fact file 36

# Type 3c diabetes

Type 3c diabetes, also termed pancreatiogenic diabetes or secondary diabetes, is characterised by concurrent pancreatic endocrine and exocrine insufficiency. The condition involves reduced production of all pancreatic hormones. As **Laura McGeeney**, Pancreatic Specialist Dietitian, Addenbrooke's Hospital Cambridge, explains, Type 3c differs from other types of diabetes and needs to be identified and managed appropriately

When someone does not produce or secrete enough pancreatic enzymes for adequate digestion, they have pancreatic exocrine insufficiency (PEI). This is treated with pancreatic enzyme replacement therapy (PERT), usually in the form of capsules containing porcine pancreatic enzymes, which are taken with meals, snacks and milky drinks to enable adequate digestion. If PEI is untreated, this leads to malabsorption and malnutrition. Inadequate digestion and absorption of carbohydrates also presents problems for someone with diabetes trying to keep their blood glucose level within a target range.

Other aspects of pancreatic disease can also make Type 3c diabetes management difficult. People may be in a lot of pain, drowsy from analgesia, nauseous from their disease or treatment, emotionally distressed by their diagnosis or prognosis, receiving chemotherapy, have a variable nutritional intake, potentially a high alcohol intake and may need to regularly travel to hospital for treatments.

## Diagnosis of Type 3c diabetes

The American Diabetes Association classification of diabetes has four main categories and sub-category 3c describes diseases of the exocrine pancreas. This includes pancreatitis, pancreatic cancer, pancreatic surgery/trauma, cystic fibrosis, haemochromatosis, fibrocalculous pancreatopathy and pancreatic agenesis.

Type 3c diabetes is frequently misclassified, mostly as Type 2 diabetes[1]. This German study showed that, using the ADA classification, in a sample of nearly 1,922 people with diabetes, 8 per cent had Type 3c. Three-quarters of these had chronic pancreatitis.

The diagnosis is made as it is with other types of diabetes. If either fasting glucose or HbA1c is high, further investigation is indicated. However, defining the condition as Type 3c is less straightforward. Ewald and Hart[2] suggested that for a diagnosis of Type 3c to be made, someone must have all of the following:

- PEI
- pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
- no Type 1 diabetes-associated autoimmune markers.

The above are termed the major criteria. There are also some minor criteria, indicating a Type 3c diagnosis, including:

- the absence of pancreatic polypeptide (PP) secretion
- impaired incretin secretion
- no excessive insulin resistance (eg HOMA-IR)
- impaired beta-cell function (HOMA-B or glucose:c-peptide ratio)
- low serum levels of lipid-soluble vitamins (A, D, E and K).

However, the details of defining a Type 3c diagnosis are not universally agreed. A recent paper[3] has critiqued these criteria, but states that they remain the best available to date. The authors propose that in classifying the type of diabetes, the following laboratory tests be carried out at least once:

- diabetes-associated autoantibodies (to distinguish from Type 1)
- C-peptide:glucose ratio and HOMA-IR
- assessments of pancreatic exocrine function and pancreatic imaging.

In clinical practice, pancreatic exocrine function is usually assessed with faecal elastase-1 measurement in a stool sample. This is a surrogate marker of pancreatic exocrine function and is fairly inexpensive, easily carried out and widely available. However, it has low sensitivity and specificity for mild to moderate PEI (200–500µg/g).

An HbA1c within the normal range does not exclude diabetes in someone with untreated PEI. Commencement of PERT can unmask diabetes by increasing digestion of starches. It is therefore good practice to check blood glucose levels after someone starts taking PERT.

## Clinical and laboratory features

Type 3c diabetes involves a range from mild to severe impairment of glucose metabolism[4]. Someone with Type 3c has low circulating levels of insulin, glucagon, PP and gastric inhibitory polypeptide, and normal or high levels of GLP-1. They also have increased peripheral insulin sensitivity and decreased hepatic insulin sensitivity. Hypoglycaemic episodes are common and can be prolonged, as people with Type 3c have impaired glucagon secretion. Ketoacidosis is rare.

Lee et al[5] suggest that clinical features could be used to distinguish pancreatic cancer-associated diabetes (Type 3c) and Type 2 diabetes. A lack of a family history of diabetes, age 65 years or older, recent weight loss of >2kg, a premorbid or usual BMI <25 kg/m$^2$ all suggest Type 3c is more likely.

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## Management of Type 3c diabetes

Therapeutic goals vary depending on diagnosis, nutritional status, prognosis, comorbidities and lifestyle. For those who are relatively well, these include a fasting serum glucose of 3.9–7.2mmol/l and HbA1c of 53mmol/mol (7 per cent), while targets are likely to be more relaxed in those with more life-limiting disease, or where frequent hypoglycaemia is prominent. Recommendations include weight loss in those who are obese, daily exercise, limiting carbohydrate intake, alcohol abstinence and smoking cessation[4]. However, these are rarely appropriate for people who are less well. Someone with pancreatic cancer and a short prognosis will be aiming to avoid or reduce hypos and symptoms of hyperglycaemia.

Research into the optimal treatment strategies for Type 3c is lacking. Those used have been adopted from treatment of Type 1 and Type 2 diabetes. Typically, medications used are the same as for Type 2, with metformin often being the initial drug of choice. Those presenting with significant hyperglycaemia (HbA1c >69.4mmol/mol (8.5 per cent), fasting glucose >10mmol/l), catabolic with glycosuria and weight loss are usually started on insulin.

There are suggestions that insulin therapy[6], sulphonylurea therapy[7] and sitagliptin or exanatide[8] confer an increased risk of pancreatic cancer. Bonelli et al[9] found that diabetes was associated with a 2.86-fold increase in the risk for pancreatic cancer, the risk increasing to 6.49-fold for those treated with insulin, compared with 2.12-fold for those treated with oral hypoglycaemic agents. The risk ratio (RR) was not affected by the duration of insulin treatment, but longer duration of oral hypoglycaemic therapy was associated with a lower RR for the development of pancreatic cancer.

Li et al[7] found insulin treatment to be associated with an increased risk of pancreatic cancer (RR 2.78 for insulin users of more than five years) and metformin therapy to be associated with a 70 per cent decreased risk (RR 0.30). Sadeghi et al[10] studied people with pancreatic cancer and diabetes and reported a longer median survival in metformin users when compared with non-users: 16.6 vs 11.5 months. Cui and Andersen[4] proposed that if there are no drug side effects (principally gastrointestinal sensitivity) or contraindications (such as renal insufficiency), metformin should be prescribed to all Type 3c patients, even if other antidiabetic medication is required for adequate glycaemic control.

The management of Type 3c requires management of PEI. and lifestyle factors as well as anti-diabetic therapies. Malabsorption not only increases malnutrition, it also presents problems for blood glucose management. If the carbohydrate consumed is not adequately digested and absorbed, it will not result in the expected rise in blood glucose.

Alterations in PERT dosing can have an impact on blood glucose levels without any changes to carbohydrate intake. It is therefore necessary to consider these in tandem and inform people of the potential impact changes to PERT dose may have on their blood glucose levels. It is important that PERT is taken with their slow-release carbohydrate hypo treatments for them to be effective.

There can be a somewhat fatalistic acceptance of cancer cachexia in people with pancreatic cancer, and accelerated, pronounced weight loss is seen as an untreatable consequence of disease. While studies evaluating the potential role of pharmacological agents and nutritional strategies in treating cachexia are ongoing, there is, as yet, no therapy for the condition. Correctly identifying and treating both exocrine and endocrine insufficiencies in people with pancreatic cancer, which contribute to weight loss and are reversible factors, may minimise weight loss, improve quality of life and address key supportive care needs.

More research is needed into the diagnosis and management of Type 3c diabetes. Identifying the diagnosis as Type 3c is often the first step to improving outcomes.

## REFERENCES


1. Ewald N, Kaufmann C, Raspe A et al (2012). Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes/Metabolism Research and Reviews* 28 (4); 338-342
2. Ewald N and Hardt PD (2013). Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World Journal of Gastroenterology* 19 (42); 7276–7281
3. Duggan SN, Ewald N, Kelleher L et al (2017). The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. *European Journal of Clinical Nutrition* 71 (1); 279–294
4. Cui YF and Andersen DK (2011). Pancreatogenic diabetes: special consideration for management. *Pancreatology* 11 (3); 279–294
5. Lee JH, Kim SA, Park HY et al (2012). New-onset diabetes patients need pancreatic screening? *Journal of Clinical Gastroenterology* 46 (7); e58–61
6. Azar M and Lyons TJ (2010). Diabetes, insulin treatment and cancer risk: what is the evidence? *F1000Reports Medicine* Jan 18
7. Li D, Yeung SC, Hassan MM et al (2009). Antidiabetic therapies affect the risk of pancreatic cancer. *Gastroenterology* 137 (2); 482–488
8. Elashoff M, Matveyenko AC, Gier B et al (2011). Pancreatitis, pancreatic and thyroid cancer with glucagon-like-peptide-1-based therapies. *Gastroenterology* 14 (1); 150–156
9. Bonelli L, Aste H, Bovo P et al (2003). Exocrine pancreatic cancer, cigarette smoking and diabetes mellitus: a case-control study in northern Italy. *Pancreas* 27 (2); 143–149
10. Sadeghi N, Abbruzzese JL, Yeung SC et al (2012). Metformin use is associated with better survival of diabetic patients with pancreatic cancer. *Clinical Cancer Research* 18 (10); 2905–2912



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