Understanding Type 3c Diabetes

Sarah Davies
GPwSI Diabetes, Woodlands Medical Centre, Cardiff
All Wales Lead for Diabetes in Primary Care

Vicki Alabraba
Diabetes Specialist Nurse
EDEN Education Team, University Hospitals Leicester
Pinfold Medical Practice, Loughborough

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Sarah Davies

Abbott, Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Dexcom, Eli Lilly, Menarini, Novo Nordisk

Vicki Alabraba

Dexcom, Novo Nordisk, Eli Lilly, Sanofi, Menarini, AstraZeneca

Declaration of Interest:

DSN Forum UK LTD Director

What this session will cover

- What is type 3c diabetes?
- Can patients be misclassified as type 1 or 2?
- How to diagnose type 3c diabetes?
- How can we recognise these patients?
- Treating type 3c diabetes, what are the differences to type 1 and 2?

Definitions

Type 3c diabetes (also known as **pancreatogenic diabetes**) is 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. *Pancreapedia: Exocrine Pancreas Knowledge Base*, DOI: 10.3998/panc.2015.35

Pancreatic diabetes includes both structural and functional loss of glucose-normalising insulin secretion in the context of exocrine pancreatic dysfunction.

- It is commonly misdiagnosed as type 2 diabetes
- True prevalence is not fully understood
- Estimated that 5-10% of western diabetes population have T3cD

What are the causes?

- Pancreatitis (acute and chronic)
- Trauma or pancreatic surgery
- Pancreatic cancer
- Cystic fibrosis
- Haemochromatosis
- Rare genetic disorders
- Idiopathic forms

…..as such, pancreatic or Pancreatogenic diabetes is the preferred umbrella terminology

However, pancreatitis is the commonest cause

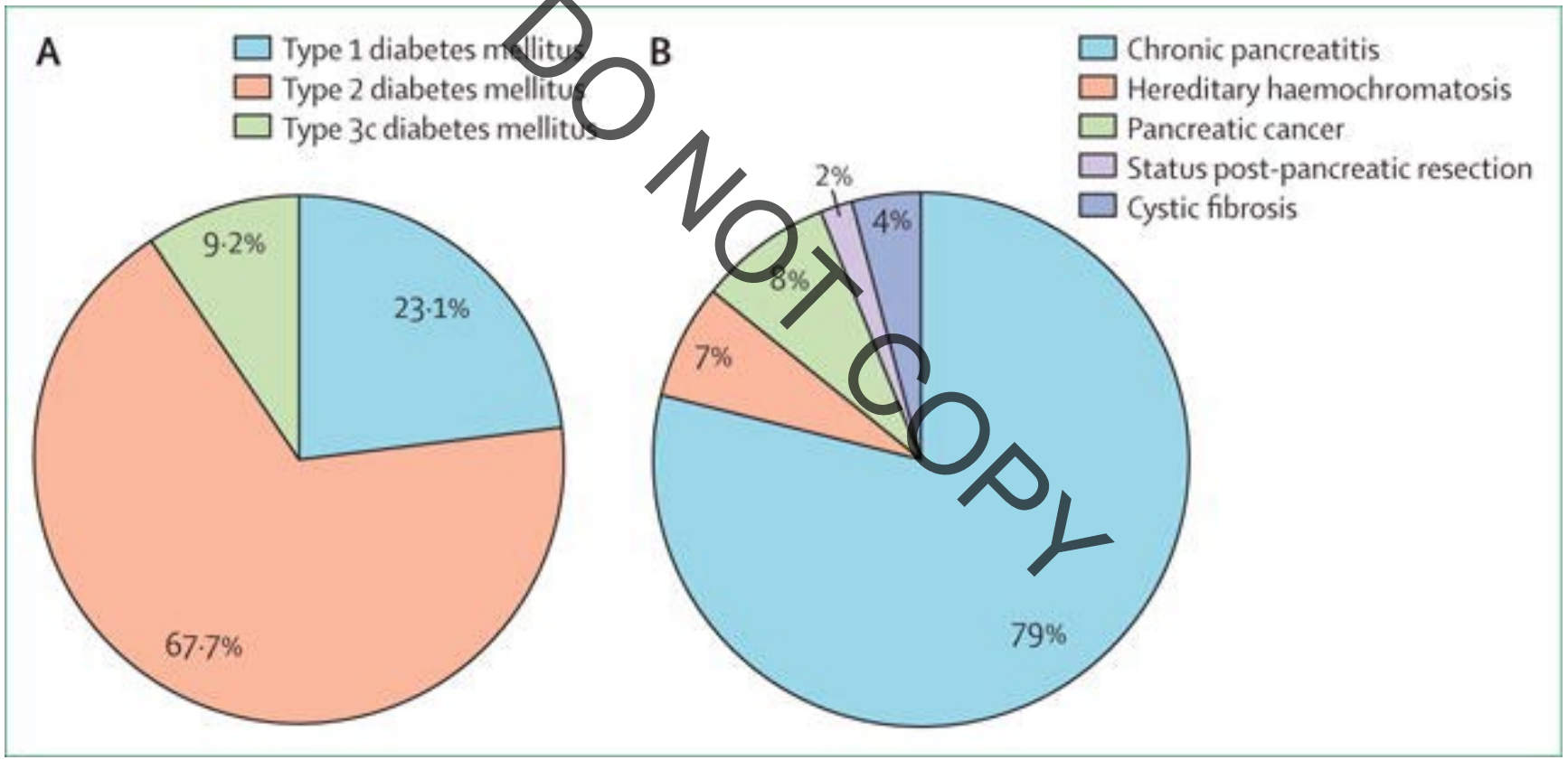
Pancreatitis, even a single episode, can lead to post-pancreatitis diabetes mellitus (PPDM)

Both acute and chronic pancreatitis can lead to PPDM

The risk is highest with recurrent episodes

Prevalence and causes of type 3c diabetes mellitus

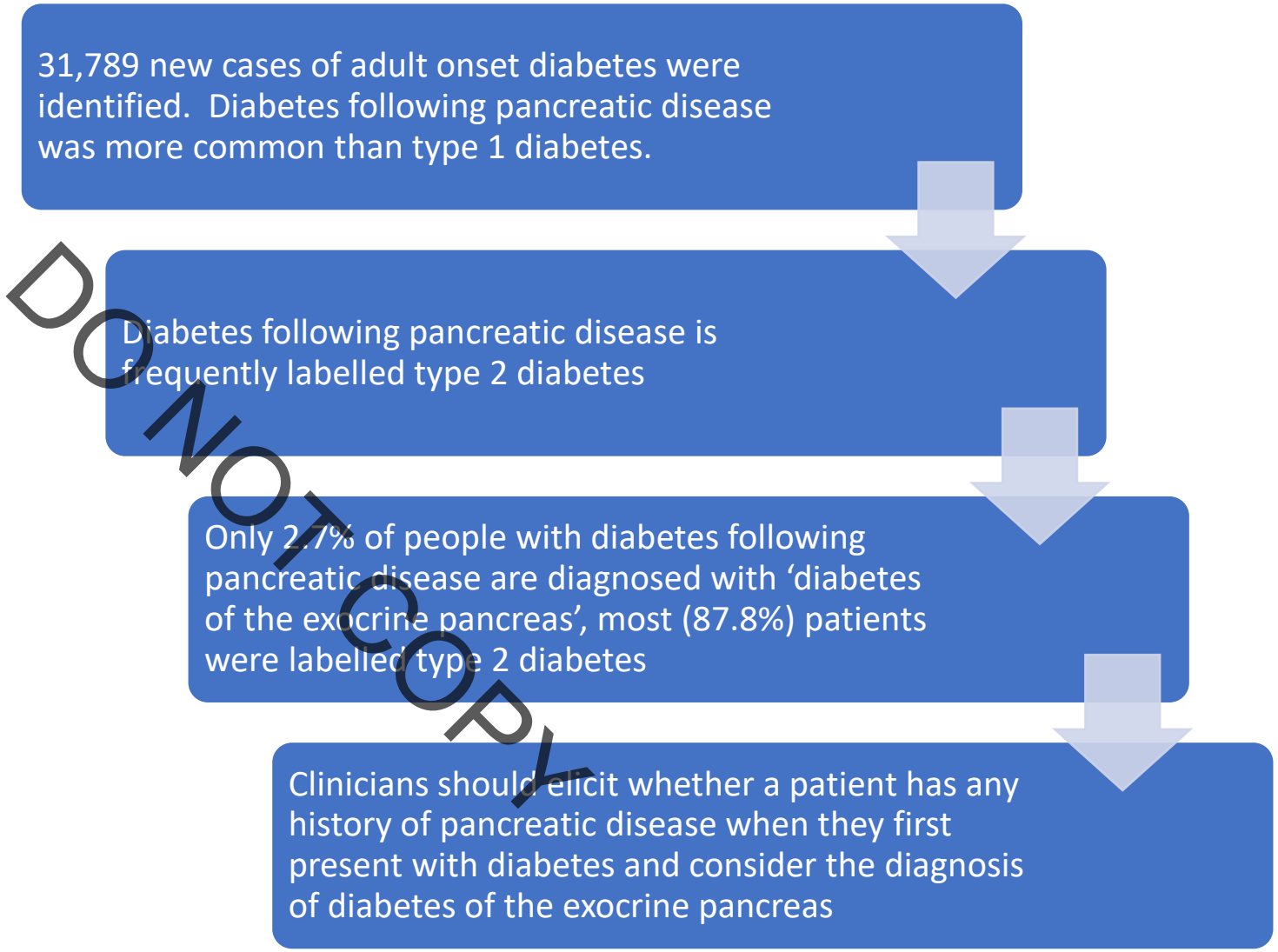
Prevalence of type 3c diabetes in a cohort of 1868 participants with diabetes



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

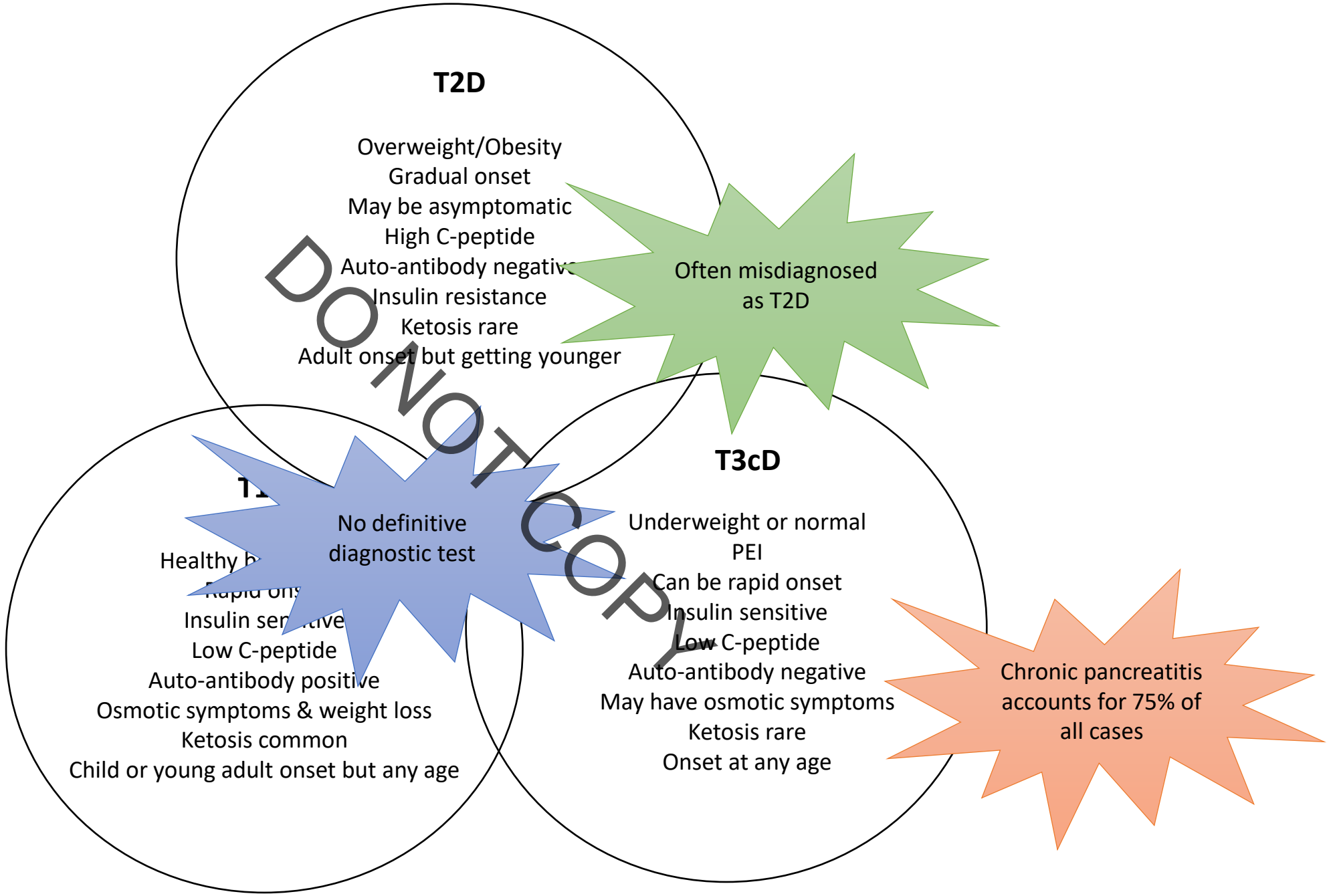
Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c):

A Retrospective Cohort Study



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. https://doi.org/10.2337/dc17-0542

How do you diagnose type 3c?

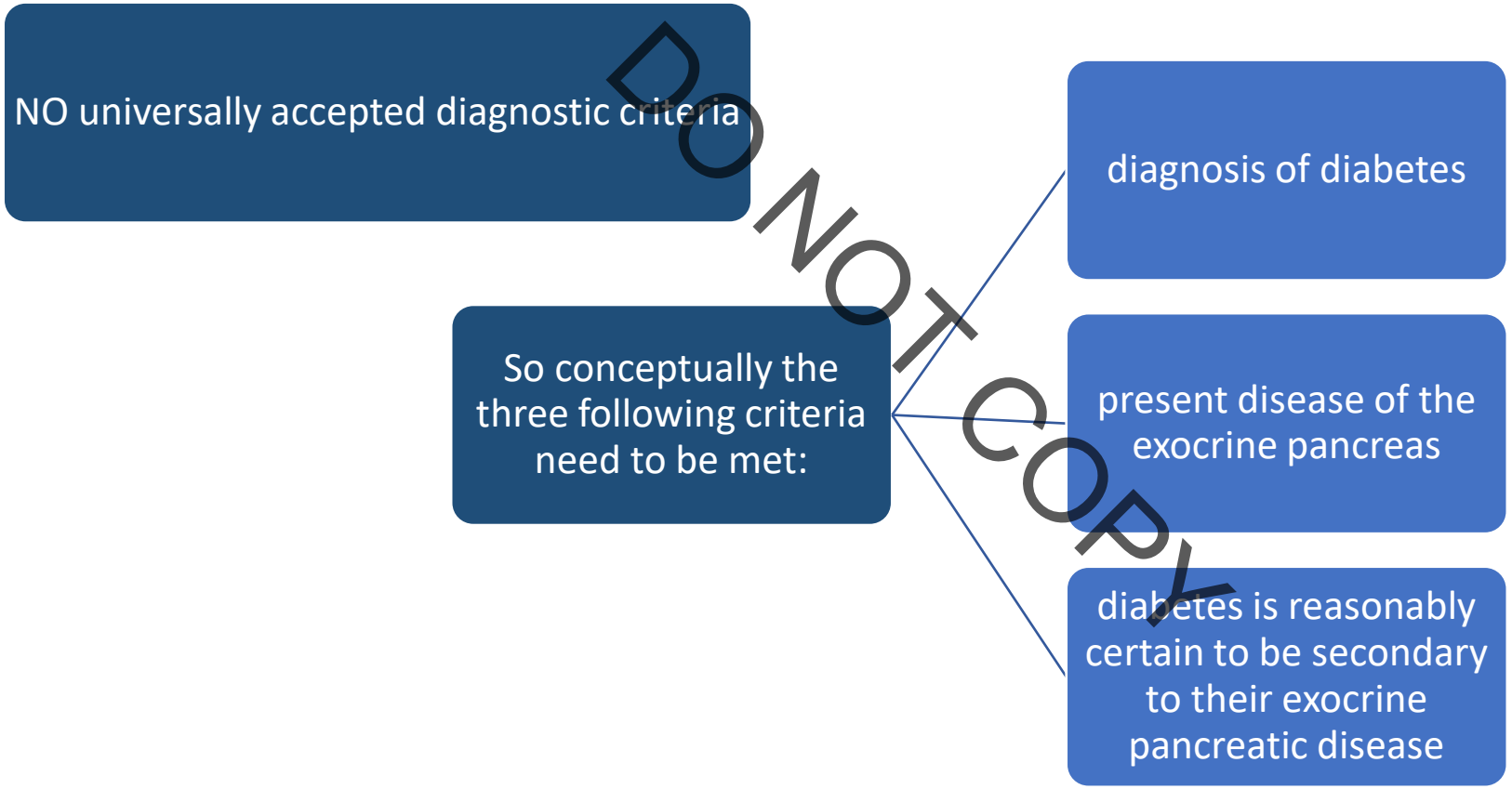

T2D
Overweight/Obesity
Gradual onset
May be asymptomatic
High C-peptide
Auto-antibody negativ
Insulin resistance
Ketosis rare
Adult onset but getting younger
Often misdiagnosed as T2D
No definitive diagnostic test
Healthy b
Insulin sen tive
Low C-peptide
Auto-antibody positive
Osmotic symptoms & weight loss
Ketosis common
Child or young adult onset but any age
T3cD
Underweight or normal
PEI
Can be rapid onset
Insulin sensitive
Low C-peptide
Auto-antibody negative
May have osmotic symptoms
Ketosis rare
Onset at any age
Chronic pancreatitis accounts for 75% of all cases
DO NOT COPY

Common Symptoms of type 3c diabetes

May include symptoms of both hyperglycaemia and exocrine insufficiency

Hyperglycaemia	Exocrine insufficiency
Polyuria	Abdominal pain/discomfort
Polydipsia	Bloating and/or wind
Tiredness/lethargy	Tiredness/lethargy
Weight loss	Weight loss
Slow healing wounds/skin infections	Fatty/greasy stools

How do we differentiate type 3c diabetes from type 1 or 2 diabetes?



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

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 recognise these patients?

Distinguishing pancreatogenic diabetes from type 1 or type 2 diabetes[4,8]

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

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

Chris Woodmansey,[1] Andrew P. McGovern,[1] Katherine A. McCullough,[1,2] Martin B. Whyte,[1,2] Neil M. Munro,[1] Ana C. Correa,[1] Piers A.C. Gatenby,[1,3] Simon A. Jones,[1,4] and Simon de Lusignan[1,5]

Diabetes Care 2017;40:1486–1493 | https://doi.org/10.2337/dc17-0542

Insulin use within 5 years was:

- 4.1% (3.8–4.4) with type 2 diabetes,
- 20.9% (14.6–28.9) with diabetes following acute pancreatitis
- 45.8% (34.2–57.9) with diabetes following chronic pancreatic disease.

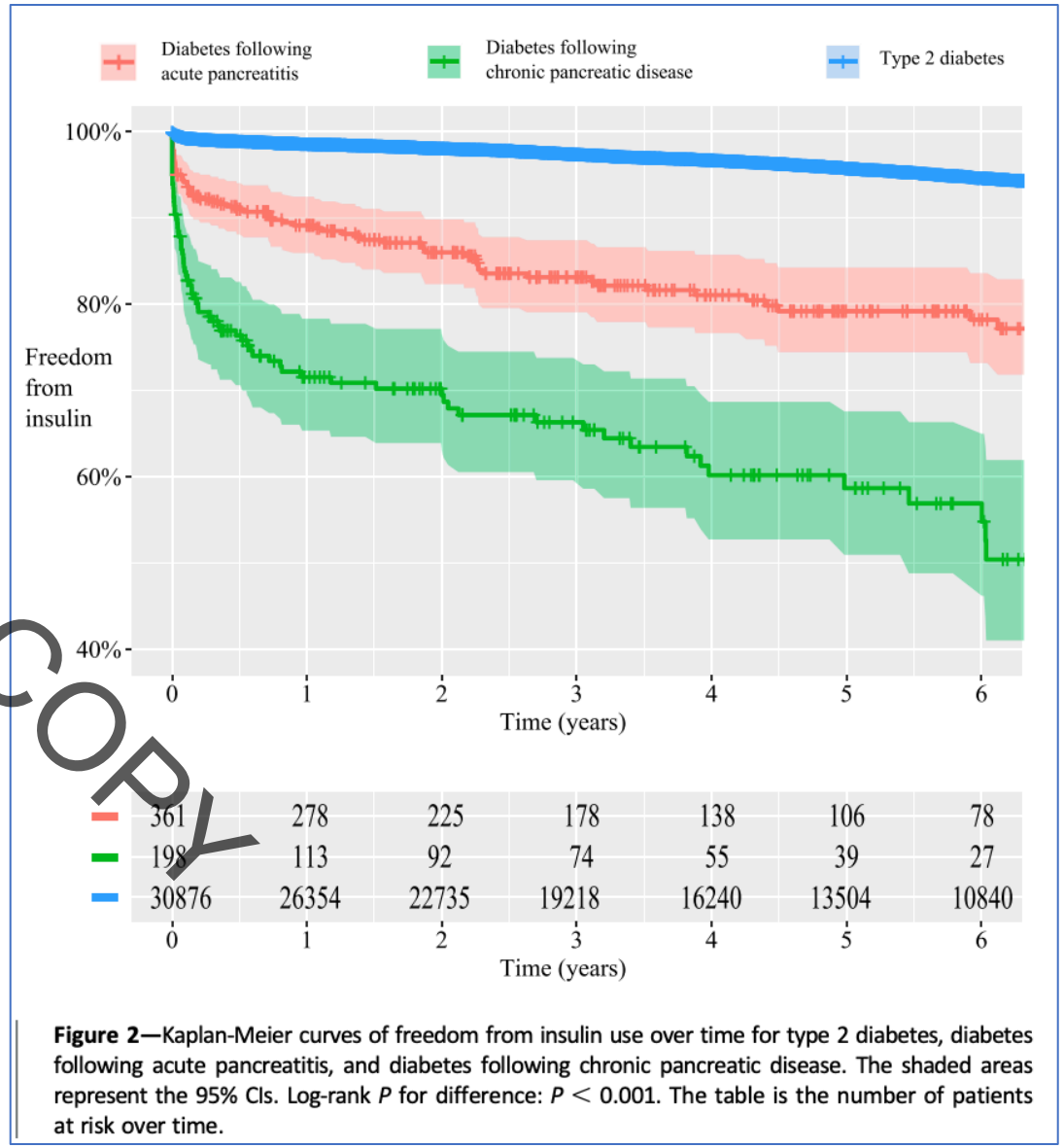
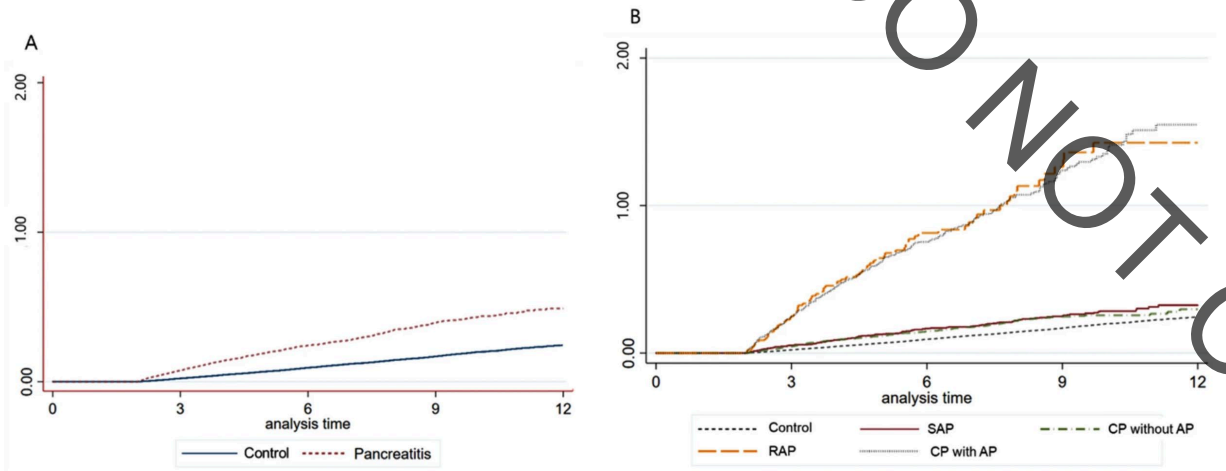


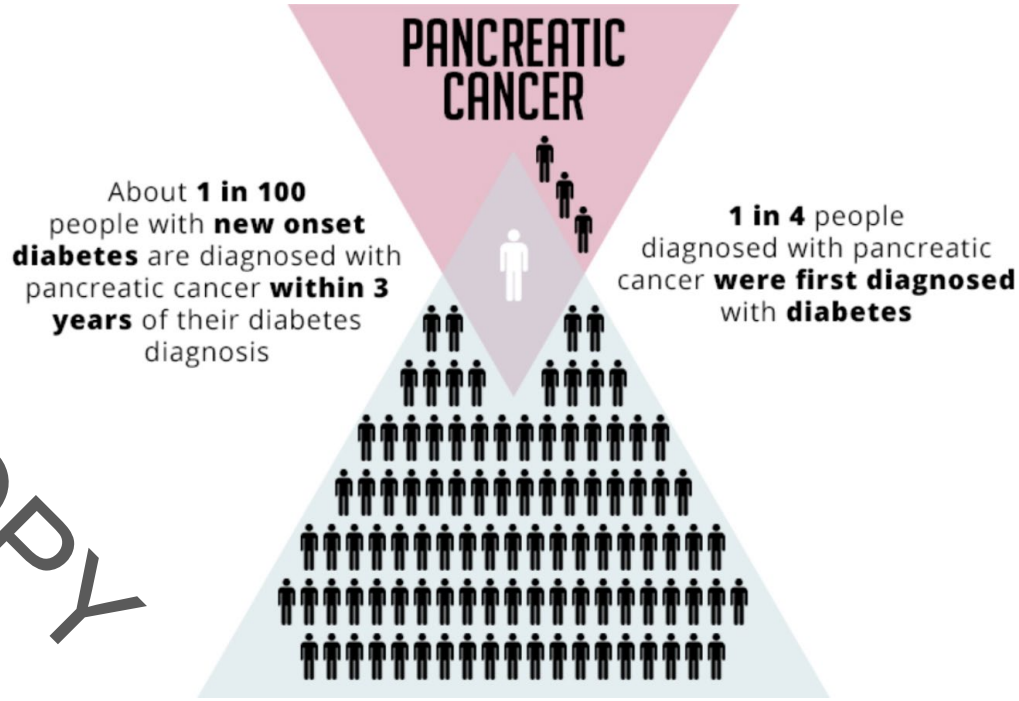
Figure 2—Kaplan-Meier curves of freedom from insulin use over time for type 2 diabetes, diabetes following acute pancreatitis, and diabetes following chronic pancreatic disease. The shaded areas represent the 95% CIs. Log-rank *P* for difference: $P < 0.001$. The table is the number of patients at risk 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



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

National Cancer Institute (2019) https://prevention.cancer.gov/news-and-events/blog/new-onset-diabetes-cohort-sought-unravel-complexities-pancreatic-cancer

Treating type 3c diabetes, what are the differences to type 1 and 2?

Management

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 management	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

1.3.15 Assess people with type 3c diabetes ev[illegible]nths for potential benefit of

1.3.16 [illegible]ging type 3c [illegible] are not using [illegible] NICE guidelines [illegible]dults and [illegible]ging diabetes in [illegible]ng people.

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

- the recommendations on insulin therapy and insulin delivery (including rotating injection sites within the same body region) in the NICE [illegible]lines on type 1 diabetes in [illegible]ing and managing [illegible]nd young [illegible]
- [illegible]aisal [illegible]s
- [illegible] infusion for the [illegible]betes mellitus.

[2018, amended 2020]

1.3.18 [illegible]and [illegible] pancreatitis [illegible]quiring insulin, see [illegible]ations on education and information in the NICE guideline on diagnosing and [illegible] diabetes in adu[illegible] managing dia[illegible] young peopl[illegible]

1.3.19 For guidance [illegible] glucose for peo[illegible] and type 3c diabet[illegible], see the recommendations on blood glucose management in the NICE g[illegible]nosing and managi[illegible]lts, and bloo[illegible]e NICE [illegible]and manag[illegible] young peop[illegible]

Nutrition

Specialist dietitian

CVD risk reduction

Blood pressure
Lipids
Smoking cessation
Urine ACR

Lifestyle

Alcohol
Smoking cessation
Physical activity

Metformin

if no contraindications

Insulin

Often needed due to insulin deficiency

Pioglitazone

Avoid in HF
Bladder cancer
Risk of fractures

SGLT-2 inhibitors

DKA risk
Little evidence

DPP4-inhibitors

Pancreatitis risk

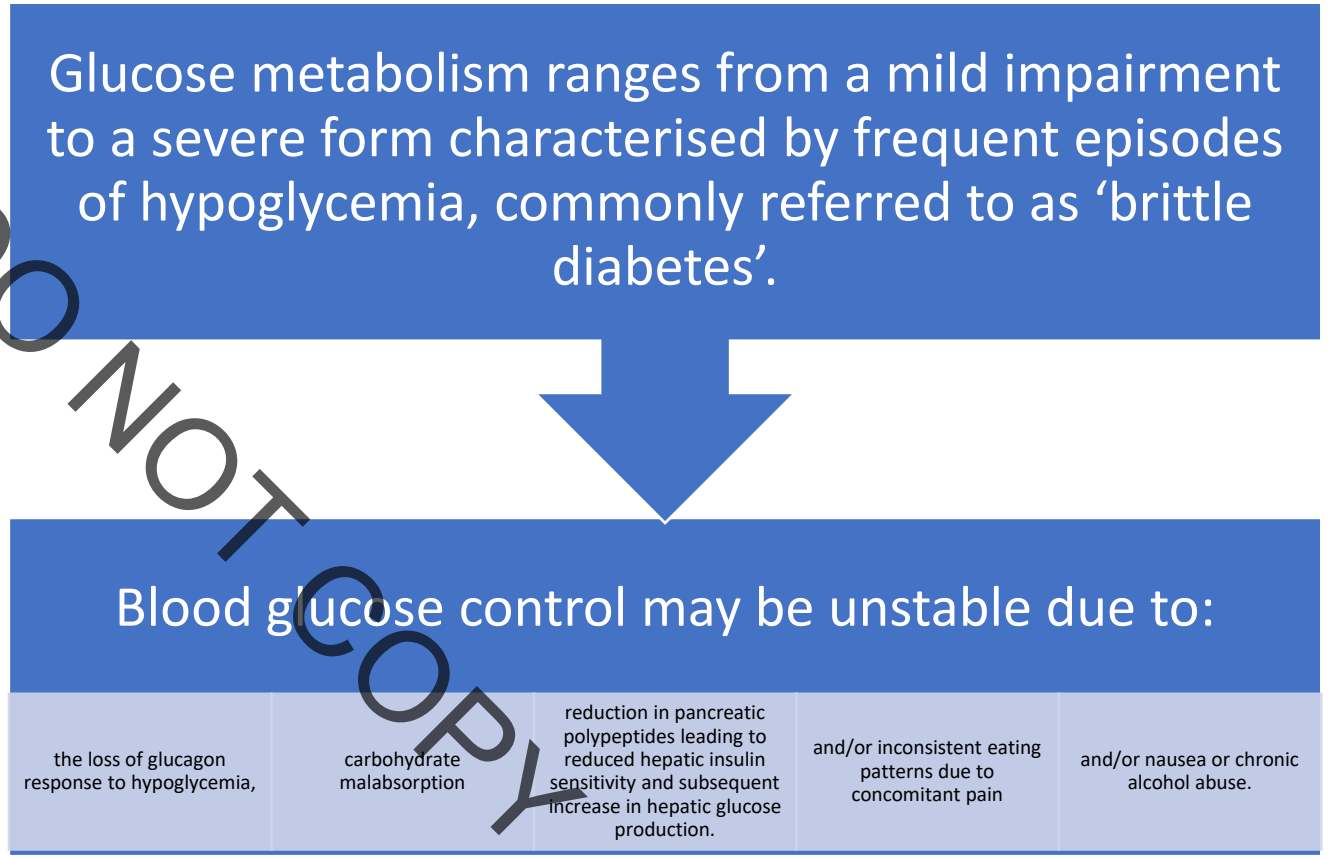
Sulfonylurea

may be less effective dependent on beta cell function

GLP-1 RA

Pancreatitis risk
Appetite suppression
Weight loss

The challenge of glucose management in type 3c



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

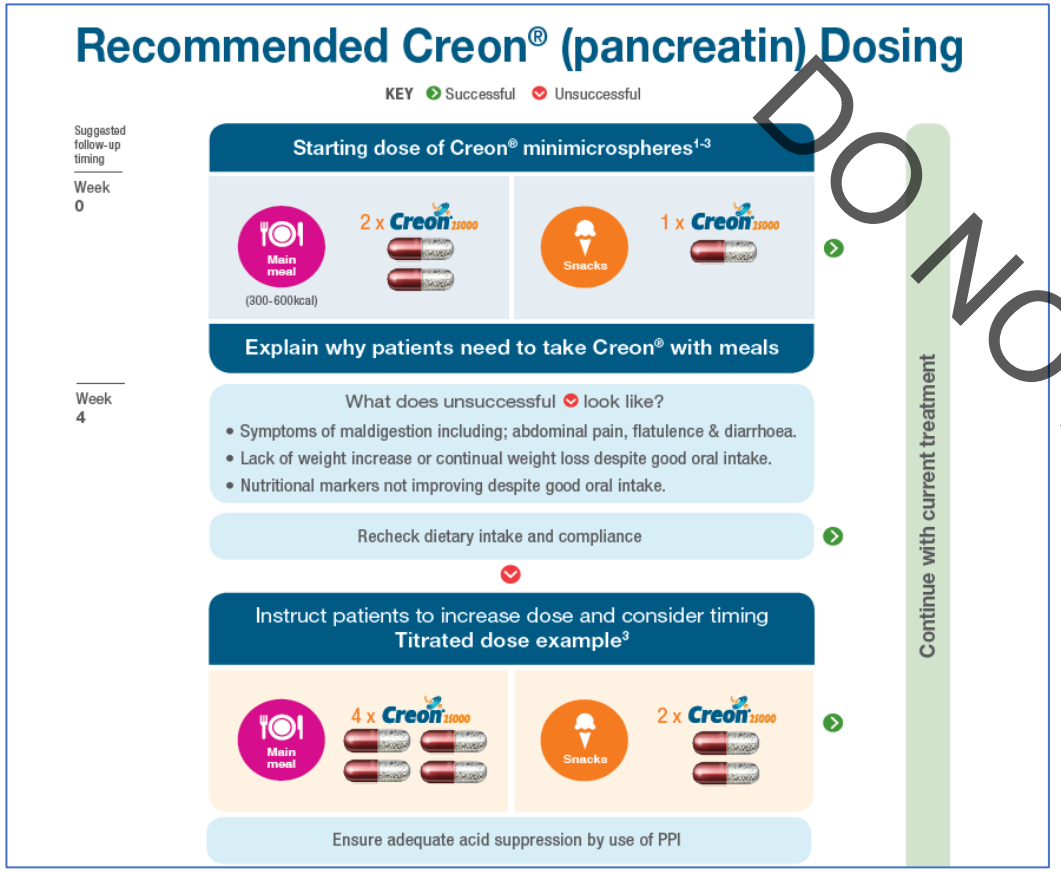
Malabsorption not only increases malnutrition, but it also presents problems for blood glucose management.

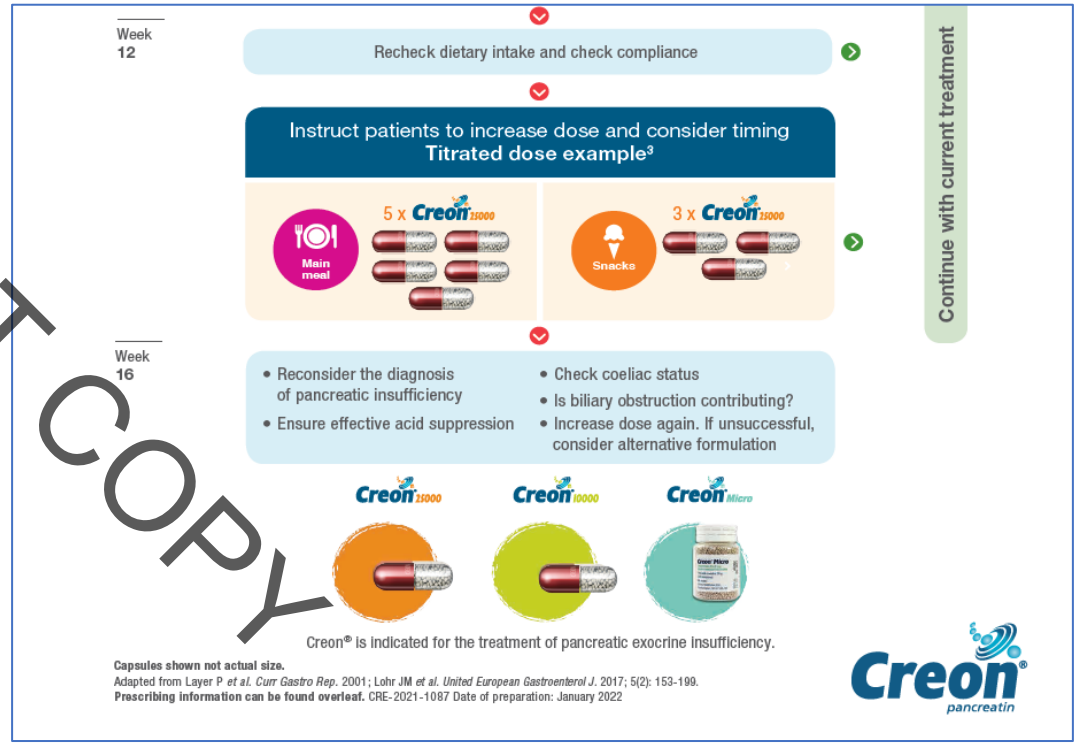
Pancreatic enzyme replacement therapy (PERT)

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

Pancreatic Enzyme Replacement Therapy (PERT)





Other brands of PERT are available: Pancrease®, Nutrizym®, Pancrex®

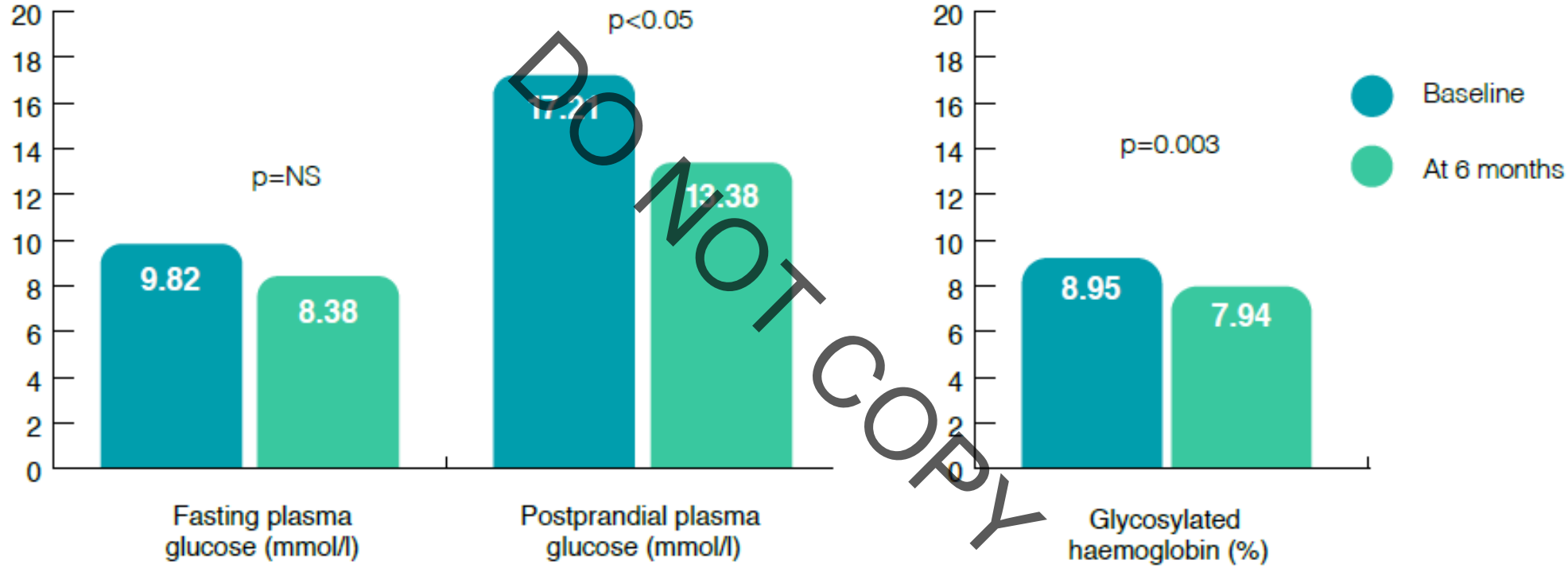
Glycaemic Management

PERT can affect glycaemic control pathways via:

The altered action of the hormones, leptin and incretins on glucose homeostasis; for example, it may improve the incretin response to food and consequently lower blood glucose levels

The patient's glycaemic response and blood glucose levels should be checked frequently during treatment as the dose of the diabetes medication may need adjusting (especially sulfonylureas and insulin)

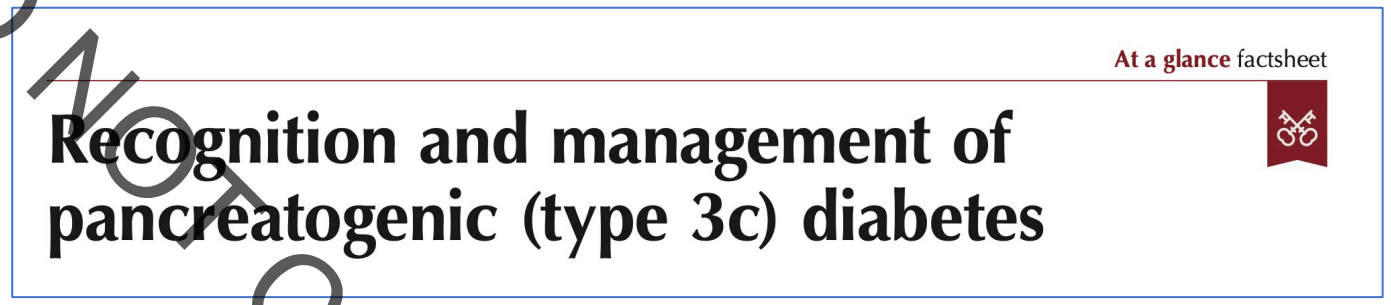
Clinical study – Could PERT improve glucose management?



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

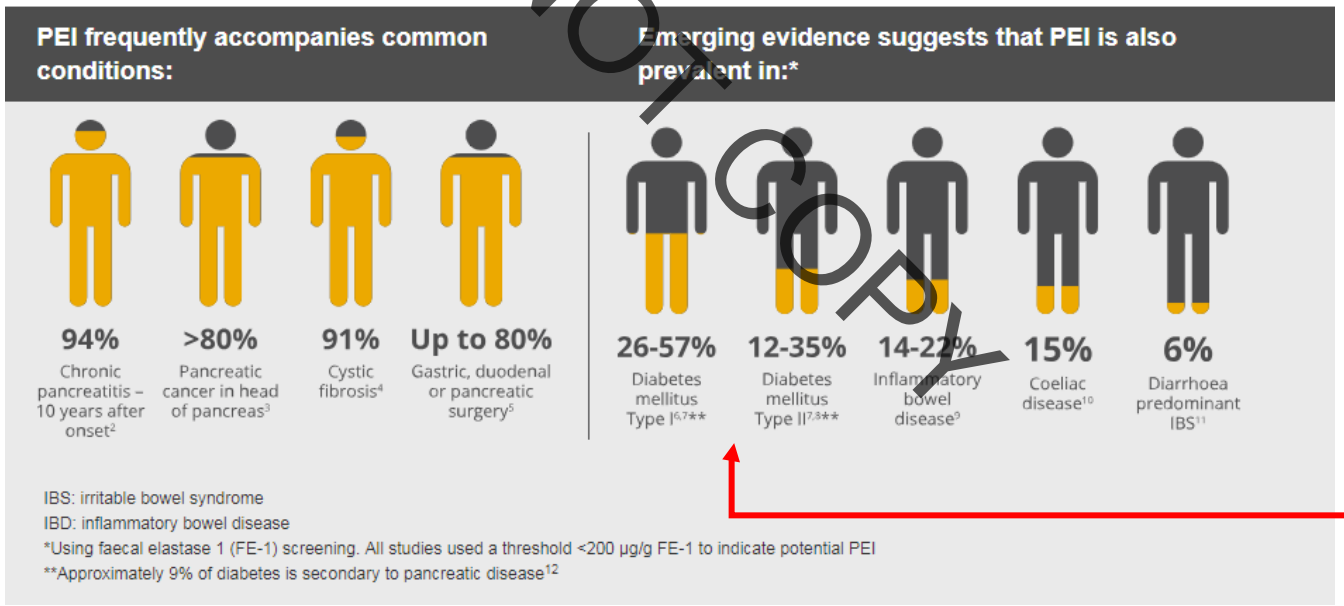


Morris D (2020) Recognition and management of pancreatogenic (type 3c) diabetes. *Diabetes & Primary Care* **22**:111–12

Remember:
Type 3c diabetes not to be confused with Pancreatic Exocrine Insufficiency (PEI) in Diabetes

Pathophysiological Concepts of PEI in Diabetes

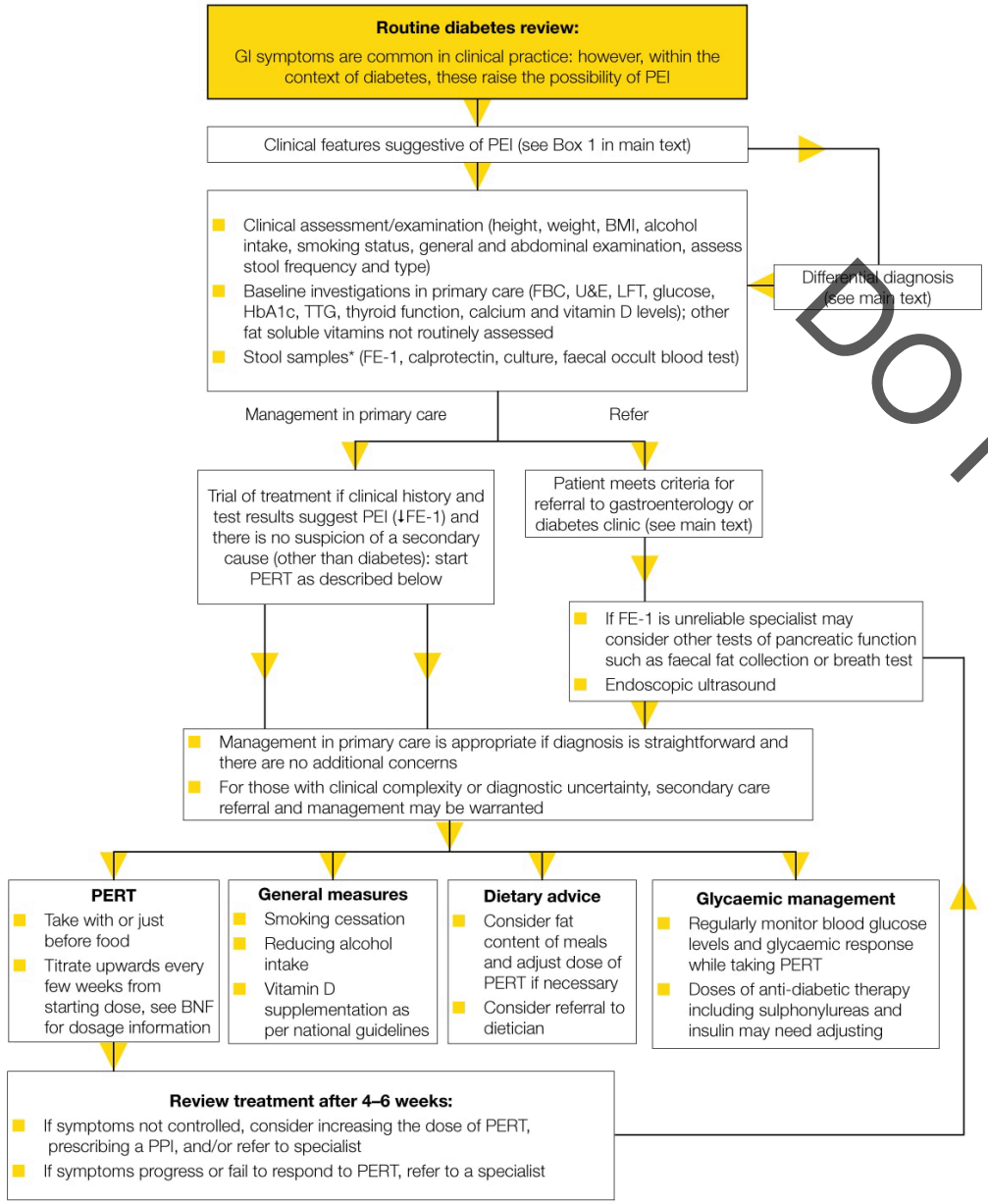
- The prevalence of PEI is reportedly higher in Type 1 DM than in T2DM
- Type 1 DM (26-57%) than in T2DM (20-36%) - *Singh V et al, World J Gastroenterol 2017*
- T1DM 38.62% vs T2DM 28.12% - *Mohapatra S et al, Pancreas 2016*



Use these figures for consistency

1.Icks A, Haastert B, Giani G, *et al*. Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol*. 2001;**39**:823-30.
2.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.
3.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.

Guidelines



* FE-1 is an unreliable measure if the patient has very loose stools; elevated levels of calprotectin are suggestive of inflammatory bowel disease and warrant specialist referral

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

Does technology help people living with type 3c diabetes?

Continuous Glucose Monitoring

Author's own image

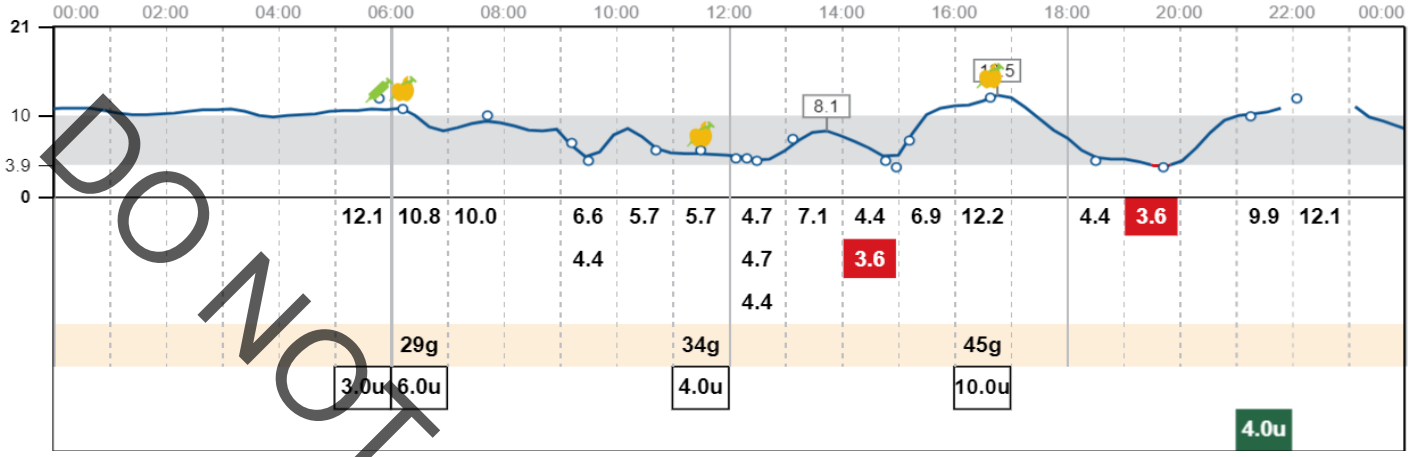
TUE **11 Jul**

Glucose mmol/L

Carbs grams

Rapid-Acting Insulin

Long-Acting Insulin



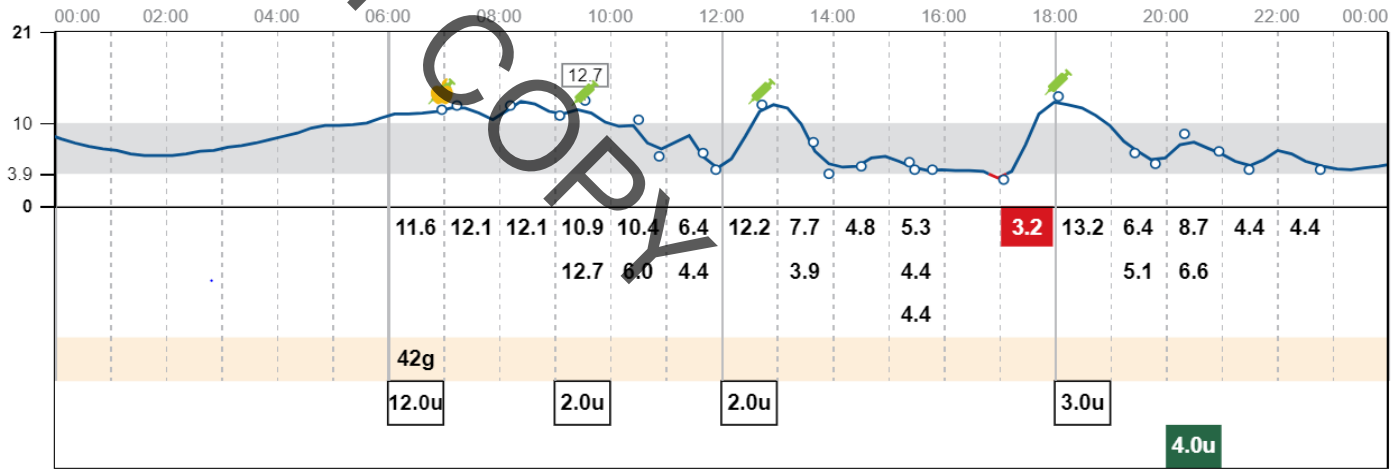
WED **12 Jul**

Glucose mmol/L

Carbs grams

Rapid-Acting Insulin

Long-Acting Insulin



Who is eligible for CGM in England or Wales?

Type 1 diabetes: NICE NG17

Type 1 diabetes

- ✓ All adults with type 1 diabetes
- ✓ All children and young people with type 1 diabetes
- ✓ Consider CGM for pregnant women who are on insulin therapy but do not have type 1 diabetes if:
  - ✓ Problematic severe hypoglycaemia (with or without impaired awareness of hypoglycaemia)
  - ✓ Unstable blood glucose levels that are causing concern despite efforts to optimise glycaemic control

Who is eligible for CGM in England or Wales?

Type 2 diabetes: NICE NG28

Type 2 diabetes

For adults with type 2 diabetes on multiple daily insulin injections if any of the following apply:

- ✓ Recurrent hypoglycaemia or severe hypoglycaemia
- ✓ Impaired hypoglycaemia awareness
- ✓ User would otherwise be advised to self-monitor capillary glucose at least 8 times a day
- ✓ A condition or disability (including a learning disability or cognitive impairment) that means the user cannot self-monitor capillary blood glucose but could use an isCGM device (or have it scanned for them) or could use rtCGM

OR

- ✓ Otherwise need help from a care worker or healthcare professional to monitor their blood glucose.

What about type 3c diabetes?

Type 3c diabetes: Pancreatitis NICE NG104

Type 3c diabetes

For guidance on self-monitoring blood glucose for people with pancreatitis and type 3c diabetes requiring insulin see:

- ✓ Type 1 diabetes NICE NG17 &
- ✓ Diabetes in children & young people NICE NG18

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
- Diabetes technology (CGM) may improve glucose management and reduce hypoglycaemia in type 3c
- Exocrine management is achieved with enzyme replacement and vitamins

Thank you for listening, any questions?