

### Diabetes shorts: Type 3c diabetes

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#### Disclaimer/disclosure



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### Content...

- What is pancreatogenic (type 3c) diabetes?
- Diagnosis and useful investigations

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- When to refer
- How to manage

### **Definitions**

Type 3c diabetes (also known

as pancreatogenic diabetes)

diabetes that comes secondary to

pancreatic diseases, involving the exocrine

and digestive functions of the pancreas.

Gudipaty, Lalitha. Rickels, Michael R. (2015). Pancreatogenic (Type 3c) Diabetes. <u>Pancreapedia: Exocrine Pancreas Knowledge Base</u>, DOI: <u>10.3998/panc.2015.35</u> Pancreatic diabetes includes both structural and functional loss of glucosenormalizing insulin secretion in the context of exocrine pancreatic dysfunction.

- It is commonly misdiagnosed as type 2 diabetes
- Hyperglycemia due to general pancreatic dysfunction has been called "type 3c diabetes"

## What are the causes?

- pancreatitis (acute and chronic)
- trauma or pancreatectomy
- neoplasia
- cystic fibrosis
- hemochromatosis
- fibrocalculous pancreatopathy
- rare genetic disorders
- idiopathic forms

.....as such, pancreatic diabetes is the preferred umbrella terminology

### However, pancreatitis is the commonest cause

Pancreatitis, even a single bout, can lead to postpancreatitis diabetes mellitus (PPDM)

Both acute and chronic pancreatitis can lead to PPDM

the risk is highest with recurrent bouts

### Prevalence and causes of type 3c diabetes mellitus

Prevalence of type 3c diabetes in a cohort of 1868 participants with diabetes



Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c) *Diabetes Metab Res Rev.* 2012;28:338–42

Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c):

A Retrospective Cohort Study 31,789 new cases of adult onset diabetes were identified. Diabetes following pancreatic disease was more common than type 1 diabetes.

Diabetes following pancreatic disease is frequently labelled type 2 diabetes

Only 2.7% of people with diabetes following pancreatic disease are diagnosed with 'diabetes of the exocrine pancreas', most (87.8%) patients were labelled type 2 diabetes

> Clinicians should elicit whether a patient has any history of pancreatic disease when they first present with diabetes and consider the diagnosis of diabetes of the exocrine pancreas

Chris Woodmansey, Andrew P. McGovern, Katherine A. McCullough, Martin B. Whyte, Neil M. Munro, Ana C. Correa, Piers A.C. Gatenby, Simon A. Jones, Simon de Lusignan; Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study. *Diabetes Care* 1 November 2017; 40 (11): 1486–1493. <u>https://doi.org/10.2337/dc17-0542</u>

### How do you diagnose type 3c?

# How do we differentiate Pancreatic diabetes from type 1 or 2 diabetes?

NO universally accepted diagnostic criteria

# So conceptually the three following criteria need to be met:

#### diagnosis of diabetes

present disease of the exocrine pancreas

diabetes is reasonably certain to be secondary to their exocrine pancreatic disease

Hart PA, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC, Pandol SJ, Yadav D, Chari ST; Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer(CPDPC). Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol. 2016 Nov;1(3):226-237.

doi: 10.1016/S2468-1253(16)30106-6. Epub 2016 Oct 12. PMID: 28404095; PMCID: PMC5495015

### So how do we do this?

A distinguishing feature is concurrent pancreatic exocrine insufficiency (defined by monoclonal faecal elastase 1 test or direct function tests)

Pathological pancreatic imaging (endoscopic ultrasound, MRI, computed tomography)

An absence of type 1 diabetes—associated autoimmunity

Ewald N and Hardt PD (2013). Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. World Journal of Gastroenterology 19 (42); 7276–7281

### **Feacal Elastase-1 test**

![](_page_11_Picture_1.jpeg)

Feacal Elastase 1 (FE-1) usually repeated to ensure accuracy of result.

<100 mcg/g indicates severe PEI

<200 mcg/g indicates mild/moderate PEI

A value of 200-250 mcg/g is considered borderline with retesting recommended

FE-1 may be reduced in patients diagnosed with coeliac disease or IBS suggesting PEI may be the cause of symptoms in these patients or the patient may have both conditions.

Be aware that this measure can be unreliable if the patient has very loose stools

If the patient has persistent, very loose stools, refer to GI services

# How do we recognize these patients?

Distinguishing pancreatogenic diabetes from type 1 or type 2 diabetes<sup>4,8</sup>

Clinical feature	Type 1 diabetes	Type 2 diabetes	Pancreatogenic diabetes
Age of onset of diabetes	Mainly children and young adults	Commonly adults >40 years	Chronic pancreatitis: usually >40 years Cystic fibrosis: usually <30 years Pancreatic resection: within 5 years of surgery
Presentation	Rapid onset, osmotic symptoms, DKA	Gradual onset, DKA rare	Can be rapid decompensation, DKA rare
Obesity	Uncommon	Common	Uncommon
Autoimmunity	Islet cell antibodies, other autoimmune diseases	Rare	Rare
Insulin levels (C-peptide)	Low	High	Low

Morris D (2020) Recognition and management of pancreatogenic (type 3c) diabetes. Diabetes & Primary Care 22: 111–12

![](_page_13_Figure_0.jpeg)

following acute pancreatitis, and diabetes following chronic pancreatic disease. The shaded areas represent the 95% Cls. Log-rank *P* for difference: P < 0.001. The table is the number of patients at risk over time.

# Pancreatic cancer is a known complication of chronic pancreatitis and sometimes manifests with new onset diabetes.

From: Incidence and risk of pancreatic cancer in patients with acute or chronic pancreatitis: a population-based cohort study

![](_page_14_Figure_2.jpeg)

Cumulative incidences of pancreatic cancer among patients with pancreatitis followed for more than 2 years and controls. (A) Comparison between pancreatitis and control groups. (B) Comparison among SAP, RAP, CP with AP, CP without AP and control groups. SAP, single episode of acute pancreatitis; RAP, recurrent acute pancreatitis; AP, acute pancreatitis; CP, chronic pancreatitis.

Park, S.M., Kim, K.B., Han, JH. et al. Incidence and risk of pancreatic cancer in patients with acute or chronic pancreatitis: a population-based cohort study. Sci Rep 13, 18930 (2023). https://doi.org/10.1038/s41598-023-45382-y

### How to manage type 3c diabetes

what are the differences to type 1 and 2?

![](_page_16_Picture_0.jpeg)

### The evidence base to guide management of type 3c diabetes is weak and there are no specific guidelines.

Treatment goals are derived from randomised controlled trials from type 1 and type 2 diabetes, and expert opinion but include the following:

Diet and lifestyle

Reducing cardiovascular risk

**Glycaemic control** 

Exocrine issues

Makuc J. Management of pancreatogenic diabetes: challenges and solutions. Diabetes Metab Syndr Obes. 2016 Aug 25;9:311-5. doi: 10.2147/DMSO.S99701. PMID: 27601927; PMCID: PMC5003514.

Morris D (2020) Recognition and management of pancreatogenic (type 3c) diabetes. Diabetes & Primary Care 22: 111–12

Type 3c diabetes

Lifestyle

Alcohol

Smoking cessation

Physical activity

Nutrition

Specialist dietitian

Metformin

if no

contraindications

1.3.15 Assess people with type 3c diabetes events for potential benefit of

> CVD risk reduction Blood pressure Lipids Smoking cessation Urine ACR

For guidance on managing type 3c diabetes for people who need insulin, ee:

the recommendations on insulin therapy and insulin delivery (including rotating injection sites within the same body region) in the Normalized on type 1 diabetes in ing and managing nd young Insulin Often needed due

Often needed due to insulin deficiency

[2018, amended 2020]

Pioglitazone 1.3.18 and Avoid in HF pancreatiti Risk of fractures uiring insulin, ations on education see and information in the NICE guideline on diagnosing and diabetes in adv DPP4managing dia inhibitors young peopl 1.3.19 For guidance Pancreatitis risk glucose for peo and type 3c diaber see the recommendations on blood glucose management in the NICE posing and managi <u>Vts</u>, and <u>bloc</u> Sulphonylurea e NICE and mar may be less young pe effective dependent on beta cell function

## SGLT-2 inhibitors

DKA risk Little evidence

GLP-1 RA

Pancreatitis risk Appetite suppression Weight loss

### The challenge of glucose management in type 3c

Glucose metabolism ranges from a mild impairment to a severe form characterised by frequent episodes of hypoglycemia, commonly referred to as 'brittle diabetes'.

Blood glucose control may be unstable due to:

- the loss of glucagon response to hypoglycemia,
- carbohydrate malabsorption
- reduction in pancreatic polypeptides leading to reduced hepatic insulin sensitivity and subsequent increase in hepatic glucose production.
- and/or inconsistent eating patterns due to concomitant pain
- and/or nausea or chronic alcohol abuse.

Alberti KGMM. Diabetes secondary to pancreatopathy: an example of brittle diabetes. In: Tiengo A, Alberti KGMM, Del Prato S, Vranic M (editors), editors. Diabetes Secondary to Pancreatopathy. Proceedings of the Post EASD International Symposium on Diabetes Secondary to Pancreatopathy, Padova, 21–22 September 1987, International Congress Series 762. Amsterdam: Excerpta Medica; 1988. p. 211–214

### **Exocrine issues**

Malabsorption not only increases malnutrition, but it also presents problems for blood glucose management.

Pancreatic enzyme replacement therapy (PERT)

- PERT can improve digestion of carbohydrates and increase glucose levels.
- PERT may unmask diabetes in an individual with previously normal HbA1c.
- Vitamin D supplements if proven deficiency. Consider investigations for osteoporosis.

Cui Y, Andersen DK (2011) Pancreatology 11: 279–94, Gudipaty L, Rickels M (2015) Pancreatogenic (Type 3c) Diabetes. APA: bit.ly/2No0Vtl, Makuc J (2016) Diabetes Metab Syndr Obes 9: 311–15, Gupte A et al (2018) BMJ 361: k2126, Duggan SN, Conlon KC (2017) Practical Gastroenterology 41: 14–23, Ewald N, Hardt PD (2103) World J Gastroenterology 19: 7276–81

### Clinical study – Could PERT improve glycaemic control?

![](_page_20_Figure_1.jpeg)

The improvement in diabetes control as shown by significant improvements in postprandial plasma glucose and HbA1c HbA1c is reduced by 11 mmol/mol

Mohan V et al. Int J Pancreatol 1998;24(1): 19-22

# For further advice

![](_page_21_Figure_1.jpeg)

# Can technology help people living with type 3c diabetes?

![](_page_23_Picture_0.jpeg)

Bwrdd Iechyd Prifysgol Hywel Dda University Health Board

![](_page_23_Picture_2.jpeg)

Type 3c not to be confused with Pancreatic Exocrine Insufficiency in Diabetes

### Pathophysiological concepts of PEI in DM

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### Pathophysiological concepts of PEI in DM

![](_page_26_Figure_1.jpeg)

- The prevalence of PEI is reportedly higher in Type 1 DM than in T2DM
- Type 1 DM (26-57%) than in T2DM (20-36%) Singh V et al, World J Gastroenterol 2017
- T1DM 38.62% vs T2DM 28.12% Mohapatra S et al, Pancreas 2016

I.Icks A, Haastert B, Giani G, *et al.* Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol.* 2001;**39**:823-30.
 Hardt PD, Krauss A, Bretz L, *et al.* Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus. *Acta Diabetol.* 2000;**37**:105-10.
 Rathmann W, Haastert B, Icks A, *et al.* Low faecal elastase 1 concentrations in type 2 diabetes mellitus. *Scand J Gastroenterol.* 2001;**36**:1056-61.

![](_page_27_Figure_0.jpeg)

BMI=body mass index; FE-1=faecal elastase-1; FBC=full blood count; GI=gastrointestinal; HbA1c=haemoglobin A1c; LFT=liver function tests; PEI=pancreatic exocrine insufficiency; PERT=pancreatic enzyme replacement therapy; PPI=proton pump inhibitor; TTG=IgA tissue transglutaminase antibody; U&E=urea and electrolytes

## Summary

- Type 3c diabetes is diabetes due to pancreatic damage, it is little recognised and often misdiagnosed
- Management of type 3c covers both endocrine and exocrine functionality
- Typically, glycaemic management is achieved with Metformin and insulin with glucose monitoring to avoid hypoglycaemia
- Exocrine management is achieved with enzyme replacement and vitamins

![](_page_29_Picture_0.jpeg)

### Thank you.

![](_page_29_Picture_2.jpeg)

pcdosociety.org

![](_page_29_Picture_4.jpeg)