Recognition and management of pancreatogenic (type 3c) diabetes

What is pancreatogenic diabetes?

- Diabetes associated with disease, trauma or surgery of the exocrine pancreas (see ***Box 1***).
- Also referred to as type 3c diabetes.
- Both endocrine (hormone-secreting) and exocrine (digestive enzyme production) functions of the pancreas can be affected.
- Endocrine dysfunction involves all the pancreatic islet cells, including loss of insulin secretion from beta-cells (causing hyperglycaemia) and loss of glucagon from alpha-cells (blunting the response to hypoglycaemia).
- Exocrine dysfunction can lead to impaired digestion and malabsorption of nutrients.

Box 1. Causes of pancreatogenic diabetes[1]

- Pancreatitis (acute or chronic)
- Pancreatectomy
- Trauma
- Pancreatic carcinoma (can develop early in the disease)
- Cystic fibrosis
- Haemochromatosis (for information, visit www.haemochromatosis.org.uk)

Prevalence

- In Western populations estimates vary, with one study suggesting that as many as 5–10% of all individuals with diabetes may have type 3c diabetes.[2]
- Type 3c diabetes is frequently misclassified (often as type 2 diabetes) and so prevalence is underestimated in practice.
- Chronic pancreatitis accounts for around 75% of all cases.[3]
- Alcohol is a common cause of pancreatitis. Other causes include smoking, toxic chemicals, autoimmune disease, genetic causes and pancreatic duct obstruction.[4]

Why is it important to recognise pancreatogenic diabetes?

- To ensure appropriate medical treatment. Insulin may be required.
- Awareness of "brittle diabetes" and risk of hypoglycaemia through loss of counter-regulatory hormone response.[5]
- Need for pancreatic enzyme replacement therapy (PERT).[6]
- Malabsorption of fat-soluble vitamins. Risk of vitamin D deficiency and osteoporosis.[6]
- Increased risk of pancreatic carcinoma.[7]
- To avoid incretin-based therapies where there is a history of pancreatitis.

Clinical recognition of pancreatogenic diabetes

- Consider type 3c if diabetes diagnosed in individuals with chronic pancreatitis or other conditions listed in ***Box 1***. Consider screening for diabetes in people with these conditions.
- Classic symptoms of diabetes: thirst, polyuria, weight loss, fatigue, recurrent infection may be present. Diagnose diabetes by usual means.
- Ask about gastrointestinal symptoms. Consider type 3c as cause of diabetes if history of upper abdominal pain, steatorrhoea, bloating and weight loss. Pancreatic enzyme insufficiency (PEI) usually pre-dates onset of diabetes.[4]
- There is no definitive diagnostic test for type 3c diabetes.

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

Useful investigations in possible pancreatogenic diabetes[9]

Investigation	Pancreatogenic diabetes
HbA_{1c}, fasting glucose, random glucose	To diagnose diabetes
Islet cell antibodies (anti-GAD, IA2 antibodies)*	Expected to be absent in type 3c and type 2 diabetes. Characteristic of type 1 diabetes
C-peptide level*	Low in type 3c and type 1 diabetes. May be raised in type 2 diabetes
25-hydroxy vitamin D level	Often low in type 3c diabetes
Faecal elastase-1 levels*	Low levels in type 3c diabetes, indicating exocrine insufficiency
Pancreatic imaging (endoscopic ultrasound, CT/MRI scan)*	To reveal pancreatic pathology

*Depending on local arrangements, some of the tests are likely to be performed in secondary care, either under endocrinology or gastroenterology.

Box 2. Proposed major diagnostic criteria for pancreatogenic diabetes[9]

- Pancreatic exocrine insufficiency (faecal elastase-1 testing)
- Pathological pancreatic imaging (endoscopic ultrasound/CT or MRI scan)
- Absence of type 1 diabetes-associated antibodies

Referral

- To confirm diagnosis of type 3c diabetes (islet cell autoantibodies, pancreatic imaging, faecal elastase testing).
- Refer to endocrinology if insulin needed to control hyperglycaemia (high HbA_{1c} at presentation, sudden rise in HbA_{1c}).
- Refer to gastroenterology if symptoms indicate need for PERT (steatorrhoea, weight loss).
- If concern over possibility of pancreatic carcinoma (weight loss, epigastric pain radiating to back, jaundice, anorexia, unexpected deterioration in glycaemic control).

Management

The evidence base to guide management of type 3c diabetes is weak. There are no specific guidelines. Treatment goals are derived from randomised controlled trials from type 1 and type 2 diabetes, and expert opinion.

1. Diet and lifestyle[10]

- High soluble fibre diet.
- Smoking cessation.
- Avoid alcohol.
- Regular exercise.

2. Reducing cardiovascular risk (as per type 1 and type 2 diabetes)

- Smoking cessation.
- Control hypertension.
- Use of statin.

3. Glycaemic control[2,4–6,8–9]

- Awareness of risk of hypoglycaemia and need for blood glucose monitoring. May need to accept higher HbA_{1c} levels.
- Metformin: first-line therapy for mild hyperglycaemia; low risk of hypoglycaemia; possible protective effect against pancreatic carcinoma.
- Sulfonylureas/glinides: less effective as beta-cell function declines in type 3c diabetes; risk of hypoglycaemia.
- Pioglitazone: option if intolerance or contraindication to metformin; avoid in heart failure, or if concerns over risk of fracture and possible small risk of bladder cancer.
- DPP-4 inhibitors and GLP-1 receptor agonists: generally avoided because of concerns over pancreatitis and pancreatic carcinoma. GLP-1 RA properties of reducing appetite and weight loss not desirable in type 3c diabetes. Also avoid if type 3c diabetes is linked to pancreatitis.
- SGLT2 inhibitors: little evidence but potentially useful; can increase risk of DKA.
- Insulin: ultimately needed in most cases to deal with insulin deficiency; may be required from outset if HbA_{1c} markedly elevated; treatment of choice in cystic fibrosis-related type 3c diabetes; basal–bolus regimen optimal (or insulin pump), carbohydrate counting appropriate.

4. Exocrine issues[2,4–6,8–9]

- Pancreatic enzyme replacement therapy (PERT; e.g. Creon, Nutrizym, Pancrease, Pancrex) with meals if PEI. Judge response by relief of steatorrhoea, weight gain.
- PERT can improve digestion of carbohydrates and increase glucose levels. PERT may unmask diabetes in an individual with previously normal HbA_{1c}.
- Vitamin D supplements if proven deficiency. Consider investigations for osteoporosis.

Resources

- TREND-UK. Patient leaflet on diabetes and pancreatic exocrine insufficiency: bit.ly/3hXy25g
- Diabetes UK. Fact file on type 3c diabetes: bit.ly/3evlqAh
- Pancreatic Cancer UK. Resources for health professionals: bit.ly/3ereDaF
- E-learning module: *Making the right diagnosis*: bit.ly/right-diagnosis_cpd

References

[1]ADA (2020) *Diabetes Care* **43**(Suppl 1): S14–53
[2]Cui Y, Andersen DK (2011) *Pancreatology* **11**: 279–94
[3]Ewald N et al (2012) *Diabetes Metab Res Rev* **28**: 338–42
[4]Gudipaty L, Rickels M (2015) *Pancreatogenic (Type 3c) Diabetes*. APA: bit.ly/2No0Vtl
[5]Makuc J (2016) *Diabetes Metab Syndr Obes* **9**: 311–15
[6]Gupte A et al (2018) *BMJ* **361**: k2126
[7]Cui Y, Andersen DK (2012) *Endocr Relat Cancer* **19**: F9–F26
[8]Duggan SN, Conlon KC (2017) *Practical Gastroenterology* **41**: 14–23
[9]Ewald N, Hardt PD (2103) *World J Gastroenterology* **19**: 7276–81
[10]Duggan SN et al (2017) *Eur J Clin Nutr* **71**: 3–8

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