Pancreatic exocrine dysfunction: common in type 3c diabetes, but don’t forget types 1 and 2 diabetes mellitus

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Abstract
It is well understood that the pancreas has two distinct roles: the endocrine and exocrine functions, that are functionally and anatomically closely related. As specialists in diabetes care, we are adept at managing pancreatic endocrine failure and its associated complications. However, there is frequent overlap and many patients with diabetes also suffer from exocrine insufficiency.

Here we outline the different causes of exocrine failure, and in particular that associated with type 1 and type 2 diabetes and how this differs from diabetes that is caused by pancreatic exocrine disease: type 3c diabetes. Copyright © 2017 John Wiley & Sons.

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Key words
pancreatic exocrine insufficiency, PEI; gastrointestinal symptoms; steatorrhoea; faecal elastase-1 levels

Introduction
Summary of pancreatic physiology.
In normal physiological states, insulin release from the islet cells is stimulated by the production of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic hormone (GIP) – known as incretins. These are released by the endocrine cells in the small bowel mucosa, in response to carbohydrate and lipid presence in the proximal gastrointestinal tract. The islet cells, responsible for the endocrine function primarily secreting insulin, glucagon and somatostatin, typically constitute only a very small proportion (1–2%) of the pancreatic mass, but are distributed throughout the pancreatic tissue.

(See Figure 1.)

The pancreas also plays a vital role in digestion. Gastric acid in the duodenum stimulates the release of secretin from duodenal mucosal cells, which in turn stimulates the release of water and bicarbonate from pancreatic ductal cells. In addition, the presence of fat and protein in the duodenum stimulates cholecystokinin (CCK) release by endocrine cells in the duodenal mucosa, which results in the release of pancreatic enzymes and pro-enzymes from pancreatic acinar cells through both direct and vagal stimulation.

The composition of pancreatic enzymes is predominantly proteases (80%), with the remainder mainly made up of amylase (7%), lipase (4%) and nucleases (1%).

Together, this combination of water, bicarbonate and enzymes forms the pancreatic juices that, once released into the duodenum, enable digestion of fat, carbohydrate and protein and constitute the pancreatic exocrine function.

For this process to work, the pancreas requires:
• Adequate stimulation.
• The ability to synthesise the pancreatic enzymes.
• A patent pancreatic duct and common bile duct to allow flow into the duodenum.
• Appropriate and timely mixing with the semi-digested food.

Pathology of pancreatic exocrine insufficiency
Pancreatic exocrine insufficiency (PEI) is not the same condition as chronic pancreatitis; rather, it is a functional state and a less well-recognised manifestation of pancreatic disease caused by a variety of aetiologies, including but not limited to chronic pancreatitis. The underlying aetiology may be associated with conditions that cause overt structural pancreatic damage, as well as those that do not, and can result from a fault in one or more of the...
steps described above. PEI is a spectrum or a continuum of disease, ranging from mild symptoms to very severe with complete absence of any residual pancreatic enzyme activity.

The most common cause of PEI is chronic pancreatitis. In chronic pancreatitis, the structure of the pancreas is damaged by chronic, patchy and progressive inflammatory and fibrotic changes. This damage can affect both the exocrine and endocrine function. Alcohol is linked to the majority of cases of chronic pancreatitis, but a significant number are idiopathic. A smaller number are caused by genetic mutations, and some cases are thought to be autoimmune in origin. The underlying pathological process that leads to chronic pancreatitis is not fully understood, although theories include the development of protein-rich plugs which cause patchy ductal obstruction, ischaemia, and antioxidant deficiency. Recurrent episodes of acute pancreatitis, a diffuse but non-progressive inflammatory condition, can also lead to chronic pancreatitis due to repeated inflammation and subsequent development of fibrosis.

Cystic fibrosis is another cause of PEI, as a result of progressive pancreatic damage from the abnormally thickened secretions that characterise cystic fibrosis. Structural changes as a result of surgical intervention can also lead to chronic pancreatitis due to repeated inflammation and subsequent development of fibrosis.

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**Type 1 and type 2 diabetes**

Gastrointestinal symptoms occur frequently in patients with diabetes (up to approximately 80% of patients)\(^1,12\) and have a number of attributable causes, including side effects from antidiabetes medications such as metformin, co-existing gastrointestinal comorbidities such as irritable bowel syndrome, and diabetes complications such as gastroparesis.

While the development of diabetes in the presence of pancreatic disease is relatively well established and understood, there are also a significant number of individuals with type 1 or type 2 diabetes who develop PEI in the absence of any other overt pancreatic disease. This can be thought of as a less-well recognised gastrointestinal complication of diabetes.

While exact prevalence rates vary by studies and by diagnostic method, studies using faecal elastase-1 (FE-1) as the diagnostic test have shown that between 25–72% of patients with type 1 diabetes and between 28–54% of patients with type 2 diabetes have PEI.\(^1,13\) A recent audit undertaken in the authors’ department found that 42% of patients with diabetes who had symptoms consistent with PEI, and who provided a stool sample, were found to have PEI.\(^14\)

A number of hypotheses regarding the cause of PEI in diabetes have been suggested, though the exact underlying aetiology, or aetiologies, is still not certain. It has been shown frequently that the pancreas is macroscopically altered in patients with diabetes, with smaller-sized organs and evidence of fibrosis and atrophy visible both histologically and on imaging.\(^2,13\) Theories regarding the underlying process leading to these changes include:

- The reduced trophic effect due to a lack of insulin.
- The effect of diabetic neuropathy (particularly autonomic neuropathy).
- Fibrosis and atrophy due to microvascular and oxidative stress damage.
- Dysregulation due to changes in other islet hormones including glucagon and somatostatin.
- Autoimmune effects.
- The presence of underlying pancreatic disease such as chronic pancreatitis that has gone undiagnosed (suggesting that the individual therefore has type 3c diabetes).\(^2,13–15\)
- Genetic factors may also be involved.\(^15\)

**Clinical features**

The clinical features of PEI can be thought of as following a spectrum of severity, depending on the extent of pancreatic exocrine function loss. While the severity may vary, the type of symptoms that are present in PEI are very similar regardless of the underlying aetiology and whether the PEI is as a result of a primary pancreatic exocrine disease, or as a result of type 1 or type 2 diabetes. However, it should be recognised that there may be additional symptoms associated with any underlying condition such as epigastric pain in chronic pancreatitis.

PEI may be asymptomatic or present with very mild, non-specific symptoms, including abdominal pain, bloating, flatulence and diarrhoea (see Box 2).\(^16,17\) Diarrhoea can be assessed using the Bristol Stool Scale and includes types 5, 6 and 7 that are compatible with PEI.\(^14\) The perhaps more typical symptoms of weight loss and the foul-smelling, grey loose stool associated with steatorrhoea occur much later in the disease course, and reflect approximately a 90% loss of pancreatic function.\(^17\) Steatorrhoea is therefore an uncommon presenting symptom at the time of diagnosis.\(^15\) Fat malabsorption is the key abnormality in PEI, and is the cause of the typical symptoms of steatorrhoea. The reasons for this are twofold. Firstly, lipase is the most unstable of all the pancreatic enzymes, and is most susceptible to intraluminal degradation, particularly at very low pH levels.\(^3,17\) Secondly, the pancreas is the predominant source of lipolytic enzymes, whereas amylase is also produced in salivary glands, and gastric pepsinogen is another key protease.

It is also possible that patients may experience difficulties with glucose metabolism and increased instability.\(^7,18\)

Other less common symptoms include those related to fat-soluble vitamin deficiencies (A, D, E and K) and osteoporosis.\(^3\) Physical examination may rarely detect features of chronic malabsorption and vitamin deficiencies, though may contribute to determining the underlying aetiology.

**Diagnosis**

There are several different diagnostic techniques that can be used to detect PEI. These techniques can be split into those that directly measure pancreatic exocrine function, and those that indirectly measure pancreatic exocrine function.

**Direct methods**

Direct methods include the secretin or CCK stimulation test. Traditionally, these involved measuring pancreatic juice output and content (either bicarbonate or enzyme concentration) through a naso-duodenal tube in response to secretin, CCK or a meal. More recently, both tests have also been conducted via an endoscopic approach. These methods are time consuming, invasive and reliant on technology, and, while they have previously been considered the gold standard test for pancreatic function according to the British Society of Gastroenterology 2003 guidelines on the diagnosis of chronic diarrhoea,\(^19\) they are not used in routine clinical practice.\(^3,19\)

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**Box 1. Classification of diseases of the pancreas causing type 3c diabetes**

- Pancreatitis
- Trauma/pancreatectomy
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Tropical fibrocalculous pancreatic diabetes
- Others

**Box 2. Symptoms of pancreatic exocrine insufficiency (PEI)**

- Abdominal pain or discomfort
- Bloating
- Flatulence
- Diarrhoea
- Weight loss
- Steatorrhoea
- Altered glycaemic control in diabetes?
Indirect methods
Indirect methods include measurement of serum enzymes, faecal analysis and breath tests. Serum levels of enzymes including trypsinogen, lipase and amylase typically only fall in very advanced pancreatic disease and have poor specificity for PEI; therefore, these are not recommended for diagnosis.\(^{19}\) Breath tests such as the C-mixed triglycerides breath test have been used to measure exhaled triglyceride breakdown products, though these tests are not standardised\(^{17}\) and are not widely available.\(^{20}\)

A number of different faecal tests can be performed to diagnose PEI. Faecal fat quantification, or the coefficient of fat absorption (CFA), can be performed accurately and with high sensitivity and specificity. However, the test is not widely available and is usually measured over 72 hours and therefore the impractical nature of this test means that it is rarely performed.\(^{3,17}\) Other tests involve measurement of pancreatic enzymes in stool. Faecal elastase-1 (FE-1) is the most reliable of these enzyme tests, as this enzyme is not degraded during its transit through the gastrointestinal tract and it has been shown to correlate well with levels of pancreatic enzymes present in the duodenum. It is more sensitive and specific than faecal chromotrypsin analysis when using direct tests for comparison.\(^{21}\)

Faecal elastase-1 sampling is a reliable and easy test that requires one random stool sample and is measured using an enzyme-linked immunosorbent assay technique. Results vary little from day-to-day, although they can be falsely positive in the presence of co-existing watery diarrhoea. Results are not affected by pancreatic enzyme supplementation since elastase is not a component of pancreatic preparations.\(^{21}\) FE-1 levels of less than 200\(\mu\)g/g are considered diagnostic for PEI, with 100–200\(\mu\)g/g indicating mild–moderate disease and less than 100\(\mu\)g/g consistent with severe PEI.\(^{22}\) Overall, FE-1 has a sensitivity of 93% and a specificity of 93%.\(^{21}\) FE-1 testing is currently the most commonly used and most widely available diagnostic test for PEI in the UK.\(^{23}\)

In addition to the above methods for diagnosing PEI, it is important to consider testing for co-existing fat-soluble vitamin deficiencies, particularly if the PEI is likely to have been long-standing and severe.

The conditions for diagnosing PEI in type 1 or type 2 diabetes are straightforward:

- A positive test confirming PEI.
- Known type 1 or type 2 diabetes.
- Absence of known underlying exocrine pancreatic or extra-pancreatic disease that causes PEI.

Conversely, diagnosing type 3c diabetes is less well defined, and may frequently go under-recognised. Type 3c diabetes is thought to account for approximately 1–3% of all cases of diabetes, but in view of poorly-defined diagnostic criteria and general lack of awareness of the ‘other types of diabetes’, it is possible that type 3c may actually account for significantly more cases of diabetes than this.\(^{15}\) Various diagnostic criteria for type 3c diabetes have been proposed, but none are standardised or widely accepted. In general, minimum requirements would be evidence of pancreatic disease, either on imaging or clinically evident, with the development of diabetes subsequent to this (often several years later),\(^{7}\) though it is important to bear in mind that patients may present with diabetes, and the pre-existing pancreatic disease may only become apparent on specific questioning or testing.

When making a diagnosis of PEI in type 1 or type 2 diabetes, it is important to remain vigilant for the possibility of underlying but previously undiagnosed pancreatic disease such as chronic pancreatitis, which could not only change the diagnosis to type 3c diabetes, but could also affect management.

Treatment/management
Once PEI is diagnosed, the treatment approach is to normalise digestion and alleviate symptoms in addition to managing the underlying cause. Normalising digestion is achieved through the use of pancreatic enzyme replacement therapy (PERT). PERT is an oral preparation, also known as pancreatic, which is taken at mealtimes and with snacks, with the dose adjusted to the fat content of the food and to clinical response. A number of different preparations are available commercially; most are enteric coated and all are of porcine origin. Commonly used preparations in the UK include Creon, Pancrex, Pancrease HL and Nutrizym.\(^{24}\)

The recommended starting dose varies depending on which preparation is used, but a typical starting regimen of Creon that the authors frequently use in their clinical practice is 25 000 units with snacks and 50 000 (2 x 25 000 capsules) with meals. This can be titrated up, depending upon clinical response, every few weeks.

Since the drug works locally within the gastrointestinal tract but is not absorbed, there is no set maximum dose. There are few side effects; gastrointestinal symptoms are most common and are usually associated with the underlying condition. Although rare, the most concerning is that of fibrosing colonopathy, which has been seen in paediatric patients with cystic fibrosis taking more than 10 000 units/kg/day; this is far higher than the typical dose in most adult patients without cystic fibrosis.\(^{17,22}\)

Monitoring is based upon clinical response (symptoms, weight change and markers of malnutrition); there is no consensus on repeated testing, particularly given that a change in FE-1 would not be expected (PERT does not contain elastase) and other tests such as faecal fat quantification face the same problems as those for initial diagnosis.\(^{17}\) Additional acid suppression therapy may be beneficial in patients who have failed to respond to adequate PERT dosing.\(^{17}\) A retrospective study has shown that approximately 80% of patients respond to treatment with PERT.\(^{22}\) In patients with no improvement in symptoms, the diagnosis should be questioned and an alternative considered.\(^{17}\)

In addition to PERT, general lifestyle advice includes smoking cessation advice and reducing alcohol intake, particularly if this is felt to be contributing to the underlying aetiology.\(^{25}\) Previously, a low-fat diet had been recommended, in part to limit the symptoms of steatorrhoea, but this is no longer recommended due to the associated calorie reduction and dietary consequences.\(^{3}\)
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Key points
- There is a close overlap, both functionally and anatomically, between the exocrine and endocrine portions of the pancreas
- Patients with pre-existing pancreatic disease, such as chronic pancreatitis, usually have pancreatic exocrine insufficiency and are at high risk of subsequently developing diabetes, known as type 3c diabetes
- Patients with type 1 and type 2 diabetes may also develop pancreatic exocrine insufficiency; there are a number of theories regarding how and why this happens
- Gastrointestinal symptoms in patients with diabetes are common and may be caused by pancreatic exocrine insufficiency, but this is often under-diagnosed
- Pancreatic exocrine insufficiency is usually straightforward to diagnose and treat, but this requires awareness among diabetes health care professionals and patients
- Pancreatic exocrine insufficiency, and subsequent enzyme replacement therapy (PERT), may affect glycaemic control; further research is needed

Glycaemic control in patients with diabetes and PEI

The exact relationship between PEI, PERT and glycaemic control is not well established. However, given the hypothesised aetiological links between PEI and diabetes and such a close functional and anatomical relationship, it is logical that treatment of the exocrine insufficiency may also impact upon the endocrine function and glucose metabolism. A relationship triad between pancreatic exocrine acinar cells, endocrine islet cells, and gut incretin hormones has been shown by Hayden et al. to demonstrate that impairment in any one of these aspects due to pancreatic interstitial fibrosis can result in abnormal glucose metabolism.2

It has been known since 1980 that pancreatic enzyme replacement in PEI enhances the release of GIP in response to oral nutrient ingestion.20 Similarly, postprandial GLP-1 and insulin have also been shown to be increased in patients with PEI who are treated with PERT.26 These findings are thought to represent the fact that GIP and GLP-1 are secreted in response to enhanced quantities of nutrients that have been digested. However, these increased incretin levels have not been found to correlate with an increased beta-cell response, though this study was based upon a small sample size26 and has not been confirmed elsewhere.

Since release of GIP and GLP-1 leads to a slower rate of gastric emptying (and therefore a more controlled rise in postprandial glucose) as well as insulin release, it is possible that this enhanced GIP and GLP-1 response in patients with PEI treated with PERT will result in improved glycaemic control,15 but to date this has not been substantiated by further studies in patients with diabetes. However, a study involving adolescents with cystic fibrosis has shown that there is an improvement in postprandial glycaemia following PERT supplementation.27 This GLP-1 response has also been shown, in addition to an improvement in HbA1c, in a study of patients with tropical chronic pancreatitis.28

In contrast, while Ewald et al. found no difference in either HbA1c or oral glucose tolerance test, they did find a reduction in mild–moderate hypoglycaemia following PERT29 which may represent improved glucose stability or variability, associated with the improved nutrient absorption that results from PERT.

Summary
When actively looked for, PEI appears to be common in patients with type 1 or type 2 diabetes, and could be considered as another complication of the condition. However, further research into the hypothesised pathophysiology of PEI in type 1 and type 2 diabetes is required to determine whether type 3c diabetes, and types 1 and 2 diabetes with co-existing PEI, are simply the same disease along a spectrum, or a separate entity. Moreover, the effect of PERT on glycaemic control remains controversial, and requires additional research to identify any potential avenues for improved glycaemic control.

Aside from any potential for improved glycaemic control, patients treated with PERT stand to benefit from a reduction in their gastrointestinal symptom burden, and improvement of their nutritional state. PEI symptoms are quick and easy to enquire about, but doing so requires awareness among all members of the diabetes team to provide opportune and timely enquiry. Patients may have a certain reluctance to raise these symptoms without prompting. However, symptomatology can and should be raised in both primary and secondary care, and may frequently be an issue that is identified first – for example, by dietitians or practice nurses. Therefore, it is essential that we raise awareness of PEI among all health care professionals involved in delivering diabetes care.

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References
References are available online at www.practicaldiabetes.com.

Letter to the Editor
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References