node metastasis, lymphovascular invasion, multifocality, capsule invasion, bilaterality) and antiTG, antiTPO values were compared in patients with and without cervical lymph node metastasis.

Results

In 419 papillary thyroid cancer patients, 52 lymph node metastases were detected. Lymphovascular invasion was present in 24 patients and capsule invasion was present in 104 patients. Extrathroidal extension was present in 32 patients. In logistic regression analysis, age (<45 years old ($P<0.001$ OR:4.193)), lymphovascular invasion ($P<0.001$ OR:7.762), capsule invasion ($P<0.002$ OR:3.054), extrathyroidal extension ($P<0.001$ OR:6.450) and bilaterality ($P<0.001$ OR: 0.217) involvement were significantly associated with cervical lymph node metastasis.

Discussion

We found that the risk of cervical lymph node metastasis was high in the presence of extrathyroidal extension, multifocality and lymphovascular invasion. In contrast to previous reports, the risk was found to be high for the age group lower than 45. Clinically, lymph node metastasis does not develop in all patients, knowing risk factors of cervical lymph node metastasis can determine the operation type, the treatment and the follow-up.

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EP1445

Theranostic management of medullary thyroid cancer (MTC) with (111In/177Lu) CP04: how close are we to a clinical solution?

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Effective targeted therapy for advanced endocrine malignancies is a goal of modern endocrinology. We herein present promising results of the first phase of clinical part of European project (Gran-T-MTC) aimed to assess the safety of gastrin analogue CP04 (DOTA-$(DGlu)_6$-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH_2) i.v. administration in dose (50 μg) useful for translation to 177In-CP04 for PRRT. CP04 has been selected for MTC therapy based on a high CCK-2 receptor expression in MTC and superior pharmacokinetics properties among gastrin analogues tested. Positive results of preclinical part of the study confirmed possibility of 111In-CP04 applying in humans.

Aim

To assess ^{111}In-CP04 safety, biodistribution and dosimetry.

Material and methods

Four patients: three with progressive/metastatic MEN2A-related MTC (^{18}F-FDG-PET/MRI positivity), one with sporadic MTC (short calcitonin doubling time) were enrolled. Basal calcitonin levels ranged between 279 and 824 pg/ml.

Study design

During the first clinical trial phase each patient received 111In-CP04 (200 MBq) in 2 different doses: a low (10 μg) and high (50 μg). Biodistribution and dosimetry data were assessed based on serial planar and SPECT/CT images over time.

Results

No side effects were observed during injection of either CP04 dose. In all patients 111In-CP04 uptake was confirmed in MTC lesions regardless of peptide dose (in one patient uptake was low). The compound showed both a renal clearance and uptake in the stomach wall with subsequent intestinal clearance with for both peptide doses similar kinetics and little variation across patients. The Effective dose was 6 mSv/200 MBq, irrespective of the amount of peptide. The kidney absorbed dose for the 50 μg therapeutic amount of CP04 if labeled with 177Lu was estimated at 0.32Gy/GBq and the stomach absorbed dose at 0.13Gy/GBq.

Conclusions

MTC metastases can be detected with 111In-CP04. Biodistribution and dosimetry data show CP04 promising radiopharmaceutical for MTC therapy if labeled with 177Lu. The confirmatory second part of clinical phase of trial has just begun.

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EP1446

Medullary thyroid carcinoma – diagnosis and outcome of patients treated in a tertiary center

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Medullary thyroid carcinoma (MTC) is a rare tumor of C cell origin, that may be sporadic or familial. Diagnosis is often delayed and its course variable.
Objectives
Evaluation of clinical characteristics and outcome of patients diagnosed with MTC.
Methods
Retrospective analysis of clinical records of patients with MTC between 2005 and 2016. We considered undetectable serum calcitonin as criteria of cure.
Results
Sixteen patients (12 women) were observed: mean age at presentation 63.8 years (46–79), mean follow-up: 2.2 years. Thyroid nodules were present in all. Four patients had compressive symptoms, three lymphadenopathy and one chronic diarrhea. Eight patients were diagnosed on the basis of histological examination without previous clinical suspicion of MTC. Genetic testing for *RET* proto-oncogene mutations was performed in nine patients and in one germinative mutation was detected (isolated familiar MTC). Eight patients with previous suspicion of MTC underwent total thyroidectomy with central lymph node dissection, and in five of these also lateral lymph node dissection. Among patients diagnosed after surgery: two had undergone total thyroidectomy with central lymph node dissection, in one of these combined with lateral node lymph dissection, three total thyroidectomy and three hemithyroidectomy. One completed thyroidectomy and the other two maintain undetectable calcitonin (follow-up: 0.5-1.3 years). After surgery seven patients were cured. One of them suffered recurrence with hepatic metastases 4 years later. Among patients with disease persistence there were six with progression in serum calcitonin, one with radiologic evidence of metastases. This patient had cervical lymph node metastases (calcitonin doubling time-CDT:6 months) 7 years after MTC diagnosis and underwent reoperation without cure.
Discussion
In this cohort of patients MTC diagnosis was made often after surgery (50%), which raises the question of presurgical calcitonin testing. MTC may have indolent or aggressive course as observed in this study, and turns difficult optimal treatment and follow-up strategy in the individual patient.

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EP1447

Papillary carcinoma of thyroglossal duct cyst with cervical lymph node metastasis

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Introduction
Neoplasias in the thyroglossal duct cyst (TDC) are rare, their prevalence varies from 1 to 1.5%. The most common cancer is papillary cancer representing 85% of cases. The diagnosis is often fortuitous following to the anatomopathological examination of the surgical specimen.
Patient and method
Our patient has 33-years-old, with no previous medical history, which underwent a resection of a TDC of 29 mm in diameter, diagnosed by an anterior cervical tumefaction. The anatomopathological examination of the cyst was in favor of papillary carcinoma. The evolution is marked by the appearance of a left cervical adenopathy. The patient has benefited by a biopsy excision, and histology was in favor of a metastasis of a papillary carcinoma. Cervical ultrasound: normal, without cervical adenopathies. The patient had a total thyroidectomy whose anatomopathology returned without anomaly. The hormonal assessment showed an undetectable level of thyroglobulin (TG). (TSH: 30.24 Uu/ml, TG: 0.55 µg/l and anti-TG antibody: 1.2 IU/ml). Levothyroxine was increased to 150 µg/day. Iratherapy is considered for our patient.
Conclusion
The papillary cancer on TDC is an exceptional localization. It can develop at the expense of residues of thyroid follicles within the cyst of the TDC, or may be secondary to thyroid papillary carcinoma metastasis. Its management consists of an excision of the cyst. Hormone replacement therapy is systematic. Total thyroidectomy is indicated in cases of thyroid suspicious of malignancy, also if extra-cystic extension. Lymph node dissection is indicated in the presence of adenopathy. A complement by Iratherapy is not systematic, however in our patient it is indicated because the presence of a lymph node metastasis. The monitoring will be on long term and generally the evolution is favorable.

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EP1448

Impact of RAC1/1b signalling on Sodium Iodide symporter regulation

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The Sodium Iodide Symporter (NIS) is responsible for active transport of iodide into thyroid cells. Its expression in thyroid tumors allows the use of radioactive iodine (131I) as co-adjuvant therapeutic tool to eliminate remaining tumor cells and metastases after total thyroidectomy. Nevertheless, certain subsets of patients with advanced forms of thyroid cancer lose the ability to respond to radioiodine therapy, which drastically reduces their survival rates. Recent studies have implicated the Rac1/p38 pathway in the stimulation of NIS expression through a mechanism that remains unclear. Additionally, the overexpression of RAC1b, a hyperactive splicing variant of RAC1, was recently shown to be overexpressed in a subset of papillary thyroid carcinomas carrying the activating mutation BRAFV600E and to be associated with unfavorable outcome. BRAFV600E mutation, in turn, has been associated with the downregulation of NIS. Here, we further investigate the role of RAC1/RAC1b on NIS expression levels, and developed new cellular models to functionally assess the impact of these GTPases on NIS-mediated iodide uptake. To evaluate whether RAC1b has a role in NIS expression modulation, we determined NIS transcript levels in a cohort of 64 follicular cell-derived thyroid tumors, comparing tumors presenting RAC1b overexpression ($n=32$) to those that did not ($n=32$). RAC1b-overexpressing tumors were defined as those with expression levels above a defined threshold (corresponding to the mean value plus two SDs of RAC1b expression level in a normal thyroid group). RAC1b and NIS expression was assessed by quantitative RT-PCR. We found that samples negative for RAC1b expression presented higher levels of NIS in comparison to RAC1b-overexpressing samples (4.402 ± 1.271 vs 1.916 ± 0.5423, respectively; $P=0.0384$, two-tailed Student's t-test). Thus, our results show an inverse correlation between RAC1b and NIS expression levels, suggesting that RAC1b might antagonize RAC1 effectiveness at stimulating NIS expression. To further explore the impact of RAC1/1b signalling on NIS expression regulation, we established a halide-sensitive YFP-based reporter in a normal thyroid cell line system, allowing us to detect differences on iodide influx upon TSH stimulation. Our preliminary results support the relevance of further studying the impact of RAC1/1b on NIS regulation.

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EP1449

The usefulness of the study of sodium iodide symporter expression in thyroid primary tumors

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Thyroid cancer therapy is based on surgery followed by radioiodine treatment of tumor remnants and metastases. The incorporation of radioiodine by cancer cells is mediated by sodium iodide symporter (NIS), normally present in thyroid follicular cells' membrane. We studied the expression of NIS in a series of 229 thyroid primary tumors using real time PCR and immunohistochemistry, and searched for possible associations between NIS expression and clinicopathological features, molecular data, response to therapy and prognosis. NIS mRNA levels were significantly lower in carcinomas than in normal adjacent thyroid; carcinomas from males or with vascular invasion presented significantly less NIS mRNA expression than carcinomas from women and non invasive carcinomas. BRAFV600E tumors and those presenting extrathyroidal extension had a tendency to display lower NIS mRNA expression than tumors BRAFWT and no extrathyroidal extention. Regarding immunohistochemistry, only 12/211 of the cases demonstrated NIS in the basolateral membrane of tumor cells; these cases showed variable outcomes concerning therapy response and prognosis. All but one of the aforementioned cases were wild type for BRAF, NRAS and TERT promoter mutations. NIS immunohistochemical expression in primary tumors did not predict tumor behavior or response to therapy. NIS mRNA expression was more informative of tumor aggressiveness than NIS protein expression. In order to validate our data we also searched possible associations between NIS mRNA expression and clinicopathological and molecular features on 378 primary papillary thyroid carcinomas of the TCGA database. Further studies are needed to confirm the association observed between the presence of the oncogenic mutations (BRAF, NRAS and TERT promoter) and both lower mRNA expression and diminished membrane targeting of NIS protein.

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EP1450

Concomitant occurrence of papillary thyroid cancer (PTC) in a branchial cleft cyst (BCC) and an occult multifocal PTC in the thyroid gland

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Introduction
BCC is a congenital epithelial neck cyst, which occurs due to failure of the second branchial cleft to obliterate during embryogenesis. Development of PTC inside the cyst is extremely rare.
Case description
A 29-year-old female presented to the endocrinology clinic with a gradually increasing painless mass in the right lateral region of the neck, identified on ultrasound examination as an anechoic cyst of size 2×2×5 cm with a smooth wall. Despite repeated biopsies and evacuation of the fluid, the cyst was a recurrent problem. Hence, a decision for surgical removal was made. The histopathological examination revealed a cystic structure with lymphatic weaving in the wall and PTC in both the lumen and lymphatic weaving. Despite no abnormalities were detected in the thyroid on ultrasound, the patient was referred for total thyroidectomy. The histopathological specimen revealed the presence of multifocal PTC within the thyroid, the largest being 1 mm, and one metastatic lymph node. Due to the increased post-surgical thyroglobulin concentration and the suspicion of metastasis to other cervical lymph nodes on ultrasound examination, the patient required two subsequent lymphadenectomies followed by radioiodine therapy to achieve remission. No further recurrence of the disease was observed in a 6-year follow-up period.
Conclusions
In such patients two scenarios should be considered: (i) PTC in BCC is a primary lesion arising from ectopic thyroid tissue concomitant with multifocal PTC of the thyroid or (ii) neck cyst is a cystic degeneration of a metastatic lymph node, while primary site is located in the thyroid. Detection of PTC in BCC requires verification of the thyroid for concomitant neoplastic lesions. Despite normal thyroid on ultrasonography, histopathological examination may reveal the presence of multifocal occult PTC in the thyroid. Therefore, following the diagnosis of PTC in BCC, completion total thyroidectomy should be the recommended procedure.

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EP1451

Comparative analysis of clinicopathological characteristics between Korean and Italian thyroid cancer patients

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Background
The incidence of thyroid cancer in South Korea has increased rapidly. Increase in medical surveillance and access to health care services have enhanced the detection of asymptomatic tumors. We investigated the differences of tumor characteristics between South Korean patients and Northern Italian patients subject to different healthcare systems.
Methods
The demographic, histopathologic and management features of thyroid cancer operated in two tertiary referral hospitals in Seoul, South Korea ($n=4,474$) and Varese, Northern Italy ($n=2,897$) from years 2000 to 2015 were analyzed.
Results
The mean age of diagnosis was similar (49 years) among the Korean and Italian patients. However, the proportion of female was higher among Korean patients (81.3 vs 74.2%, $P<0.001$). The proportion of papillary subtype was higher (99.2 vs 92.6%, $P<0.001$) and the size of tumor was smaller (1.03 ± 0.83 vs 1.79 ± 1.01 cm, $P<0.001$) in the Korean subjects. Interestingly, the prevalence of multifocality (37.8 vs 8.2%), extrathyroidal extension (41.6 vs 13.1%) and lymph node metastasis (34.8 vs 6.7%) was also higher in the Korean patients ($P<0.001$). Most of the Italian cases received total thyroidectomy (96.0%). In comparison, a considerable number of the Koreans (21.9%) received hemithyroidectomy as initial surgical treatment ($P<0.001$). The proportion of the patients who received radioactive iodine therapy was significantly higher among the Korean patients (53.3 vs 29.7%, $P<0.001$).
Conclusion
We have identified distinct lineaments of thyroid gland cancer between the two different nationalities which could not be explained entirely by early detection from screening. Further prospective studies with controlled treatment strategies are needed to determine long-term prognosis.

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EP1452

Malignant struma ovarii and synchronous tumour of thyroid gland in the same patient: a single pathway for two different tumours?

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Background
Struma ovarii (SO) is the presence of thyroid tissue as a major cellular component in an ovarian tumour.
Case report
A 35-year-old, Caucasian female, asymptomatic and with normal physical examination was submitted to left oophorectomy due to an ovarian mass (8.2× 7.0×6.0 cm) detected in routine pelvic examination. Her mother also had history of oophorectomy for an ovarian tumour and partial thyroidectomy for benign thyroid nodule. The histological examination of the mass showed a totally intra-ovarian neoplasia predominantly composed of thyroid tissue (95%) with areas of follicular variant of papillary thyroid carcinoma (FVTPC) which was compatible with malignant SO. She was tested for thyroid function which was normal and thyroid ultrasound revealed a slightly hypoechogenic nodule with 1.7 cm in the right lobe. Fine needle cytology of this nodule was performed and was compatible with FVTPC. She underwent total thyroidectomy and histology revealed a well differentiated thyroid tumour of uncertain malignant potential. No vascular or capsular invasions were recorded. She was treated with ^{131}I and suppressive doses of levothyroxine and remains asymptomatic, without signs of clinical or biochemical recurrence of thyroid and ovarian tumours. The search for BRAF mutations was negative.
Discussion
Three other cases of synchronous thyroid and ovarian thyroid tumours have been described so far to the best of our knowledge. In this case, since both tumours were confined and no invasion was documented they were probably synchronous tumours instead of metastasis. These two tumours are embryologically related so we cannot exclude a common mechanism of genomic origin that possibly explains the synchronous tumours and even the familiar history.

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EP1453

Does Preoperative Serum Neopterin Level Predict Differentiated Thyroid Carcinoma?

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Introduction
The frequency of thyroid surgery for suspected malignancy but postoperative resulted with benign pathology tends to increase in the worldwide. Therefore, additional preoperative markers are needed to prevent excessive surgery. Neopterin is a new molecule secreted by monocytes and macrophages and indicates the activation of cellular immunity. Therefore it can be used as a marker of immune activation. We aimed to evaluate the diagnostic value of serum neopterin levels to determinedifferentiated thyroid cancers (DTC).
Material and method
This prospectivestudy included 86 patients (67 female and 19 male) who underwent thyroidectomy due to nodular goiter between March 2015 and November 2015. Patients who had overt hyperthyroidism or hypothyroidism andrenal or hepatic dysfunction were excluded from the study. Weight, height and body mass index (BMI) were measured prior the surgery. A fasting blood sample obtained from all study participants prior the surgery to measure serum neopterin levels. Post-thyroidectomy, according to pathology results patients were divided into two groups,as DTC and benign pathology.
Results
Of thesepatients, 39 were diagnosed with DTC and 47 had benign pathology according to postoperative histologic evaluation. There were no significant differences between the two groups in terms of age, weight, height and body mass index. Demographical data and laboratory results are given in the table. There was a positive correlation with neopterin levels and tumor size ($r=0.776$, $P<0.001$).
Discussion
Our study indicates that there is a strong association between plasma neopterin levels and DTC. Thus, if it is supported with high volume larger studies, neopterin may be a useful marker forpredicting the DTC preoperatively.

Table The comparison of demographical data and neopterin levels between groups.

	Group 1 (n:39)	Group 2 (n:47)	*P*
Age (year)	47.2±12.8	48.4±12.9	0.719
Weight (kg)	79.3±15.5	76.6±15.5	0.455
BMI (kg/m^2)	30±5.9	28.8±5.2	0.362
Preoperative TSH (mIU/lt)	1.57±1.47	1.21±1.27	0.127
Plasma neopterin (ng/ml)	50.8±48.2	22.1±20.7	**0.009**

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EP1454

Unexpectedly low thyroglobulin levels in differentiated thyroid carcinoma – case report

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Case report
66 year old male with a neck growing mass performed an ultrasonography and fine-needle aspiration biopsy which was suspicious for papillary carcinoma. The patient was submitted to total thyroidectomy and central and left lateral compartments lymph node dissection. The histological report showed a follicular carcinoma of 9 cm, with multiple lymphovascular invasions and skeletal muscle invasion. There was a focally positive surgical margin and resected lymph nodes had no metastases. Thoracic CT showed multiple lung nodules; PET showed faint uptake in a single nodule in the upper lobe of the right lung. Five months after surgery, 5,5 GBq (150 mCi) of iodine-131 (RAI) were administered. Forty-eight hours after therapy whole-body scintigraphy (WBS) was performed: moderate thyroid remnant and faint uptake in the lower third of the right thoracic area were visible. Non-stimulated serum thyroglobulin (Tg) was undetectable and stimulated levels were 1.5 ng/ml; anti-thyroglobulin antibody (ATg) was negative. Two years after RAI, Tg levels increased to 15.2 and to 43.1 ng/ml six months thereafter. ATg remained negative. Neck and thorax CT showed a new lesion in D3 and no progression of lung nodules. The patient referred light numbness in his left arm and hand. A second RAI was performed under thyroid hormone withdrawal. Stimulated serum Tg was 229.0 ng/ml. PET-CT (Default 1) was performed just before RAI administration: uptake in lytic lesions in D3 and D4 was found (SUVmax =11.3). Post-therapeutic WBS (Default 2) also showed intense uptake in the dorsal spine and faint uptake in pulmonary lesions.
Conclusion
Serum thyroglobulin is usually useful to monitor disease progression. In patients with aggressive differentiated thyroid carcinoma, Tg alone may not reflect

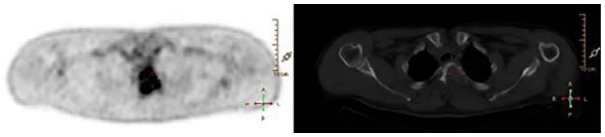

Fig. 1 18F-FDG PET-CT.

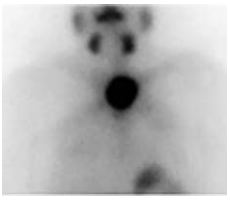

Fig. 2 WBS.

accurately disease progression, as in this patient with documented bone and pulmonary disease that is both differentiated and aggressive.

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EP1455

Papillary thyroid microcarcinoma: is it worth ablating the patients with radioiodine?

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Objective
Recently, radioablation has been offered for patients with thyroid microcarcinoma, however some authors favor just follow-up as the prognosis of this disease is excellent. In this study, we compared the long-term follow-up results, for a period of 16 years, in patients with thyroid microcarcinoma in a group of patients with thyroidectomy only and in another both thyrodectomized and radioablated.
Methods
Two hundred sixty five patients with a proven diagnosis of thyroid cancer <10 mm among 1755 thyroid cancer cases were included in the study. Any patients with unfavorable characteristics such as capsular or perithyroidal invasion, intrathyroidal spread, lymph node invasion or multicentirity were excluded. In group IA, 18 patients (14 female, 4 male; mean age 74), patients were hemi-thyroidectomized only and 64 patients (43 female, 21 male, mean age 66) in group IB had total or near-total thyroidectomy. In group II, 183 patients (123 female, 60 male; mean age; 61) underwent total or near total thyroidectomy and ingested I-131 (dose range; 30-85 mCi) while they were in ahypothyroid state (TSH >40 uIU/L). In the surveillance period, all patients were monitored with periodical serum Tg/ATg measurement and ultrasound of the neck for a period of two to 16 years.
Results
In group IA and IB, lymph node metastasis was detected in 9 patients (11%) with US-guided fine needle aspiration in the surveillance period. No patient asked for additional treatment including surgical intervention and followed by L-T4 suppression only. Serum Tg levels were less than 2 ng/dl (range; 0.2 to 3.9 ng/dl) in 56 patients an in the remaining 26, ranged from 2.0 to 9.8 ng/dl. Serum Tg levels decreased to lower values than 9.8 ng/dl after no more than one year. In group II, lymph node invasion were detected in 19 patients (10%) and 9 of them had neck dissection for a complete cure. Initial serum Tg levels ranged from 2.1 to 19.8 ng/dl in those patients. In 19 patients with lymph node invasion serum Tg levels ranged between 2.2–19.8 ng/dl.
Conclusion
In both groups, approximately 1/10 of patients presented with recurrent or metastatic disease to regional lymph nodes. As the difference between radioablated and not ablated groups is statistically not significant, we do not recommend completion thyroidectomy and radioablation for patients with thyroid microcarcinoma (excluding any poor prognostic factor) and follow-up unless the disease becomes clinically apparent.

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EP1456

Anaplastic thyroid carcinoma and multinodular toxic goiter

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A 69 years old female with cervical radiotherapy 25 years ago for an unknown condition, known with multinodular goitre and hyperthyroidism for 6 years, presented with a 6 months history of enlarged right supraclavicular mass, local pain with difficulty in mobilization of the right arm and weight loss. She also reported progressive bilateral exophtalmia especially on the right side, no dysphagia, hoarseness or dyspnoea. Thyroid hormone levels were normal on antithyroid drugs and the thyroid auto-antibodies and parathyroid levels were all normal. Neck CT showed an inhomogeneous large gland with several hypoechoic nodules, compression of the trachea and oesophagus, severe compression of the right internal jugular vein with collateral blood flow and a right supraclavicular adenopathy with no cleavage plan from the thyroid tissue. No significant head, chest and abdominal lesions were described. Fine needle aspiration of the thyroid and the supraclavicular mass revealed anaplastic carcinoma, with no expression of the thyroid transcription factor 1, mamoglobin 1 and positive expression for CK7, CK19 and CK5. The tumour was considered unresectable and the patient was started on chemotherapy with paclitaxel and carboplatin for 4 months. After the first 2 rounds of chemotherapy she had an initial good response, with shrinkage of the supraclavicular mass. The CT after the completion of chemotherapy showed an increased volume of both the thyroid gland and the supraclavicular mass, with thrombosis of the internal jugular vein and supraclavicular bone erosion. She is under evaluation for external radiotheraphy. The association between a toxic nodular goiter and anaplastic thyroid carcinoma after cervical radiotherapy, with no distant metastases has apparently not been reported so far.

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EP1457

Evaluate the effectiveness of the Bethesda system for reporting thyroid cytopathology in the prediction of thyroid cancer (TBSRTC) on fine needle aspiration (FNA) in Moscow region, Russia

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Aim
To evaluate the effectiveness of the Bethesda system for reporting thyroid cytopathology in the prediction of thyroid cancer on fine needle aspiration (FNA).
Materials and methods
This is retrospective study of 70 detected thyroid cancer. Thyroid ultrasound and FNA were performed on all patients. 66 of them with cancer suspicion were communicated to the thyroid surgeon, 4 cases of papillary carcinoma were accidentally diagnosed after hystological investigation. 65 patients underwent total thyroidectomy with or without lymph node dissection. One patient refused surgical treatment. 69 intraoperative samples were subjected to hystological examination.
Results
In the group with cancer suspicion category VI by TBSRTC was assigned in 51 (77.3%) cases, category V in 13 (19.7%) cases, 1 case (1.5%) with category V and VI with multinodular goitre, and 1 case (1.5%) with category VI and IV with multinodular goitre too. Hystological examination of 60 (91%) cases confirmed thyroid cancer: papillary carcinoma in 56 (85%) cases; medullary carcinoma in 3 (4.5%) cases; mixed follicular and papillary carcinoma in 1 (1.5%) case. In 6 (9%) cases the cancer wasn't detected. 2 (3%) of these 6 cases were classified as category VI and 4 cases (6%) as category V. Thyroid cancer was not detected in all the cases of categories II-III found after thyroidectomy for other reasons.
Conclusion
Category VI corresponds with 97% of diagnosed thyroid cancer, and category V - 94%. Thyroid cancer was confirmed in only 4 of all cases with category IV. This result indicates the need for additional diagnostic methods in the preoperative period for category IV – for which molecular genetic tests may have potential. To determine the risk of malignancy of thyroid nodules with categories II-III requires long-term monitoring.

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EP1458

Outcomes and imaging results in patients with medullary thyroid cancer

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Medullary Thyroid Cancer (MTC) is sporadic in approximately 75% whilst 25% of MTC occurs as hereditary forms due to RET mutations. Prognosis is relatively good with 10-year survival rates of 65%. However, many patients develop recurrent disease and imaging is critical to localise the site of recurrence. Eighty-eight MTC patients, attending the Royal Marsden Hospital NHS Trust were

included in an analysis of overall survival. Median Follow-up duration was 7.5 years (IQR: 4.5–13.5). Twenty cases were hereditary and had a median survival 12 year (7.7–22.5 95%CL). Sixty-eight patients with Sporadic MTC had a shorter survival outcome, median survival 5. 7 year (5.0–7.7 95%CL). Overall median survival rate was 7.3 years (5.3–9.3 95%CL). Hazard Ratio for Sporadic Hereditary is 2.1 (1.2–3.5, $P=0.005$). According to Kaplan-Meier estimate, 65%($n=13$) of these Hereditary MTC survive 10 years. In contrast, 10 year survival rate of sporadic cases was 28% ($n=19$). We also evaluated the sensitivity of different imaging modalities within three bands of calcitonin levels (0–100, 100–400, and > 400 ng/l). The findings demonstrated that USS neck had a superior sensitivity for localising diseases in those with calcitonin with less than 400: 0.25 (.0.073–.0.524 95%CL, calcitonin 0–100), 0.857 (0.421–0.996 95%CL calcitonin 100–400,) and .0 556 (.0.308–785 95%CL calcitonin > 400). In contrast, in patients with calcitonin > 400, CT neck and body has a higher sensitivity 0.667 (.0.49–0.814 95%CL) and .0745 (.0.604–0.857 95%CL) respectively. Thus, USS neck should be considered as first line imaging modality in follow-up in MTC in those with calcitonin < 400 and CT should be considered at higher calcitonin levels in order to identify site of disease relapse. In addition, Hereditary MCT has better prognosis than sporadic cases.

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EP1459

Lymph node metastasis of differentiated thyroid cancer: role of thyroglobulin in the washout fluid of fine-needle aspiration biopsies

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Introduction
Thyroglobulin (Tg) measurement in needle washouts from fine-needle aspiration biopsies (FNA-Tg) increases the sensitivity of lymph node (LN) metastasis diagnosis in differentiated thyroid cancer (DTC). However, the cutoff value for FNA-Tg has not been clearly established and there are large differences between clinical studies, which hinders its interpretation. Our study aimed to investigate the optimal cutoff value of FNA-Tg and evaluate its utility in the diagnosis of LN metastasis of DTC.
Methods/design
This was a retrospective study of 211 consecutive cases of FNA from 143 patients identified from our institutional database, who underwent FNA citology and Tg measurement in needle washout for suspicious LN, between 2012 and 2016.
Results
From the total of 211 cases, 121 (57%) had personal history of DTC. FNA citology was benign in 114 (54%) and malignant in 64 (30%). The median FNA-Tg was 1168 ng/ml (interquartile range 27–11974) in malignant LNs, and 0.1 ng/ml (interquartile range 0–0.27) in benign LNs. LN ressection was performed in 55 patients (38.4%), based on the combined results of FNA-Tg and FNA citology. Histology reported LN metastasis of DTC in 45 of these (81%). Compared to FNA-Tg values above 0.2 ng/ml, FNA citology showed superior specificity (95.4% vs 67.1%) but slightly inferior sensitivity (88.7% vs 91.5%). FNA-Tg values above 10 ng/ml showed 80.3% sensitivity and 100% specificity. Combining both diagnostic strategies (FNA citology and FNA-Tg above 0.2 ng/ml) showed superior diagnostic power than using either strategy alone (specificity 96.4% and sensitivity 91.5%). We evaluated the optimal cutoff values of FNA-Tg in determining malignant LNs from ROC analysis and the optimal cutoff value was 0.98 ng/ml (sensitivity, 85%; specificity, 95.4%).
Conclusion
Our results show that combining FNA citology and Tg measurement is useful for the investigation of LN metastasis of DTC. A FNA-Tg cutoff value above 1 ng/ml should lead to its diagnosis.

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EP1460

The epidemiology of thyroid cancer within a center of excellence in Athens: Real life data

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Thyroid cancer is the most frequent endocrine cancer. Its incidence has been found to increase in recent years. Additionally, environmental factors, which may be implicated in the pathogenesis of thyroid disorders, such as iodine deficiency and salt iodine supplementation are changing and may have an impact on the epidemiology of thyroid cancer. The aim was to study the epidemiology of thyroid within a center of excellence in Athens in the modern world setting. A cohort of 63 patients, aged 46.3 ± 1.77 (mean ± S.E.M), range 16–81 years with thyroid cancer was studied. The histology of the cancer was recorded. The histological subtypes of papillary thyroid cancer were evaluated and recorded. Within a cohort of 63 patients with thyroid cancer 60 were found to have papillary thyroid cancer, three were found to have follicular thyroid cancer, one was found to have a mixed medullary follicular-derived thyroid cancer and one was found to have a B cell lymphoma of the thyroid. Within the group of the patients with papillary thyroid cancer, 39 (67.24%) were found to have papillary, 19 (32.8%) were found to have the follicular variant of papillary thyroid cancer, 1 (1.72%) had encapsulated papillary thyroid carcinoma, and 1 (1.72%) was found to have the tall cell variant of papillary thyroid carcinoma. It appears that in the modern world setting within a center of excellence in Athens papillary thyroid cancer was the commonest type. Although papillary thyroid cancer and the follicular variant of papillary thyroid cancer were the commonest forms of thyroid cancer recorded, more aggressive types of thyroid cancer such as the tall cell variant were also recorded.

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EP1461

Is thyroglobulin at ablation a good predictor of the thyroid remnant size in differentiated thyroid cancer?

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Aim
Stimulated thyroglobulin (sTg), measured at radioiodine remnant-ablation (RRA) in patients with differentiated thyroid cancer(DTC), is an important predictive factor of persistent disease. However, Tg produced by normal thyroid cells may also contribute to the sTg value.
We aimed to study the relationship between sTg-level in RRA and the thyroid remnant size (TRs), using post-therapy whole-body scan (131I-ptWBS), at different TSH stimulation method.
Materials and methods
We review DTC cases referred for RRA, either prepared with recombinant-human TSH (rhTSH) or after 4-weeks levothyroxine withdrawal (hipo). Anti-thyroglobulin antibodies (TgAb) and sTg were measured. Patients with positive TgAb, 131I-uptake outside the thyroid bed and suspected to have persistent disease on the first 6–12 months were excluded. Four hundred patients (331 women, 69 men;mean age sd:49.8 14.1 years-old) were selected. TRs was assessed by 131I-ptWBS, using a fixed circular region-of-interest (ROI) placed in thyroid bed. The geometric mean (GM) of the total counts (cts) in the ROI was calculated, corrected for the thigh background and normalized for the treatment activity (nGM). Based on nGM, remnants were classified into small(S)-nGM < = 10cts/MBq; medium(M)-10cts/MBq < nGM < = 50cts/MBq and large (L)-nGM > 50cts/MBq. Spearman's rank correlation coefficient was used to test the association between TRs and the sTg normalized for TSH(nTg). SPSS version-23 was used for statistical analyses.
Results
A moderate positive correlation between nGM and nTg was found in rhTSH and hipo patients ($rs=0.55$, $P<0.001$ and $rs=0.59$, $P<0.03$ respectively). For the all population we found a strong positive correlation($rs=0.61$,$P<0.002$). A positive moderate correlation was found in group-S and L ($rs=0.58$, $P<0.01$; $rs=0.42$, $P<0.034$ respectively); a weak positive correlation in group-M ($rs=0.08$, $P<0.19$).
Conclusion
Radioiodine-scintigraphy and sTg are important tools to evaluate the functional status of both normal and neoplasic thyroid tissue. Our results suggest that TRs and sTg values are correlated, in the absence of clinical/imagiological disease, regardless the method of TSH stimulation. We hypothesize that sTg values are a better predictor of TRs in patients with less TRs.

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EP1462

Prevalence of thyroid cancer in malaga and province

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Introduction
Thyroid cancer is the most common endocrine neoplasia, being its papirally version the most frequent. (90% of all differentiated thyroid neoplasms). It is usually multifocal and metastasizes normally to regional lymph nodes.
Objectives
To describe the prevalence of thyroid cancer and its histopathological variants in the different regions of the province of Malaga.
Material and methods
We performed a retrospective descriptive study. We collected the thyroid cancer diagnoses in the databases of pathological Anatomy of the different hospital centers of the province between 2010 and 2015.
Results
545 cases were collected, it is more frequent in women (79.63%) than in men (20.37%); the average age at diagnosis was 50 ± 15 years. Analyzing in different areas: 30.1% East Málaga; 12.5% West Málaga, 30.1% Costa del Sol, 1.3% Guadalhorce Valley, 1.5% Serranía de Ronda/ Sierra de las Nieves, 7.3% Axarquía, 3.1% Antequera, 2.4%, 2.7% Melilla. The most frequent histological variant was papillary (69.72%) and in the different areas: East Málaga: 76.22% papillary, 9.15% follicular, 6.71% micropapillary, 3.65% medullary, 1.83% anaplastic, 1.22% Hurtle cel, 1.22% oncocytic. West Málaga; 63.25% were papillary, 11.76% were follicular, 13.23% were micropapillary, 4.41% were medullary, 4.41% were oncocitic, 2.94% were Hurtle; Or anaplastic. Axarquia 73.17% papillary, 4.88% follicular, 9.76% micropapillary, 9.76% medullary, 2.44% anaplasic. Gualdalhorce Valley 77.59% were papillary, 6.89% follicular, 10.34% micropapillary, 1.72% medullary, 3.45% no data. Antequera, 64.71% papillary; 17.65% follicular, 11.76% micropapillary, 5.88% medullary. Serranía Ronda/Sierra Nevis: 75% papillary, 12.5% follicular, 12.5% micropapillary. In Costa del Sol 59.76% papillary, 12.20% follicular, 8.54% micropapillary, 1.22% medullary, 0.61% anaplastic, 4.27% Hurtle cel, 13.41% no data. Melilla: 80.02% papillary, 6.66% follicular, 6.66% micropapillary, 6.66% anaplasic In other provinces: 84.62% papillary, 7.14% follicular, 7.14% medullary. Tumor tissue was noticed to surpass the resection capsule in 19.08% (without data 11.93%). In 33%, no ganglia were removed, 21.6% of affected nodes and distant metastases $> 1\%$.
Conclusions
The prevalence of thyroids cancer in our population was similar to those described in Spain. In the analysis of different types, papilar was the most frequent, followed by follicular and micropapillaries. The overall prognosis is good.

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EP1463

Lymph node metastases location (central vs lateral neck) in well-differentiated thyroid carcinoma: Is it important?

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Introduction
Regional lymph node (LN) metastases have prognostic significance in differentiated thyroid cancer (DTC). Several studies demonstrated that lateral neck LN metastasis, classified as N1b, have a greater impact on overall survival than central LN metastasis. Our study aimed to assess the risk of N1a vs N1b involvement on outcome in patients with differentiated thyroid cancer (DTC), according to the 7th edition of the TNM staging system.
Methods/design
This was a retrospective study of 276 patients identified from our institutional database, who underwent surgery for DTC between 2000 and 2013. All patients had: lymph node metastasis, apparent complete tumour resection, without distant metastasis at diagnosis and nonaggressive histologic variant. The association between variables was assessed using chi-square and Student's *t*-tests.
Results
All patients were followed for a minimum of 3 years postoperatively (146.3 ± 87.1 months). Most patients had papillary thyroid cancer (99%). One hundred and twenty seven patients (46%) were classified as N1b and mean age was similar in both groups (46.6 years in N1b patients vs 47.5 in N1a; $P = 0.560$). There was no significant association between N1b classification and extra-thyroid extension (44.9% of N1b patients vs 46.3% of N1a patients; $P = 0.812$), tumour size (mean size was 23.3 vs 23.2 mm; $P = 0.958$), persistence of disease (29.4% vs 21.1%; $P = 0.163$), recurrence of disease (14.5% vs 9.1%; $P = 0.182$) and disease specific-mortality (5% vs 1.5%; $P = 0.1$).
Conclusion
Our results suggest that there is no difference in patients' outcome with LN metastasis in the central neck compared to LN metastasis in the lateral neck or mediastinum, namely disease specific mortality, recurrence and persistence of disease. These data support the recently updated TNM classification in which lymph node metastases location is not considered for staging purposes.

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EP1464

Two cases with metastatic thyroid cancer

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Although the thyroid gland has an abundant blood supply, metastasis to the thyroid gland is a rare condition. Its incidence varies from 0.1% and 3% in clinical series. First case. A 56-year-old man presented to emergency service with neurological symptoms. CT of brain revealed multiple hyperdens lesions. Posteroanterior chest X-ray showed increased opacity in the left lung. Metastatic lung cancer was considered as a preliminary diagnosis and PET/CT was performed. PET/CT showed a mass lesion of $15.8 \times 7.6 \times 8.5$ cm in the upper lobe of the left lung and multiple pathologic involvements with metastatic appearance were present in many organs, especially in thyroid gland. A biopsy was performed from the mass lesion and biopsy revealed squamous cell lung cancer. FNA was performed from a nodule located in the right thyroid lobe and cytopathological analysis of aspiration material showed metastatic epithelial carcinoma. Second case. A 42-year-old man presented with fatigue, dyspnea and cough. Thorax CT revealed a nodular lesion of 27×17 mm in posterior segment of the right upper lobe. PET/CT showed increased FDG uptake in the lung, mediastinum and abdominal multiple lymph node regions, thyroid gland and skeletal system. Biopsy was performed with fiberoptic bronchoscopy and the result was consistent with primary adenocarcinoma of the lung. FNA was performed from a nodule located in the right thyroid lobe and from a suspicious right cervical lymph node in level III. Cytopathological analysis of both aspiration materials revealed metastasis of malign epithelial carcinoma. It was thought that medical palliative approach would be more appropriate treatment option for two cases when presence of multiple synchronous metastases, absence of local symptoms, characterization of primary diseases, general condition and life expectancies of the patients considered. Discussion. It should be known that the treatment approach in patients with metastatic thyroid cancer affects survival and treatment should be individualized.

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EP1465

Isolated bone metastases: a rare form of presentation of papillary thyroid carcinoma

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Background
Papillary thyroid cancer (PTC) is the most frequent type of well-differentiated thyroid cancer (WDTC) and frequently poses a management dilemma. Its indolent behavior associated with high long term survival support the trend towards a more conservative management approach. The authors present a case of isolated bone metastases as the form of presentation of papillary thyroid carcinoma. A 61-year-old man was admitted with complaints of lower back pain for the previous 3 months. A lumbosacral spine CT and sacral MRI were performed, showing a $9 \times 9 \times 7{,}5$ cm mass centered on the sacrum infiltrating the sacral canal, with soft tissue density associated with extensive lytic lesions of the sacral vertebra, suggestive of chordoma. The patient was submitted to a sacrectomy with reconstruction. The histology of the removed specimen revealed involvement of the sacrum by thyroid cancer, namely papillary type (follicular variant), with positivity for thyroglobulin and TTF-1 on the

immunohistochemistry study. The thyroid ultrasound showed multiple nodes bilaterally and the FDG-PET scan showed increased uptake in the left thyroid lobe and in the area of the sacral surgery, without other areas of high uptake. The patient was submitted to a total thyroidectomy, with the histologic study of the thyroid revealing a multifocal papillary thyroid cancer (follicular and oxyphilic variants). Ablative treatment with radioactive iodine was administered after the surgery.
Conclusion
Distant metastatic disease at presentation is rare in WDTC, with these patients having less favorable outcomes. For this reason, many risk stratification algorithms include metastatic disease as a high risk factor. This clinical case reports a rare form of presentation, showing us that, although most PTC are indolent, there are still factors about this type of tumor we need to study in order to be able to single out these specific cases for more aggressive treatment.

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EP1466

Association between preoperative serum MMP-9 and histopathological features of thyroid tumors

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Introduction
Matrix metalloproteinase-9 (MMP-9) is a zinc dependent proteolytic enzyme used by cells for degradation of the extracellular matrix during invasion and migration. There are only a few reports regarding the role played by MMP-9 in papillary thyroid carcinoma (PTC).
Aim
To evaluate the association between MMP-9 secretion, reflected by preoperative serum levels and the histopathological features of thyroid tumors.
Materials and methods
We assessed serum MMP-9 in 329 subjects: 309 patients with thyroid tumors and 20 healthy controls (C). Patients were divided into 2 groups, following the pathology report: benign disease group (BD) ($n=176$, aged 50.5 ± 12.88 years) and PTC group ($n=133$, aged 48.6 ± 14.92 years). In the PTC group histopathological features of thyroid tumors were analyzed according to pathological stage, histological subtype, multifocality and invasion. The histology showed classic PTC (cPTC) in 49 patients, follicular variant (fvPTC) in 52 and aggressive forms (AGR) in 32 patients. Sera were collected before patients underwent surgery. MMP-9 was measured by Quantikine Elisa kit (R&D System). The study was approved by Ethics Committee of the Institute.
Results
We found a significant difference in serum MMP-9 levels between controls and thyroid tumors (BD+PTC) (mean$\pm$S.E.M.: 561.45 ± 49.37 ng/ml vs 787.47 ± 31.24 ng/ml, $P<0.0001$). According to the pathology tumor stage (T1–T4), we found higher MMP-9 levels in T3 (869 ± 79.48 ng/ml) compared to more incipient stages (T1 vs T3 $P<0.01$, T2 vs T3 $P<0.03$ respectively). fvPTC showed lower MMP-9 levels vs cPTC or AGR (596.38 ± 34.76 ng/ml vs 760.35 ± 70.54 ng/ml or vs 835.75 ± 109.9 ng/ml, respectively, $P<0,05$). There was no significance between cPTC and AGR. There was no difference in MMP-9 in terms of multifocality, but patients with invasive tumors had significantly higher serum MMP-9 than non-invasive ones (838.14 ± 80.3 ng/ml vs 618.68 ± 30.9 ng/ml, $P<0.02$).
Conclusions
Preoperative serum MMP-9 might differentiate patients at risk for invasive and more aggressive tumor behavior, with implications in post-surgical radioiodine treatment and follow-up.

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EP1467

Follicular thyroid carcinoma and follicular variant papillary thyroid carcinoma: Clinical and histological features depending on the initial size

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Introduction
Follicular Thyroid Carcinomas (FTCs) and Follicular Variant Papillary Thyroid Carcinomas (FVPTCs) may present absence of suspicious ultrasonography features more frequently than classic papillary carcinomas. Thus, some cases may be identified with the pattern of 'low suspicion' rather than intermediate or high suspicion defined in the American Thyroid Association (ATA) guidelines of 2015. These guidelines establish a size cutoff of 1.5 cm to recommend fine-needle aspiration in nodules belonging to this category of low suspicion, justified because the probability of distant metastasis in FTCs <2 cm is rare. The aim of this study is to analyze the perithyroidal extension and the presence of variables associated with greater aggressiveness in cases of FTC and FVPTC as a function of the initial size.
Description of methods
A retrospective study of 76 patients with diagnosis of FTC or FVPTC was conducted. The presence of the followings clinical and histological parameters were evaluated: initial perithyroidal extension; aggressive histologic variants (extensive capsular invasion, oncocytic features, undifferentiated foci); presence of vascular invasion, presence of lymph node metastases and distant metastases at diagnosis and during follow-up. The differences between the 2 groups were analysed according to nodular size: <1.5 cm (group A) and ≥ 1.5 cm (group B).
Results
76 cases with a mean age of 53 ± 16 years, 75% women. Group A: 40 cases, size 0.72 ± 0.34 cm, 8% FTC and 92% FVPTC. Group B: 36 cases, size 2.76 ± 1.04 cm, 33% FTC and 67% FVPTC. Extrathyroidal extension 5% vs 19.4% (p0,052); aggressive histologic variants 0% vs 22.2% (P0.002); vascular invasion 0% vs 19.4% (P0.003), lymph node metastases 10% vs 13.9% (P0.6); distant metastasis 0% vs 2.3% (P0.28).
Conclusion
The presence of aggressive histologic variants and vascular invasion was significantly greater in the carcinomas ≥ 1.5 cm. None of the carcinomas <1.5 cm presented aggressive histological, vascular invasion or distant metastases at diagnosis or during follow-up. Our data agree with the recommendation established by the ATA to choose a size cutoff of 1.5 cm for low suspicion pattern nodules.

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EP1468

Ten years of TSH suppression therapy in differentiated thyroid cancer analysed by HR-pQCT

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Introduction
TSH suppression therapy by thyroid hormones (TST) in patients with differentiated thyroid cancer (DTC) could be associated with adverse effects on bone metabolism in post-menopausal women. Recent recommendations suggest therefore to minimize time passed under TSH suppression therapy. However data in literature are controversial and few shows results on microarchitecture. This study evaluated bone microarchitecture using High-resolution peripheral quantitative computed tomography (HR-pQCT, XtremeCT; Scanco Medical AG, Switzerland), in post-menopausal women under TST for more than ten years.
Patients and methods
We conducted a descriptive, case-control, cross-sectional study, in 22 menopausal women under TST for more than 10 years (patients), compared with 32 menopausal women without any bone disease (controls). We measured Bone Mineral Density (BMD) by Dual-energy X-ray absorptiometry (DXA), Bone Microarchitecture by HR-pQCT, bone markers (serum osteocalcin and cross laps).
Results
BMI were similar in both groups. PTH was higher in patients (37.2 ± 2.2 ng/l) compared with controls (29.4 ± 2.4 ng/l), $P=0.03$. TSH was at 0.10 ± 0.03 mUI/L, with duration of TST of 17.9 ± 1.2 years. No differences were observed between the two groups for bone markers. Hip and lumbar spine BMD were not impaired in patients group. However radial cortical bone density value (Dcomp) was lower in patients (Dcomp at the radius: 816.7 ± 24.5 g/cm^3 vs 863.3 ± 11.3 g/cm^3 in controls, $P=0.04$).
Conclusions
This preliminary study shows an adverse effect of TST on radial Dcomp, while BMD is not affected. The trabecular micro architecture is preserved. These preliminary results need to be confirmed and impact of bone breaks need to be studied.

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EP1469

Metastatic papillary thyroid carcinoma with intraglandular dissemination in remission of Graves' disease

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A 26-year-old woman was referred to our outpatient clinic, presenting with growing left sided neck mass. She was in remission of Graves' disease for the last two years.Ultrasound examination revealed isoechogenic nodule with micro-calcifications in the upper third of the left thyroid lobe measuring 9×6×6 mm and conglomerate of lymph nodes on the left side of the neck, the largest node measuring 37×21×13 mm. Behind the lower pole of the left thyroid lobe we found lymph node. Fine needle aspiration of the isoechogenic nodule in the left thyroid lobe, conglomerate of lymph nodes on the left side of the neck and lymph node behind the lower pole of the left thyroid lobe revealed papillary carcinoma. Total thyroidectomy with left modified radical neck dissection was performed. Histopathological examination confirmed papillary thyroid carcinoma with intraglandular dissemination and metastases to 18 out of 26 lymph nodes. Patient recived ablative-therapeutic dose of 3.83 GBq of I-131. Now, 6 years later, the patient is disease free.

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EP1470

Thyroid nodule size and the risk of malignancy

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Introduction
Thyroid nodule size is routinely assessed and has been a cause for concern, if it is a carcinoma or not.
Aim
Our aim was to evaluate the relationship between thyroid nodule size and cancer risk. It was a retrospective analysis of 386 patients with thyroid nodules who referred to surgery in our hospital from January 2011 to March 2016. Patient's demographic data, nodules size, and final pathology were recorded. All data were analyses using SPSS18.
Results
From the total of 386 patients, female were 86% and male 14%, with mean age of 46.75 years old ±14.24 DS were included for this study. Based on final pathology 179 patients (46.5%) had malignant nodules. The mean size of malignant and benign nodules were 3.07±1.52 cm and 3.6±1.59 cm respectively ($P<0.003$). For the purposes of this investigation, thyroid nodules <1 cm in diameter provided baseline cancer risk for comparison (5.6% risk of cancer). The overall prevalence of cancer in nodules 1.0–1.9 cm was 20.1%; 2–2.9 cm was 30.8%; in nodules 3.0–3.9 cm, 23.4%; and in nodules ≥4.0 cm, 20.1%. The primary influence of this association was the low malignancy rate in nodules under 1.0 cm. When comparing nodules 1.0–1.9 cm, 2.0–2.9 cm, 3.0–3.9 cm, no difference in malignancy rate was demonstrated ($P=0.5$). For nodules >4 cm the differences was statistically significant (OD: 3.17; CI95%: 1.01–10.02; $P<0.04$).
Conclusion
These data provide strong evidence that thyroid nodule size >4 cm is associated with an increased risk (three fold) of well-differentiated thyroid cancer and can be applied in medical decision for thyroid surgery.

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EP1471

Lateral cervical lymph node metastasis from papillary thyroid cancer of undetected primary: a case report

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Background
Lymph node metastasis from papillary thyroid cancer without detectable primary within the thyroid gland is extremely rare. We describe a case of a young woman with a cervical metastasis, without detectable orthotopic or ectopic thyroid focus.
Case report
A 30-year old woman with a history of adenocarcinoma of the ascending colon six years previously, presented at the 15th week of a normal second pregnancy, for management of subclinical Hashimoto's thyroiditis. She had received thyroxine replacement during her first pregnancy 2 years earlier. She had a family history of colon cancer in her maternal grandmother and her mother's two cousins. On examination she had a palpable node at the right lateral compartment and her thyroid was not palpable. Ultrasound examination of the neck showed a small, mildly hypoechoic, heterogeneous gland and a well-defined, hypoechoic mass 30×15×13 mm, lateral to the right carotid artery at level IV. The mass was finally excised one year postpartum and was found to be a lymph node occupied extensively by follicular variant of papillary thyroid cancer. She subsequently underwent total thyroidectomy with central and right lateral node dissection without complications. Thorough histologic examination of the thyroid failed to reveal cancer, central compartment nodules were negative (0/17) and one more node harbored microscopic metastasis (1/18) on the right side. The contralateral nodes dissected were negative (0/9). MRI of the oropharynx, mediastinum, abdomen and pelvis and non-contrast CT of the lungs (scheduled for follow up of the bowel carcinoma) were normal. The patient has been referred for radioactive iodine treatment.
Conclusions
Papillary thyroid cancer presenting as a cervical mass in the absence of a thyroid primary, needs to be differentiated from ectopic thyroid cancer in the neck or elsewhere. A picocarcinoma or one that has spontaneously regressed cannot be excluded.

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EP1472

Birt–Hogg–Dubé and papillary thyroid carcinoma: a case report

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Background
Birt–Hogg–Dubé (BHD) syndrome has been reported to be associated with neoplastic conditions. Its association with thyroid carcinoma has been reported but remains controversial. Here we report the case of a BHD patient with a thyroid papillary carcinoma.
Case report
A 47-year-old man presented with asymptomatic facial papules, which had been gradually increasing in number for 6 years. A biopsy was taken from a papule on the nose and histology examination showed epithelial proliferation. Mutation in exon 4 of FLCN was identified which confirmed the diagnosis of BHDS. A systematic ultrasound examination of his neck showed a 2 cm solid isoechoic nodule of the right thyroid lobe. The left thyroid lobe and the isthmus appeared to be normal. Serum levels of free thyroxine, and thyrotrophin were within normal ranges. Fine needle aspiration of the nodule revealed papillary clusters that had atypical nuclei and intranuclear inclusions and that appeared to be a papillary carcinoma. Our patient underwent a total thyroidectomy with neck exploration. The pathologic examination confirmed the diagnosis of papillary carcinoma classified T1NXMX. The patient was put on L-thyroxine and a radioiodine therapy will be considered.
Discussion
Birt–Hogg–Dubé syndrome consists of multiple fibrofolliculomas traditionally associated with trichodiscomas and acrochordons. Medullary carcinoma of the thyroid was the most reported type of cancers. Eventhough, other types of carcinoma as papillary carcinoma et carcinoma were not the common form of BHD syndrome could also occur. Our report is of high scientific interest because it will increase awareness of BHD in the medical community, as this syndrome is too often overlooked even when obvious clinical manifestations are present. So the neck ultrasound is recommended for BHD patients and family members.

Among others BHD patients followed in our hospital, we will look for the frequency and results of ultrasounds.

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EP1473

Diagnosis of papillary thyroid carcinoma: Is it time to reconsider?

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Aim
The aim of this retrospective study was to evaluate the diagnostic significance of presurgical thyroid ultrasound in comparison with FNAC of thyroid nodules and their contribution in detecting thyroid cancer.
Patients and methods
We retrospectively studied the files of 118 thyroid cancer patients, 18 men (15.2%) and 100 women (84.8%), who underwent thyroidectomy from January 2013 until December 2016, in the Department of Surgical Oncology of Theagenio Cancer Hospital, Thessaloniki, Greece. All patients were diagnosed and followed up by the Section of Endocrinology and were operated upon by the same surgical team. The mean patient age was 55 years ($\pm$12.26). We evaluated the suspicious ultrasound findings according to the ATA Guidelines of 2015 (hypogenicity, microcalcifications, taller than wide shape, irregular margins, extrathyroidal extension) and the results of FNAC (in accordance to Bethesda Score), in association with the pathology report. All ultrasounds were scored based on the suspicious characteristics.
Results
Mean tumor size was 7.1 mm ($\pm$8.73 mm), multifocallity was found in 69 patients (58.5%). The Bethesda score was positive for malignancy in 45% of the cases. On the other hand, the suspicious ultrasound findings were in accordance with the pathology report in 78.8% of the cases. Almost all patients with Bethesda II or III presented at least one or more suspicious ultrasound characteristics and those with Bethesda VI at least three or more suspicious for cancer ultrasonographic findings. Based on our statistical analysis, ultrasound as a diagnostic tool is more significant ($P<0.05$) and has a more positive predictive value in detecting thyroid cancer compared to FNAC.
Conclusions
Ultrasound characteristics and clinical suspicion are considered more valuable in the diagnosis of papillary thyroid carcinoma, especially for small lesions (<10 mm) and multinodular goiter. Therefore, an ultrasound scoring system should be adopted by the clinicians coping with thyroid cancer.

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EP1474

Patient with thyroid carcinoma showing thymus-like differentiation: a case study

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Thyroid carcinoma showing thymus-like differentiation (CASTLE) is an extremely rare thyroid neoplasm. This type of tumour may arise from branchial pouch remnants or ectopic thymus and is considered as independent clinicopathological entity of thyroid neoplasms. There have been only about 100 cases described in the literature, so far. Here, we have retrospectively analyzed the data from histopathology and clinics of a 70 year old female patient with thyroid CASTLE who underwent total thyroidectomy in 2009 due to thyroid nodule in the right lobe ($25\times25\times30$ mm) and suspicion of papillary thyroid carcinoma in the fine needle aspiration biopsy. At that time histopathological examination suggested presence of metastasis to the thyroid likely from the ovary or thymus however, the detailed clinical and imaging study did not confirm that these organs could be the source of this lesion. In February 2011 patient underwent neck lymphadenectomy that revealed metastases to the lymph nodes with unknown origin but thyroid carcinoma was ruled out. Patient was all time under control of endocrinologist and oncologist. In May 2014 patient was again hospitalized and next lymphadenectomy was done. At that moment histopathology of the lymph nodes indicated CASTLE (HMWCK+, p63+, CD5+, bcl2+, CEA+, synaptophysin+, Calc−, THY−, TTF1−). Therefore, the thyroid specimens were reevaluated again, and the presence of CASTLE in the gland was also confirmed. In subsequent follow-ups there were no signs and symptoms of the disease recurrence. Thyroid CASTLE might be easy overlooked because of its rarity and similarity to some thyroid cancers like squamous cell carcinoma or anaplastic carcinoma. Complete thyroid resection and lymphadenectomy are important to improve the long-term survival and the locoregional recurrence rate, although CASTLE course is usually clinically indolent. The short review of the already published data regarding CASTLE was done.

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EP1475

Minimally and widely invasive follicular thyroid carcinomas: are there significant differences in clinical behaviour and prognosis?

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Introduction
The existence of clear differences between the biological course and clinical behaviour of minimally invasive (MI) and widely invasive (WI) follicular thyroid carcinomas (FTC) is still debatable. The present study was conducted to outline the clinical differences between MI and WI-FTC and evaluate outcomes in both tumors.
Methods
We conducted a retrospective cohort study involving 80 cases of FTC. The comparison between MI-FTC and WI-FTC included an evaluation of clinic-pathologic characteristics, including tumor staging, and outcome assessment.
Results
The cohort included 65 patients with MI-FTC and 15 patients with WI-FTC. Patients whose age at diagnosis was $\geq$45 years more frequently had WI-FTC (27.3% Vs 4.0%, $P=0.023$). Mean tumor size was significantly greater in WI-FTC patients than in the MI-FTC (43.07 vs 30.94 mm, $P=0.007$). At univariate analysis, vascular invasion, infiltrative margins and invasion of thyroid capsule were significantly related to the presence of WI-FTC ($P<0.001$, $P<0.001$ and $P=0.010$, respectively). A higher cancer stage (III–IV) was also associated with the occurrence of WI-FTC (50% vs 8.6%, $P<0.001$). After a mean follow-up of 52.6 and 76.4 months in MI and WI-FTC, respectively, one patient of the first group and two patients of the second died of FTC. Patients with MI and WI tumors respectively presented a disease-free survival of 100% and 84% at 10 years.
Conclusions
The study reported a good outcome in both MI and WI patients, probably related to an aggressive therapeutic strategy and strict follow-up. Our data confirm previous studies which showed that WI-FTC are typically larger tumors with higher stage, more frequent vascular invasion and invasion of the thyroid capsule. Accordingly, we believe that the tumor grade of invasiveness must be taken into account on the staging process of disease.

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EP1476

Cystic masses of neck: a case report

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Introduction
Cystic masses of neck consist of a variety of pathologic entities. The age of presentation and clinical examination narrow down the differential diagnosis. In adults are considered to be malignancies until proven otherwise (thyroid lesions, salivary gland neoplasms, metastatic squamous cell carcinoma and lymphatic malformations such as the cystic lymphangioma. Ultrasound (US) is often used for initial evaluation. Computed tomography (CT) and MRI provides additional information. FNAC has a supplementary role for confirmation of diagnosis but its accuracy may depend on the experience of the cytopathologist.
Case report
A 41 years old woman presented with a left-side neck mass that had slowly enlarged over the past 6 months with a serious burner. MRI showed a 72*57*47 mm septate mass, with solid and cystic components with contralateral airway displacement and posterior displacement of the carotid. Thyroid US had revealed a normal gland. FNAC was nondiagnostic but the inicial diagnosis was a cystic lymphangioma and the patient was treated with Picibanil (OK-432) without any result. Six months later she underwent surgical excision. The histopathology report came out as Cystic metastatic lymph node from Papillary carcinoma of the thyroid. US demonstrated a poorly defined nodule with micro-calcification in the left lobe of the thyroid. One week later she underwent a total thyroidectomy and bilateral cervical lymphadenectomy. The final diagnosis was a 12 mm Papillary Carcinoma with bilateral metastatic lymph nodes.
Discussion
Metastatic nodes from head-and-neck malignancy, especially papillary carcinoma of the thyroid, are the most common types of nodal metastases presenting as cystic masses in the neck. Eighty percent of the cystic masses in patients over 40 years of age are due to necrotic lymph nodes. On US presence of punctate calcification within the solid component of the cystic node warrants careful search for primary papillary carcinoma in the thyroid gland. In our patient the diagnosis unfortunately was a challenge.
Conclusions
Cystic lesions of the neck are commonly encountered on imaging studies. Clinical presentation along with imaging features as assessed by Doppler US or CT help in accurate diagnosis. These imaging modalities also aid in optimal pre-operative planning. Imaging is essential for accurate diagnosis and pretreatment planning.

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EP1477

Staging of thyroid cancer at the time of its diagnosis in a single clinical centre

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Medical documentation of 976 patients treated and followed-up over the years 2001–2006 at our 131- radioiodine treatment centre was analysed with respect to their thyroid cancer staging. The mean age at their time of diagnosis was 59 ± 15.1 years. From histopathology, papillary, follicular or poorly differentiated cancer was diagnosed in 87.6, 11.7, and 0.7% of these patients, respectively. The mean ages of patients with papillary, follicular or poorly differentiated cancer were 58.4 ± 15.0, 62.9 ± 15.7 and 70.6 ± 14.6 years, respectively, the age differences between these patient groups being statistically significant ($P = 0.0014$). On their admission, patients were TNM- staged. Patients with microcarcinoma pT1a formed the largest group – 38.9%, followed by T1b- 32.3%, T2 − 10.0%, T3 − 12.3%, T4 − 3.0%, and Tx – 3.5%. In the last case the tumour diameter was not established by the surgeon or pathologist. Most patients were staged at N0 – 88.9%, followed by N1a − 9.7%, and N1a + b – 1.4%. At the time of diagnosis, distant metastases to lungs or bones was staged as M1in only 0.6% of patients. On chi-square analysis of percentage distribution of tumour size (T) in papillary cancer patients, pT1a was most frequent (42.8%), while T_2 dominated in the follicular cancer group (32.3%). This difference was statistically significant ($P = 0.0000$). No differences were found with respect to N or M classes. In the follow-up of this patient group, 77 patients were re-operated due to lymph node or lung metastases, and 23 patients were operated three times. Multiple I-131 treatment (2–6 times) was applied in this last group. Three patients died due to thyroid cancer progression.
Conclusion
On their diagnosis, patients with papillary cancer and follicular cancer significantly differed with respect to age and stage of disease.

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EP1478

Cystic nodule and carcinoma of thyroid gland, diagnosis and treatment of cistic nodule

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The cystic nodule is by its origin a real or pseudo cyst. According to the date of literature the papillary thyroid carcinoma is being detected in the cystic nodule in up to 27% of the cases. Ultrasound is the best diagnostic method of the cystic nodule and fine needle aspiration under ultrasound examination is a diagnostic method for cytological diagnosis.
Results
Seventy patients with detected cystic nodule underwent fine needle aspiration and the aspirational content was cytopathologically examined. In 31/70/ (44.3%) of patients there was a complete discharge of the cyst. In 4/70/ (5.7%) there was partial discharge but without recidivans and in 35/70/ (50%) of patients there were recidivates of cystic contents. According to the fine needle pathohystological findings in nine patients was detected a malignancy (eight patients had papillary and one follicular carcinoma).
Conclusion
Cystic nodule in thyroid gland is diagnosed by using ultrasound. Fine needle aspiration is used for discharging of the cyst. Cysts which recidivate after few needle aspiration should be operated surgically, and the patient with proved carcinoma are cured according to the protocol for the treatment of thyroid malignant disease.

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EP1479

Incidence of thyroid cancer in the gray bethesda categories

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Objective
The recommendations for action in a Bethesda category III are to repeat the cytology or to perform molecular tests, and if these are inconclusive, surveillance or surgical indication may be maintained, depending on the risk factors, ultrasound characteristics of the nodule and patient preference. In case of category IV of Bethesda, the recommendation is the surgery. The objective of this study was to evaluate the impact of age, gender and nodule size on the incidence of malignant lesions in patients with thyroid nodules with Bethesda III and IV classification.
Material and methods
Retrospective observational study of patients undergoing Total Thyroidectomy between July 2014 and June 2016. Totalizations were excluded. Descriptive analysis and statistical treatment with SPSS 20.
Results
Four hundred ninety two patients were submitted to Total Thyroidectomy after their presentation at the Multidisciplinary Thyroid Group consultation. The mean age of the patients was 54.6 years, being 82.7% female. Bethesda III was indicated in 52 patients, and Bethesda IV in 125 patients. In category III, in seven patients (13.5%) the histology revealed to be a malignant lesion, 71.4% female, mainly in the 5th decade of life; the majority of patients were T1b. In category IV, in 20 patients (16%) the histology revealed a malignant lesion, 65% female, mainly in the 6th decade of life; the majority of patients were T1b.
Conclusions
In our series, 13.5 and 16% of patients with a category III and IV Bethesda surgical indications were found to be malignant lesions, respectively, according to the literature (5–15% for Bethesda III, 15–30% for Bethesda IV). It was not possible to find a statistically significant difference between the variables tumor size, age group of patients and gender.

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EP1480

Sentinel lymph node biopsy in medullary thyroid microcarcinoma after methylene blue dye mapping – a pilot study

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Introduction
The aim was to analyse usefulness of sentinel lymph node (LN) biopsy of jugulo-carotid regions after methylene blue dye mapping for selection of clinically N0 patients with medullary thyroid microcarcinomas (MTMC) and lateral LN metastases for one-time modified radical neck dissection (MRND).
Materials and methods
From 2007 to 2016th, 15 patients were operated in our institution due to MTMCs with serum calcitonin levels lower than 1000 pg/ml, tumors under or 10 mm in size and clinically negative regional LNs. Total thyroidectomy with central neck dissection was done in all patients. Sentinel LN mapping was performed by injecting 0.2–0.5 ml of 1%-methylene blue dye in the thyroid lobes. Blue stained sentinel LNs were removed from II/III levels and examined by frozen section. In case sentinel LNs were benign, additional non-colored LNs were removed for standard pathological analysis. If sentinel LNs were positive on frozen section, one-time MRND was performed.
Results
One patient had hereditary form of medullary thyroid carcinoma, with bilateral subcentimeter tumors, while others had sporadic, unilateral MTMC. Sporadic MTMCs showed neither central nor lateral LN metastases on bilateral sentinel LN biopsy, with no indication for MRND. Hereditary MTMC had central LN metastases, with positive sentinel LNs on both sides, thus one-time bilateral MRND was performed. This patient had metastases in other dissected LNs, as well, and serum calcitonin level of 221 pg/ml. Frozen section and definite pathological analysis were 100% match.
Conclusion
Sentinel LN biopsy after methylene blue dye mapping can be precisely used for intraoperative assessment of lateral neck LNs. It optimizes surgery of MTMCs, selecting clinically N0 patients with metastases on frozen section for one-time MRND. This pilot study is the first reported experience with sentinel LN biopsy of jugulo-carotid regions in medullary thyroid carcinomas using methylene blue dye, focusing on the subgroup of microcarcinomas.

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EP1481

Lymph node categorization as a prognostic factor in a historical series of medullary thyroid cancer cases within a regional hospital

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Introduction
Medullary thyroid cancer (MTC) TNM classification categorizes lymph nodes (LN) according to their location, but does not consider number and size of LN.
Objective
To analyze the relationship between number and size of LN in MCT persistent disease (PD).
Material and methods
Retrospective study of patients with MTC followed up in a regional hospital from 1985 to 2015. The main variables (expressed as qualitative in frequency and quantitative as mean ± s.d. or median (min-max)): size of largest LN, number of node, extracapsular involvement and number of LN surgical procedures undertaken. Univariate analysis was used to assess the relationship between LN number and TMN stage with PD or remission. A *P*-value less than <0.05 was considered significant.
Results
Thirty-five patients were included (age at diagnosis 51 ± 18 years; 57% women). Time to follow up:8.6 ± 7.2 years. Presentation: 24% cervical mass, 38% through family screening, 8% as incidentalomas. Before surgery, calcitonin levels were 391 pg/ml (2-46022) and carcinoembryonic antigen levels were 11.8 ng/ml (0-2009). TNM stage: I:47%; II:6%; III:12%; IV:35%. N0:37%; NX:20%, N1:43%(N1a:33%; N1b:67%). Size of greatest LN:2.5 ± 1.6 cm (< 1 cm: 23%; 1–3 cm: 46%; >3 cm: 31%). Number of node: 1(0–22) (< 5 LN:64%; 5–9 LN:14%; ≥10 LN:22%). Extracapsular involvement: 29%. Number of LN surgery: 1 ± 0.67 (0–4). At the last visit, 47% had PD.
Univariate analysis:
We found clinical differences, although they were not significant, in LN size (PD 31 ± 15 mm vs remission 10 ± 14 mm (*P* 0.058)). The percentage of patients who reached remission was 0%(0/5) with extracapsular involvement vs 50%(5/10) without extracapsular involvement (*P* 0.053). Among 15 patients with N1category, only three were cured (all had < 5 LN and a size LN < 2 cm).

Table 1

	LN Number	*P*	N0	Nx	N1a	N1b	*P*
PD	7 (1–22)	0.01	0%	50%	75%	80%	0.002
Remission	1 (0–2)		100%	50%	25%	20%	

Conclusion
In our case series we observed that N category and number of LN is associated with PD in the long term. Furthermore, there was a linear trend between the size of the greatest LN and the extracapsular imvolvement with the PD. This reinforces the importance of a correct characterization of LN involvement.

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EP1482

A case of bilateralmetastaticrenal tumorof thyroid carcinoma

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Introduction
Distant metastasis caused by thyroid carcinoma is common and usually found in lung or bone. Clinically detectebale, welldifferenciated metastatic thyroid carcinoma to the kidney is rare. Only 16 cases have been reported in the littérature. We describe a case of metastatic vesicular thyroid carcinoma to the bilateral kidneys in a 61 years women, with bone, pulmonary lever and lynph nodes metastasis.
Case report
A 61 old women with a past history of thyroid tumor that had been surgically treated 19 years earlier She underwent a total thyroidectomy, radiotherapy, s ablation treatment with iodine 131 and thyroxin suppression therapy (200 µg/day) and has been diagnosed as vesicular thyroid cancer developped a left renal metastasis with chest pain. The lesion was detected with iodine 131 scintigraphy which measured in the CT Scan 68/60/13 mm. Biological tests showed: The thyroglobulin 3000 ng/ml (0.8–55) - TSH = 0.02 µUI/ml. Subsequent surgery and histopathology analysis of the renal lesion confirmed the diagnosis of vesicular thyroid metastatic carcinoma. Four years later a second metastasis of the right kidney appeared with pulmonary, bone, leaver and lymph nods metastasis. She underwent surgery where metastatic carcinoma was confirmed (3 cm of diameter).
Discussion - Conclusion
Only few cases of metastatic spread to the kidneys are described in the literature. 16 cases have been reported. They are mostly unique and rarely bilateral. The common use of the ultrasound and the CT Scan in assessment of monitoring of a cancer, patient allowed bringing to light more frequently this kind of lesion. The concomitant existence of metastasis in the other sites is variously appreciated in the literature. They varies from 50 to 100% observed cases and pejorative from the point of view of the prognosis. The most frequent locations are pulmonary, mediastinal and bone. The patient has benefited a dialysis treatment and deceased a year later.

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EP1483

Is prophylactic central cervical dissection in papillary carcinoma of the thyroid justified?

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Objective
Thyroid cancer is the most common of the endocrine tumors, with papillary being the most frequent. There is no consensus about prophylactic central cervical dissection in patients with papillary carcinoma of the thyroid. The aim of this

study is to analyze surgical complications and the rate of recurrence of papillary carcinoma in patients undergoing total thyroidectomy and prophylactic central cervical dissection, and patients submitted to total thyroidectomy alone.
Material and methods
Prospective study of consecutive patients submitted to total thyroidectomy and prophylactic central cervical dissection between January 1993 and December 1999, and consecutive patients submitted to total thyroidectomy alone, in the same period of 7 years, for papillary carcinoma of the thyroid. The groups were compared in relation to surgical complications and the rate of disease recurrence. Totalizations of thyroidectomy were excluded. Statistical analysis with SPSS 20
Results
Fifty-nine patients underwent total thyroidectomy and prophylactic central cervical dissection (mean age 46.3 years, 86.4% female), 43 patients underwent total thyroidectomy alone (mean age 46.2 years, 95.3% female). Recurrent laryngeal nerve injury occurred in 10 patients after CCD and in two patients after TT. Hypoparathyroidism occurred in 24 patients (20.8% definitive) after CCD and in seven patients (14.3% definitive) after TT. Disease-free survival rates were of 84.3% of patients 10 years after CCD, and 88.6% after TT alone.
Conclusions
In our series, it was not possible to establish a statistically significant difference between groups regarding recurrence of the disease, but a statistically significant difference regarding surgical complications. According to our results, we consider prophylactic central cervical dissection in papillary carcinomas thyroid not justified.

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EP1484

Thyroid cancer frequency over three decades

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Aim
To investigate the frequency of thyroid carcinoma and its subtypes in one region over three decades.
Material and methods
Data retrospectively collected from a tissue bank where all hospitals in a region with a little above 1 million inhabitants should send samples from all operated tumors, from 1981 to 2010.
Results
From 1981 to 1990 there where 156 thyroid cancers; 206 from 1991 through 2000 and 362 from 2001 through 2010, with a 132% rise from the first decade to the last one. Papillary cancer accounted for just 42% in the first decade, rising to 65% in the 2000s. There was also an absolute 50% rise in follicular cancer incidence, although the relative percentage fell from 40% in the first decade to 26% in the last one. Medullary cancer incidence rised by 150%, but relative percentage remained stable between 3 and 4%. Frequency of other rare types of thyroid neoplasms such as anaplastic, lymphoma or squamous carcinoma remained stable.
Conclusions
Thyroid carcinoma incidence is rising, mainly due to a rise in papillary carcinoma, as previously reported, but we also observed an increased incidence in follicular cancer.

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EP1485

Thyroid nodules: a huge dilemma!

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Current UK guidelines for thyroid nodules advise a thyroid ultrasound (ThyUSS) with U-Classification with or without Fine Needle Aspiration (FNA) with Thy-Classification to determine malignancy risk. We report four cases where thyroid carcinoma was diagnosed histologically following reassuring cytology and radiological examination. This is a case of 28-year-old female who presented with neck swelling. ThyUSS showed an enlarged left thyroid with cystic and solid components; FNA was Thy2. Surveillance ThyUSS showed additional right-sided nodules without pathological features; FNA was Thy1. The patient opted for thyroidectomy; histology showed two small foci of papillary carcinoma. 53-year-old female referred with a right dominant nodule following ThyUSS; FNA was Thy2. Subsequent ThyUSS showed a mildly hypoechoic, vascularised nodule with peripheric halo; FNA was Thy1. The patient opted for right thyroid lobectomy; histology showed benign follicular nodules with the dominant nodule containing an incidental papillary microcarcinoma. 60-year-old female had an incidental finding of a left thyroid nodule on CT neck on a background of autoimmune hypothyroidism and a family history of thyroid cancer. ThyUSS showed a left-dominant nodule with increased peripheral vascularity and smaller right-sided nodules; FNA was Thy2. The patient opted for a left thyroid lobectomy; histology showed papillary thyroid carcinoma and subsequent right thyroidectomy histology also showed papillary micro-carcinoma. 41-year-old female presented with T3-thyrotoxicosis with positive thyroglobulin antibodies and swelling corresponding to the thyroid. ThyUSS showed a right-sided, solid homogenous nodule and two small left-sided nodules. Repeated ThyUSS over nine months were stable; FNA was Thy2 and Thy1c. Technetium scan showed a right-sided toxic nodule and co-existent cold nodule. Following right hemi-thyroidectomy histology showed benign follicular adenoma and an incidental papillary microadenoma.
Conclusion
These cases demonstrate that whilst the U- and Thy-Classifications are reassuring they do not exclude malignancy. This uncertainty should be highlighted to patients when discussing management of thyroid nodules.

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EP1486

Timing to repeat thyroid fine-needle aspiration after a follicular lesion of undetermined significance result - does it matter?

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Introduction
Regarding thyroid nodules, in case of follicular lesion of undetermined significance (FLUS), performing repeat fine-needle aspiration (FNA) is a common follow-up strategy. It has been suggested that a waiting period of at least 3 months between FNAs would increase the diagnostic yield. Our study aims to clarify the optimal time for repeat FNA in case of an initial FLUS result.
Methods
We identified retrospectively all thyroid FNA FLUS results that occurred in our institution in 2016 and analysed only the patients who were submitted to repeat FNA. We recorded cytologic diagnosis, time between FNA and histologic results in case of surgery.
Results
A total of 79 patients were included, with ages between 34 and 86 years. Mean nodule diameter was 26.7 ± 11.7 mm. After the second FNA, 8 (10.18%) patients also underwent a third one. A total of 6 (7.6%) had surgery performed at some time during follow-up – 2 cases with malignant histology results. The result of the second FNA was non-diagnostic in 27.8% of cases and remained FLUS in 26.6%. Mean time interval between the first and second FNA was 3.8 ± 1.4 months. We did not find a statistically significant difference in diagnostic yields ($P = 0.267$) or diagnostic non-FLUS results ($P = 0.523$) between second FNA's performed 3 months or earlier (36 patients) compared to those preformed later (43 patients). Timing (as well as sex, age and nodule diameter) remained not correlated with diagnostic yield or diagnostic non-FLUS results after regression analysis using time between FNAs as a continuous variable.
Conclusion
Although our study had limited numbers, its results suggest that in case of a first FLUS FNA result, and if the decision to repeat is considered by the clinician, the timing of the second FNA does not seem to affect its diagnostic yield or the likelihood of another FLUS result.

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EP1487

Development of hypoparathyroidism due to targeted therapies

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Due to inhibition affect on proliferation, motility, resistance to apoptosis and growth of metastasis, the epidermal growth factor receptor (EGFR) inhibitor erlotinib and vascular endothelial growth factor receptor (VEGF) and EGFR inhibitor vandetanib are viable treatment options for treatment of advanced non-small cell lung cancer and thyroid cancer respectively. Advanced non-small cell lung carcinomas (NSCLC) or medullary and differentiated thyroid carcinomas (MTC and DTC) may present with bone metastatis in the presence of bone pain, elevated serum calcium or elevated alkaline phosphatase levels. We, hereby represent two patients who had diagnosis of NSCLC and MTC with bone metastatis, both treated with EGFR inhibitors and presented surprisingly with hypocalcemia in our outpatient clinic as a result of hypoparathyroidism. Sudden declines in calcium levels after initiating EGFR inhibitors contrary to the evidence of bone metastasis in these cases preoccupied that these agents may prevent parathyroid cell growth and decreased PTH levels lead to hypocalcemia.

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