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EDUCATIONAL SERIES

Pancreatic enzyme replacement therapy

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About the Experts

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Undiagnosed pancreatic exocrine insufficiency (PEI) results in malabsorption, which can quickly lead to gastrointestinal symptoms, weight loss, malnutrition, osteoporosis and fat-soluble vitamin deficiencies. Pancreatic replacement therapy (PERT) eliminates this malabsorption and sequelae by approximating the exocrine secretory response of a normal healthy pancreas. Dosing and administration of PERT is inextricably linked to diet, meaning that dietitians are ideally placed to prescribe and monitor this therapy. This review is supported by an educational grant from Viatris.

PEI occurs when the quantities of enzymes secreted into the duodenum in response to a meal are not sufficient to maintain normal digestion and absorption.[1] This can occur due to reduction of pancreatic exocrine parenchyma by atrophy or resection, reduced stimulation of enzyme production (which may be anatomical or physiological), and/or obstruction of the pancreatic duct or ampulla by stones or strictures.[2]

Which patients are at risk of pancreatic exocrine insufficiency?

In some patients this risk is obvious, including those with **cystic fibrosis** or **total pancreatectomy.** All of these patients will develop PEI and require PERT. There are other patients where the risk is sometime less obvious, and PEI can ensue.

- **Chronic pancreatitis:** these patients with atrophy and calcification all eventually develop PEI.
- **Acute pancreatitis:** these patients only develop PEI when there has been significant pancreatic necrosis as part of the acute disease.
- **Pancreatic adenocarcinoma**: these most common pancreatic cancers usually develop in the main pancreatic duct and cause obstruction and malabsorption. In a New Zealand study of patients with advanced pancreatic cancer, 68-92% developed PEI but only 21% were on PERT.[3]
- **Pancreatic resection:** patients after pancreaticoduodenectomy (Whipple's procedure) can develop PEI, and postoperative PERT is now recommended for routine use.[4]
- **Gastric surgery:** there is a reduction of bicarbonate and lipase secretion following gastrectomy. There is also likely to be asynchrony, with post-prandial gastric emptying not occurring at the same time as the release of pancreatic enzymes into the small intestine. This leads to insufficient mixing of chyme with pancreatic juices and reduced contact time for digestion of nutrients resulting in PEI.
- **Bowel resection:** depending on the site and extent of resection, the complex interaction between secretions of the gut, stomach and pancreas are interrupted e.g. altered transit time, reduced stimulation of the pancreas to secrete digestive enzymes, bacterial overgrowth and compensatory gastric hyperacidity. It is therefore reasonable to expect patients who have had extensive small bowel resection to experience a degree of PEI.
- **Elderly patients:** increasing age is associated with a reduction in pancreatic parenchymal volume, structure and function. This can lead to a reduction in exocrine function and enzyme secretion in otherwise healthy older adults and PERT should be used if PEI is established.[5]

Diagnosis of pancreatic exocrine insufficiency

Diagnosis involves careful clinical assessment of the patient with a history that includes enquiry about gastrointestinal symptoms, bowel habit, weight loss and fat-soluble vitamin status. Symptoms of PEI include postprandial pain, bloating, flatulence and steatorrhoea. The presence of steatorrhoea is the usual basis for commencing PERT. PEI can often be diagnosed on the basis of the patient's clinical history even if the presence of steatorrhoea cannot be firmly established.[1] Thus PEI can be present without overt symptoms, and diagnosis may be made on the basis of a high index of suspicion.

Cross sectional imaging of the pancreas will allow morphological assessment. PEI is usually associated with obvious changes in pancreatic morphology, including reduced parenchymal mass, atrophy, fibrosis, obstruction of duct, and calcification (both parenchymal and/or ductal).

Pancreatic function tests can be considered, and the most commonly performed measure of pancreatic exocrine function is the Faecal Elastase (FE-1) assay. This pancreas specific protease is not degraded by intestinal passage and is measured in the stool. However, it only becomes positive when significant PEI is present, is prone to false positives and it is not useful in patients who have asynchrony.[1]

The 2015 APC guidelines for the management of PEI classify patients with clinically suspected PEI into three subgroups – PEI definite, PEI possible and PEI unlikely, and present recommendations for diagnosis according to these subgroups (see **Table 1**).[1,6]

Table 1. Australian Pancreatic Club 2015 recommendations for diagnosis of PEI according to aetiology.[1,6]

	PEI definite	PEI possible	PEI unlikely
Aetiology	Total pancreatectomy	Mild and moderate chronic pancreatitis	Irritable bowel syndrome
	Severe chronic pancreatitits	After severe acute pancreatitis	Coeliac disease
	Tumour destroying head of pancreas	After Whipple procedure	Inflammatory bowel disease
	Acute pancreatitis destroying head of pancreas	Cystic fibrosis	Weight loss in older people
		Gastrectomy with postprandial asynchrony	Type 2 diabetes
		Vitamin A, E, D, K deficiency	Bowel resection
Diagnosis	In the presence of severe steatorrhoea and weight loss, diagnosis can be made on clinical grounds alone	In the presence of moderate pancreatic structural changes, a diagnosis of PEI is suggested if nutritional impairment and diarrhoea are also present	Symptoms of PEI occur in < 10% of patients. Tests of lower sensitivity and specificity may result in under- or over-diagnosis
	Probability of a positive objective test for PEI is 100%	Probability of a positive objective test for PEI is 30-70%	Probability of a positive objective test for PEI is < 10%

Dietary management in pancreatic exocrine insufficiency

Carbohydrate and protein digestion is not overtly compromised in PEI, unlike fat digestion, which is mostly dependent on availability of sufficient pancreatic enzymes. As a result, fat digestion is the primary focus of dietary assessment and intervention.

Historically, patients with PEI have been advised to follow a diet of less than 20g of fat per day.[7] However, evidence has shown that high fat diets (100 g fat/day) are tolerated in patients with PEI as long as sufficient enzyme therapy is prescribed.[8] **Therefore, it is now recommended that individuals with PEI aim to obtain 30% of their energy from fat, just as it is recommended for the general population, but, at the same time, ensuring adequate enzyme replacement is prescribed**.[9,10]

A careful dietary history taken by a dietitian, including timing, size and content of meals, is essential before prescribing PERT. It is also important to determine the overall protein and energy intake to ensure that it is sufficient for weight and lean muscle mass preservation.

The recommended dose for commencing PERT is 25,000–50,000 units of lipase with each meal, with half the dose for snacks, and titrated based on the presence of malabsorption to the lowest effective dose (with restoration of normal stools).

In adults, the maximum recommended dose of PERT is 75,000–80,000 units of lipase per meal. PERT is most effective when taken during the meal in order to replicate normal pancreatic secretion in response to ingestion of food.[11]

When a patient is enterally fed and unable to take PERT orally, enzymes need to be provided through the feeding tube with the enteral feed. This requires careful consideration of the size of the tube, the location of the tube in the gut and the enteral feeding regime (rate, continuous or bolus).

The recommended dose is 1000 units of lipase for every gram of fat administered as a starting dose, provided every 2–3 hours as a bolus while a continuous feed is running.[12] Guidelines for administering PERT with enteral feeds have been published.[13]

Monitoring of patients on PERT

Patients with PEI are at risk of developing nutrient deficiencies from any combination of poor intake, malabsorption or maldigestion of nutrients. Therefore, serum fat-soluble vitamin concentrations should be measured at the commencement of PERT, and at least annually following this. Other micronutrients should also be monitored depending on the patient's clinical history, for example vitamin B12 in patients post gastrectomy. Iron and other trace elements such as zinc, copper, calcium, thiamine and selenium should additionally be monitored in patients that have had procedures that bypass or remove the duodenum, severe malnutrition or symptoms of deficiency. In general, when a patient has multiple nutrient deficiencies, it should be assumed that others are present and it is wise to recommend a multivitamin with minerals (e.g. vitABDECK) in addition to repletion of specific nutrients.

If a patient continues to experience symptoms of PEI despite adequate enzyme prescription and appropriate administration, a trial of acid suppression (i.e. proton pump inhibitor or H2 receptor antagonist) may be beneficial. However, other reasons for a poor response should also be considered and discussed with the medical team.

Patients with PEI are also at risk of pancreatic endocrine insufficiency (i.e. prediabetes and diabetes). Patients should be screened for diabetes by checking HbA1c, and patients should be educated on what symptoms to look out for.

Pancreas Clinic

At Auckland District Health Board, a dedicated pancreas clinic has been set up where all patients with pancreatic disease or suspected PEI can be referred to be seen by a specialist team of pancreatic surgeons and dietitians. On-going assessment with close monitoring and attention to the clinical signs and symptoms of PEI is essential for optimising long-term success for these patients to both improve quality of life and to prevent the complications of untreated PEI.

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REFERENCES

1. Australasian Pancreatic Club. Australasian guidelines for the management of pancreatic exocrine insufficiency. 2015.
2. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. Gut 2005; 54 Suppl 6:vi1-28.
3. Landers A, et al. Pancreatic enzyme replacement therapy (PERT) for malabsorption in patients with metastatic pancreatic cancer. BMJ Support Palliat Care. 2016 Mar; 6(1):75-9.
4. Gianotti L, et al. Nutritional support and therapy in pancreatic surgery: A position paper of the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2018; 164(5): 1035-1048.
5. Löhr JM, et al. The ageing pancreas: a systematic review of the evidence and analysis of the consequences. J Intern Med. 2018 May;283(5):446-460.
6. Nikfarjam M, et al. Diagnosis and management of pancreatic exocrine insufficiency. Med J Aust. 2017 Aug 21;207(4):161-165.
7. Dominguez-Munoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. Curr Gastroenterol Rep 2007; 9(2):116-122.
8. Safdi M, et al. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo controlled, parallel group trial in subjects with chronic pancreatitis. Pancreas 2006; 33(2):156-162.
9. de-Madaria E, et al. The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). Pancreatology 2013; 13(1):18-28.
10. Ministry of Health. 2015. Eating and Activity Guidelines for New Zealand Adults. Wellington: Ministry of Health.
11. Smith RC, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. Pancreatology 2016;16(2): 164-180.
12. Anthony H, et al. Pancreatic enzyme replacement therapy in cystic fibrosis: Australian guidelines. Pediatric Gastroenterological Society and the Dietitians Association of Australia. J Paediatr Child Health 1999; 35(2):125-129.
13. Ferrie SC, et al. Pancreatic enzyme supplementation for patients receiving enteral feeds. Nutr Clin Pract. 2011; 26(3): 349-351.

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