

Pancreatic exocrine insufficiency in type 1 and type 2 diabetes – more common than you think?

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Citation: Cummings M (2014) Pancreatic exocrine insufficiency in type 1 and type 2 diabetes – more common than you think? *Journal of Diabetes Nursing* 18: 320–3

Article points

1. Pancreatic exocrine insufficiency (PEI) is a condition that is often missed in people with diabetes and gastrointestinal symptoms.
2. The classical symptoms of steatorrhoea and weight loss only tend to occur in people with very severe PEI. More commonly, people will present with loose bowel movements, abdominal discomfort and flatulence.
3. If the individual has symptoms plus a low faecal elastase-1 level, PEI should be suspected and further evaluation of the pancreas may be warranted to exclude other pathological causes. PEI can be readily treated with pancreatic supplements, such as pancrelipase capsules.

Key words

- Gastrointestinal symptoms
- Pancreatic exocrine insufficiency

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As diabetes clinicians, we rarely ask people with diabetes about gastrointestinal symptoms. Symptoms such as loose bowel movements, abdominal discomfort or flatulence should alert us to causes such as drug-induced gastrointestinal changes, Coeliac disease, small bowel bacterial overgrowth or autoimmune disease; however, a condition that is rarely considered is pancreatic exocrine insufficiency (PEI). PEI is a deficiency of the exocrine pancreatic enzymes, resulting in an inability to digest food properly. Some research suggests that approximately 50% of people with type 1 diabetes and 32% of those with type 2 diabetes have some degree of PEI. This article discusses the diagnosis and management of PEI in people with type 1 and type 2 diabetes and describes the results of a recent PEI audit in Portsmouth.

As diabetes clinicians, we do not routinely ask people with diabetes whether they have any gastrointestinal symptoms. If an individual volunteers symptoms, such as loose bowel movements, abdominal discomfort and flatulence, for example, we may consider diabetes-related causes. These causes may include: drug-induced gastrointestinal changes that may be caused by medications such as metformin; Coeliac disease, which is six-times more common in people with type 1 diabetes than the general population; gastroparesis; small bowel bacterial overgrowth; or autoimmune disease, such as thyrotoxicosis. We may also consider non-diabetes related causes, such as gastroenteritis (if there is a short history), irritable bowel syndrome, inflammatory bowel disease or neoplastic bowel disease.

A condition that is often not considered, however, is pancreatic exocrine insufficiency (PEI). This condition may be more readily

considered in people with primary pancreatic disorders, such as recurrent pancreatitis, pancreatic cancers or those undergoing a pancreatectomy. We should, however, be considering PEI as a cause of gastrointestinal problems in people with type 1 and type 2 diabetes.

How common is PEI in people with diabetes?

Some studies have examined the prevalence of PEI in people with diabetes. In studies that assessed PEI using direct pancreatic function tests (for example, the secretin–pancreozymin test) it was demonstrated that overall these tests were abnormal in 52% of people with type 1 type 2 diabetes (Hardt and Ewald, 2011). A literature review examined some recent studies that looked at the use of indirect pancreatic function tests with faecal elastase-1 levels. Collectively, these studies involved approximately

250 people with diabetes and found that approximately 50% of people with type 1 diabetes and 32% of people with type 2 diabetes may have some degree of PEI (Hardt and Ewald, 2011). These studies, however, did not correlate symptoms with low faecal elastase-1 levels.

Why might people with diabetes have PEI?

In studies that have examined the morphological changes of the pancreas in people with diabetes, there are a number of structural changes observed that are consistent with an increased risk of PEI. These include pancreatic fibrosis, atrophy, fatty infiltration, pancreatitis and reduction in pancreatic size compared with a normal pancreas gland (Hardt and Ewald, 2011).

A number of mechanisms have been proposed by which exocrine function may occur and these are shown in *Box 1*. In addition, it has been shown that we may mislabel people as having type 2 diabetes when, in fact, they have secondary (or type 3c) diabetes, which is traditionally associated with a high incidence of PEI (Ewald et al, 2012). PEI may potentially be responsible for variable glycaemic control in patients with diabetes.

How might we assess for PEI and manage the condition?

The classical symptoms steatorrhea and weight loss only tend to occur in people with very severe PEI (Sikkens et al, 2010). More commonly, people will present with loose bowel movements, abdominal discomfort and flatulence. The Bristol Stool Chart (Heaton and Lewis, 1997; *Figure 1*) can be used to assess bowel movements and people reporting abnormal stools (type 5–7) should be screened for PEI.

There are several tests that can be used to screen for PEI. These include the coefficient of fat absorption test (Domínguez-Muñoz, 2011) and the 13C-mixed triglyceride breath test (Sikkens et al, 2010). For pragmatic reasons and larger scale testing, however, the most common test used within the UK in the faecal elastase-1 measurement (Domínguez-Muñoz, 2011), which typically costs approximately £10 per test.

Box 1. Potential mechanisms that may lead to PEI in people with diabetes.

1. Insulin has a trophic effect upon pancreatic tissue and its lack may cause pancreatic atrophy.
2. Pancreatic islet hormones have a regulatory function on exocrine tissue, which may be impaired.
3. Diabetic autonomic neuropathy, specifically within the pancreas, affecting exocrine function.
4. Diabetic angiopathy causing impaired blood flow and pancreatic fibrosis/atrophy.
5. Elevated hormone and peptide concentrations, for example, glucagon and somatostatin, which may suppress exocrine function.
6. Simultaneous damage of exocrine and endocrine tissue by viral infections, autoimmune or genetic changes.
7. Pancreatitis (sometimes leading to a mislabel of type 2 diabetes.)

“PEI may potentially be responsible for variable glycaemic control in patients with diabetes.”

Bristol Stool Chart








Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. Entirely liquid

Figure 1. The Bristol Stool Chart (Heaton and Lewis, 1997).

Page points

1. If the individual has symptoms plus a low faecal elastase-1 level, PEI should be suspected and further evaluation of the pancreas may be warranted to exclude other pathological causes.
2. PEI can be readily treated with pancreatic supplements, such as pancrelipase capsules. The starting dose should be 50 000 units with each meal and 25 000 units with a snack. The aim of treatment is to alleviate gastrointestinal symptoms.

Levels below 200 mcg/g are consistent with mild PEI and more severe PEI, often associated with steatorrhoea, is associated with faecal elastase-1 concentrations below 100 mcg/g. In addition to the effects of fat malabsorption (including fat soluble vitamin malabsorption, such as vitamin D, which is linked to the development of osteoporosis) there is a possible impact of fat maldigestion upon glucose metabolism that may lead to variability in glycaemic control. If the individual has symptoms as well as a low faecal elastase-1 level, PEI should be suspected and further evaluation of the pancreas may be warranted to exclude other pathological causes. This investigation could include a CT scan or endoscopic ultrasound of the pancreas.

PEI can be readily treated with pancreatic supplements, such as pancrelipase capsules. The starting dose should be 50 000 units with each meal and 25 000 units with a snack. The typical costs for pancrelipase capsules are: 40 000 units (100 capsules) £41.80, 25 000 units (100 capsules) £28.25 and 10 000 units (100 capsules) £12.93 (British National Formulary, 2014).

These capsules dissolve in the stomach releasing enteric-coated pancreatic enzymes that

mix with ingested food. The enteric coating inhibits gastric digestion but on reaching the duodenum, the former dissolves releasing the enzymes to digest the nutrients. The aim of treatment is to alleviate gastrointestinal symptoms. Dosing can be titrated further if required in order to alleviate clinical symptoms.

One study has also suggested that pancrelipase capsules may improve HbA_{1c} by up to 11 mmol/mol (1%), see *Figure 2* (Mohan et al, 1998).

Another study by Ewald et al (2007) showed that pancreatic supplements can be used safely in people with diabetes and do not result in problems of diabetes control. In addition, this study showed that after 16 weeks, pancrelipase capsules led to reduction in mild or moderate hypoglycaemic episodes in people with pancreatic-induced diabetes, compared to baseline data for this group (*Figure 3*).

Other studies in diabetes have shown that pancrelipase capsules augment glucagon-like peptide-1 (GLP-1) production, thereby enhancing insulin secretion (Ebert and Creutzfeldt, 1980). Further large-scale evaluation is required, however, to fully assess the impact of pancreatic supplements on glycaemic control.

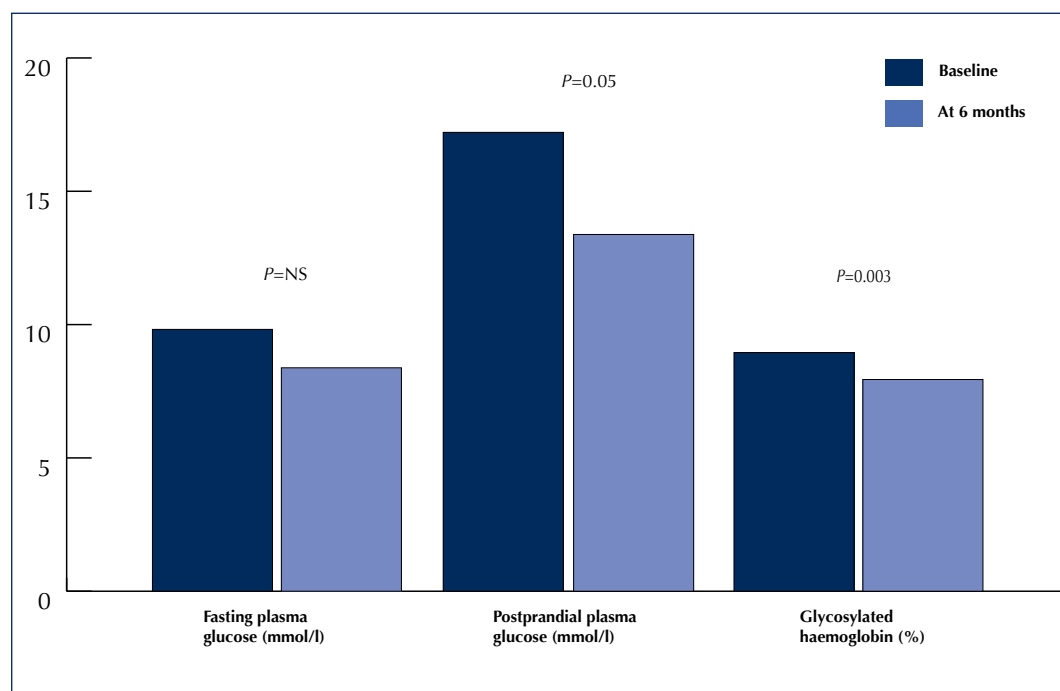


Figure 2. Blood glucose following treatment with pancreatic enzyme supplementation therapy (adapted from Mohan et al, 1998).

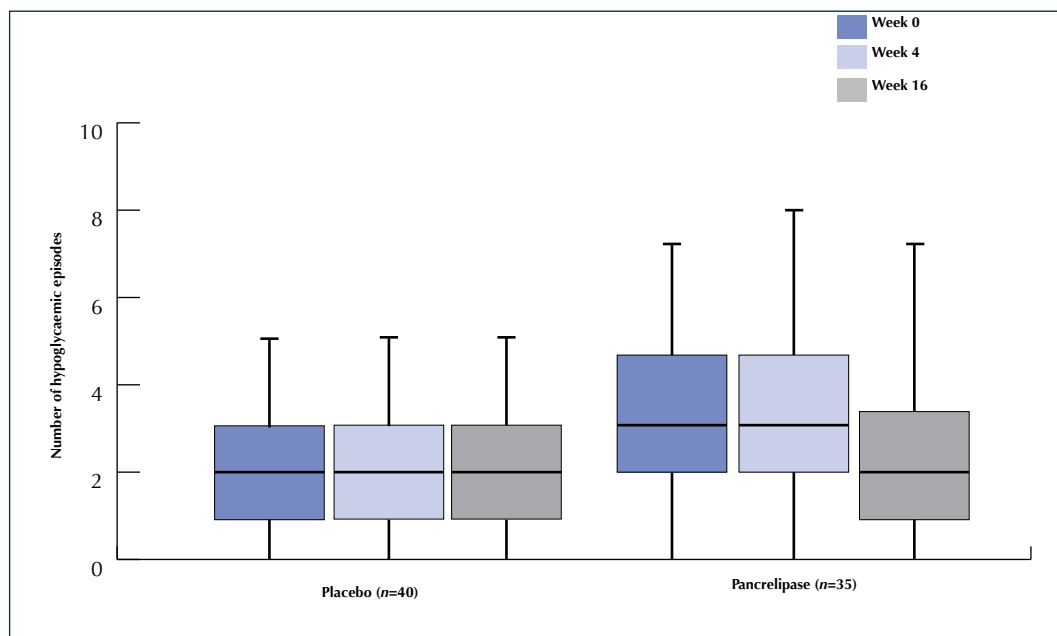


Figure 3. After 16 weeks of treatment with pancrelipase, there was reduction in number of hypoglycaemic episodes. At study end, both groups were equal ($P>0.05$; adapted from Ewald et al, 2007).

“Further large-scale studies are required to fully determine the incidence of PEI in people with type 1 and type 2 diabetes.”

People with diabetes and gastrointestinal symptoms: How many have PEI?

In Portsmouth, we recently undertook an audit evaluating the management of gastrointestinal symptoms in 156 people with diabetes. Of these, 34 people (22%) described abnormal stools (Bristol Stool Chart type 5–7), steatorrhea or unexplained weight loss. In those who elected to provide a faecal sample, 7 out of 19 (37%) symptomatic patients had low faecal elastase-1 levels. Two of the 7 people (29%) had severe PEI (<100 mcg/g), and 5 of the 7 people (71%) had moderate PEI (100–200 mcg/g).

Three individuals had type 1 diabetes, three had type 2 diabetes and one had secondary diabetes. Six out of 7 patients (86%) had an HbA_{1c} level greater than 69 mmol/mol (8.5%), diabetes duration more than 5 years and at least one other diabetes complication. This data supports the concept that gastrointestinal symptoms are common in diabetes and PEI may explain these symptoms in a number of cases. Clinical outcomes for this group of people, including impact on HbA_{1c} levels, will be the focus of a future study.

Summary

Further large-scale studies are required to fully determine the incidence of PEI in people with type 1 and type 2 diabetes. In the meantime, it would be prudent to consider routinely asking people with diabetes about gastrointestinal symptoms and evaluate the possible causes, including PEI. ■

Declaration

Professor Cummings has received an unconditional educational grant and honoraria from Abbott.

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