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Diagnosis and Management of Pancreatic Exocrine Insufficiency in Primary Care

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About the Expert

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This publication is intended as an educational resource for primary care physicians. It aims to assist with identification of pancreatic exocrine insufficiency (PEI), and presents guidelines for diagnosis and management, based on recent recommendations from the Australasian Pancreatic Club (APC). Dosing and administration guidelines for the pancreatic enzyme replacement therapy (PERT) preparations approved for use in New Zealand are also included. This review is supported by an educational grant from Mylan.

Introduction

PEI is due to a deficiency in pancreatic digestive enzyme production and/or delivery to the small intestine, leading to maldigestion and malabsorption.[1,2] PEI is most commonly associated with chronic pancreatitis, cystic fibrosis, pancreatic tumours and surgical resection of the pancreas.[1,3] Symptoms of PEI are non-specific and are shared with other pancreatic and gastrointestinal diseases, meaning that the disease may go undetected in clinical practice.[2,3] However, PEI is a serious condition that leads to malnutrition-related complications if left untreated, including osteoporosis, coagulation disorders and peripheral neuropathy.[4,5] PEI is also an independent risk factor for cardiovascular events in patients with chronic pancreatitis and has a significant impact on quality of life.[1,4,6] Therefore, an early and accurate diagnosis of PEI is of high clinical importance.[2,3] PERT is the backbone of treatment for PEI,[1,7] and has been in use for several decades, with a recent high-quality meta-analysis confirming its effectiveness in patients with chronic pancreatitis.[8] New guidelines from the APC on the management of PEI were published in 2015, and provide recommendations for diagnosis and treatment based on the aetiology of PEI.[7] Careful attention to dosing and administration of PERT is essential in ensuring optimal treatment outcomes.[7,9,10]

Aetiology

Any pathological events, including extrapancreatic conditions, that interrupt the sequence required for the normal digestion of food by pancreatic enzymes may lead to PEI.[2] Aetiologies include the following:

- Damage – the pancreatic parenchyma is no longer able to synthesise the required amounts of digestive enzymes
- Asynchrony – dissociation of normal postprandial digestive enzyme secretions and intestinal meal delivery. This can occur in conditions such as short bowel syndrome and Crohn's disease or after gastric, biliary or pancreatic resections or bypass procedures
- Obstruction – pancreatic duct blockage affects the transport of digestive enzymes and other secretions to the duodenum
- Decreased endogenous stimulation – decreased stimulation of enzyme production is particularly noted with coeliac disease.[1,11]

The most dramatic clinical symptom of PEI, steatorrhoea, does not usually manifest until pancreatic lipase levels fall below 5-10% of normal postprandial levels, due to compensatory enzyme mechanisms and the high reserve capacity of the pancreas.[12]

Prevalence

PEI is estimated to occur in 94% of patients with chronic pancreatitis, >85% of patients with cystic fibrosis, 74% of patients after pancreatic resection surgery, and 92% of patients with unresectable pancreatic cancer.[1] Maldigestion occurs in up to 80% of patients following upper gastrointestinal surgery, and PEI contributes to pathogenesis, but the causes are most likely multifactorial.[4,7]

Among the less common aetiologies of PEI, 35-50% of patients with type 1 diabetes have faecal elastase-1 levels <200 µg/g (including 20-30% with levels <100 µg/g), and 20-35% of patients with type 2 diabetes have faecal elastase-1 levels <200 µg/g (including 10-20% with levels <100 µg/g).[7] However, PEI in these patients is typically mild to moderate and not associated with overt steatorrhoea.[4] By definition, all patients with type 3c (pancreatogenic) diabetes, which accounts for 5-10% of diabetes cases in Western populations, have PEI.[4] PEI associated with this form of diabetes is typically more severe.[4] Patients with coeliac disease may have pancreatic dysfunction, but this is usually transient and normalises with a gluten-free diet.[4] It is estimated that 12-18% of patients with coeliac disease and chronic diarrhoea while on a gluten-free diet have PEI.[4] Low faecal elastase-1 levels have been found in 14-30% of patients with Crohn's disease and 22% of patients with ulcerative colitis, but this test is known to have poor diagnostic accuracy for PEI in patients with diarrhoea.[4] PEI may also occur in patients with rare genetic diseases such as Schwachman-Diamond syndrome and Johanson-Blizzard syndrome.[3,5]

There are no reliable estimates of the prevalence of PEI in the general population,[2] although prevalence appears to increase with age.[3]

Consequences

The most common clinical consequence of PEI is fat maldigestion and malabsorption, leading to low circulating levels of micronutrients, fat-soluble vitamins and lipoproteins and increasing the risk of malnutrition-related complications.[7,13] These complications include hypoalbuminaemia, coagulation disorders, ataxia and peripheral neuropathy, night blindness and xerophthalmia, and contraction or muscle spasms, osteomalacia and osteoporosis.[5] The prevalence of osteoporosis or osteopenia in patients with chronic pancreatitis is 65%.[14] PEI is an independent risk factor for cardiovascular disease in patients with chronic pancreatitis.[1,3] PEI contributes to the malnutrition commonly observed in patients with pancreatic ductal adenocarcinoma, and severe PEI is associated with decreased survival in patients with advanced pancreatic cancer.[3] Further clinical consequences of PEI can include hyperoxaluria, urinary oxalate stones, renal insufficiency and impairment of cognitive functioning.[6]

PEI also has a significant negative impact on quality of life, as a result of persistent gastrointestinal symptoms and pain, as well as other factors such as inability to work and financial strain.[1,6]

Diagnosis

Clinical presentation

Symptoms of PEI are nonspecific and vary from patient to patient, depending on severity and aetiology.[2] The classic clinical picture is a patient presenting with foul-smelling, loose and fatty stools that are difficult to flush away, weight loss (or lack of weight gain in children), muscle wasting and flatulence.[1,2] Patients may also have abdominal pain and distension, especially after meals.[7]

Patients with chronic malabsorption may exhibit nail leukonychia due to hypoalbuminaemia, ecchymoses due to vitamin K deficiency, ataxia and peripheral neuropathy due to vitamin E deficiency, night blindness and xerophthalmia due to vitamin A deficiency, and contraction or muscle spasms, osteomalacia and osteoporosis due to hypocalcaemia.[5]

It is important to differentiate maldigestion/malabsorption due to pancreatic causes from other possible causes, including the following:

- Coeliac disease
- Inflammatory bowel disease
- Inflammatory bowel syndrome
- Microscopic colitis
- Small intestinal bacterial overgrowth
- Short bowel syndrome
- Zollinger-Ellison syndrome
- Bariatric bypass surgery
- Giardiasis.[3]

Testing

Morphological and functional assessments can be used to confirm the diagnosis of PEI.[1] Computed tomography can identify pancreatic tumours and evidence of chronic pancreatitis (atrophy, calcification). Further investigation may be required with magnetic resonance imaging, endoscopic ultrasound (EUS) and/or secretin-magnetic resonance imaging. The best way to delineate the main pancreatic duct is endoscopic retrograde cholangiopancreatography (ERCP).[1,13]

Direct pancreatic function tests, including the secretin-cholecystokinin stimulation test and the endoscopic pancreatic function test, are sensitive and specific, but these are too expensive, cumbersome and invasive for routine clinical use.[1,13]

Indirect functional tests include faecal, breath and blood tests, and these are cheaper and easier to use than direct tests, although they are generally less sensitive and less specific.[1,13] The three-day faecal fat test is the "gold standard" for diagnosing steatorrhoea, but its use is limited because it is unpopular with patients and lab technicians.[13] The faecal elastase-1 test is more popular as only a single stool sample is required, but it is best used as screening test for PEI.[13] The ^{13}C breath test is a new test which, when PEI is present, demonstrates a reduction in the amount of ^{13}C released after a meal containing triglyceride labelled with ^{13}C.[13] Blood tests for magnesium, nutritional markers, bone mineral density and fat-soluble vitamins A, D, E and K are important in the diagnostic workup as they may suggest the presence of PEI.[13]

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**).[1,7]

Table 1. Australian Pancreatic Club 2015 recommendations for diagnosis of PEI according to aetiology.[1,7]

	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%

EXPERT COMMENTARY

Because PEI is often insidious, there is the need for a high index of suspicion. In practice it is often overlooked, and as a result PERT can be too little and too late. Identifiying those at risk of PEI requires vigilance and the APC guidelines (as shown in Table 1) are helpful by categorising patients into those with definite and possible PEI.

The panel of tests recommended when the diagnosis of PEI is sought is important, and should be kept close to hand. The metabolic and nutritional consequences of PEI have been emphasised in the text. Involvement of a dietitian with expertise in pancreatic disease is encouraged for patients with definite PEI, and the diagnostic tests should be repeated at regular intervals (3-6 monthly) for the early detection of these metabolic and nutritional consequences.

Faecal elastase-1 should be done in all patients with possible PEI, but it should not be used as the final or only arbiter of whether a patient requires PERT. It is a useful guide, but many patients have subclinical PEI before the test is positive. This means that a trial of supplemental PERT is often offered to patients without a diagnostic faecal elastase-1 test.

Management

The primary goal of treatment for PEI is to restore normal digestion in order to maintain adequate nutrition.[1,7] In addition, symptoms must be alleviated and malnutrition-related disease progression prevented.[1,2] Key aspects of PEI management will be discussed and include the following:

- PERT
- Lifestyle modification, including alcohol abstinence, smoking cessation and consumption of a well-balanced diet
- Trial of acid-suppressing agents in patients with continued symptoms despite high doses of PERT
- Diet adjustments, including smaller frequent meals, normal fat intake and supplementation of fat-soluble vitamins A, D, E and K
- Patient follow-up to detect nutritional deficiencies, symptoms of maldigestion, treatment of associated diseases and adherence with PERT.[1,2,7]

PERT

PERT is the backbone of treatment for PEI. APC 2015 guidelines state that steatorrhoea, either proven or implied, must be present before PERT is initiated – a decrease in pancreatic enzyme secretion alone does not mandate treatment.[7] However this is debated, as it is possible to have the consequences of PEI without overt symptoms. Thus steatorrhoea and a positive faecal elastase-1 test result are not absolute requirements for PERT. If the presence of steatorrhoea cannot be confirmed by faecal elastase-1 testing, other diagnostic tests can be undertaken. Its presence can often be inferred by the clinical context, imaging and patient characteristics, including suggestive changes in stool habit, weight loss, measured deficiencies in fat-soluble vitamins and osteoporosis.[7]

The guidelines present recommendations for the use of PERT according to PEI aetiology (see **Table 2**).[7]

Table 2. Australian Pancreatic Club 2015 recommendations for use of PERT according to PEI aetiology.[7] Also provided is the level of evidence on which the recommendations are based: 1b, individual randomised controlled trials (with narrow confidence interval); 2a, systematic reviews (with homogeneity) of clinical studies; 2b, individual cohort study or low quality randomised controlled trials; 3b, individual case-control study; 3c, critical review of the literature, including multiple experimental and observational studies; 5, expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles".

PEI aetiology	Recommendations for use of PERT
Acute pancreatitis	The use of PERT in the initial stages of acute pancreatitis is not recommended. **Level of evidence: 1b** All patients recovering from acute pancreatitis should undergo a nutritional assessment and those with continuing symptoms suggestive of ongoing malabsorption should be considered for PERT. **Level of evidence: 5**
Chronic pancreatitis	PERT can improve the symptoms of PEI in patients with chronic pancreatitis **Level of evidence: 1b** PERT can improve quality of life in patients with chronic pancreatitis **Level of evidence: 1b**
Cystic fibrosis	Aggressive nutritional management with a high-energy, high fat diet and PERT is recommended for cystic fibrosis patients with documented fat malabsorption or PEI found on pancreatic function testing **Level of evidence: 1b, 2b**
Bowel resection	PERT should be considered for those with clinical evidence of PEI and its ongoing requirement reviewed regularly because of possible intestinal adaptation **Level of evidence: 3c**
Gastric surgery	After gastric surgery, patients whose wellbeing is not severely affected do not require long term PERT **Level of evidence: 5** PEI can contribute to maldigestion and weight loss, and impact on quality of life in gastric surgery patients with more severe bowel symptoms. Adequate and appropriate PERT should be trialled here and continued if patients respond and experience improved wellbeing, bearing in mind the risk of a placebo effect **Level of evidence: 3b**
Pancreatectomy	Patients having total or subtotal pancreatectomy, including pancreatic head resection, require PERT postoperatively **Level of evidence: 2b** PERT is required in patients after pancreatico-gastrostomy because of the effect of acid on endogenous enzymes **Level of evidence: 2b**
Unresectable pancreatic cancer	PERT and dietary guidance from a dietitian should be used to treat PEI in patients with unresectable pancreatic cancers from the time of diagnosis in order to maintain weight and improve quality of life **Level of evidence: 2a**
Diabetes	Rarely is there a need to use PERT in patients with diabetes. Limited randomised controlled trial data do not support treating patients with PERT simply on the basis of very low faecal elastase-1 levels (<100 mg/g) **Level of evidence: 2b**
Coeliac disease	After establishing impaired pancreatic secretion in coeliac disease patients, or where pancreatic function testing is not feasible, a trial of PERT might be an option **Level of evidence: 3b**
Irritable bowel syndrome	PERT may lead to clinically significant improvements in diarrhoea-predominant irritable bowel syndrome where there is evidence of pancreatic exocrine insufficiency **Level of evidence: 3b**

Effectiveness

PERT has been used in the treatment of PEI for several decades, and many clinical trials have been conducted.[15] The primary endpoint for assessing efficacy in clinical trials is usually the coefficient of fat absorption, but this does not directly translate to clinical symptoms.[9] European guidelines for enteral nutrition in patients with pancreatitis recommend clinical endpoints such as improvement in steatorrhoea and maintenance of body weight.[9,16]

In practice, there is room to improve efficacy. Steatorrhoea is difficult to resolve completely with PERT and a 60-70% reduction is all that is usually achieved.[5] Recent studies from the Netherlands indicated that 68-70% of patients with PEI secondary to chronic pancreatitis or pancreatic surgery had steatorrhoea-related symptoms while receiving PERT.[17,18] The important reasons for this suboptimal efficacy are insufficient use of PERT, suboptimal scheduling in relation to meals or insufficient control of gastric acid output.[2] Furthermore, persistent deficits in blood nutritional parameters, fat-soluble vitamins and bone mineral density have been found in patients with chronic pancreatitis despite receiving PERT.[19,20]

Careful attention to dosing and administration of PERT is crucial in achieving the best outcome for patients with PEI, with individual titration necessary.[7,9,10] Determining response to treatment is further complicated by the lack of practical, objective outcome measures, and no clear guidance on this issue is offered by the APC.[7] Most guidelines recommend a re-evaluation of symptoms and body weight and a re-evaluation of serum tests of malnutrition.[2]

The PERT preparation Creon® has been well studied in randomised controlled trials of patients with *chronic pancreatitis*, patients with *cystic fibrosis* aged ≥7 years and following *pancreatic surgery*.[21,22] Creon® has also been studied in open-label trials of patients with cystic fibrosis aged 1 month to 6 years.[21,22] Trials of Creon® and other PERT formulations have shown that this treatment improves the coefficient of fat absorption and clinical symptoms in patients with PEI secondary to chronic pancreatitis, cystic fibrosis and following pancreatic surgery.[15,21,22] However, most trials have enrolled relatively small numbers of patients and were of short duration.[15] A recently published, high quality meta-analysis has confirmed the effectiveness of PERT for the treatment of PEI in patients with chronic pancreatitis.[8] The meta-analysis included quantitative data from 14 randomised controlled trials, published between 1979 and 2012. PERT significantly improved the coefficient of fat absorption compared with placebo (83.2 ± 5.5 vs 67.4 ± 7.0; p=0.0001; $I^2 = 86\%$).[8] PERT also improved the coefficient of nitrogen absorption, reduced faecal fat excretion, faecal nitrogen excretion, faecal weight and abdominal pain.[8] Quality of life was significantly improved in a 1-year extension to one of the randomised controlled trials.[8,23]

In *unresectable pancreatic cancer*, PERT reduced weight loss in a randomised, double-blind, placebo-controlled trial,[24] although these findings were not borne out in a more recent randomised, open-label trial.[25] A newly published retrospective study has shown that PERT improves survival in patients with unresectable pancreatic cancer, particularly in those with significant weight loss.[26]

A randomised, double-blind crossover trial in patients after *total gastrectomy* demonstrated that PERT improved stool consistency and decreased faecal fat excretion in patients with considerable steatorrhoea.[27] However, another similarly controlled trial showed only marginal improvements in symptoms and steatorrhoea with PERT after total gastrectomy.[28]

While reviews and case series have recommended the use of PERT in the management of *small bowel resection*, there are a paucity of randomised controlled trials demonstrating specific beneficial effects, and it is unclear whether PERT has any effect in the absence of PEI.[7]

Evidence is lacking for the use of PERT to treat PEI associated with other conditions such as *coeliac disease, inflammatory bowel disease, inflammatory bowel syndrome* and *types 1 and 2 diabetes*, and randomised controlled trials are needed.[7,15]

Safety

PERT is well tolerated. The most commonly reported adverse events are gastrointestinal disorders and allergic skin reactions, reflecting the porcine origin of PERT.[15,21,22,29] Patients with known hypersensitivity to porcine products should not be given PERT.[22,29] A recent meta-analysis found that the safety and tolerability profile of PERT was similar to that of placebo.[8]

Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been reported in patients with cystic fibrosis taking high doses of PERT.[7,22,29] The New Zealand Data Sheet for Creon® notes that unusual abdominal symptoms or changes in abdominal symptoms should be medically assessed to exclude the possibility of fibrosing colonopathy.[22]

Dosing and administration

Two preparations of PERT have approval for use in New Zealand and are funded by Pharmac – Creon® (available in two different strengths) and Panzytrat®.[22,29,30] Both contain porcine pancreatic enzymes. Minimum pancreatic enzyme activity levels are show in **Table 3.**[22,29]

Table 3. PERT preparations with approval for use in New Zealand.[22,29]

Enzyme activity (Ph Eur Units)	Creon® 10,000	Creon® 25,000	Panzytrat® 25,000
Lipase	10,000	25,000	25,000
Amylase	8000	18,000	22,500
Protease	600	1000	1250

Creon® and Panzytrat® have a pH-sensitive coating to allow the pancreatic enzymes to mix with chyme, while being protected from inactivation by gastric acid.[22,29] Intact enzymes then pass into the alkaline pH of the duodenum where the enteric coating rapidly dissolves and the enzymes are released.[7]

A low duodenal pH, for example in patients with bicarbonate deficiency, may affect the dissolution of the enteric coating and reduce the effectiveness of PERT.[1,7] Acid suppression with H_2-antagonists and proton pump inhibitors may be tried in patients who do not achieve an adequate response to PERT, although this is not an approved indication for these agents.[1,7,22,29] To ensure that the alkalinity of acid-suppressing agents does not destroy the enteric coating of PERT, at least 1 hour should elapse between the administration of both agents.[29]

The possibility of small intestinal bacterial overgrowth should be considered in patients with a poor response to PERT despite dose titration and acid suppression.[2,5,7]

Recommended dosing

The following recommendations are offered by the manufacturer of Creon®:

For children and adults with PEI associated with cystic fibrosis:

- Starting dose 1000 units lipase/kg bodyweight per meal (patients aged <4 years) or 500 units lipase/kg bodyweight per meal (patients aged ≥4 years)
- Adjust dose according to disease severity, control of steatorrhoea and maintenance of good nutritional status
- Maximum dose 4000 units lipase/g dietary fat intake OR 10,000 units lipase/kg bodyweight per day.[22]

For adults with PEI associated with other conditions:

- Starting dose 25,000-40,000 units lipase with each meal; half of meal dose with each snack
- Assess patient for clinical response and adherence with therapy
- If necessary, increase dose to 80,000 units lipase with each meal and half of meal dose with each snack
- Maximum dose 10,000 units lipase/kg bodyweight per day.[22]

The following recommendations are offered by the manufacturer of Panzytrat®:

For children and adults with PEI:

- Starting dose 50,000 lipase units/day for infants aged ≤18 months
- Starting dose 100,000 lipase units/day for children
- Starting dose 150,000 lipase units/day for adults
- Adjust dose according to individual severity of PEI; in the case of total pancreatic insufficiency this may be up to 400,000 lipase units/day.[29]

For patients with PEI associated with cystic fibrosis:

- The dose should not exceed that required for adequate fat absorption, taking into account the size and composition of meals. Increases in dose should be conducted under medical supervision with the aim of improving symptoms, and should not exceed 15,000-20,000 lipase units/kg bodyweight per day.[29]

APC 2015 guidelines note that infants may be given 2000-4000 units lipase per breastfeed or 120ml of infant formula.[7]

Method of administration

PERT should be taken either during or immediately after meals.[22,29] Capsules should be swallowed intact, without crushing or chewing, and with plenty of fluid.[22,29] For patients unable to swallow capsules, advice for Creon® is to open capsules and mix the contents with acidic soft food or liquid, such as apple sauce, yogurt or fruit juice with a pH of <5.5 (apple, orange or pineapple juice).[22] Advice for Panzytrat® in patients unable to tolerate capsules is to open and swallow the unchewed contents of the capsules.[29]

Crushing or chewing capsules or their contents, or mixing with food or fluid with a pH >5.5, can dissolve the protective enteric coating, leading to early release of enzymes in the oral cavity, reduced effectiveness and irritation of the oral mucosa.[22,29]

Nutritional management

Given that the main consequence of PEI is malabsorption of fat, and therefore vitamins and trace elements, routine nutritional assessment to ensure early detection of malnutrition is essential.[1,7,13] Such assessments should be carried out by a dietitian, and should include the following:

- Aetioloy of PEI – nutritional management varies according to diagnosis, particularly for meal size, frequency and the potential need for nutritional supplementation
- Diet history – to establish baseline diet, how the patient eats and define alcohol habits. Zero alcohol intake is recommended for patients with PEI; this is particularly important for patients with PEI secondary to chronic pancreatitis
- Malnutrition assessment – should include anthropometric measures such as mid-arm circumference, mid-arm muscle circumference, triceps skinfold or subjective global assessment in addition to body mass index
- Nutritional deficiencies – screening for markers such as magnesium, fat-soluble vitamins, vitamin B_{12}, iron and lipoproteins should be conducted at diagnosis so that appropriate supplements can be given and their status monitored
- Bone health – bone mineral density should be measured using dual-energy X-ray absorptiometry at diagnosis and every 2 years, with vitamin D and calcium supplementation given and referral to a bone specialist made when necessary
- Fat requirement – low fat or reduced fat diets are not recommended for patients receiving optimised PERT. A target of 30% total energy from dietary fat is considered appropriate, but a higher fat content may be recommended for some patients who are having difficulty gaining or maintaining weight. Adverse symptoms such as steatorrhoea need to be closely monitored.[1,7,13]

The APC recommendation for dietary protein intake in patients with PEI is 1.0-1.5 g/kg bodyweight/day.[7,13] Although total daily energy requirements can vary greatly between individuals, guidelines from the Spanish Pancreatic Club suggest a target of 30 kcal/kg bodyweight/day.[7,31]

EXPERT COMMENTARY

PERT is effective in patients with PEI. However, important reasons for suboptimal efficacy are insufficient use of PERT, suboptimal scheduling in relation to meals or insufficient control of gastric acid output.[2]

While the coefficient of fat absorption is the primary efficacy parameter used in clinical trials of PERT, this does not directly translate to clinical symptoms.[9] European guidelines for enteral nutrition in patients with pancreatitis recommend clinical endpoints such as improvement in steatorrhoea and maintenance of body weight.[9,16]

Trials of Creon® and other PERT formulations have shown that this treatment improves the coefficient of fat absorption and clinical symptoms in patients with PEI secondary to chronic pancreatitis, cystic fibrosis and following pancreatic surgery.

Regarding dietary fat intake in patients with PEI, some is essential, but too much is harmful.

CONCLUSIONS

While there is clear evidence for the effectiveness of PERT in the treatment of PEI in patients with chronic pancreatitis, cystic fibrosis and after pancreatic surgery, more randomised controlled trials are needed for patients with PEI associated with other conditions. Long-term studies across all areas are needed to establish the effects of PERT on morbidity and mortality, and to determine optimal PERT regimens.[7,9,10]

New biotechnology-derived PERT formulations that avoid the use of animal products have recently been approved by the US Food and Drug Administration, and more are in clinical development.[7] These new formulations are liquid- rather than capsule-based, making them potentially more palatable in those who find it difficult to swallow capsules.[7]

REFERENCES:

1. Nikfarjam M, et al. Diagnosis and management of pancreatic exocrine insufficiency. Med J Aust. 2017 Aug 21;207(4):161-165.
2. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol. 2013 Nov 14;19(42):7258-66.
3. Othman MO, et al. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. Int J Clin Pract. 2018 Feb;72(2). doi: 10.1111/ijcp.13066. Epub 2018 Feb 5.
4. Singh VK, et al. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol. 2017 Oct 21;23(39):7059-7076.
5. Pezzilli R, et al. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. World J Gastroenterol. 2013 Nov 28;19(44):7930-46.
6. Löhr JM, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J. 2017 Mar;5(2):153-199.
7. Australasian Pancreatic Club. Australasian guidelines for the management of pancreatic exocrine insufficiency October 2015. Available at: http://pancreas.org.au/wp-content/uploads/2016/01/APC-GUIDELINES-2015.pdf [Accessed November 2018].
8. de la Iglesia-García D, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. Pancreatology. 2016 Mar-Apr;16(2):164-80.
9. Windsor JA. Pancreatic enzyme replacement therapy in chronic pancreatitis: a long way to go. World J Gastroenterol. 2017 Oct 21;23(39):7059-7076.
10. Struyvenberg MR, et al. Practical guide to exocrine pancreatic insufficiency - Breaking the myths. BMC Med. 2017 Feb 10;15(1):29.
11. Keller J & Layer P. Human pancreatic exocrine response to nutrients in health and disease. Gut. 2005 Jul;54 Suppl 6:vi1-28.
12. DiMagno EP, et al. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. N Engl J Med. 1973 Apr 19;288(16):813-5.
13. Working Party of the Australian Pancreatic Club, et al. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. Pancreatology. 2016 Mar-Apr;16(2):164-80.
14. Duggan SN, et al. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2014 Feb;12(2):219-28.
15. Nakajima K, et al. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. Core Evid. 2012;7:77-91.
16. Meier R, et al. ESPEN Guidelines on Enteral Nutrition: Pancreas. Clin Nutr. 2006 Apr;25(2):275-84.
17. Sikkens EC, et al. Patients with exocrine insufficiency due to chronic pancreatitis are undertreated: a Dutch national survey. Pancreatology. 2012 Jan-Feb;12(1):71-3.
18. Sikkens EC, et al. The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery: a northern European survey: enzyme replacement after surgery.
19. Sikkens EC, et al. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. Pancreatology. 2013 May-Jun;13(3):238-42.
20. Domínguez-Muñoz JE & Iglesias-Garcia. Oral pancreatic enzyme substitution therapy in chronic pancreatitis: is clinical response an appropriate marker for evaluation of therapeutic efficacy? JOP. 2010 Mar 5;11(2):158-62.
21. Kuhn RJ, et al. CREON (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency. Adv Ther. 2010 Dec;27(12):895-916.
22. Medsafe. New Zealand Data Sheet. Creon® 10,000 Creon® 25,000. Available at: http://www.medsafe.govt.nz/profs/datasheet/c/CreonCreonFortecap.pdf [Accessed November 2018].
23. Ramesh H, et al. A 51-week, open-label clinical trial in India to assess the efficacy and safety of pancreatin 40000 enteric-coated minimicrospheres in patients with pancreatic exocrine insufficiency due to chronic pancreatitis. Pancreatology. 2013 Mar-Apr;13(2):133-9.
24. Bruno MJ, et al. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut. 1998 Jan;42(1):92-6.
25. Saito T, et al. A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. Pancreas. 2018 Aug;47(7):800-806.
26. Domínguez-Muñoz JE, et al. Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: a retrospective analysis. BMC Cancer. 2018 May 5;18(1):534. doi: 10.1186/s12885-018-4439-x.
27. Ambrecht U, et al. The benefit of pancreatic enzyme substitution after total gastrectomy. Aliment Pharmacol Ther. 1988 Dec;2(6):493-500.
28. Brägelmann R, et al. The effect of pancreatic enzyme supplementation in patients with steatorrhoea after total gastrectomy. Eur J Gastroenterol Hepatol. 1999 Mar;11(3):231-7.
29. Medsafe. New Zealand Data Sheet. Panzytrat® 25,000. Available at: http://www.medsafe.govt.nz/profs/Datasheet/p/panzytratcap.pdf [Accessed November 2018].
30. Pharmac. Online Pharmaceutical Schedule November 2018. Pancreatic enzyme. Available at: https://www.pharmac.govt.nz/wwwtrs/ScheduleOnline.php?osq=Pancreatic%20enzyme [Accessed November 2018].
31. de-Madaria E, et al. The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). Pancreatology. 2013 Jan-Feb;13(1):18-28.

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