Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
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The Diagnosis and Management of Type 3c Diabetes

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Aim of presentation

To provide an overview of the characteristics, diagnosis, and management of type 3c diabetes

Classification of DM

World Journal of Gastroenterology

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bpgoffice@wjgnet.com
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World J Gastroenterol 2013 November 14; 19(42): 7276-7281
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

Asbjørn Mohr Drewes, MD, PhD, DMSc, Professor, *Series Editor*

Diagnosis and treatment of diabetes mellitus in chronic pancreatitis

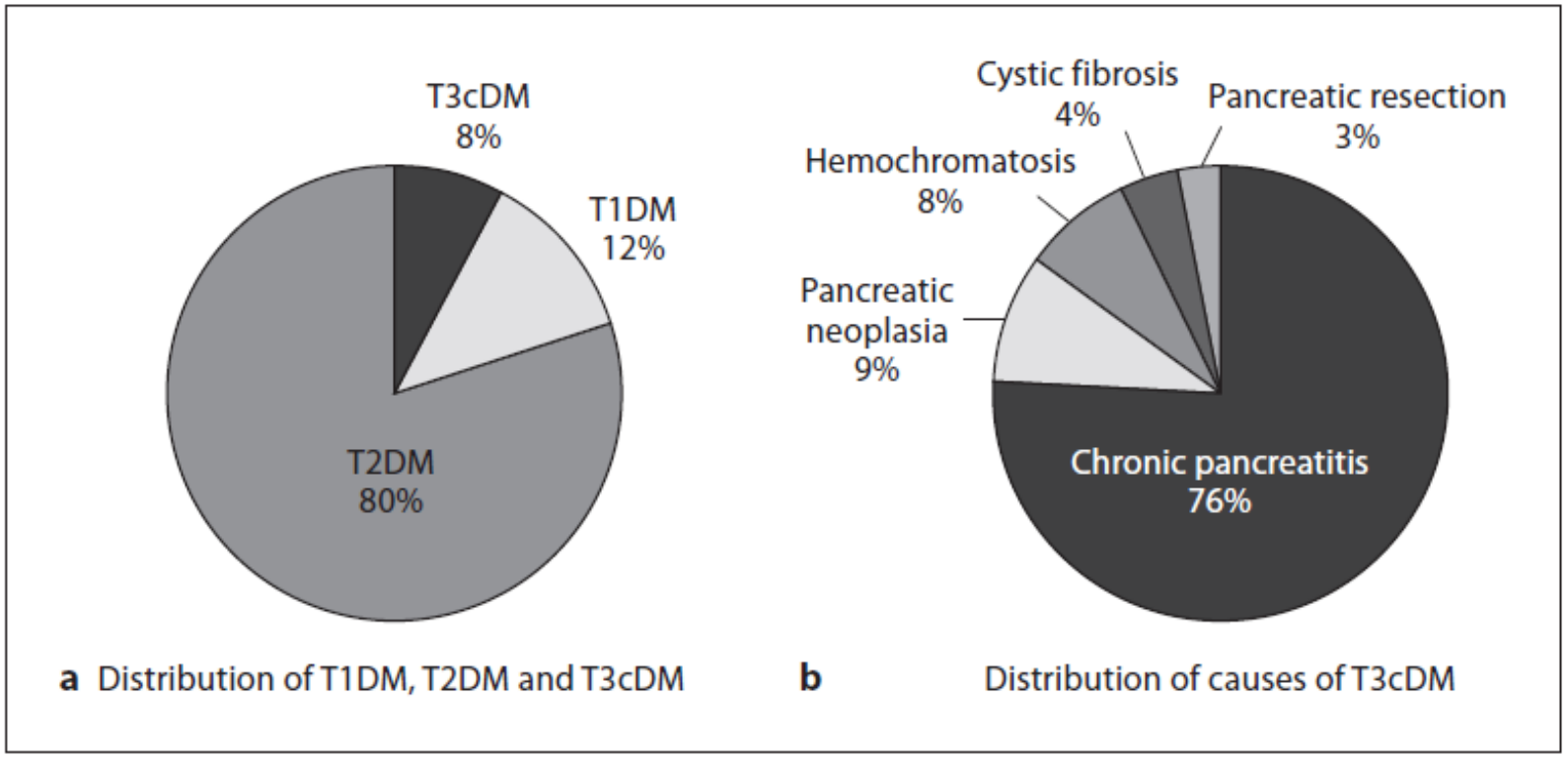
Table 1 Current classification of diabetes mellitus

I	Type 1 Diabetes Mellitus (β-cell destruction, usually leading to absolute insulin deficiency)
	A: Immune mediated
	B: Idiopathic
II	Type 2 Diabetes Mellitus (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with insulin resistance)
III	Other Specific Types Of Diabetes Mellitus
	A: Genetic defects of β-cell function
	B: Genetic defects in insulin action
	C: Diseases of the exocrine pancreas
	1: Pancreatitis
	2: Trauma/pancreatectomy
	3: Neoplasia
	4: Cystic fibrosis
	5: Hemochromatosis
	6: Fibrocalculous pancreatopathy
	7: Others
	D: Endocrinopathies
	E: Drug- or chemical-induced
	F: Infections
	G: Uncommon forms of immune-mediated diabetes
	H: Other genetic syndromes sometimes associated with diabetes
IV	Gestational Diabetes Mellitus

Type 3c Diabetes
(Diabetes of the Exocrine Pancreas)

American Diabetes Association: Diagnosis and classification of diabetes. Diab Care 2011;34(suppl 1): S62-S69

Prevalence



Pancreatology

Review

Pancreatology 2011;11:279–294
DOI: 10.1159/000329188

Published online: July 9, 2011

Pancreatogenic Diabetes: Special Considerations for Management

YunFeng Cui[a, b] Dana K. Andersen[a]

Based on Hardt et al, Diab Care. Feb 2008. 31: 1,922 hospitalised DM patients

Conditions associated with type 3c DM

Chronic pancreatitis

Pancreatic cancer

Type 3c DM

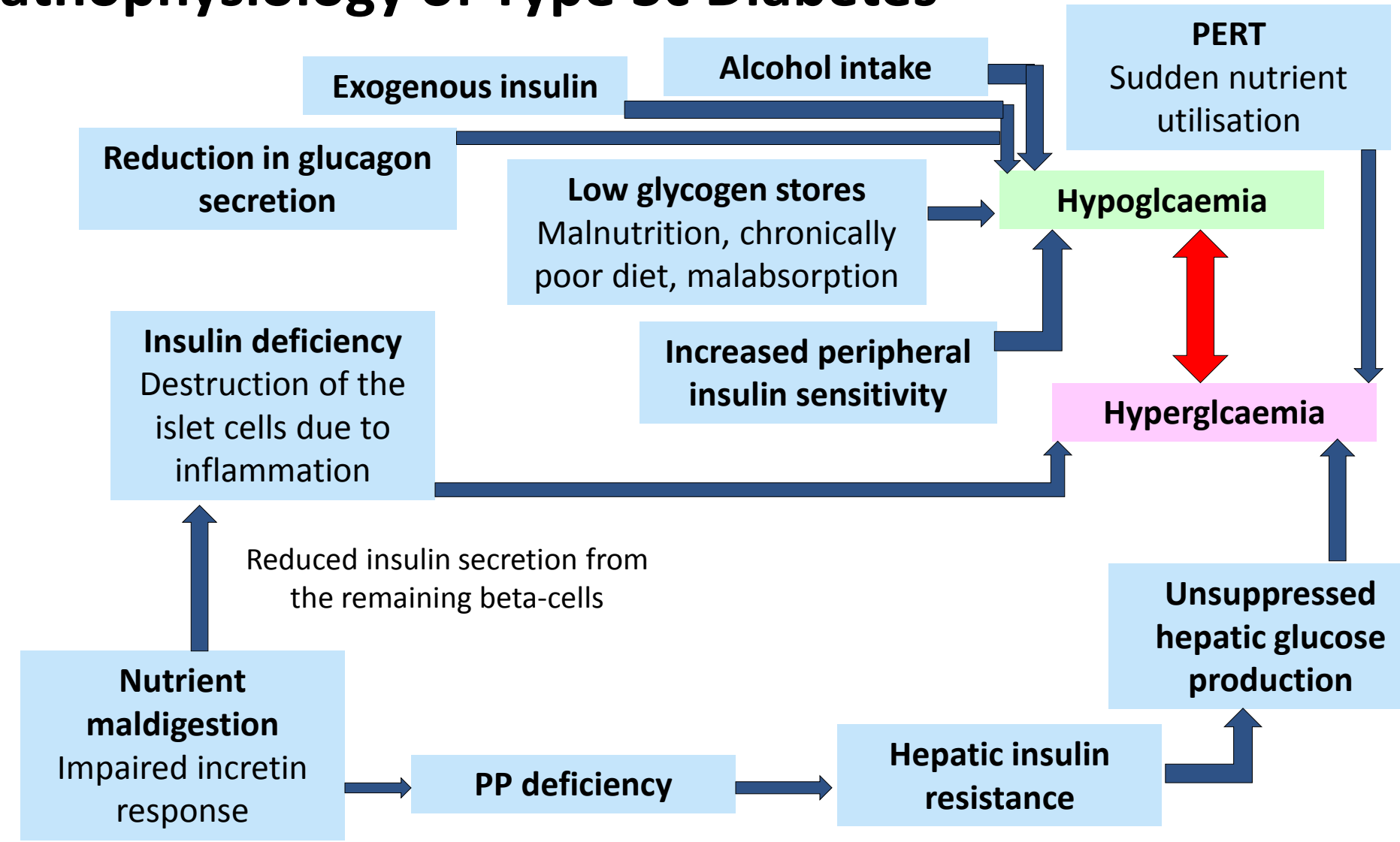
Pancreatic surgery

Acute pancreatitis

Other:
Haemochromatosis, Fibrocalculous Pancreatopathy, Pancreatic Agenesis

Cystic Fibrosis

Pathophysiology of Type 3c Diabetes



Brittle Diabetes

Risk of developing DM in CP?

What is the risk of developing DM in CP?

- 5-80%, depending on aetiology, geography, duration of follow-up
- Common consequence of alcohol-related and idiopathic/tropical CP

Supplement

United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU)

J Matthias Löhr[1], Enrique Dominguez-Munoz[2], Jonas Rosendahl[3], Marc Besselink[4], Julia Mayerle[25], Markus M Lerch[5], Stephan Haas[1], Fatih Akisik[6], Nikolaos Kartalis[7], Julio Iglesias-Garcia[2], Jutta Keller[9], Marja Boermeester[4], Jens Werner[10], Jean-Marc Dumonceau[11], Paul Fockens[4,8], Asbjorn Drewes[12], Gürlap Ceyhan[13], Björn Lindkvist[14], Joost Drenth[15], Nils Ewald[16], Philip Hardt[16], Enrique de Madaria[17], Heiko Witt[18], Alexander Schneider[19], Riccardo Manfredi[20], Frøkjer J Brøndum[21], Sasa Rudolf[22], Thomas Bollen[23] and Marco Bruno[24]; HaPanEU/UEG Working Group

United European Gastroenterology Journal
0(0) 1–47

DOI: 10.1177/2050640616684695
journals.sagepub.com/home/ueg
SAGE

What factors affect the risk?

- Surgery (distal pancreatectomy) (1B)
- Age (1B)
- Duration of disease (1B)
- Heavy smoking (1C)
- Calcifications (1C)
- Gender (2A)
- Family history (2A)

Not enough evidence /no evidence

- BMI
- Zinc status
- High fat intake
- Genetic mutations

Comparing Type 3c diabetes to Types 1 and 2

Table 1. Comparing and Contrasting the Characteristics of Types 1, 2 and 3c Diabetes*

Characteristic	Type 1 Diabetes	Type 2 Diabetes	Type 3c Pancreatogenic Diabetes
Hyperglycemia	Severe	Usually Mild	Mild, or severe in 'brittle diabetes' • Due to unsuppressed hepatic glucose production • Exaggerated (peripheral) sensitivity to insulin
Hypoglycemia	Common	Rare	Common and may be severe • Deficiency in glucagon secretion o Impaired activation of gluconeogenesis • Hepatic insulin sensitivity is reduced, due to deficiency in polypeptide secretion o Exogenous insulin delivery exaggerates this • Peripheral sensitivity to insulin enhanced from relative hyperinsulinemia & reduced counter-regulatory hormone release (glucagon) • Poor dietary intake due to pain, smoking, alcohol or symptom avoidance • PEI with malabsorption • Persistent alcohol intake in some
Ketoacidosis	Common	Rare	Rare
Diabetes-associated antibodies	Yes	Rare	No
Insulin Levels	Low	High	Low
Glucagon Levels	Normal or High	Normal or High	Low
Peripheral Insulin Sensitivity	Normal or Increased	Decreased	Increased
Hepatic Insulin Sensitivity	Normal	Normal or Decreased	Decreased
Pancreatic Polypeptide Levels	Normal or Low (may be low or absent in those with severe autonomic neuropathy[27])	High (may be decreased in those with severe autonomic neuroapthy[27])	Low
Incretin Secretion			Incretin secretion is impaired in the setting of maldigestion, hence diminished insulin release from remaining beta-cells
• Gastric Inhibitory Polypeptide (GIP) Levels	Normal or Low	Normal or High	Low
• Glucagon-like Peptide-1 (GLP-1) Levels	Normal	Low or normal[16] (may increase with metformin therapy or with PERT[28])	Normal or High[14]
Age of Onset	Childhood or Adolescence	Mainly in Adulthood	Any (chronic pancreatitis usually presents in adulthood)
Overweight/Obese	Rare	Common	Uncommon. However, patients with chronic pancreatitis may be overweigh or obese, but have muscle depletion compared to matched controls[3]
Undernutrition	Uncommon	Rare	Common[25,26,29]
Nutrient Deficiency	Rare	Rare	Deficiency of fat-soluble vitamins is common in chronic pancreatitis due t PEI and poor diet[3,30,31]
Bone Mineral Density / Risk of Fracture	Risk of low bone mineral density and higher fracture risk, especially at the hip[32]	May have low bone mineral density, although may also have increased fracture risk despite normal/high bone mineral density (could be related to falling risk due to complications such as poor eyesight, neuropathy)[32]	Depending on the type of pancreatic disease, the risk of low bone mineral density is substantial. In chronic pancreatitis, 65% of patients have either osteoporosis or osteopenia[33], and there is a high risk of atraumatic fractur compared to controls[34,35]
Risk of Pancreatic Cancer	No higher risk[29]	Twofold risk of developing pancreatic cancer[36]	5% of patients with chronic pancreatitis will develop pancreatic cancer ov a 20-year period Risk of pancreatic cancer higher for patients with both chronic pancreatitis and diabetes, than for those with chronic pancreatitis alone (although diabete could be a manifestation of pancreatic cancer rather than a risk factor)[37]

Duggan & Conlon. Practical Gastroenterology May 2017 (163) 14-23

Based on earlier tables by Slezak & Andersen, and Cui YF & Andersen DK

Diagnosis

Pancreatology 13 (2013) 336–342

Contents lists available at SciVerse ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: Recommendations from *PancreasFest 2012*

Michael R. Rickels [a], Melena Bellin [b], Frederico G.S. Toledo [c], R. Paul Robertson [d], Dana K. Andersen [e], Suresh T. Chari [f], Randall Brand [c], Luca Frulloni [g], Michelle A. Anderson [h], David C. Whitcomb [c,i,j,*] for the PancreasFest Recommendation Conference Participants [1]

Initial evaluation:

- Fasting glucose and HbA1c
- Repeated annually
- Impairment in either requires further evaluation

Diabetes

- HbA1c >48 (6.5%) *(but HbA1c <6.5% does not exclude DM, measure is limited)*
- Glucose >7 mmol/L

Impaired glucose tolerance

- HbA1c 38.8-46.4 (5.7-6.4 %)
- Glucose 5.5 – 6.9 mmol/L

Impairment in fasting glucose or HbA1c should be further evaluated by a 75g OGTT

Based on ADA Guidelines

Proposed diagnosis of Type 3c DM

Table 2 Proposed diagnostic criteria for type 3c diabetes mellitus

Major criteria (must be present)
Presence of exocrine pancreatic insufficiency (monoclonal fecal elas tase-1 test or direct function tests)
Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
Absence of type 1 diabetes mellitus associated autoimmune markers
Minor criteria
Absent pancreatic polypeptide secretion
Impaired incretin secretion (*e.g.*, GLP-1)
No excessive insulin resistance (*e.g.*, HOMA-IR)
Impaired beta cell function (*e.g.*, HOMA-B, C-Peptide/glucose-ratio)
Low serum levels of lipid soluble vitamins (A, D, E and K)

MRI: Magnetic resonance imaging; CT: Computed tomography; GLP-1: Glucagon-like peptide-1; HOMA-IR: Homeostasis model assessment of insulin resistance; HOMA-B: Homeostasis model assessment of beta-cell.

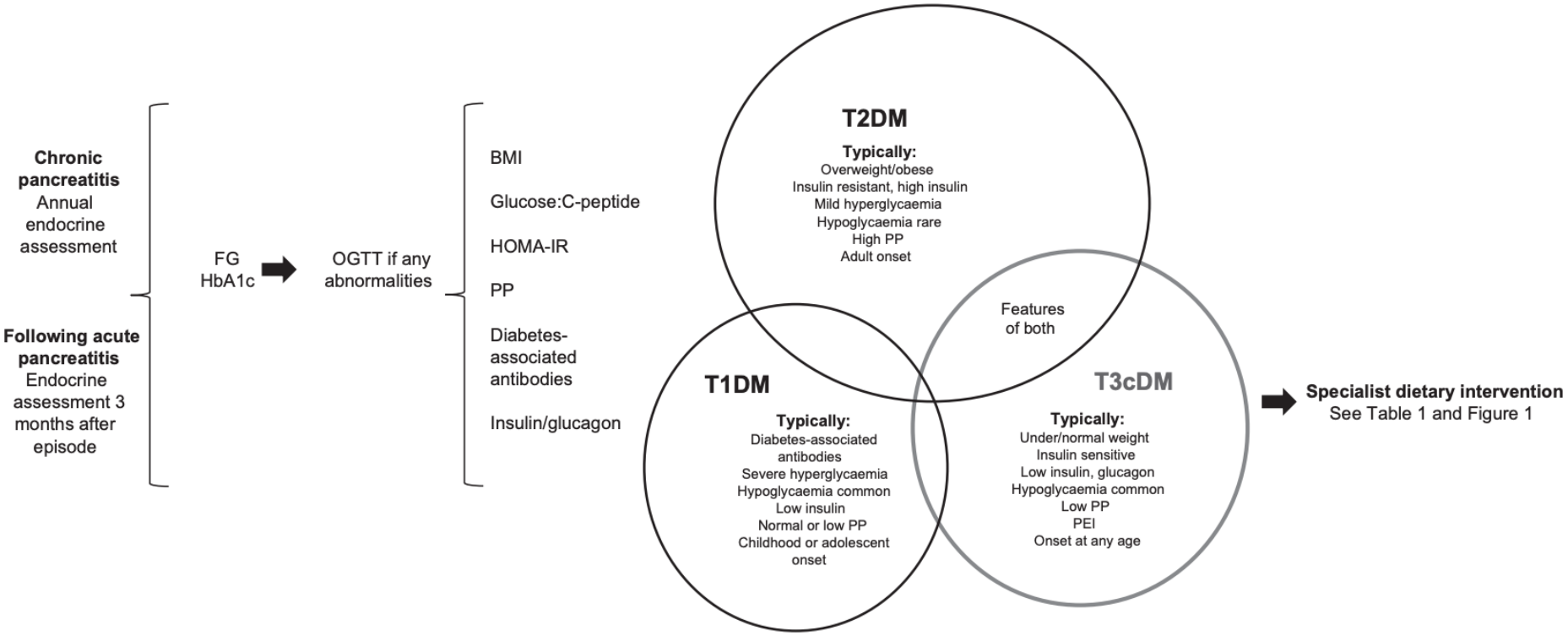
Problems with diagnostic criteria

- How best to measure insulin resistance?
- Timing of c-peptide measurement?
- PP may also be decreased in type 1/2
- Fat soluble vitamins may not always be low

- In many cases, these data are not available

Ewald N, Hardt PD. *World J Gastroenterol*. 2013;19(42):7276–7281.

Guidelines for pancreatitis-related type 3c diabetes: *Screening and assessment*



Duggan et al. Eur J Clin Nutr. 2016; 1-6

Special considerations for CP-related type 3c diabetes

Risk of pancreatic cancer in CP patients

- 4-5% develop pancreatic cancer over the life-time of the disease, x10-20 higher risk than normal
- Early-onset CP have x 50 higher risk
- Smoking: risk factor

Pancreatogenic DM with CP = 'pre-malignant state' (Cui *et al*)

- *'Avoid insulin, Insulin Secretagogues'*
- Weight loss, exercise, drugs which reduce circulating insulin may have a protective effect
- More research required

Pharmacological treatment options

Drugs typically used are the same as for Type 2

- Few studies have examined therapeutic efficacy for Type 3c vs type 2
- Type 3c DM patients specifically excluded from studies

Insulin

- May be required for hyperglycaemia
- Anabolic effects may be beneficial
- Insulin *vs* no insulin depends on clinical presentation
  - Profound hyperglycaemia (HbA1c >69.4 (8.5%), glucose >10 mmol/L) with catabolic with glycosuria and weight loss – insulin preferred

Metformin

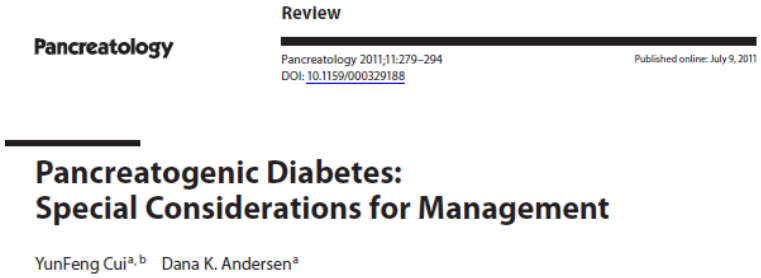
- GI side effects
- May reduce the requirement for insulin

Suggested algorithm for treatment of Type 2 DM *(Cui et al, 2011)*

At diagnosis of T3cDM	→	Escalation of treatment based on A1c levels >7%							
Lifestyle Δ + Metformin + Panc Enz Rx	→	Lifestyle Δ + Metformin + TZD or αGI + Panc Enz Rx	→	Lifestyle Δ + Metformin + Basal insulin + Panc Enz Rx	→	Lifestyle Δ + Metformin + Intensive insulin Rx + Panc Enz Rx	→	Lifestyle Δ + Metformin + Intensive insulin Rx + Adjunct Rx + Panc Enz Rx	

Both exocrine and endocrine insufficiency likely to co-exist

Therapeutic goals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Pancreatogenic Diabetes: Special Considerations for Management

YunFeng Cui[a, b] Dana K. Andersen[a]

Inferred from best practice as applied to type 1 and 2 DM

Principal goal of therapy:

- Reduce HbA1c <53 (7%), fasting glucose 3.9-7.2 mmol/L
- For all patients, concentrated effort to correct lifestyle factors (reinforced at every visit)
  - Weight loss in obese, daily exercise, limit CHO, abstain from alcohol and smoking

Management Guidelines for Type 3c Diabetes

ADA Guidelines on standards of care in diabetes

Individualised treatment programme by RD

Patient should actively engage with self-management, education and treatment planning with healthcare team

- Including the collaborative development of individualised eating plans

Those on intensive insulin regimens

- Self-monitoring of blood glucose 6-10 times per day

Duggan et al. Eur J Clin Nutr. 2016; 1-6

Self-monitoring in type 3c diabetes

Table 3. Suggested Self-Monitoring Regimen for Blood Glucose Testing in T3cDM*

Minimum 6-10 blood glucose testing occasions per day:

- Prior to all meals and snacks
- Occasionally post-prandially
- Before bed
- After physical activity
- In the presence of suspected hypoglycemic symptoms
- After treating for hypoglycemia until normoglycemia is maintained
- Before critical tasks e.g. driving, swimming, using dangerous equipment, etc.

**Based on ADA self-monitoring blood glucose testing for T1DM and T2DM patients on intensive insulin regimens[38]*

Duggan & Conlon. Practical Gastroenterology May 2017 (163) 14-23

Dietary management

Suggested management guidelines *(Duggan & Conlon, 2013)*

Principles of Management	Management Strategies
Prevent: • Hypoglycemia • Hyperglycemia • Exacerbation of malnutrition • Co-morbidities associated with diabetes (e.g. retinopathy, renal disease)	• Do not skip meals • Take small, frequent meals • Measure glucose levels frequently, particularly after physical activity, and if diet is poor • Avoid alcohol • Ensure adequacy of enzyme therapy • Minimize high-sugar/ high-glycemic index food or fluids • Consider a diary to record diet, glucose levels, enzymes, exercise, at least until acceptable glucose control is maintained • Dietitian assessment/ monitoring

PRACTICAL GASTROENTEROLOGY • JUNE 2013

Diabetes and **pancreatic cancer**

Diabetes and PDAC strongly associated

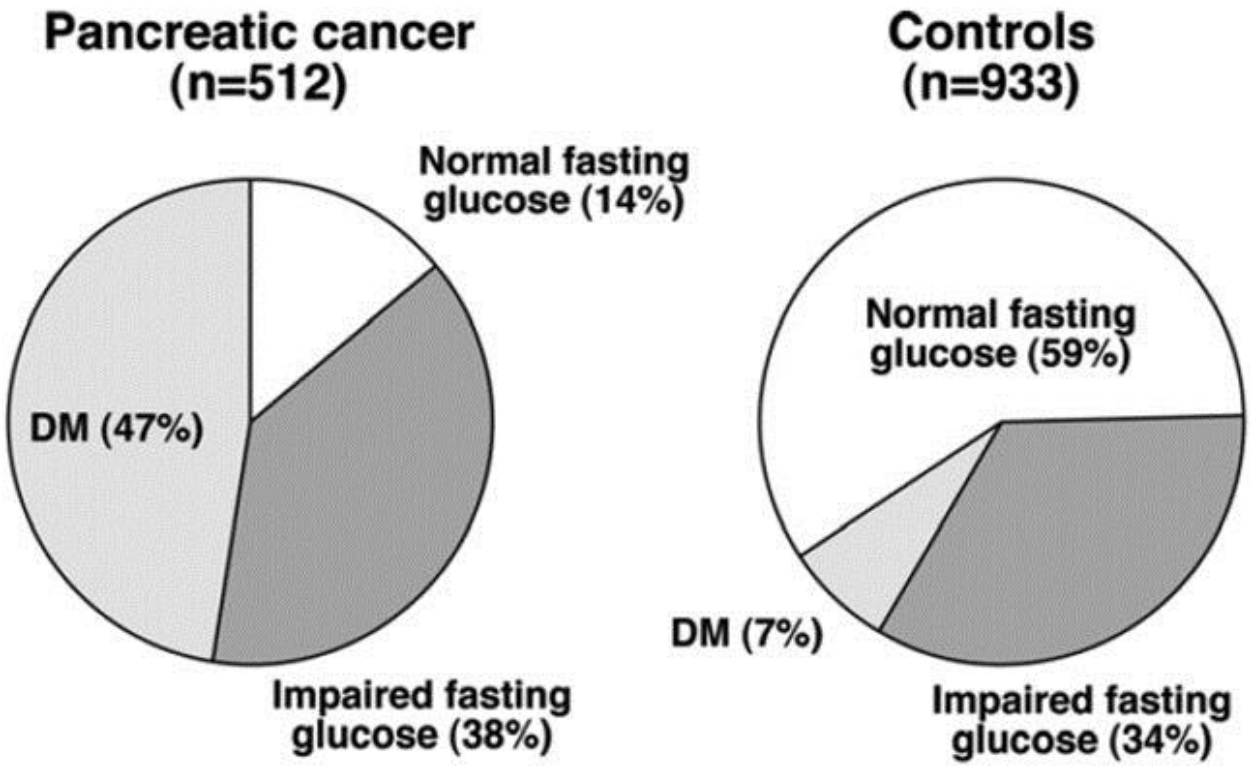
Study of n=100 cancer patients (lung, breast, prostate, pancreas)

- **PDAC 68%**
- **Other cancers 15-21%**
- **Age-matched controls 24%**
- **Most patients with PDAC/DM diagnosed with DM <2 yr prior**

‘Dual causality’

Aggarwal G et al. Pancreas 2013; 42:198-201

PDAC and DM



Pannala et al. Gastroenterology 2008; 134:981-987

Obesity and weight

Diabetes Volume 66, May 2017 1103

Diabetes, Pancreatogenic Diabetes, and Pancreatic Cancer

Dana K. Andersen,[1] Murray Korc,[2] Gloria M. Petersen,[3] Guido Eibl,[4] Donghui Li,[5] Michael R. Rickels,[6] Suresh T. Chari,[7] and James L. Abbruzzese[8]

Diabetes 2017;66:1103–1110 | DOI: 10.2337/db16-1477

Obesity

- **Hyperinsulinaemia**
- **Adipokines**

Clinical scenario

- **PDAC associated with weight loss rather than gain**
- **Deteriorating glycaemic control, weight loss, >50 years**
  - Atypical of T2DM – should consider pancreatic cancer

Endocrine function
following acute pancreatitis

Pancreas

ORIGINAL ARTICLE

Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis

Stephanie L M Das,[1] Primal P Singh,[1] Anthony R J Phillips,[1] Rinki Murphy,[2] John A Windsor,[1] Maxim S Petrov[1]

Systematic review **Das et al, 2013**

24 studies (post acute pancreatitis) (n=1,102)

- Pre-DM or DM in 37% (pooled prevalence)
- New DM in 15% 12 months after 1st attack, increased risk after 5 years
- 8/24 studies included *'all severe AP'* subjects

Pancreatology 13 (2013) 336–342

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Original article

Research gaps I

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Michael R. Rickels [a], Melena Bellin [b], Frederico G.S. Toledo [c], R. Paul Robertson [d], Dana K. Andersen [e], Suresh T. Chari [f], Randall Brand [c], Luca Frulloni [g], Michelle A. Anderson [h], David C. Whitcomb [c,i,j,*] for the PancreasFest Recommendation Conference Participants [1]

Guidance Statement 1.1: Further refinement of risk stratification is needed for diabetes that could influence clinical decision making, such as, for example, earlier consideration of TPIAT prior to loss of islet function. Areas for investigation include the molecular genetics of recurrent acute or chronic pancreatitis, their relationship with type 2 diabetes susceptibility alleles, and canonical risk factors for type 2 diabetes.

Refinement of risk stratification that may influence clinical decisions

Guidance Statement 1.2: During the discussion, it was recognized that while pathophysiologic defects that distinguish between pancreatogenic (type 3c), type 1, and type 2 diabetes have been described, further research is needed to determine whether metabolic tests of islet cell hormone secretion and action or other biomarkers can better distinguish among these three forms of diabetes, and whether treatment based on proper classification improves clinical outcomes.

Distinguishing between types of DM

Guidance Statement 2.1: Additional research is needed to determine whether earlier case identification can result in improved long-term glycemic control and a consequent reduction in diabetes-associated complications.

Earlier identification of T3DM

Pancreatology 13 (2013) 336–342

Contents lists available at SciVerse ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Research gaps II

Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: Recommendations from *PancreasFest 2012*

Michael R. Rickels [a], Melena Bellin [b], Frederico G.S. Toledo [c], R. Paul Robertson [d], Dana K. Andersen [e], Suresh T. Chari [f], Randall Brand [c], Luca Frulloni [g], Michelle A. Anderson [h], David C. Whitcomb [c,i,j,*] for the PancreasFest Recommendation Conference Participants [1]

Guidance Statement 2.2: Further research is needed into whether the one-hour glucose level during a standard 75 g oral glucose tolerance test can improve risk stratification and, if so, using what criteria. In addition, investigation into the potential role for simultaneous measurement of C-peptide and insulin during the oral glucose tolerance in assessing insulin secretion and sensitivity, respectively, is warranted to evaluate the discriminatory value of this test for identifying impaired beta-cell function or insulin resistance.

Role of OGTT, C-peptide, insulin

Guidance Statement 2.3: Further research is needed to better define the PP response compared with measures of fasting glucose, HbA1c, and oral glucose tolerance in the determination of risk for progression to pancreatogenic diabetes.

PP response

Guidance Statement 2.4: Future research is needed to determine whether the insulin or C-peptide response to glucose-potentiated arginine testing is predictive of islet yield and metabolic functional outcomes when assessed prior to TPIAT.

Predicting islet yield for TPIAT

Guidance Statement 3: Additional studies should examine the efficacy, safety, and tolerability of metformin compared with sulfonylurea therapy early in the course of pancreatogenic diabetes. Furthermore, studies are needed to evaluate the long-term glycemic control and rate of diabetes-associated complications of early insulin compared with oral therapy for pancreatogenic diabetes.

Metformin, other OHAs, insulin

Our recent study

N=26 SAP patients (1= episode, min 1 year post SAP)

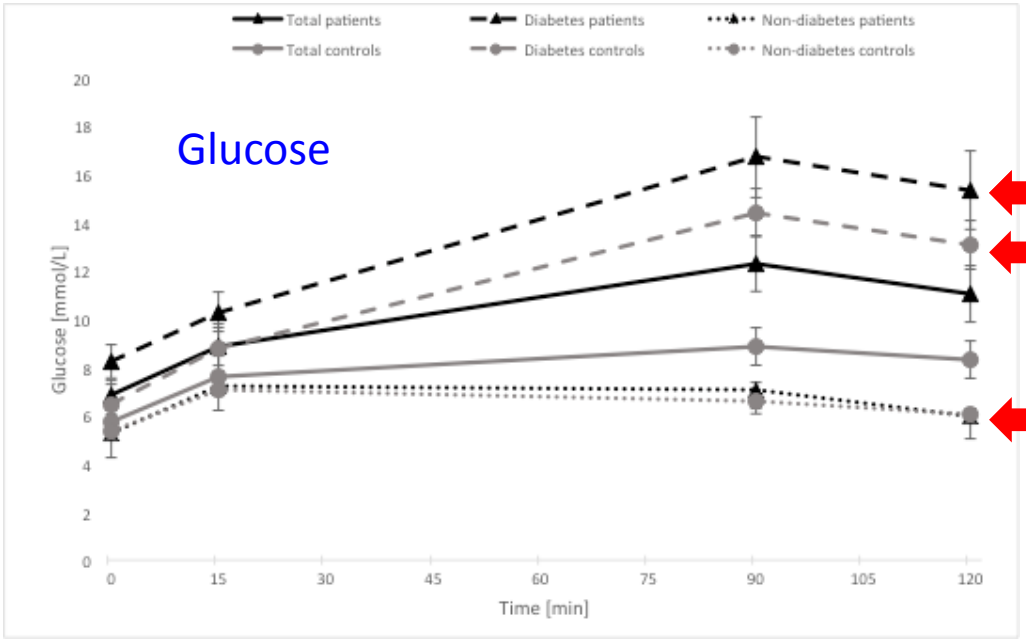
N=26 matched controls (age, BMI, DM status)

No difference in waist circ, W:H, family history, smoking status

54% diabetes in post SAP group, 35% in controls

27% diagnosed using fasting glucose

46% using HbA1c

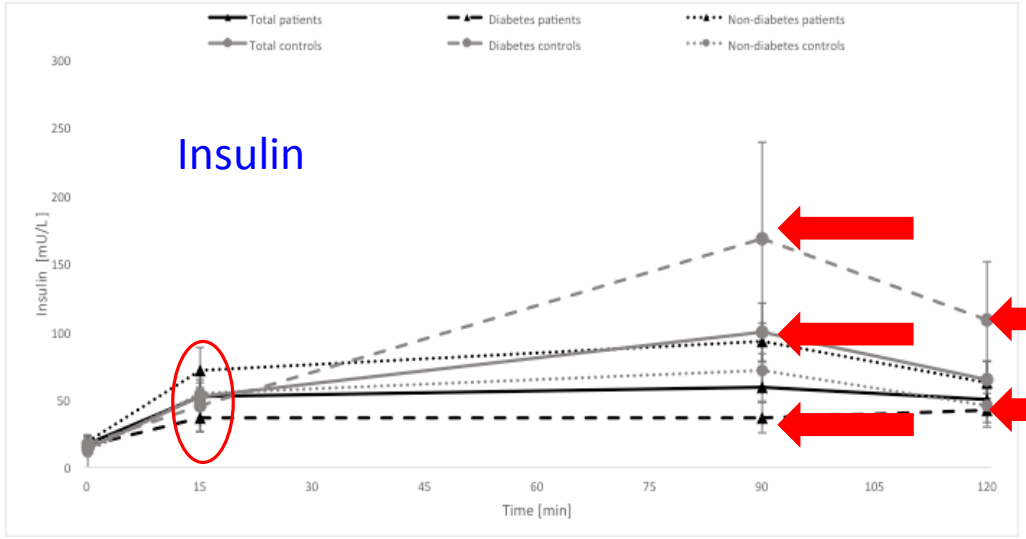


DM
hi
ti

No sig difference in

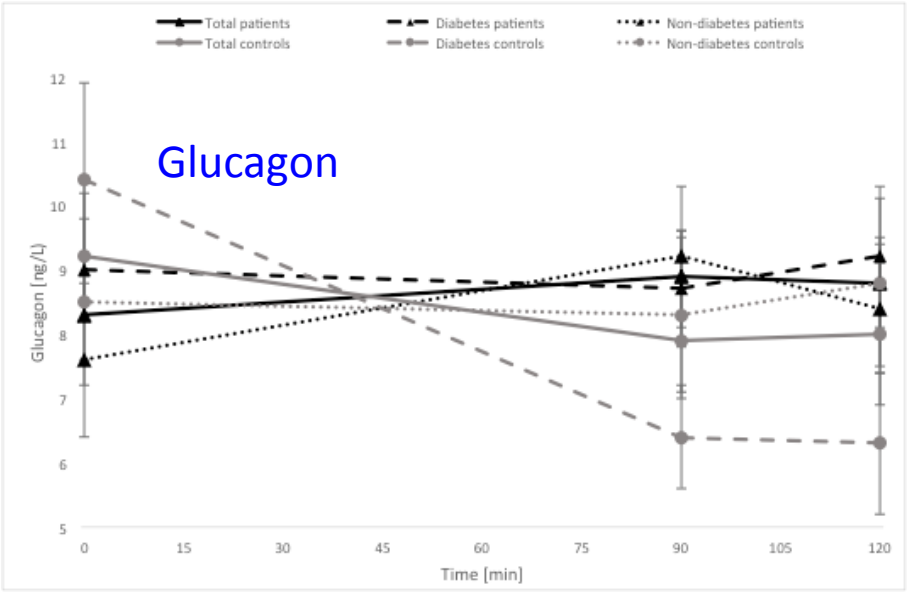
Differences marked at 90, 120 min

control subjects

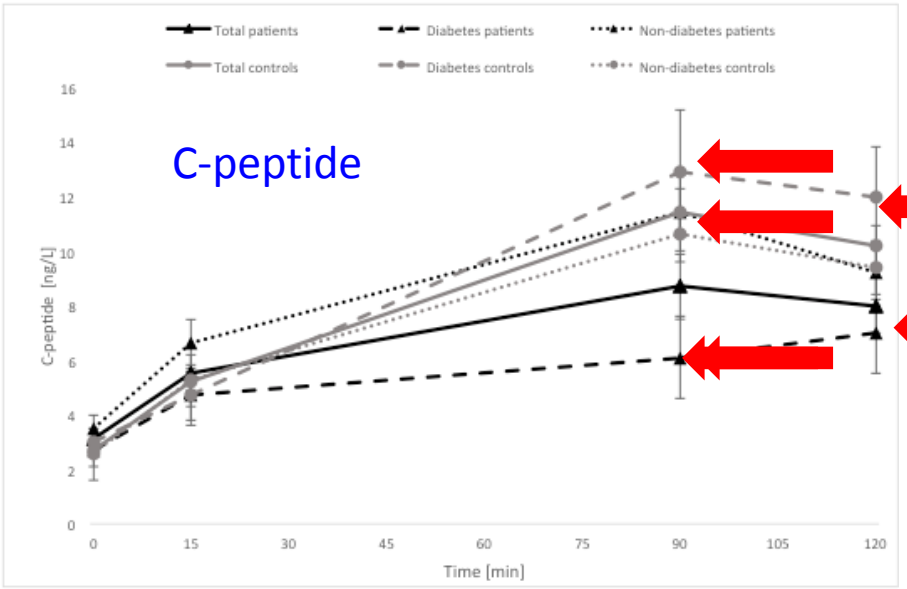


Insulin lower in diabetic CP than in controls with DM at 90 mins and 120 mins

Duggan & Conlon, Unpublished

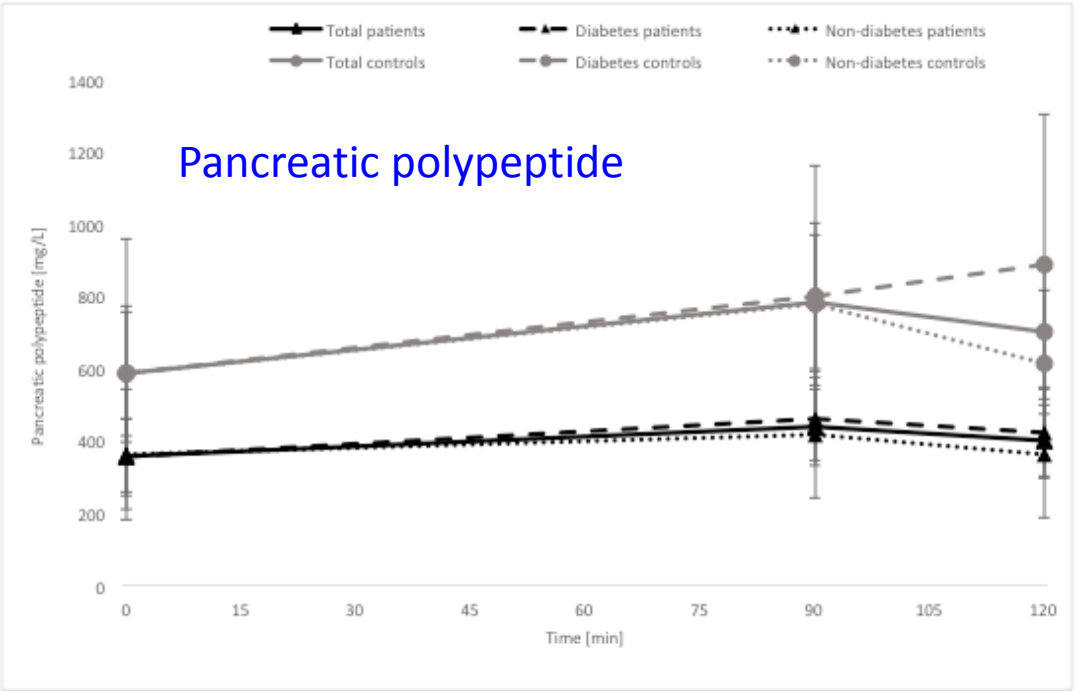


Poor response to OGTT
Glucagon suppression?



C-peptide is sig. lower in diabetic CP patients compared to diabetic control subjects at 90 / 120 mins

Duggan & Conlon, Unpublished



Not significantly different

Duggan & Conlon, Unpublished

- First study to investigate behavior of glucose, insulin, PP, c-peptide and glucagon over 2 hour OGTT in patients following SAP
- Potential for differentiating type 3c from types 1 and 2
- High prevalence of DM following SAP, OGTT required to diagnose all cases

Summary

Type 3c DM

Principle goal of therapy:
HbA1c <7%, fasting glucose 3.9-7.2 mmol/L

Increased risk of pancreatic cancer:
'Premalignant state'
Consideration prior to insulin use

Metformin is drug of choice

Initial evaluation:
Glucose, HbA1c, repeat annually.
Any impairment requires further evaluation

'Brittle DM'
Careful dietary management, in context of overall condition

Distinct from types 1 and 2:
Shares characteristics with both

Many research gaps

Conditions:
CP, post AP, pancreatic cancer, pancreatic surgery, CF

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Thank you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