GUIDELINES ON MALE HYPOGONADISM

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Introduction

Male hypogonadism is a clinical syndrome caused by androgen deficiency which may adversely affect multiple organ functions and quality of life. Androgen deficiency increases slightly with age. In middle-aged men the incidence is 6%. Hypogonadism is more prevalent in older men, in men with obesity, those with co-morbidities, and in men with a poor health status.

Aetiology and classification

Male hypogonadism can be classified in accordance with disturbances at the level of:

- the testes (primary hypogonadism);
- the hypothalamus and pituitary (secondary hypogonadism);
- the hypothalamus/pituitary and gonads (hypogonadism in adult men);
- androgen target organs (androgen insensitivity/resistance).

Table 1: Most common forms of primary hypogonadism

Disease	Pathophysiology
Maldescended or ectopic testes	Failure of testicular descent, maldevelopment of the testis
Testicular cancer	Testicular maldevelopment
Orchitis	Viral or unspecific orchitis
Acquired anorchia	Trauma, tumour, torsion, inflammation, iatrogenic, surgical removal
Secondary testicular dysfunction	Medication, drugs, toxins, systemic diseases
(Idiopathic) testicular atrophy	Male infertility (idiopathic or specific causes)
Congenital anorchia (bilateral in 1 in 20,000 males, unilateral 4 times as often)	Intrauterine torsion is the most probable cause
Klinefelter syndrome 47,XXY	Sex-chromosomal non-disjunction in germ cells

Table 2: Most common forms of secondary hypogonadism

Disease	Pathophysiology
Hyperprolactinemia	Prolactin-secreting pituitary adenomas (prolactinomas) or drug-induced
Isolated hypogonadotrophic hypogonadism (IHH) (formerly termed idiopathic hypogonadotrophic hypogonadism)	SGnRH deficiency specific (or unknown) mutations affecting GnRH synthesis or action

Kallmann syndrome (hypogonadotrophic hypogonadism with anosmia) (prevalence 1 in 10,000)	GnRH deficiency and anosmia, genetically determined
Secondary GnRH deficiency	Medication, drugs, toxins, systemic diseases
Hypopituitarism	Radiotherapy, trauma, infections, haemochromatosis and vascular insufficiency or congenital
Pituitary adenomas	Hormone-secreting adenomas; hormone-inactive pituitary adenomas; metastases tothe pituitary or pituitary stalk

Recommendation	**LE**	**GR**
The two forms of hypogonadism (primary and secondary) have to be differentiated (LH levels), as this has implications for patient evaluation and treatment and makes it possible to identify patients with associated health problems and infertility.	1b	B

LH = luteinising hormone.

Diagnostic evaluation

Table 3: Signs and symptoms suggesting prepubertal-onset hypogonadism

Small testes
Cryptorchidism
Gynaecomastia
High pitched voice
Unclosed epiphyses
Linear growth into adulthood
Eunuchoid habitus
Sparse body hair/facial hair
Infertility
Low bone mass
Sarcopenia
Reduced sexual desire/activity

Table 4: Signs and symptoms associated with adult-onset hypogonadism

Loss of libido
Erectile dysfunction
Fewer and decreased morning erections
Overweight or obesity
Sarcopenia
Low bone mass
Depressive thoughts
Fatigue
Loss of body hair
Hot flushes
Loss of vigour

Recommendations diagnostic evaluation	LE	GR
The diagnosis of testosterone deficiency should be restricted to men with persistent symptoms suggesting hypogonadism (Table 3).	3	C
Testosterone should be measured in the morning before 11.00 hours in the fasting state.	2	A
Total testosterone assessment should be repeated at least on two occasions with a reliable method. In addition, in men with: - Total testosterone levels close to the lower normal range (8-12 nmol/L), the free testosterone level should be measured to strengthen the laboratory assessment. - Suspected or known abnormal sex hormone-binding globulin (SHBG) levels, free testosterone should also be included.	1	A
Testosterone assessment is recommended in men with a disease or treatment in which testosterone deficiency is common and in whom treatment may be indicated. This includes men with: - Obesity. - Metabolic syndrome (obesity, hypertension, hypercholesterolaemia, type 2 diabetes mellitus). - Pituitary mass, following radiation involving the sellar region and other diseases in the hypothalamic and sellar region. - End-stage renal disease receiving haemodialysis. - Treatment with medications that cause suppression of testosterone levels - e.g. corticosteroids and opiates. - Moderate to severe chronic obstructive lung disease.	2	B

- Infertility. - Osteoporosis or low-trauma fractures. - HIV infection with sarcopenia. - Type 2 diabetes mellitus.		
LH serum levels should be analysed to differentiate between primary and secondary forms of hypogonadism.	2	A

Recommendations for screening men with adult-onset hypogonadism	**LE**	**GR**
Screening of testosterone deficiency is only recommended in adult men with consistent and multiple signs and symptoms listed in Table 3 and 4.	3	C
Adult men with established hypogonadism should be screened for concomitant osteoporosis.	2	B

Disease management

Table 5: Indications for testosterone treatment

Delayed puberty (idiopathic, Kallmann syndrome)
Klinefelter syndrome with hypogonadism
Sexual dysfunction and low testosterone
Low bone mass in hypogonadism
Adult men with low testosterone and consistent and preferably multiple signs and symptoms of hypogonadism (listed in Table 3 and 4) following unsuccessful treatment of obesity and comorbidities
Hypopituitarism
Testicular dysgenesis and hypogonadism
Type 2 diabetes mellitus with hypogonadism

Table 6: Contraindications against testosterone treatment

Prostate cancer
PSA > 4 ng/mL
Male breast cancer
Severe sleep apnoea
Male infertility-active desire to have children
Haematocrit > 0,54%
Severe lower urinary tract symptoms due to benign prostatic hyperplasia
Severe chronic cardiac failure/New York Heart Association Class IV
Uncontrolled cardiovascular disease

Table 7: Testosterone preparations for replacement therapy

Formulation	Administration	Advantages	Disadvantages
Testosterone undecanoate	Oral; 2-6 cps every 6 h	Absorbed through the lymphatic system, with consequent reduction of liver involvement.	Variable levels of testosterone above and below the mid-range. Need for several doses per day with intake of fatty food.
Testosterone cypionate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Possible fluctuation of testosterone levels.
Testosterone enanthate	Intramuscular; one injection every 2-3 weeks	Short-acting preparation that allows drug withdrawal in case of onset of side-effects.	Fluctuation of testosterone levels.

Testosterone undecanoate	Intramuscular; one injection every 10-14 weeks	Steady-state testosterone levels without fluctuation.	Long-acting preparation that cannot allow drug withdrawal in case of onset of side-effects.
Transdermal testosterone	Gel or skin patches; daily application	Steady-state testosterone level without fluctuation.	Skin irritation at the site of application and risk of interpersonal transfer.
Sublingual testosterone	Sublingual; daily doses	Rapid absorption and achievement of physiological serum level of testosterone.	Local irritation.
Buccal testosterone	Buccal tablet; two doses per day	Rapid absorption and achievement of physiological serum level of testosterone.	Irritation and pain at the site of application.
Subdermal depots	Subdermal implant every 5-7 months	Long duration and constant serum testosterone level.	Risk of infection and extrusion of the implants.

Recommendations for testosterone replacement therapy	LE	GR
The patient should be fully informed about expected benefits and side-effects of the treatment option. The selection of the preparation should be a joint decision by an informed patient and the physician.	3	A
Short-acting preparations are preferred to long-acting depot administration when starting the initial treatment, so that therapy can be adjusted or stopped in case of adverse side-effects.	3	B
Testosterone therapy is contraindicated in patients with male infertility and a desire for children since it may suppress spermatogenensis.	1b	A
HCG treatment can only be recommended for hypogonadotrophic hypogonadal patients with simultaneous fertility treatment.	1b	B
In patients with adult-onset hypogonadism, testosterone treatment should only be attempted in men with major symptoms and if weight loss, lifestyle modification and good treatment balance of comorbidities have proven unsuccessful.	2	A

HCG = human chorionic gonadotrophin.

Recommendations on risk factors in testosterone treatment	LE	GR
Haematological, cardiovascular, breast and prostatic assessment should be performed before the start of treatment.	1a	A
Haematocrit and haemoglobin monitoring and PSA are recommended assessments at the start and during TRT therapy.	3	A
Symptomatic hypogonadal men who have been surgically treated for localised prostate cancer and who are currently without evidence of active disease (i.e. measurable PSA, abnormal rectal examination, evidence of bone/visceral metastasis) can be cautiously considered for a TRT: treatment should be restricted to those patients with a low risk for recurrent prostate cancer (i.e. Gleason score <8; pathological stage pT1-2; preoperative PSA <10 ng/ml) and should not start before 1 year of follow-up.	3	B
Assessment for cardiovascular risk factors should be performed before commencing TRT and optimisation of secondary prevention in men with pre-existing cardiovascular disease should be performed.	1a	A
Men with hypogonadism and either pre-existing cardiovascular disease, venous thromboembolism or chronic cardiac failure who require TRT should be treated with caution, monitored carefully with clinical assessment, haematocrit (not exceeding 0.54) and testosterone levels maintained as best possible for age within the mid-normal healthy range.	1b	A

PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

Recommendations for follow-up	LE	GR
The response to treatment should be assessed 3, 6 and 12 months after the onset of treatment, and thereafter annually.	4	C
Haematocrit should be monitored at 3, 6 and 12 months and thereafter annually. The testosterone dosage should be decreased, or therapy discontinued if the haematocrit increases above 0,54.	4	C
Prostate health should be assessed by digital rectal examination and PSA before the start of TRT. Follow-up by PSA at 3, 6 and 12 months and thereafter annually.	4	C
Men with cardiovascular diseases should be assessed for cardiovascular symptoms before TRT is initiated. There should be close clinical assessment during TRT.	1b	A

BMD = bone mineral density; PSA = prostate-specific antigen; TRT = testosterone replacement therapy.

This short booklet text is based on the more comprehensive EAU Guidelines (978-90-79754-80-9), available to all members of the European Association of Urology at their website, http://www.uroweb.org.