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Pancreatic enzyme replacement therapy (PERT) for the treatment of pancreatic exocrine insufficiency (PEI)

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This publication is an educational resource for healthcare professionals focusing on the treatment of pancreatic exocrine insufficiency (PEI) with pancreatic enzyme replacement therapy (PERT). This is an under-diagnosed and under-treated condition with multiple aetiologies that can cause serious complications. To optimise treatment, it is essential that the dose of PERT is individualised according to the patient's disease severity and adjusted according to their response. Multiple studies have shown that PERT is associated with improvements in symptoms, nutritional parameters and survival in patients with PEI. This review is supported by an educational grant from Viatris.

Background

The pancreas produces enzymes (e.g. lipase, amylase, trypsin and chymotrypsin) and bicarbonate, both of which are important for macronutrient digestion.[1] These secretions enter the second portion of the duodenum via the pancreatic duct following mediation by hormonal and neuronal mechanisms.[2] Inadequate pancreatic secretion can result in maldigestion and malabsorption referred to as pancreatic enzyme insufficiency (PEI).[1–4]

PEI is primarily caused by a wide range of pancreatic-related conditions such as chronic pancreatitis, cystic fibrosis, pancreatic obstruction, pancreatic tumours, pancreatic resection, and diabetes (type 1, 2 and pancreatogenic diabetes).[2,3] Other conditions where PEI may arise include gastric resection and bariatric surgery, coeliac disease, IBD, short bowel syndrome and in older adults due to an aging pancreas (**Table 1**).[2,3,5] The prevalence of PEI is unknown due to its multiple causes, however, it is widely considered an under-diagnosed condition.[3,6]

Regardless of the underlying disorder, there are four possible mechanisms causing PEI:[6,7]

1. Damage to the pancreatic parenchyma making it unable to synthesise sufficient enzymes
2. Asynchrony between digestive enzyme secretion and meal delivery
3. Obstruction of the pancreatic duct
4. Decreased endogenous stimulation

DEFINITE (100%)	Total pancreatectomy, severe chronic pancreatitis (with calcific changes, steatorrhoea, weight loss), head of pancreas cancer or acute pancreatitis destroying head of pancreas.
POSSIBLE	Cystic fibrosis, mild and moderate chronic pancreatitis, after severe acute pancreatitis or severe pancreatitis, after pancreatic surgery (46-100% depending on procedure), bariatric surgery, small intestinal bacterial overgrowth, elderly with weight loss.
UNLIKELY (<10%)	Type 2 diabetes, irritable bowel syndrome, coeliac disease, inflammatory bowel disease, bowel resection.

Table 1: The likelihood of pancreatic exocrine insufficiency in different populations of patients. Adapted from Nikfarjam *et al* (2017).[5,6,8–11]

Abbreviations used in this review

CCK = cholecystokinin
CFA = coefficient of fat absorption
CI = confidence interval
CNA = coefficient of nitrogen absorption
GI = gastrointestinal
GIQLI = gastrointestinal quality of life index
HIV = human immunodeficiency virus
HR = hazard ratio
IBD = inflammatory bowel disease
ITT = intention to treat
PEI = pancreatic exocrine insufficiency
PERT = pancreatic enzyme replacement therapy
PPI = proton pump inhibitor
QoL = quality of life
RCT = randomised controlled trial
TEAE = treatment-emergent adverse effects

Diagnosing PEI

The clinical symptoms of PEI are generally not observed until duodenal lipase levels fall below 5-10% of normal postprandial levels (**Figure 1**).[1,12]

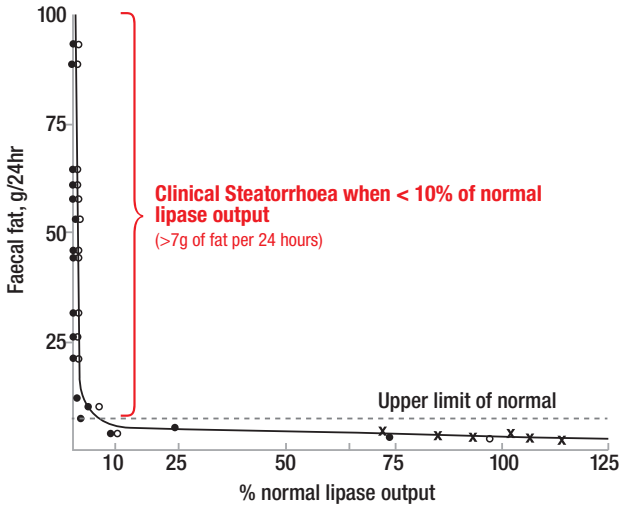

Figure 1: The relationship between pancreatic lipase output and the development of steatorrhoea. Adapted from DiMagno *et al* (1973).[12]

Patients with PEI may present with steatorrhoea, abdominal pain, weight loss, and diarrhoea, all of which can result in GI motor disturbances, further disruption to secretory functions, malabsorption and malnutrition.[1,4,13] Steatorrhoea and weight loss are the principle symptoms of PEI and specific inquiry regarding additional symptoms should be made in any patients reporting frothy, foul smelling and buoyant stools, as patients may not self-report all symtpoms.[1] PEI can also occur in the absence of obvious symptoms.

It is difficult to assess pancreatic exocrine function, therefore a diagnosis of PEI begins with the patient's self-reported bowel movements, bodyweight, history, and a clinical assessment (**Figure 2**).[1] It is important to differentiate malabsorption due to PEI from non-pancreatic causes.[1] PEI may also be misdiagnosed as another GI disorder such as irritable bowel syndrome.[13] The initial assessment should include a CT scan to assess pancreatic structure.[1]

The need for diagnostic testing in suspected PEI is determined by the patient's clinical characteristics. No test is required for patients with total pancreatectomy, severe calcific pancreatitis or malignancy in the pancreatic head, as PEI occurs in 100% of these cases.[1]

Direct tests of pancreatic function are the most sensitive and specific methods of assessing pancreatic function, e.g. secretin-CCK stimulation, the Lundh test, and endoscopic pancreatic function, however, these are invasive and the potential adverse effects of testing should be considered, particularly in patients where PEI is unlikely.[1]

Indirect functional assessments include breath, faecal, blood and urine tests, although these are less accurate.[6] Deficiencies in fat-soluble vitamins, lipoproteins and magnesium can assist in the diagnosis of PEI.[1]

A diagnostic trial of PERT may be considered if an objective marker of PEI is not available.[1]

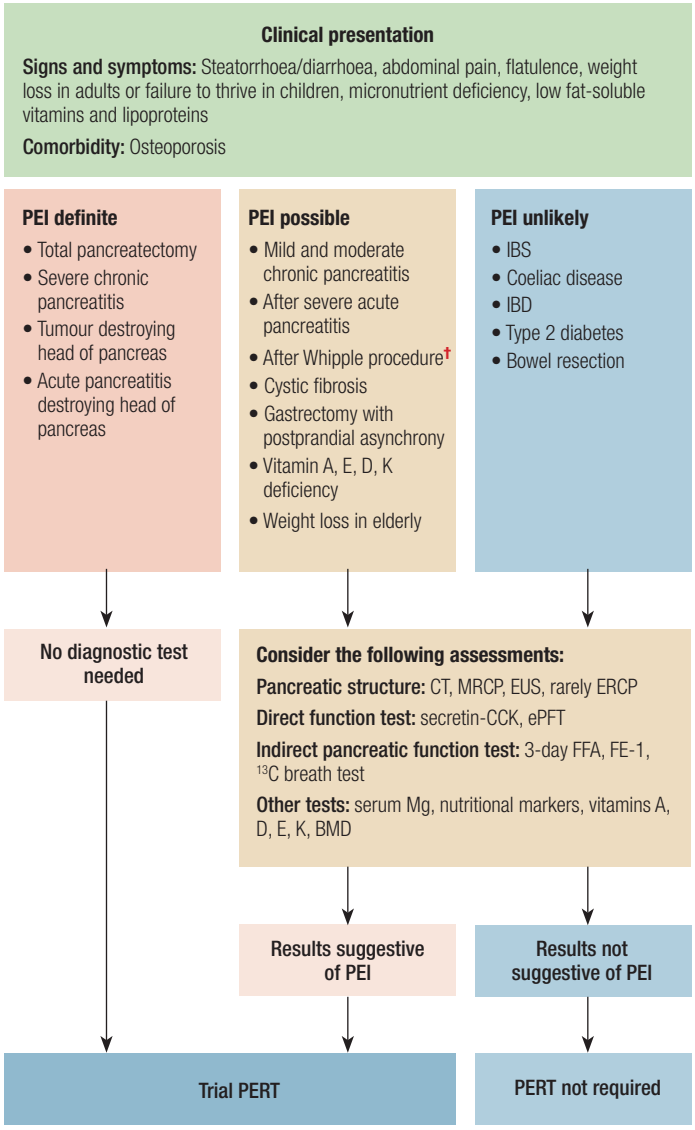

Figure 2: Diagnostic pathway for pancreatic exocrine insufficiency. Adapted from Nikfarjam *et al* (2017).[6]

BMD = bone mineral density, CCK = cholecystokinin, CT = computed tomography, ePFT = endoscopic pancreatic function test, ERCP = endoscopic retrograde cholangiopancreatography, EUS = endoscopic ultrasound, FE-1 = faecal elastase-1, FFA = faecal fat analysis, IBD = inflammatory bowel disease, IBS = irritable bowel syndrome, Mg = magnesium, MRCP = magnetic resonance cholangiopancreatography

† = After pancreatic surgery due to pancreatic cancer

The consequences of untreated PEI

In a healthy digestive system, the quantity of postprandial enzymes secreted by the pancreas far exceeds the amount required for digestion.[1] In a patient with PEI, reduced lipase production and/or an abnormally low pH due to decreased bicarbonate secretion mean that lipase activity in the GI tract is reduced and fat digestion is impaired.[4]

Adults with PEI often experience weight loss and children who are affected may not gain weight and fail to thrive.[1] The symptoms of PEI and the consequences of the resulting malnutrition are often associated with a reduced QoL.[13] In all patients with PEI, the absorption of fat-soluble vitamins (A,D, E and K) is suboptimal and deficiencies in calcium, folic acid, magnesium, thiamine and zinc may occur.[14] The risk of osteopenia and osteoporosis is therefore high and 60% of patients with PEI are diagnosed with reduced bone density.[14] In patients with cystic fibrosis, PEI has been associated with decreased survival, compared to patients who are pancreatic-sufficient.[13]

Treatment with PERT (see below) can prevent malnutrition, improve bodyweight and reduce the burden of abdominal symptoms, thereby improving QoL.[13]

PERT is under-used

Despite evidence that PERT is a safe and effective treatment for PEI it is frequently under-prescribed, dosed inadequately or taken irregularly by patients.[1,4,15] Prescribers and patients need to be aware of the importance of optimal dosing and treatment compliance in order to maximise the effectiveness of therapy. Referral to a dietitian (see below) is recommended to improve patient compliance with PERT.[1]

Data from a large medical insurance database in the United States revealed that 30.4% of people with chronic pancreatitis collected a prescription for PERT while 21.9% of those with pancreatic cancer and PEI filled a prescription for PERT.[16] In these two groups of patients, 8.5% and 5.5% respectively were prescribed an adequate dose of PERT.[16] A systematic review found that PERT was frequently not offered to patients with pancreatic cancer and that it was under-prescribed due to a lack of education at the health professional and public level.[15] A Dutch survey of 161 patients with chronic pancreatitis reported steatorrhoea-related symptoms were experienced by 70% of patients despite treatment with PERT and only 25% had been referred to a dietitian.[17] Several retrospective analyses of patients with pancreatic cancer reported that 21% were prescribed PERT, despite 70% of patients in one study having malabsorption-related symptoms.[13,18,19]

A qualitative investigation of the perspectives and experiences of 35 people affected by pancreatic cancer revealed "strong feelings of frustration and anger" regarding the symptoms of untreated PEI.[20] These feelings often centred on inadequate dietary advice and a lack of basic information about PEI and how it should be treated. Distress was often exacerbated by a perceived reluctance of clinicians to prescribe PERT. The few patients who were prescribed PERT were often confused about dosing, were unable to modify the dose and often did not time dosing with food intake.

Expert commentary: The underuse and underdosing of PERT results in a substantial and unnecessary burden to patients. It is a simple and cheap therapy that makes an immense difference to patient's QoL. From the patient's perspective, untreated, or inadequately treated PEI often results in them having to stay home-based, so they are always near a toilet. This can lead to feelings of social isolation, at a time when individuals might be struggling the most. Prescribing PERT and enabling patients to return to their normal activities of daily living, with dignity, has been one of the most rewarding aspects of this therapy in our practice.

Treatment of PEI

Pancreatic enzyme replacement therapy (PERT) is the cornerstone of PEI treatment.[1,2,6]

The goals of therapy are to prevent malabsorption and maldigestion-related symptoms, maintain adequate nutrition and improve QoL.[1,21] This is achieved by delivering enough active enzymes into the duodenal lumen, as close as possible to the arrival of the meal. It is estimated that supplementation of at least 10% of normal pancreatic lipase activity is required for treatment to be effective.[2]

PERT is given as a combination of pancreatic enzymes derived from the porcine pancreas.[21] Different formulations are available including microspheres or microtablets of varying size with a pH-sensitive enteric coating that prevents gastric acid from denaturing the lipase.[21] Once the intact enzymes reach the alkaline pH of the duodenum, the enteric coating rapidly dissolves to release the enzymes into the lumen.[1]

In New Zealand, fully-funded PERT can be prescribed as pancreatin or pancrelipase.[22] Pancreatin is available in the following formulations:[23,24]

- CREON® 10,000®, 150 mg pancreatin capsules containing not less than 8,000 Ph.Eur. units amylase, 10,000, Ph.Eur. units lipase and 600 Ph.Eur. units protease
- CREON® 25,000®, 300 mg pancreatin capsules containing not less than 18,000 Ph.Eur. units amylase, 25,000, Ph.Eur. units lipase and 1,000 Ph.Eur. units protease
- CREON® Micro modified-release granules with each 100 mg of minimicrospheres containing lipase 5000 Ph.Eur. units, amylase 3600, Ph.Eur. units and protease 200 Ph.Eur. units

PANZYTRAT® (pancrelipase) 25,000 modified-release capsules containing 25,000 Ph. Eur. units of lipase, 22,000 Ph. Eur. units of amylase and 1,250 Ph. Eur units of protease will no longer be available in New Zealand from early 2023.[25,26]

Non-porcine enzyme supplements (liprotamase) for PEI have been trialled and limited evidence suggests they may have a beneficial effect on fat and protein absorption in patients with cystic fibrosis.[27] However, a randomised trial found liprotamase was inferior to pancrelipase as assessed by CFA.[28]

Dosing

Fixed dosing is not used for PERT as the requirements vary between patients and depend on the clinical context.

- In patients with cystic fibrosis, fat-based (500-4000 U lipase/g dietary fat) or weight-based (maximum of 2,500 IU lipase/kg/meal) dosing might be used.[29]
- In all other (non-cystic fibrosis) patients the recommended adult starting dose for Creon® is 25,000-40,000 units of lipase with each meal and half this dose with snacks.[30] From a practical perspective, however, a starting dose of 25,000-50,000 units lipase may be more appropriate due to PERT preparations currently on the market in New Zealand, i.e. 50,000 with meals and 25,000 with snacks.

Meal-based dosing should be up-titrated as necessary depending on the size of the meal and any ongoing symptoms. Patients should be educated about how to adjust dosing on a meal-by-meal basis. The upper limit of PERT dosing is 10,000 units of lipase per kg of bodyweight per day, which equates to 28 x Creon® 25,000 capsules per day for a 70 kg person.[31]

Whichever dosing strategy is employed, the essential components are[1]

1. PERT is optimised by dose adjustments
2. PERT is taken as prescribed
3. A PPI is considered as an adjunctive treatment.

This means that patients require quality education and close monitoring to individualise treatment according to PEI severity and the fat content of meals.[31,32] Due to the differing dosages of PERT that are available, confusion regarding dosing is common.[21]

The efficacy of PERT should be assessed by the effect on both the patient's GI symptoms and nutritional markers.[3,4,32] If the patient's response is not sufficient, adherence should assessed and the dose increased if necessary or the addition of a PPI considered.[3,4,32] Multiple studies show that approximately half of patients prescribed PERT are adherent with treatment.[33,34] If an inadequate response persists, additional factors should be considered such as bacterial overgrowth of the small intestine or an alternative diagnosis considered, e.g. abnormal intestinal motility, liver disease or an alternative GI condition.[3,4,6,32,35]

Patient education

Education about the administration of PERT should be provided to all patients.[36] The reason for taking PERT with a meal is to mimic the endogenous secretions of the pancreas.[21] Therefore, PERT should always be taken with food and water and the greater the quantity of food that is eaten, the longer the meal or the higher the content of fat, the more the dose needs to be increased.[21,31] As a general rule, the patient can be guided by the length of their meal to determine the timing of administration:[31]

- Less than 15 minutes – take the full dose with the first few mouthfuls
- 15-30 minutes – take half the dose at the start of the meal and the other half in the middle
- 30-45 minutes – take one-third at the start, one-third in the middle and the final third toward the end of the meal
- Meals longer than 45 minutes may require an increased dose of PERT

Acid suppression

Patients with pancreatic disease may have a pH level in their duodenum that is lower than normal due to a deficiency of bicarbonate.[1] An abnormally low pH may prevent the release of the enteric coated enzymes and limit the effectiveness of PERT.[7] Furthermore, lipase is irreversibly inactivated at a pH <4. A PPI or other acid-suppressing treatment may be beneficial to patients using PERT who continue to experience PEI symptoms, particularly steatorrhoea, despite adequate dosing.[1]

Dietary management

All patients taking PERT should be under the dietary management of a dietitian to determine their nutritional and bodyweight status, to assess for macro and micronutrient deficiencies, to tailor an ongoing dietary plan and to assess PERT dosing and adherence.[1] Typically, the dietitian assessment will involve a detailed food, symptom and PERT history to determine what and how the patient eats and the appropriateness of the PERT regimen. It is within the scope of practice for dietitians in New Zealand to prescribe PERT as well as vitamins and supplements to treat micronutrient deficiency and malnutrition (if their practicing certificate is endorsed with prescribing rights).

In general, it is better to distribute nutrient intake across the day in six smaller meals with an appropriate dose of PERT at each.[1] This strategy will reduce the amount of fat in each meal that can be malabsorbed and is particularly helpful for patients with nausea or anorexia who may find a large meal unappealing.

Patients taking PERT should not reduce their fat intake without consulting their dietitian as this may cause unintentional weight loss.[36] Historically, reduced fat diets were recommended for patients taking PERT, however recent studies using higher fat diets have produced encouraging results and a target of 30% of total energy from dietary fat is now recommended.[1,6] In the palliative population, e.g. unresectable pancreatic cancer, the diet should be unrestricted.

Carbohydrate and protein digestion are not severely affected in PEI due to the action of salivary amylase and the secretion of enzymes from brush borders.[1] Impaired glucose tolerance may develop due to endocrine dysfunction which may require treatment. In some patients with severe PEI supplementation of dietary protein may be necessary.[1]

Avoiding alcohol intake is recommended for patients with PEI as this will reduce the risk of further deterioration in pancreatic function.[1,2,6]

Adverse effects

The main adverse effects associated with PERT are gastrointestinal, i.e. abdominal pain, nausea, vomiting, constipation, abdominal distension and diarrhoea.[24] However, these are also symptoms of PEI and similar or lower incidences compared to placebo have been reported for abdominal pain and diarrhoea.[24] Strictures of the ileo-caecum and large bowel (fibrosing colonopathy) have been occasionally reported in patients taking high doses of earlier forms of PERT over prolonged periods.[1,13]

PERT should not be prescribed to patients with pork allergies and non-porcine alternatives could be considered.[1] An elemental diet may be required if the non-porcine preparations are not effective.

Expert commentary: A step-up approach for PERT dosing is often used, but this may mean a delay in reaching an effective dose for many patients. This prolongs the consequences of untreated PEI for patients, especially if there is a long period between consultations. Step-down dosing may therefore be considered in patients with severe PEI as there are no short-term consequences for excessive dosing.

In our practice, we have also found that prescribing just the one capsule size of PERT (Creon® 25,000) has reduced confusion and improved compliance. Historically, we used to prescribe a mixture of Creon® 10,000 and Creon® 25,000 for meals and snacks respectively, however, many patients found this difficult to follow, especially in the context of all their other medications. Given the large percentage of patients in the literature still reporting symptoms of PEI despite being on PERT, we suspect that much of this is due to underdosing of the therapy. Moving to the one, higher dosed capsule (Creon® 25,000), therefore also makes sense for this reason.

Clinical studies of PERT

Multiple clinical trials demonstrate that PERT results in long-term improvements in PEI-related symptoms, nutritional parameters and bodyweight in patients with PEI due to chronic pancreatitis, pancreatic resection, cystic fibrosis and pancreatic cancer.[13] These data indicate that PEI is common in patients with these underlying conditions and that correct dosing and adherence are critical to optimise the benefits of PERT.

PEI and malnutrition rates following pancreatic resection

An Australian prospective study of consecutive patients undergoing pancreatic resection examined the prevalence of PEI, micronutrient deficiency, diabetes, osteoporosis and malnutrition.[37] There were 98 patients in the analysis and most had been diagnosed with cancer (73%). Patients who underwent pancreaticoduodenectomy were more likely to require PERT than those who underwent distal pancreatectomy (97% vs 48%, $p<0.001$). In the pancreaticoduodenectomy group, 19% required PERT pre-operatively and by 5 months post-operatively 97% of all patients required PERT. PPIs were required to optimise PERT efficacy in 71% of pancreaticoduodenectomy patients and 50% of distal pancreatectomy patients.

In the same study, 72% of patients had a deficiency of ≥1 micronutrient (iron, trace elements, fat-soluble vitamins) and 40% were malnourished. From bone density data, 29% of patients were diagnosed with osteoporosis and 49% with osteopenia.[37]

This study demonstrates that most patients following pancreaticoduodenectomy and around half following distal pancreatectomy will develop PEI and require PERT.[37] Furthermore, micronutrient deficiencies are common following pancreatic resection and close post-surgical monitoring is important.[37]

PERT and chronic pancreatitis

Two double-blind, randomised placebo-controlled trials assessed the safety and tolerability of PERT in patients with PEI due to chronic pancreatitis.[38,39] After one week, 61 patients receiving pancreatin experienced significant improvements in fat absorption (18.5%; 95% CI 15.8-21.2 vs 4.1%; 1.0-7.2 respectively) and nitrogen absorption, as well as greater reductions in mean stool fat, stool frequency and stool weight compared to placebo.[38] Following a 51-week, open-label extension of a double-blind RCT, significant improvements were reported in 48 patients taking CREON® for CFA (22.7 +/-12.2%), CNA (6.5 +/-7.9%), bodyweight (4.9 +/-4.9kg) and BMI (1.9 +/-1.9 kg/m^2) and for most nutritional markers that were measured ($p\leq0.001$ for all).[39] The daily mean stool frequency decreased from 2.8 to 1.6 ($p<0.001$) and improvements in clinical symptoms, clinical global impression of symptoms, and QoL were also reported.[39] PERT was well tolerated in both studies and no unexpected TEAE were reported.[38,39]

Collectively, these data and other studies provide good evidence that in patients with PEI due to chronic pancreatitis, PERT improves malabsorption, bodyweight, PEI-related symptoms and QoL.[13]

PERT and cystic fibrosis

An analysis of seven short-term, double-blind RCTs found that PERT was associated with significant increases in fat and protein absorption in children aged ≥7 years with cystic fibrosis ($p<0.001$).[13] In one study, a target dose of 4,000 lipase units per gram of fat resulted in significantly higher coefficient of fat absorption (CFA) and coefficient of nitrogen absorption (CAN) in patients randomised to CREON® or placebo ($p<0.001$).[40] There was also a reduction in stool frequency, abdominal pain, stool consistency ($p<0.001$ for all) and flatulence ($p=0.013$) that was noticeable on the first day of treatment and persisted.

Another double-blind RCT in 16 children aged 7-11 years with PEI and cystic fibrosis found the CFA for pancrealipase-treated patients was significantly higher compared to placebo (82.8% vs 47.4%; $p<0.001$), with similar results for CNA (80.3% vs 45.0%; $p<0.001$).[41] Again, significant improvements were seen in stool fat, stool weight and nitrogen, as well as a reduction in stool frequency ($p<0.001$ for all). Improvements in height, weight and BMI parameters have been reported by another study of 40 children aged <4 years with PEI due to cystic fibrosis who were treated for 3 months with CREON®.[42]

Together these results suggest that by preventing malnutrition and maintaining bodyweight, PERT improves long-term outcomes in children with cystic fibrosis.[13]

The importance of dose adjustments and adherence to treatment

A double-blind RCT enrolled 304 patients who had undergone pancreatoduodenectomy and recorded a faecal elastase ≤200 µg/g.[43] Participants were randomly assigned to 40,000 IU pancreatin 3 times daily during meals or placebo.[43] The protocol was completed by 71 patients in the PERT group and by 93 in the placebo group (the ITT population).[43] PERT patients in the per protocol population achieved a 1.09 kg weight gain after three months while those taking placebo recorded a loss of -2.28 kg (**Figure 3**; p<0.001). However, there was no difference between treatments in the ITT population (-0.68 kg vs -1.19 respectively; p=0.302). Multivariate analysis indicated that poor treatment adherence was the strongest risk factor for weight loss (HR 4.018; p<0.001).[43] The medication compliance rate in the study was 69.1%.

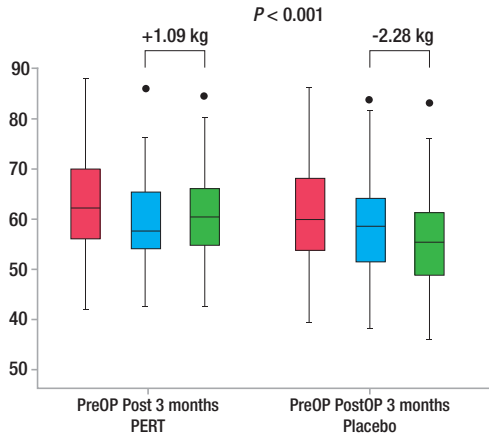

Figure 3: Change in bodyweight in the per protocol population of treated with PERT or placebo following pancreatoduodenectomy. Adapted from Kim *et al* (2020).[43]

It was concluded that PERT was associated with significant improvements in bodyweight in the per protocol population, but not in the ITT population.[43] This suggests that improving patient adherence with education and active monitoring may increase the effectiveness of PERT and this is consistent with non-adherence being the strongest risk factor for weight loss. The authors noted the dose of PERT may have been suboptimal, therefore further gains might have been made in the PERT group if the dose was titrated up according to symptoms.

A one-week, double-blind RCT enrolled 58 adult patients with severe PEI following pancreatic resection.[44] In the double-blind phase, the CFA for the pancreatin arm increased and the placebo arm decreased, with a treatment difference of 32.6% (95 CI 19.9-45.4; p<0.001).[44] Statistically significant differences from baseline in the CNA and stool fat favoured pancreatin (p<0.001 for both). The stool frequency for patients taking pancreatin decreased by -0.9 stools per day during the double-blind period and increased by 0.5 stools per day in the placebo group. Following one year of open-label pancreatin, statistically significant improvements from baseline were reported for CFA, CNA, stool fat, stool nitrogen, stool weight, stool frequency, bodyweight and BMI.

It was concluded that PERT resulted in statistically significant improvements in fat and nitrogen absorption in patients with PEI due to pancreatic surgery, compared to placebo.[44] These improvements were clinically modest but in practice the dose would be adjusted to patient response, meaning that greater improvements would be expected in clinical practice. The relatively small improvement in clinical symptoms may have been due to low adherence (not recorded), disease progression or mild symptoms at baseline due to PERT prior to study initiation.

PERT and pancreatic cancer

A pilot study was conducted to assess the efficacy of PERT in improving symptoms and QoL in patients with metastatic pancreatic cancer.[45] The study was completed by 29 patients and within one week of beginning PERT there were significant reductions in diarrhoea scores (p<0.005) and pancreatic and hepatic pain (p<0.05 for both).[45]

After 3 weeks, there were significant improvements in pancreatic pain and symptoms of bloating/gas (p<0.005 for both). Diarrhoea was found to have worsened at week 3, despite the initial improvement, which may have been due to increased food intake. It was concluded that PERT showed potential for improving QoL for patients with metastatic pancreatic cancer.

PERT and survival

There are no well-designed prospective studies reporting on PERT and survival in patients with pancreatic cancer, although several retrospective analyses have been published.[18,46]

A Spanish analysis identified 160 patients with unresectable pancreatic adenocarcinoma who were either treated according to standard oncology protocols (Group 1) or were also prescribed PERT if needed (Group 2).[46] PERT was administered to 66.2% of patients in Group 2. Palliative chemotherapy was offered and accepted by 46.5% in Group 1 and 71.6% in Group 2 (p<0.001). The median survival in Group 2 (189 days; 95% CI 167-211 days) was significantly longer than in Group 1 (95 days; 75.4-114.6 days; HR 2.12; p<0.001; **Figure 4**).[46] Univariate and multivariate analysis found that palliative chemotherapy and PERT were significantly and independently associated with longer survival. When all patients with weight loss >10% in both groups were analysed (n=95), the median survival of the 40 patients who received PERT was 199 days (95% CI 152-246 days) compared to 99 days (68-130 days; p<0.001) in patients with significant weight loss who did not receive PERT.

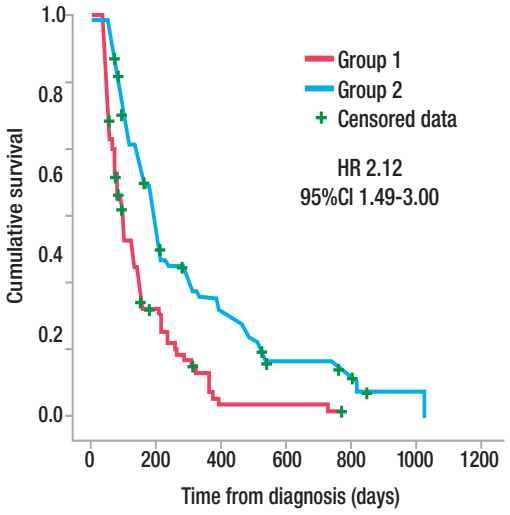

Figure 4: Kaplan-Meier survival curves for patients with unresectable pancreatic cancer. Adapted from Domínguez-Muñoz *et al* (2018).[46]

Another retrospective analysis of a UK dataset created 807 matched pairs of patients with pancreatic adenocarcinoma who did and did not receive PERT.[18] There were 1,403 deaths in total, with the adjusted survival time ratio being 2.62 (95% CI 2.27-3.02) in cases treated with PERT, compared to non-PERT treated controls. The survival of cases treated with PERT remained significantly longer regardless of the use of chemotherapy or surgery.

Expert commentary: The improvement in survival in patients with pancreatic cancer treated with PERT is the standout finding in the literature above and in our view supports routine prescription in these patients on diagnosis. The risks associated with weight loss and poor QoL due to steatorrhoea and other gastrointestinal disturbances almost always outweighs the burden or inconvenience of taking PERT with food. The relatively modest clinical benefits reported in the clinical study should not be used as a reason to not prescribe PERT in patients having pancreatic resection. Greater benefits would have occurred if optimisation of PERT had been permitted, to ensure adequate dosing, appropriate timing, and acid suppression if required.

TAKE-HOME MESSAGES

- Pancreatic exocrine insufficiency (PEI) is a frequently under-diagnosed condition with multiple causes, the most common being chronic pancreatitis, pancreatic cancer and cystic fibrosis
- The consequences of PEI may include steatorrhoea, deficiencies in fat-soluble vitamins and micronutrients, osteoporosis, malnutrition and weight loss, a reduced QoL, and potentially reduced survival
- Diagnostic testing is not required for patients with total pancreatectomy, severe calcific pancreatitis or malignancy in the pancreatic head as PEI occurs in 100% of these cases. Direct measures of pancreatic function are invasive, while indirect tests are less sensitive and less specific. Deficiencies in fat-soluble vitamins, lipoproteins and magnesium can assist in making a diagnosis.
- PERT is the first-line treatment for PEI, but it is frequently under-used and/or under-dosed
- The involvement of a dietitian is recommended for all patients taking PERT
- Optimised dosing and patient education are essential for PERT to be effective. Dosing should be individualised and patients taught to up-titrate their dose according to their diet and symptoms.
- The main adverse effects of PEI tend to be gastrointestinal, e.g. abdominal pain, nausea, vomiting, constipation, abdominal distension and diarrhoea
- If PERT is not effective, compliance should be reviewed and consideration given to increasing the dose and/or initiating a PPI
- Clinical studies show that PERT is associated with improvements in nutritional parameters, reduced symptoms, increased bodyweight and survival in patients with PEI
- Most patients following pancreaticoduodenectomy and around half following distal pancreatectomy will develop PEI and require PERT
- Multiple studies provide good evidence that PERT results in patients with chronic pancreatitis experiencing significant improvements in stool frequency, malabsorption, bodyweight, PEI-related symptoms and QoL.

EXPERTS' CONCLUDING REMARKS

The benefits of treating PEI with PERT are well established, however, to achieve effective treatment the dosing, timing and patient education needs to be optimised. Specialised dietitians working in this area can be a useful resource to provide support to general practitioners and other medical professionals to follow up with patients commenced on PERT by providing further education and up titrating of prescription.

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