

Pancreatic exocrine insufficiency and diabetes



There is increasing awareness that a simple explanation of relative or absolute insulin deficiency does not fully explain why glycaemic control is easier to manage in some people compared to others. The production of insulin is an “endocrine” function of the pancreas, but it is clear that the pancreas’ “exocrine” function, which involves effective food digestion, may also impact on glycaemic control. Pancreatic exocrine insufficiency is a condition characterised by a deficiency of the exocrine digestive enzymes, and it may be more common in people with diabetes than we realise.

This booklet will cover the following:

- Pancreatic exocrine insufficiency (PEI) explained.
- Causes of PEI.
- Link between PEI and diabetes.
- Signs and symptoms.
- Diagnosis.
- Treatment: pancreatic enzyme replacement therapy.
- Managing diabetes and PEI.
- Useful resources and references.

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What is pancreatic exocrine insufficiency?

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The pancreas gland has two main functions: an exocrine function that helps in food digestion and an endocrine function that regulates blood glucose. The pancreas produces digestive enzymes, which are secreted directly into the gut (exocrine). Digestive enzymes are needed to break down food in the gut to release essential nutrients, which are then absorbed into the bloodstream. The pancreas also produces hormones involved in blood glucose regulation, which pass directly into the bloodstream (endocrine); insulin is the most important hormone produced by the pancreas.

Pancreatic exocrine insufficiency (PEI) occurs when the amount of digestive enzymes (e.g. proteases, lipases and amylases) produced by the pancreas in relation to the meal consumed is insufficient to digest food adequately. This results in maldigestion, malnourishment and nutrient deficiencies, especially malabsorption of fat-soluble vitamins as the digestion of fats is particularly affected. Depending on the severity and duration of PEI, a number of nutrient-deficient complications can occur (Sikkens et al, 2013):

- **Vitamin A deficiency** reduces the effectiveness of the immune system and can cause night blindness.
- **Vitamin D deficiency** leads to bone problems (such as osteopenia and osteoporosis).
- **Vitamin E deficiency** results in neurological disorders, such as peripheral neuropathy.
- **Vitamin K deficiency** results in blood coagulation disorders.

What causes PEI?

Damage to the pancreas is the leading cause of PEI. The destruction or removal of pancreatic tissue, inadequate stimulation of pancreatic enzyme-producing tissue caused by nerve damage, impaired delivery of enzymes into the gut due to blocked pancreatic ducts (e.g. by a tumour or fibrosis), auto-immune damage or damage caused by infection are all potential causes of pancreatic damage and structural change.

Why might PEI be more common in people with diabetes?

Post-mortem examinations of the pancreases of people with diabetes show structural changes and signs of damage: fibrosis, shrinkage, fatty infiltration, evidence of chronic inflammation and a reduction in size (Hardt and Ewald, 2011). Genetic aberrations, infection or auto-immune conditions can damage the exocrine and

endocrine tissues of the pancreas and thus cause insulin deficiency and a reduction in digestive enzymes, resulting in both diabetes and PEI to be present.

It is estimated that 80–90% of people with a history of chronic pancreatitis have some degree of PEI (Keller et al, 2005), as will 80% of people who have had pancreatic surgery for cancer (Sikkens et al, 2012). Loss of pancreatic tissue means many of these people will develop diabetes. It has been estimated that in about 9% of people with diabetes, pancreatic disease (e.g. chronic pancreatitis and pancreatic cancer) is the cause of diabetes. Often, this type of diabetes is incorrectly classified as type 2 diabetes (Ewald et al, 2012).

As well as pancreatic disease, there are several other theories about the association between diabetes and PEI:

- Insulin has an anabolic (growth) effect on pancreatic tissue. An absolute lack of insulin, seen in type 1 diabetes, or partial deficiency, seen in type 2 diabetes, may lead to a loss of pancreatic tissue.
- Nerve damage caused by diabetic neuropathy may interfere with the stimulation of the pancreatic cells and neurons that are involved with the secretion of pancreatic enzymes. Diabetic neuropathy can cause gastroparesis, diabetes diarrhoea and faecal incontinence, but the diarrhoea and bloating associated with this diabetic complication may be symptoms of PEI.
- The same microvascular damage associated with neuropathy, nephropathy (kidney disease) and retinopathy (eye disease) may reduce blood flow to pancreatic tissue leading to fibrosis, atrophy and loss of function.
- Abnormally increased glucagon production caused by decreased insulin levels or effectiveness may lead to exocrine damage and dysfunction (Cummings, 2014).

How common is PEI in people with diabetes?








Previous studies using direct pancreatic function tests have shown that about 50% of people with type 1 and type 2 diabetes have abnormal pancreatic function; however, these tests are not routinely used to diagnose PEI (Hardt and Ewald, 2011). Other studies using indirect pancreatic function tests have shown similar results where 51% of people with type 1 diabetes and 32% of people with type 2 diabetes were found to have PEI (Hardt and Ewald, 2011). These results are based on FE levels and not on the presence of symptoms. ■

Depending on the severity of PEI, the symptoms may range from vague gastrointestinal discomfort to severe debilitating problems significantly affecting quality of life. The following may be indicative of PEI and are worth further investigation:

- Loose bowel movements.
- Abnormal stools, often of a pale yellow colour.
- Abdominal discomfort.
- Flatulence and bloating.
- Fatigue.
- Erratic blood glucose control in severe, untreated PEI (Mohan et al, 1998).

If severe, PEI can result in weight loss and frothy, oily and foul-smelling buoyant stools containing undigested fats (steatorrhea). This type of stool occurs when over 90% of the exocrine pancreatic function is lost (Fieker et al, 2011). Ideally, PEI should be diagnosed before this stage. The Bristol Stool Chart is a useful tool for patients to describe their stool consistency:

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 its 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

Diagnosing PEI

People with diabetes often describe symptoms of fatigue and difficulty controlling blood glucose levels; however, these are non-specific symptoms and may not be related to PEI. If they complain of diarrhoea and gastrointestinal discomfort, there are a number of other causes to exclude before considering PEI:

- Side effects of blood glucose-lowering medication, in particular metformin and glucagon-like peptide-1 receptor agonist injections.
- Gastroparesis is a relatively rare complication of diabetes, where nerve damage to the stomach results in delayed emptying, bloating, vomiting or dumping, which leads to erratic blood glucose levels.
- Coeliac disease affects 1–7.8% of people with type 1 diabetes (Cronin and Shanahan, 1997). The inability to digest and absorb gluten results in shorter duodenal villi and a reduced ability to absorb nutrients, which presents symptoms like PEI (Leeds et al, 2007).

There are also several non-diabetes-related causes of PEI-like symptoms that also should be discounted:

- Gastroenteritis (if the diarrhoea is a recent problem).
- Irritable bowel syndrome.
- Inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis.
- Bowel cancer.

How to diagnose PEI

Once other causes are excluded, the usual test for diagnosing PEI is measuring the amount of elastase-1 in a stool specimen. Elastase-1 is a protein-digesting enzyme secreted into the duodenum by the pancreas to break down connective tissue. It passes through the gut and collects in the faeces unchanged, so it is a useful marker of pancreatic insufficiency.

A single spot stool specimen should be placed in a plain universal container with patient identification information and the appearance of stool noted on the form (e.g. loose or watery) as it may be frozen before analysing (South Tees Hospitals, 2016).

Levels of faecal elastase-1 between 100 µg/g and 200 µg/g indicate mild PEI, while less than 100 µg/g indicates severe PEI. Further investigations may include a CT scan or endoscopic ultrasound of the pancreas to investigate the cause of PEI. ■

PEI treatment: Pancreatic enzyme replacement therapy

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Pancreatic enzyme replacement therapy (PERT) replaces the digestive enzymes that are lost due to PEI. Pancreatic supplements contain proteases, lipases and amylases to mimic the action of the digestive enzymes. There are a number available on prescription in the UK.

PERT is usually taken in capsule form and must be **swallowed whole**. Treatment will only work if taken with food, so the meal should be completed within 30 minutes of consuming the PERT capsules, or if more than 1 capsule is taken, the patient should space them out throughout the meal. **Hot drinks should be avoided** at mealtimes as these may make the PERT less effective.

If an individual is unable to swallow capsules whole, the capsule can be opened and the contents mixed with soft acidic food (like apple puree, yoghurt, or orange or pineapple juice). A cold drink should follow to wash the enzymes from the mouth to prevent residual enzymes from damaging the buccal mucosa and causing ulcers.

A healthy pancreas typically produces around 720 000 lipase units in response to a 300 to 600 kcal meal (Keller, 2005). **The starting dose for PERT is 50 000 units with every meal** (although a higher dose may be needed with very fatty meals, such as fried foods, takeaways, cheese and pastry). A total of 25 000 units is recommended with every snack and milky drink. The number of units sounds large, especially if your patient is using insulin and dialling up their doses in much smaller unit increments. The dose is adjusted until the symptoms of PEI resolve.

PERT is manufactured from pork pancreases sourced from pork for human consumption, so this should be discussed with people who do not eat pork for cultural reasons or who have an allergy to pork products.

The capsules should be kept at **room temperature** as heat will denature the contents. Even keeping them in a pocket should be avoided due to body heat.

Side effects of PERT include gastrointestinal effects (e.g. constipation, nausea, vomiting, diarrhoea and abdominal distension); however, these are also symptoms of PEI. Mouth ulcers may occur if capsules are chewed instead of swallowed whole.

Everyone should eat a nutrient-rich diet, but this is particularly important for someone with PEI. **A referral to a dietitian is essential** to ensure the individual gets the most out of their treatment. Fat-soluble vitamins (A, D, E and K) and mineral supplements may be required, but if the PERT is effective, effective digestion and absorption of essential nutrients will be adequate without further supplements.

Managing PEI and diabetes

PERT in people with severe PEI, such as people with pancreaticogenic diabetes, may significantly improve the attainment of glycaemic targets and so more frequent

blood glucose monitoring may be required to titrate doses of insulin and oral hypoglycaemic agent appropriately. PERT can improve HbA_{1c} by up to 11 mmol/mol (1%; Mohan et al, 1998) and a study in people with diabetes associated with exocrine function demonstrated a reduction in episodes of mild to moderate hypoglycaemia (Ewald et al, 2007).

Although PERT is required for meals and snacks, it is not required when treating episodes of hypoglycaemia with glucose, non-diet fizzy drinks, jelly babies etc. It would be required if a follow-on starchy snack is needed.

Effective and consistent digestion of meals in people with PEI will help to stabilise blood glucose levels and may cause weight gain, which will also affect insulin sensitivity and insulin requirements. PERT also appears to increase insulin production in people with type 2 diabetes who still have functioning insulin-producing beta cells (Ebert and Creutzfeldt, 1980).

Useful resources

- **TREND-UK:** www.trend-uk.org
- **Diabetes UK:** www.diabetes.org.uk
- **The Pancreatitis Supporters' Network:** www.pancreatitis.org.uk
- **The National Pancreas Foundation:** www.pancreasfoundation.org
- **Pancreatic Cancer UK:** www.pancreaticcancer.org.uk
- **Royal Brompton & Harefield NHS Foundation Trust:** www.rbht.nhs.uk

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