

Pancreatic exocrine insufficiency after pancreaticoduodenectomy: Current evidence and management

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Abstract

Pancreaticoduodenectomy (PD) is the commonest procedure performed for pancreatic cancer. Pancreatic exocrine insufficiency (PEI) may be caused or exacerbated by surgery and remains underdiagnosed and undertreated. The aim of this review was to ascertain the incidence of PEI, its consequences and management in the setting of PD for indications other than chronic pancreatitis. A literature search of databases (MEDLINE, EMBASE, Cochrane and Scopus) was carried out with the MeSH terms "pancreatic exocrine insufficiency" and "Pancreaticoduodenectomy". Studies that analysed PEI and its complications in the setting of PD for malignant and benign disease were included. Studies reporting PEI in the setting of PD for chronic pancreatitis, conference abstracts and reviews were excluded. The incidence of PEI approached 100% following PD in some series. The pre-operative incidence varied depending on the characteristics of the patient cohort and it was higher (46%-93%) in series where pancreatic cancer was the predominant indication for surgery. Variability was also recorded with regards to the method used for the diagnosis and evaluation of pancreatic function and malabsorption. Pancreatic enzyme replacement therapy is the mainstay of the management. PEI is common and remains undertreated after PD. Future studies are required for the identification of a well-tolerated, reliable and reproducible diagnostic test in this setting.

Key words: Pancreatic exocrine insufficiency; Pancreaticoduodenectomy; Pancreatic enzyme replacement therapy; Pancreatic cancer; Malabsorption; Steatorrhoea

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Core tip: Pancreatic exocrine insufficiency is highly prevalent after pancreaticoduodenectomy and has significant implications to patients' quality of life, nutrition, post-operative survival and cancer related outcomes. The published literature reveals no uniform definition of pancreatic exocrine insufficiency after surgery and patients are often under diagnosed. Pancreatic enzyme replacement therapy is effective, well tolerated and is indicated routinely in this cohort of patients. Future studies need to focus on the identification of a well-tolerated, reliable and reproducible diagnostic test in this setting that will facilitate a uniform definition and management approach.

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INTRODUCTION

Pancreatic enzymes are an essential component of normal digestion, without which severe malnutrition occurs. Nonetheless, pancreatic exocrine insufficiency remains widely under-diagnosed and undertreated. The physiological secretion of pancreatic enzymes is in response to nutritional intake in healthy individuals. The stimulation occurs through three phases: Cephalic, gastric and the most important intestinal phase^[1]. The pancreatic enzyme secretion peaks at about 30 min after the exposure of the duodenum to nutrients and returns to baseline after about 2-4 h. The presence of undigested food, especially fat, in the terminal ileum exerts a robust negative feedback mechanism^[2-7].

Pancreatic exocrine insufficiency (PEI) is a common and recognized outcome after pancreatic surgery. Multiple definitions have been used in the published literature based on various evaluation parameters. The "broadest" definition was presented in a systematic review by the Spanish pancreatic association and defined PEI as the inability of the pancreas to perform digestion in association with disturbed pancreatic function^[8].

Pancreaticoduodenectomy (PD) is an operative procedure that involves resection of the pancreatic head in addition to the duodenum and bile duct. It is the most common pancreatic resection performed, especially in the setting of pancreatic malignancy. The effect of PD on pancreatic exocrine secretion is multifactorial. The degree of insufficiency is influenced by the pancreatic remnant^[9], preservation or resection of the gastric antrum and duodenum^[10], the use of a roux-en-Y loop with asynchrony of delivery of the pancreatic enzymes^[11,12] and other factors, such as the peri-operative use of Octreotide^[13]. In the context of pancreatic surgery, PEI has been associated with prolonged hospital stay^[14], increased complication rates^[15], reduced survival^[16], worse quality of life^[8] and nutritional deficiencies^[17]. Furthermore, the presence of PEI may also impede the progression of patients to adjuvant chemotherapy in the setting of resections performed for malignancy.

The purpose of this paper is a comprehensive review of the current evidence on the incidence and management of PEI specifically in the setting of PD for indications other than chronic pancreatitis.

STUDY SELECTION

The intention was to proceed with a systematic review of the incidence and management of PEI in the setting of PD. Studies were selected in accordance with Preferred Reporting of Systematic Reviews and Meta-analyses (PRISMA) 2009 guidelines^[18].

A literature search of databases (MEDLINE, EMBASE, Cochrane and Scopus) was carried out by two separate authors (AP and JA). The search was constructed by using the Medical Subject Heading (MeSH) terms "pancreatic exocrine insufficiency" and "Pancreaticoduodenectomy". Studies that analysed the incidence of PEI in the setting of PD were included. Studies that focused on complications of PEI after PD were also

included. Case reports, reviews, consensus statements, conference abstracts and articles in languages other than English were excluded. Studies on pancreatic resections for chronic pancreatitis were excluded, as well as studies that did not subclassify patients according to the type of pancreatic resection and therefore data on PEI after PD could not be extracted.

The search led to a total of 746 hits. After removal of duplicates and articles in languages other than English, 556 articles remained. Further screening and full text review of articles resulted in a total of 34 articles eligible for inclusion in the review. The steps of the selection process are collated in [Figure 1](#).

APPRAISAL OF LITERATURE

An attempt at data extraction revealed that studies used different parameters to define PEI as explained below in the results. This meant that a quantitative analysis of the results was not possible. Narrowing down studies further with stricter inclusion criteria meant that a large body of evidence would be left out of the analysis thereby subjecting the review to significant bias. A recent systematic review on the same subject, which included a total of only 9 studies, highlighted this aspect^[19]. It was therefore decided to proceed with a qualitative narrative review of the subject.

DEFINITION OF PANCREATIC EXOCRINE INSUFFICIENCY

In chronic pancreatitis, PEI is defined by the presence of steatorrhoea and commonly assessed by the concentration of faecal elastase-1 (FE-1) in a random stool sample^[20]. In this setting, FE-1 is known to reflect the level of pancreatic function and water reabsorption in the gastrointestinal tract^[21,22]. It has been validated and correlates well with radiological findings and steatorrhoea in chronic pancreatitis^[23-26]. FE-1 in the setting of chronic pancreatitis has also been used to grade the severity of PEI (Normal- > 200 µg/g stool; mildly impaired - 100-200 µg/g stool and severe - < 100 µg/g stool)^[27].

Following pancreatic surgery, however, there is no consistent definition for PEI. Furthermore, various diagnostic tests have been used in this setting, while the accuracy of FE-1 is reduced making it an unreliable test. [Table 1](#) highlights some of the most common parameters used to define PEI in patients undergoing pancreatic surgery and especially PD^[28-34].

PARAMETERS FOR THE CLINICAL ASSESSMENT OF PANCREATIC EXOCRINE INSUFFICIENCY FOLLOWING PANCREATODUODENECTOMY

The most characteristic clinical presentation of PEI is steatorrhoea, defined as the presence of more than 7 g of stool fat/day^[35]. However, steatorrhoea is a late sign and associated with severe PEI (occurring after a loss of more than 90% of pancreatic function). Therefore, a methodical diagnostic approach is warranted, including complete medical and dietetic history, physical examination and serial anthropometric measurements, supplemented by biochemical tests and in some scenarios by relevant imaging investigations^[36].

Due to the low diagnostic sensitivity of steatorrhoea, other PEI-related (but also not specific) symptomatology is important. A history of flatulence, bloating, urgency and abdominal discomfort or post-prandial abdominal pain may assist in the diagnosis of PEI. PEI is also associated with weight loss and reduction in muscle mass^[10,37]. Other symptoms such as nausea, early satiety, vomiting, oral thrush and ulcers (secondary to concurrent chemotherapy) may adversely affect the dietary intake contributing to malnutrition in these patients. Dietary modifications (consciously or subconsciously by the patients), such as restriction of protein and/or fat intake, may result in masking the symptomatology, including steatorrhoea, and therefore lead to late or misdiagnosis^[17,36].

A previous history of endocrine disorders (importantly diabetes mellitus), bowel conditions (such as coeliac disease, irritable bowel syndrome *etc.*), food intolerances or eating disorders is relevant. Previous surgery to the bowel (*e.g.* gastrectomy, small bowel resection, and colectomy) can also affect the gut function and alter microbiota causing symptoms that may aggravate or mimic PEI. Drugs like probiotics, antibiotics, laxatives, anti-diarrhoea agents also influence gut function, while others,

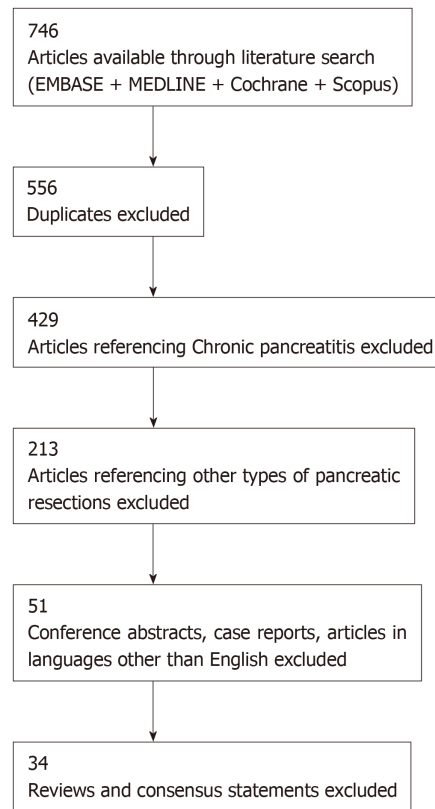


Figure 1 Literature review and selection process.

such as steroids and insulin, can also have an additional impact on the patient's weight in addition to affecting gut absorption^[36]. Serial anthropometric measurements are invaluable to monitoring the nutritional status and important to assess the response to therapeutic interventions. Functional assessments, such as grip strength, mid arm circumference and triceps skin fold, together with weight changes, must be evaluated in the context of the patient's symptoms and caloric intake.

BIOCHEMICAL PARAMETERS FOR THE ASSESSMENT OF PANCREATIC EXOCRINE INSUFFICIENCY

Relevant laboratory investigations fall into two main categories: (1) Evaluation of the nutritional status, and (2) Evaluation of the pancreatic function (Table 2). The first category includes tests such as the assessment of fat soluble vitamins, bone profile (calcium, parathyroid hormone), anaemia screen and glycaemic control. These can be used for the initial diagnosis, as well as for follow-up and evaluation of the treatment response. The second category includes tests that evaluate the pancreatic function and are further broadly sub-classified into those that evaluate the exocrine function of the pancreas and tests that measure the degree of malabsorption secondary to PEI. The latter ones focus mainly on fat malabsorption with the limitation that they cannot distinguish between pancreatic and extra-pancreatic causes. Currently there are no tests available to diagnose nitrogen malabsorption also known to occur in PEI^[38], while colonic mechanisms exist to compensate for the malabsorption of carbohydrates^[39,40].

The 2018 ISGPS position statement considered 72 h faecal fat collection with a standard intake of fat as the gold standard test to diagnose fat malabsorption^[17]. FE-1 measurement is one of the most commonly used methods to evaluate and subsequently define PEI. It is quick, non-invasive, and relatively easy to carry out in the clinical setting (on a spot faecal sample). Additionally, it is not influenced by the intake of pancreatic enzyme supplements. However, in the setting of PD, steatorrhoea occurs at a much higher FE-1 level (207 µg/g in patients post PD *vs* 15 µg/g in patients without a resection)^[41], therefore its usefulness in this setting is questionable. Kato *et al*^[32] detected PEI in 93% patients prior to PD (most of which with a diagnosis of pancreatic cancer) on the basis of the secretin stimulation test. The comparison of

Table 1 Definitions of Pancreatic Exocrine Insufficiency after pancreaticoduodenectomy

Ref.	Definition of pancreatic exocrine insufficiency
Sabater <i>et al</i> ^[8]	Condition wherein the amount of pancreatic secretions is not enough to maintain normal digestion
Ghaneh <i>et al</i> ^[26]	Need for new pharmacological intervention for exocrine insufficiency <i>i.e.</i> PERT
Sikkens <i>et al</i> ^[11]	Faecal elastase-1 < 0.200 mg/g of faeces
Halloran <i>et al</i> ^[29]	Coefficient of fat absorption < 93%
Domínguez-Muñoz <i>et al</i> ^[30]	¹³ C-mixed triglyceride test (Percent cumulative dose of < 5% of ¹³ CO ₂ at 7 h)
Yamaguchi <i>et al</i> ^[31]	BT-PABA excretion rate of < 70%
Kato <i>et al</i> ^[32]	Abnormal secretin stimulation test
Perez <i>et al</i> ^[33]	72 h faecal fat estimation
Fang <i>et al</i> ^[34]	Faecal chymotrypsin estimation

PERT: Pancreatic enzyme replacement therapy.

this test was with ¹³C- labelled trioctanoin breath assay and with parallel testing of para-aminobenzoic acid (PABA) and faecal chymotrypsin excretion. The sensitivities of both these tests were between 60% and 70% in the setting of obstructive jaundice and PD^[32]. The current review thus, reveals a lack of consensus on the parameters used to evaluate PEI after PD.

INCIDENCE OF PANCREATIC EXOCRINE INSUFFICIENCY IN THE SETTING OF PANCREATICODUODENECTOMY

Due to the nature of this review, studies reporting outcomes among patients undergoing PD for chronic pancreatitis were excluded. The reported incidence of PEI after PD varied widely between 38% and 93% (Table 3)^[42-55]. This is probably attributed to the heterogeneity of the patient cohorts and the diagnostic tests used.

Halloran *et al*^[29] showed an improvement in FE-1 after PD for pancreatic cancer, however, this was in the setting of a diminishing patient cohort (exclusion of patients with mortality) introducing the possibility of bias. Additionally, FE-1 did not compare accurately to the standard measure of PEI (Coefficient of Fat absorption). Other studies have consistently recorded improving pancreatic function in patients with ampullary cancer post-PD^[56,57]. The proposed hypothesis in these studies was the relief of the obstruction by the ampullary tumour to the pancreatic duct draining a healthy pancreas.

The correlation of pre-operative PEI to post-operative PEI is difficult to assess as FE-1 is the most frequently used marker and has been shown to underestimate PEI after pancreatic resection^[19]. Matsumoto *et al*^[47] noted a significant post-operative drop in FE-1 levels in patients with normal pre-operative values, while FE-1 levels in those with pre-existing PEI remained relatively unchanged post-operatively. It is possible that these findings are limited not only by the use of FE-1 in post-operative assessment, but also by the short follow-up period. This is further supported by the diagnosis of PEI in all patients at a median post-operative time of 52 mo^[58].

There are several studies that have investigated possible predictors of PEI after PD, such as the presence of a dilated pancreatic duct on computerized tomography (CT) scans or endoscopic ultrasound pre-operatively^[59]. One study reported that a dilated pre-operative duct diameter (> 3 mm) was more likely to result in exocrine dysfunction at 2 mo after surgery measured by reduced PABA excretion^[45]. This finding was however, not corroborated by Matsumoto *et al*^[47] who suggested that the diminishing pancreatic parenchyma was the main reason for the reduced post-operative FE-1 levels. Furthermore, post-operative parenchymal thickness on CT was shown to be a predictor of PEI (based on the ¹³C-labelled mixed triglyceride test) with a sensitivity of 88.2% and specificity of 88.9% when the cut off was set at 13 mm^[60]. Nonetheless, the use of imaging findings to clinically predict PEI remains in use predominantly in the setting of chronic pancreatitis^[25,61,62].

Table 2 Biochemical tests in the assessment of pancreatic exocrine insufficiency

Nutritional assessment	Evaluation of pancreatic function	
	Exocrine markers	Markers of malabsorption
Fat soluble vitamins	Faecal elastase-1	72 h faecal fat estimation
Bone profile	Faecal chymotrypsin	BT-PABA absorption
Iron and Ferritin studies	Secretin stimulation test	¹³ C labelled trioctanoin breath test
Micronutrient status		
Glycaemic status		

PABA: Para-aminobenzoic acid.

TECHNICAL OPERATIVE FACTORS INFLUENCING PANCREATIC EXOCRINE INSUFFICIENCY

The pre- and post-operative incidence of PEI was studied with a BT-PABA test in patients undergoing classical PD versus Pylorus preserving PD (PPPD). The short term post-operative incidence was similar in both groups. The exocrine function recovered to pre-operative levels in the PPPD group, while this was not observed in the classical PD group. The study, however, was limited by the small patient cohort (10 classical PD *vs* 44 PPPD) and the potential for selection bias across the two groups, while the indications included both benign and malignant diagnoses^[45].

The effect of the type of reconstruction, pancreatico-gastrostomy or pancreatico-jejunostomy, on PEI has also been studied (Table 4). Two retrospective studies reported that patients undergoing pancreatico-jejunostomy reconstruction for pancreatic head malignancy were significantly less likely to have PEI^[54,63]. Others have also shown a similarly high incidence of PEI after pancreatico-gastrostomy in retrospective cohorts^[9,44]. However, the retrospective comparative study by Jang *et al*^[51] showed no significant difference between the two reconstruction methods (100% *vs* 95%). This conflicting evidence is most likely attributed to the use of different methods to measure and report the incidence of PEI, including 72 h faecal fat estimation, ¹³C-labelled mixed triglyceride breath test and measurement of FE-1.

CONSEQUENCES OF PANCREATIC EXOCRINE INSUFFICIENCY AFTER PANCREATICODUODENECTOMY

In the perioperative setting, PEI can lead to malnutrition and this in turn to higher morbidity and mortality including a greater risk of a pancreatic leak^[59,64,65]. Additionally, it may significantly affect quality of life and it has been shown to be an independent predictor of survival in advanced pancreatic cancer^[66]. Similarly, cachexia, has shown to be associated with decreased survival with unresectable pancreatic cancer, with weight stabilization showing better prognosis^[67-69].

There is increasing evidence that untreated PEI negatively affects survival following PD for cancer. Among consecutive patients undergoing PD for periampullary cancer those without treatment had significantly reduced survival; this was even more pronounced among the cohort with pancreatic duct dilation (≥ 3 mm)^[70]. A further population based study used propensity matched analysis to adjust for key variables and in that study lack of treatment of PEI was associated with reduced survival and the survival benefit of pancreatic enzyme replacement therapy (PERT) was of a similar magnitude to surgery or chemotherapy^[71].

The symptoms and consequences of PEI after PD are mainly related to the malabsorption of undigested food and nutrients, especially fat soluble vitamins (Vitamins A, D, E and K)^[17] in the distal small bowel^[72]. The classical symptoms of steatorrhea, abdominal pain with bloating and cramping, flatulence, dyspepsia and nausea are however, not seen in patients with mild to moderate PEI^[73]. Vitamin malabsorption may lead to symptoms such as xerophthalmia and night blindness (Vitamin A), neurological symptoms, ophthalmoplegia and ptosis (Vitamin E), abnormal bleeding (Vitamin K), osteomalacia and metabolic bone disease (Vitamin D). It is important to recognize these as potential complications of PEI early and start supplementation (parenterally if necessary) on a long term basis. Other complications such as weight loss, electrolyte imbalances and poor wound healing may also occur^[17]. In cases where the indication for PD is cancer, malnutrition can delay the start of the

Table 3 Incidence of pancreatic exocrine insufficiency before and after pancreaticoduodenectomy

Ref.	Pre-operative incidence of PEI	Post-operative incidence of PEI	Diagnostic test
Kato <i>et al</i> ^[32]	93%	80%	Secretin stimulation
Halloran <i>et al</i> ^[29]	-	55%	Coefficient of fat absorption
Yuasa <i>et al</i> ^[42]	-	64%	¹³ C- mixed triglyceride test
Nakamura <i>et al</i> ^[9]	-	62.3%	
Hirono <i>et al</i> ^[43]	-	51%	
Benini <i>et al</i> ^[41]	-	87.5%	72 h faecal fat estimation
Lemaire <i>et al</i> ^[44]	-	94%	
Sato <i>et al</i> ^[45]	46%	33%	BT-PABA excretion
Fujino <i>et al</i> ^[46]	-	75%	
Matsumoto <i>et al</i> ^[47]	68%	50%	Faecal elastase-1
Van der Gaag <i>et al</i> ^[48]	-	59%	
Tran <i>et al</i> ^[49]	-	91%	
Pessaux <i>et al</i> ^[50]	-	95%	
Jang <i>et al</i> ^[51]	-	100%	
Falconi <i>et al</i> ^[52]	-	24%	Faecal chymotrypsin
Fang <i>et al</i> ^[34]	-	33%	
Bock <i>et al</i> ^[53]	-	52.8%	Steatorrhoea
Rault <i>et al</i> ^[54]	-	42%	
Van Berge Henegouwen <i>et al</i> ^[55]	-	64.5%	

PEI: Pancreatic exocrine insufficiency; PABA: Para-aminobenzoic acid.

recommended adjuvant chemotherapy or worse, render the patient unfit for the same. Finally, NAFLD is a rare and poorly recognized possible consequence of PEI after PD. It is believed to occur secondary to the malabsorption of essential amino acids leading to decreased plasma levels of apoprotein B^[74], which, when combined with sub-optimal insulin secretion lead to peripheral lipolysis and greater hepatic fat deposition^[75]. These changes have been shown to be reversible with the administration of PERT and subsequent improvements in body weight^[76].

MANAGEMENT OF PANCREATIC EXOCRINE INSUFFICIENCY AFTER PANCREATICODUODENECTOMY

PERT is the mainstay of treatment of PEI. However, in the post-operative setting, there is a lack of consensus over the timing of initiation of PERT. While some authors recommend routine post-operative PERT^[36,77], others advocate in favour of PERT only after clinical or biochemical diagnostic evidence of PEI^[8,78]. In pancreatic cancer, due to the high incidence of PEI and obstructive jaundice, peri-operative use of PERT for all patients has been shown to be beneficial^[36] and is recommended by the United Kingdom National Institute of Clinical Excellence guidelines^[79].

Patient education is important for the correct use of PERT. Enzymes use is advisable with all meals, snacks and milky drinks, including various supplements. The conventional timing of administration is during or immediately after a meal in order to achieve optimal timing for mixing with the chyme. This hypothesis however, has not been studied in the setting of pancreatic surgery and the presence of pancreato-biliary reconstruction and digestive asynchrony^[16].

PERT is usually commenced at a dose of 50000-75000 units lipase with a meal and 25000-50000 units with each snack^[10,80-82]. This may be titrated to the needs of the individual patient. In common clinical experience, patients over time learn to adjust the dose of PERT on the basis of their symptoms and diet. Nonetheless, close follow-up is required to ensure that management remains on track in the setting of changing (recovering or deteriorating) pancreatic function and/or patient diet (as some patients may compromise on the nutritional value of their diet rather than the PERT dose). The use and effectiveness of PEI should be monitored with serial anthropometric measurements and nutritional blood tests^[36], including measurements for glycaemic control, as the use of effective PERT may result in manifestation of diabetes^[83]. In addition to PERT, supplementation with vitamins and other micronutrients is

Table 4 Incidence of pancreatic exocrine insufficiency after pancreaticoduodenectomy—evidence on the role of the type of pancreatic reconstruction

Ref.	Diagnostic test	Incidence of PEI–Pancreaticogastrostomy	Incidence of PEI–Pancreaticojejunostomy
Nakamura <i>et al</i> ^[9]	¹³ C Triglyceride breath test	62.3%	-
Lemaire <i>et al</i> ^[44]	Faecal Fat excretion and faecal elastase-1	100%	-
Jang <i>et al</i> ^[51]	Faecal elastase-1	100% (severe)	75% (severe); 20% (mild)
Roeyen <i>et al</i> ^[63]	Need for PERT +/- any abnormal pancreatic function test	75%	45.7% (<i>P</i> < 0.001)
Rault <i>et al</i> ^[54]	Steatorrhoea	70%	21.7% (<i>P</i> < 0.025)

PEI: Pancreatic exocrine insufficiency; PERT: Pancreatic enzyme replacement therapy.

recommended^[84].

The gastrointestinal environment and acidity is important for the appropriate function of PERT. The lipase in PERT is inactivated by gastric acid activity. Consequently, commercially available PERT formulations are covered with pH sensitive, acid resistant microspheres that release the lipase at a pH of 5-6, similar to what is present in the native duodenum. Based on studies about the optimal sphere size required to produce the best dissociation in the duodenum, most commercial preparations have sphere size that varies from 1-2 mm^[85,86]. In the post-operative PD setting, failure of the pancreas to produce bicarbonate is hypothesized to lead to an acidic environment in the duodenum and proximal jejunum, leading to inefficient activation of lipase^[35,87]. The concurrent use of gastric acid suppression is therefore recommended. The use of a proton pump inhibitor is known to reduce faecal fat losses^[88] and may also help reduce precipitation of bile salts^[36].

PERT is generally well tolerated with minimal adverse effects. Rare reports on fibrosing colonopathy with the use of PERT are limited to paediatric patients, especially in the setting of cystic fibrosis^[89-91]. There have been no such reports in the adult post-operative population. Many studies including open label PERT trials have not found significant adverse drug reactions^[92-94].

Failure of PEI to improve after escalation of PERT dosage and gastric acid suppression must prompt further investigations for concurrent problems. The two commonest diagnoses in this setting are bile salt malabsorption and small bowel bacterial overgrowth^[30,80,82]. Bile salt malabsorption occurs due to the change in the pH in the proximal small bowel secondary to deficiency of bicarbonate secretion from the pancreas. The cholecystectomy performed during PD may also contribute to the development of this condition^[36,95]. The presence of a blind loop of bowel used for reconstruction is known to occur after PD and is documented in up to 65% of patients leading to small bowel bacterial overgrowth^[36].

CONCLUSION

This literature review confirms that PEI is prevalent after PD even for indications other than chronic pancreatitis and may have severe implications with respect to patients' survival, quality of life, nutrition and subsequent management. The lack of a uniform definition of PEI in this setting and the low diagnostic accuracy of the available tests introduce a wide variability in the reported results and suggested management. Pancreatic enzyme replacement therapy is effective, well tolerated and is indicated routinely in this cohort of patients. Future studies need to concentrate on the identification of a well-tolerated, reliable and reproducible diagnostic test that will facilitate a uniform definition and management approach.

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