Pancreatic Exocrine Insufficiency as a Complication of Gastrointestinal Surgery and the Impact of Pancreatic Enzyme Replacement Therapy

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Abstract

Background: Pancreatic exocrine insufficiency (PEI) is characterized by inadequate production, insufficient secretion, and/or inactivation of pancreatic enzymes, resulting in maldigestion. The aim of this review was to analyze the prevalence and pathophysiology of PEI resulting from gastrointestinal (GI) surgery and to examine the use of pancreatic enzyme replacement therapy (PERT) for effectively managing PEI. *Summary:* A targeted PubMed search was conducted for studies examining the prevalence and pathophysiology of PEI in patients following GI surgery and for studies assessing the effects of PERT in these patients. PEI is a common complication following GI surgery that can lead to nutritional deficiencies, which may contribute to morbidity and mortality in patients. Timely treatment of PEI with PERT can prevent malnutrition, increase quality of life, and possibly reduce the associated mortality. Treatment of PEI should aim not only to alleviate symptoms but also to achieve significant improvements in nutritional parameters. Dose optimization of PERT is required for effective management of PEI, in addition to regular assessment of nutritional status, appropriate patient education, and reassessment if symptoms return. *Key Messages:* Difficulties in detecting PEI following GI surgery can result in undiagnosed and untreated maldigestion, leading to metabolic complications and increased morbidity. Both are preventable by early administration and monitoring for optimal doses of PERT.

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Introduction

Pancreatic exocrine insufficiency (PEI) is associated with disorders of the pancreas such as chronic pancreatitis, acute necrotizing pancreatitis, and pancreatic cancer, but can also occur as a consequence of gastrointestinal (GI) and pancreatic surgery [1]. However, in patients who have undergone GI surgery, PEI appears to be underrecognized and undertreated [2]. PEI is characterized by maldigestion, usually due to structural or functional changes to GI tissue, resulting in inadequate production, insufficient secretion, limited activation, and/or inactivation of pancreatic enzymes [1, 3]. Additionally, structural

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changes to the GI tract following surgery can lead to asynchronization between the release of enzymes and passage of nutrients (pancreaticocibal asynchrony) [1, 3]. Changes to pancreatic enzyme secretion result in the malabsorption of nutrients, with malabsorption of fats and fat-soluble vitamins usually causing the initial symptoms [4]. Typically, PEI presents as steatorrhea, abdominal pain, flatulence, and bloating [2]; however, these symptoms can vary and usually only present themselves when the amount of fat, protein, and carbohydrate ingested exceeds the digestive ability of the pancreas [5]. Additionally, patients with PEI often change their diet to reduce the intake of foods that are hard to digest and to decrease steatorrhea; as a result, symptoms of malabsorption are not consistently present [5].

The correlation between PEI, secondary to a causal disease or condition, and chronic malnutrition resulting from nutrient deficiency and fat malabsorption should be a focus for physicians due to the risk of long-term complications [6]. Malnutrition arising from PEI is associated with increased risk of infection, cardiovascular disease, sarcopenia, and osteoporosis [7–14] and can lead to increased morbidity, reduced patient quality of life (QoL), and increased mortality [2, 6, 15, 16]. Since PEI-associated malnutrition also has a high patient and healthcare burden, timely treatment of patients with this condition is imperative [2, 6].

The diagnosis of PEI can be performed using invasive direct tests of pancreatic function, such as the secretin stimulation test, or noninvasive tests, including fecal elastase-1, fecal chymotrypsin, fecal fat, and ^{13}C-mixed triglyceride breath test (^{13}C-MTG-BT) [5, 17]. Direct tests of pancreatic function have the highest accuracy for detecting pancreatic secretion, but are invasive, time-consuming, expensive, and not fully standardized [5, 17]. While the fecal elastase-1 test is useful in detecting PEI in certain patient populations [18], its diagnostic accuracy is limited following pancreatic surgery as PEI may occur in these patients from nonpancreatic mechanisms and not only because of reduced exocrine secretion [19]. In contrast, the fecal fat test and the ^{13}C-MTG-BT are useful for detecting PEI following gastric and duodenal resection as they detect levels of undigested or digested products, respectively, and not pancreatic secretions [1].

The estimated prevalence of PEI in patients after pancreatic surgery is 46–100%, depending on the type of resection [20–22], and there is evidence that pancreatic secretion and fat absorption are impaired in patients after gastric surgery [23–25]. Patients undergoing GI surgery are at high risk of developing PEI; therefore, the effective management of this complication and associated malnutrition needs to be a key part of postoperative patient care [26].

This review aims to outline current evidence describing the pathophysiology and prevalence of PEI resulting from GI surgery and to examine the management of patients with PEI post-surgery, specifically the use of pancreatic enzyme replacement therapy (PERT) and the potential impact this may have on health and QoL in patients with PEI.

Materials and Methods

To identify publications describing the prevalence and pathophysiology of PEI in patients having undergone GI surgery, a PubMed literature search was conducted (cutoff date July 3, 2018) using the following search terms: ([pancreatic exocrine insufficiency] OR [PEI OR EPI] AND [prevalence OR pathophysiology] AND [pancreatic surgery] OR [gastric surgery]). Articles not focused on the prevalence or pathophysiology of PEI following pancreatic or gastric surgery were excluded, as well as non-English language publications. The PubMed search yielded 335 results; of these, 19 eligible publications on the prevalence of PEI were included in the review. To identify clinical trials assessing the effects of PERT on patients having undergone GI surgery, a PubMed literature search was conducted (cutoff date July 3, 2018) using the following search terms: ([pancreatic exocrine insufficiency] OR PEI OR EPI) AND ([pancreatic surgery] OR [gastric surgery]) AND (PERT OR [pancreatic exocrine replacement therapy] OR pancreatin OR pancrelipase). Articles not focused on clinical outcomes and PERT following pancreatic or gastric surgery were excluded, as well as non-English language publications. The PubMed search yielded 98 results; of these, 9 eligible publications were included in the review. The results of the abovementioned searches form the basis of this narrative review.

PEI as a Complication of GI Surgery

Pancreatic Surgery
Pathophysiology
Anatomical changes due to pancreatic surgery often lead to the development of PEI (see examples in Fig. 1) [1]. Reduction in exocrine secretion may arise after resection of the pancreas due to the removal of pancreatic parenchyma and/or potential damage to remaining pancreatic tissue, while blockage of the pancreatic duct can result from anastomosis [2]. Postprandial pancreatic secretion is initially stimulated by a vagal reflex triggered by fundus relaxation and then by the hormone cholecystokinin released by the duodenum [1]. The duodenum also releases secretin, which stimulates the production of bicarbonate from the pancreas and increases the volume of pancreatic
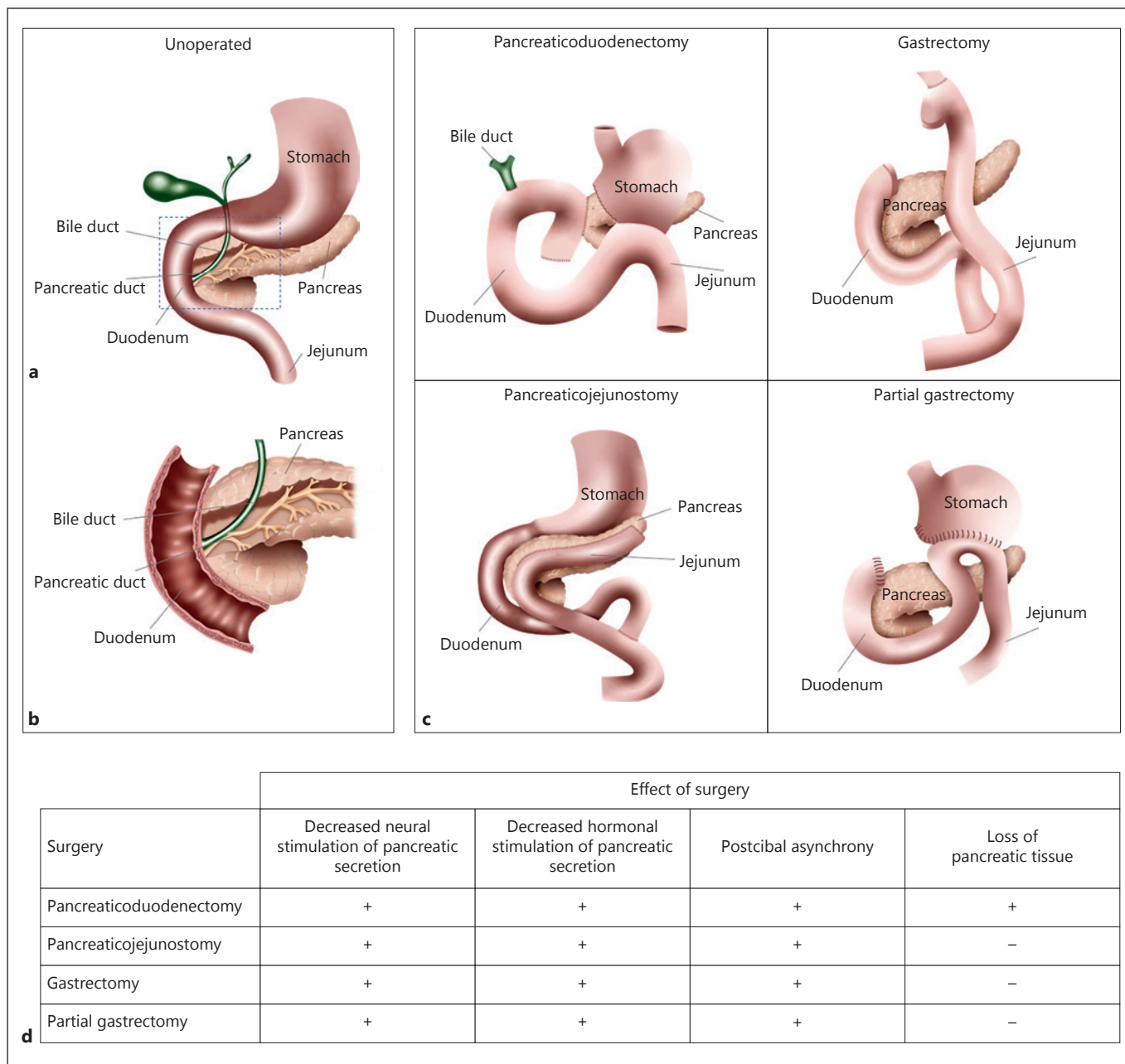
Fig. 1. Pathophysiology of common GI surgeries [1, 3, 72]. (**a**) Unoperated; (**b**) cross-section of where the pancreatic duct and the bile duct meet the duodenum; (**c**) anatomical changes following GI surgeries; (**d**) possible effects of anatomical changes on pancreatic function. Plus sign indicates an effect of surgery, minus sign indicates no or minimal effect of surgery.

secretions [27]. Thus, some pancreatic resection procedures may result in a loss of antro-fundic and duodeno-fundic reflexes as well as a loss of duodenal tissue, which may decrease pancreatic exocrine secretions and result in PEI [1, 2]. Additionally, asynchrony between the secretion of pancreatic enzymes and bile can also result from the anatomical reconstruction caused by pancreaticoduode-

nectomies [1, 2]. Such reconstructions may also contribute to malabsorption by causing the binding of bile salts to maldigested protein, carbohydrates, and fiber; these reconstructions may also predispose patients with PEI to bacterial overgrowth in the small intestine (further contributing to GI symptoms) [2]. Therefore, the type of pancreatic resection and reconstruction undertaken affects

the risk of developing PEI post-surgery. Overall, the factors that influence the degree of PEI after surgery include: the disease for which the surgery was indicated [28]; the type and extent of resection of the pancreas, stomach, and/or duodenum [2, 28, 29]; the quantity and quality of the remaining pancreatic tissue; the use of exocrine inhibitory medications such as octreotide; and the type of pancreatic anastomosis [2]. It should be noted that changes to gut pH can arise from pancreatic resection due to reduced bicarbonate secretion from the pancreas, leading to decreased activity and/or irreversible inactivation of pancreatic enzymes [28] and the precipitation of bile salts [2].

Prevalence of PEI after Pancreatic Surgery

The reported prevalence of PEI after pancreatic surgery varies widely, in part due to the type of surgical procedure [20, 21, 30–44] (Table 1), with duodenum-preserving pancreatic head resection procedures generally being associated with a lower prevalence of PEI than non-duodenum-preserving pancreaticoduodenectomy procedures [22, 45].

PEI prevalence rates of 75–86% have been reported after duodenum-preserving resections of the pancreatic head [20, 21, 33, 35]. Distal pancreatectomies are associated with much more variable prevalence of PEI, with reported prevalence rates ranging between 19.1 and 80% [33, 34, 36, 37]. A systematic review of 94 studies with 963 patients found that, compared with distal pancreatectomy, there was a lower risk of PEI following central pancreatectomy, which had a prevalence of 11.9% [37]. By their nature, total pancreatectomy procedures always result in PEI [36].

Studies describing the development of PEI following pancreaticoduodenectomies have reported prevalence rates of between 34.7 and 100% [21, 33–36, 38–44]. There is conflicting evidence regarding whether pancreaticogastrostomy or pancreaticojejunostomy after pancreaticoduodenectomy results in a higher risk of PEI, with a wide range of prevalence rates of 62.0–100% reported for pancreaticogastrostomy [38–42] and 44–100% for pancreaticojejunostomy [39, 40, 43]. A prospective, nonrandomized study ($n = 34$) that compared patients who underwent pancreaticogastrostomy ($n = 14$) or pancreaticojejunostomy ($n = 20$) found that all those in the pancreaticogastrostomy group developed severe PEI, whereas for the pancreaticojejunostomy group, 75 and 20% developed severe and mild PEI, respectively ($p = 0.05$) [39]. Even though this study was conducted in a small number of patients, the results suggest that both procedures lead to PEI and that a greater deterioration of exocrine function was observed following pancreatico-

gastrostomy [39]. Further prospective evidence in 42 patients treated for periampullary lesions by pylorus-preserving pancreaticoduodenectomy found that 63% in the pancreaticogastrostomy group developed PEI compared with 44% in the pancreaticojejunostomy group [40]. Acid-mediated inactivation of pancreatic enzymes following pancreaticogastrostomy should be considered as a cause of PEI in these patients.

Based on the abovementioned studies, it is evident that pancreatic surgery is associated with an increased risk of PEI, with pancreaticoduodenectomies and total pancreatectomies associated with the greatest risk [36].

Gastric Surgery
Pathophysiology

Although gastric surgery does not directly involve the removal of pancreatic exocrine tissue, it leads to physiological changes that contribute to the development of PEI (see examples in Fig. 1). Like duodenal resection, gastric resection can result in the loss of antro-fundic reflexes involved in fundus relaxation, thereby disrupting neural stimulation of pancreatic secretion [1]. In addition, decreased cholecystokinin and secretin release may occur after gastric surgery due to the exclusion of the duodenum from the aboral transit of nutrients, resulting in decreased postprandial stimulation of pancreatic secretion [1, 46]. Anatomical changes and accelerated or delayed transit of nutrients through the esophagojejunal anastomosis (in cases of esophagojejunostomy and total gastrectomy) or remaining stomach (in cases of partial gastrectomy), and/or decreased endogenous stimulation by products undergoing digestion, lead to asynchrony between gastric emptying and biliopancreatic secretion (postcibal asynchrony) [3, 28]. This asynchrony results in the inadequate mixing of nutrients with pancreatic enzymes, causing incomplete digestion and the transit of large and hard-to-digest nutrients to the jejunal lumen [1]. The development of PEI due to gastrectomy may be further propagated by the loss of nerve supply to the pancreas due to dissection of lymph nodes in the stomach and truncal vagotomy [28]. Similar to observations in cases of pancreatic surgery, the degree and likelihood of PEI development may be determined by the type and extent of resection and/or reconstruction [2].

Prevalence of PEI after Gastric Surgery

Although there are limited clinical data regarding the prevalence of PEI after gastric surgery, 2 small trials were identified that demonstrated a link between gastric surgery and PEI (Table 2) [23, 24].

Table 1. Estimated prevalence of PEI after pancreatic surgery

Type of pancreatic surgery	Study	Study type	Study population	Test for diagnosing PEI	Subtype of surgery (n)	PEI prevalence post-surgery, %
Any type of pancreatic surgery	[30]	Prospective cohort study with a 6-month median follow-up	29 Patients[1] treated for cancers of the pancreas, ampulla of Vater or bile duct (52% male, 48% female; median age of 62 years)	FE-1 test (≤200 µg/stool)	Distal pancreatectomy (3 patients) or pancreaticoduodenectomy (26 patients)	89[2]
	[31]	Prospective study with a 12-month follow-up	40 Patients treated for pancreatic cancer (55% male, 45% female; median age of 65 years)	CFA ≤93%; FE-1 test (<200 µg/stool)	Left pancreatectomy (3 patients), Whipple (16 patients) or PPPD (21 patients)	77% at 6 weeks; 83% at 12 months
	[32]	Systematic review of 19 studies	301 Patients with benign tumors and 163 patients with malignant tumors who underwent pancreaticoduodenectomy	Assessment methods were not used as inclusion/exclusion criteria	Pancreaticoduodenectomy (464 patients)	25.2% benign tumor group; 49.1% malignant tumor group
Comparison of pancreatectomy procedures	[21]	Prospective, randomized study with a >5-year median follow-up	85 Patients treated for chronic pancreatitis (85% male, 15% female; median age of 42 years)	PEI was defined as the presence of steatorrhea and/or the need for oral pancreatic enzyme supplementation[3]	Beger or Frey (42 patients)	76
					PPPD (43 patients)	61
	[33]	Prospective study with a 56-month median follow-up	222 Patients treated for chronic pancreatitis (80% male, 20% female; median age of 44 years)	Pancreatic imaging (i.e., CT, MRI, ERCP, and endoscopic ultrasound)	Beger or Frey (92 patients)	75[4]
					Distal pancreatectomy (21 patients)	66[5]
					PPPD (109 patients)	62[6]
					Overall (222 patients)	65[7]
	[34]	Prospective study with a 17-month median follow-up	110 Patients treated for pancreaticobiliary disease (55% male, 45% female; median age of 68 years)	^{13}C-MTG-BT	Distal pancreatectomy (30 patients)	30
					Pancreaticoduodenectomy (80 patients)	64
	[35]	Long-term results of a randomized trial with a 7-year median follow-up	47 Patients treated for chronic pancreatitis	Fecal chymotrypsin test	Frey (24 patients)	86
					PPPD (23 patients)	96
	[36]	Retrospective analysis of prospectively collected data	133 Patients treated for pancreatic disease (52% male, 48% female; mean age of 61 years)	FE-1 test and serum beta-carotene test	Distal pancreatectomy (20 patients)	80
					Total pancreatectomy (19 patients)	100
					Pancreaticoduodenectomy (49 patients)	98
					Non-resective procedures (45 patients)	82

Table 1. (continued)

Type of pancreatic surgery	Study	Study type	Study population	Test for diagnosing PEI	Subtype of surgery (n)	PEI prevalence post-surgery, %
Pancreatectomy (Beger, Frey, necrosectomy) procedures	[20]	Long-term results of a closed randomized controlled trial with a 16-year follow-up	45 Patients (at 16-year follow-up) treated for chronic pancreatitis	Not described	Beger (22 patients) Frey (23 patients)	77 83
	[37]	Systematic review of 94 studies	963 Patients treated by central or distal pancreatectomy	Assessment methods were not used as inclusion/exclusion criteria	Distal pancreatectomy (480 patients) Central pancreatectomy (359 patients)	19.1 11.9
	[38]	Prospective study with a 16-month median follow-up	52 Patients treated by pancreaticogastrostomy (60% male, 40% female; mean age of 68 years)	^{13}C-MTG-BT	PPPD: pancreaticogastrostomy	65
	[39]	Prospective study in patients ≥1 year after surgery	34 Patients treated with PPPD who survived >1 year without evidence of recurrence (56% male, 44% female; mean age of 58 years)	FE-1 test	PPPD: pancreaticogastrostomy (14 patients) PPPD: pancreaticojejunostomy (20 patients)	100% with severe PEI 75% with severe PEI; 20% with mild PEI
	[40]	Prospective study with a 37- and 103-month mean follow-up for pancreaticogastrostomy and pancreaticojejunostomy, respectively	42 Patients treated for periampullary lesions (50% male, 50% female; median age of 56 and 67 years for pancreaticogastrostomy and pancreaticojejunostomy groups, respectively)	PEI was defined as the presence of steatorrhea and/or the need for oral pancreatic enzyme supplementation[3]	PPPD: pancreaticogastrostomy (19 patients) PPPD: pancreaticojejunostomy (23 patients)	63 44
	[41]	Study with a 32-month median follow-up	19 Patients[8] treated for benign or malignant pancreatic tumors (37% male, 63% female; mean age of 55 years)	Fecal fat analysis and FE test	PPPD: pancreaticogastrostomy	100
	[42]	Retrospective study with a 17-month median follow-up	61 Patients mostly treated for carcinomas or neoplasms (61% male, 39% female; mean age of 68 years)	^{13}C-MTG-BT	PPPD: pancreaticogastrostomy	62
	[43]	Cross-sectional study with a 52-month median follow-up	26 Patients treated by pancreaticojejunostomy (38% male, 62% female; mean age of 61 years)	FE-1 test	PPPD: pancreaticojejunostomy	100
	[44]	Retrospective analysis with a 19.6-month median follow-up	678 Patients treated by partial pancreatectomy	Not specified	Pancreaticoduodenectomy and distal pancreatectomy	34.7

[1] n = 27 completed follow-up.
[2] 45% presurgery.
[3] Exocrine function was not measured using quantitative tests.
[4] 34% developed de novo PEI post-surgery.
[5] 29% developed de novo PEI post-surgery.
[6] 34% developed de novo PEI post-surgery.
[7] 33% developed de novo PEI post-surgery.
[8] Exocrine function tests were carried out in 17 patients out of 19.
PEI, pancreatic exocrine insufficiency; FE-1, fecal elastase-1; CFA, coefficient of fat absorption; ERCP, endoscopic retrograde cholangiopancreatography; CT, computed tomography; MRI, magnetic resonance imaging; ^{13}C-MTG-BT, ^{13}C-mixed triglyceride breath test; PPPD, pylorus-preserving pancreaticoduodenectomy.

Table 2. Estimated prevalence of PEI after gastric surgery

Type of gastric surgery	Study	Study type	Study population	Test for diagnosing PEI	Subtype of surgery (n)	PEI prevalence post-surgery, %
Gastrectomy	[23]	Prospective study with a 3-month follow-up	15 Patients[1] treated for gastric cancer (80% male, 20% female; median age of 62 years)	Secretin-cerulein test	Total gastrectomy	100
	[24]	Comparative study with an 18-month median follow-up	31 Patients treated for gastric cancer compared to 15 healthy controls (71% male, 29% female; mean age of 64 years for treatment groups)	^{13}C-MTG-BT	Roux-en-Y reconstruction after subtotal gastrectomy (14 patients) Billroth I reconstruction after subtotal gastrectomy (17 patients)	62.3

[1] Exocrine function tests were carried out in 9 patients out of 15.
PEI, pancreatic exocrine insufficiency; ^{13}C-MTG-BT, ^{13}C-mixed triglyceride breath test.

A prospective study in 15 patients who had undergone total gastrectomy for gastric cancer and received an exocrine function test found that all developed severe PEI within 3 months post-surgery [23]. A comparative study of 31 patients who underwent Roux-en-Y ($n = 14$) or Billroth I ($n = 17$) reconstructions after subtotal gastrectomy found that fat digestive and absorptive function was reduced following both procedures compared to 15 healthy controls [24]. The Roux-en-Y reconstruction led to a greater reduction in fat digestion and absorption, as assessed by the percentage of $^{13}CO_2$ cumulative dose at 7 h (% CD-7 h), compared to the Billroth I reconstruction (8.1 [±3.4] vs. 11.1% [±3.4], respectively, $p = 0.02$, compared with 13.9% [±7.2] for controls) [24]. Based on the abovementioned data regarding the prevalence of PEI after gastric surgery, the type and extent of surgery may contribute in varying degrees to the development and prevalence of PEI.

Impact of PEI after GI Surgery
PEI following pancreatic surgery, if left untreated or undertreated, is associated with considerable morbidity related to GI symptomatology, malnutrition, and reduction in the patient's QoL and can ultimately lead to decreased long-term survival [31, 36]. A retrospective analysis of prospectively obtained data in 133 patients undergoing pancreatic surgery for pancreatic disease concluded that the development of PEI was associated with substantially reduced patient QoL [36]. A prospective study in 40 patients undergoing pancreatic surgery for pancreatic cancer found that those with PEI had lower QoL scores using the EORTC QLQ-C30 questionnaire (of note, the reduction in QoL was only statistically significant in the case of insomnia [$p = 0.001$]) [31]. It should be noted that the decrease in QoL in patients with PEI was not significant in this patient population (with the exception of insomnia) [31] likely due to the effects of progressing pancreatic cancer, which would further reduce QoL to a greater extent than PEI.

Post-surgery, the presence of PEI may also lead to increased pain. A prospective study in 224 patients undergoing pancreatic surgery for chronic pancreatitis found a strong association between the presence of PEI and frequent pain (at least once a week) at follow-up [33]. Further retrospective analysis of 147 patients with chronic pancreatitis undergoing pancreatic surgery demonstrated that untreated PEI at hospital discharge ($p = 0.04$; Exp[B] = 2.102; 95% CI 1.04–4.26) along with postoperative insulin dependence ($p = 0.03$; Exp[B] = 2.111; 95% CI 1.09–4.09) were significant risk factors for reduced long-term survival [15]. Although well-designed prospective studies are clearly needed, the abovementioned data highlight the clinical relevance of PEI in patients following pancreatic surgery, a patient group in which PEI is underrecognized and undertreated. Physicians need to be more aware of the importance of diagnosing and adequately treating this condition as soon as it arises.

Management of PEI with PERT

PERT is considered the standard treatment for PEI [4, 7, 47]. It involves the supplementation of pancreatic lipase, amylase, and protease at doses leading to improvement of symptoms and nutritional status [47]. Modern formulations of PERT comprise enteric-coated pH-sensitive mini-microspheres, microspheres, or micro-tablets, which prevent the degradation of enzymes in the stomach and allow their release in the duodenum at pH >5.5 [4, 28]. PERT facilitates the improvement of nutritional status and weight gain in patients with PEI, by effectively correcting the cause of malabsorption [4]. A recent large retrospective observational study showed that PERT was independently associated with improved survival following pancreaticoduodenectomy for cancer [48]. In this study, the effect of PERT on improved survival was predominantly observed among patients with a dilated pancreatic duct ($\geq$3 mm) [48]. In line with this study, undertreatment with PERT following pancreatic surgery is associated with reduced survival and QoL [15]. A prospective, cross-sectional study in 91 patients who had undergone pancreatic surgery, and who received PERT, found that 68% of these patients still suffered from steatorrhea symptoms and 39% lost weight, suggesting that they were being undertreated [49]. Of note, the median dose of PERT was 150,000 units of lipase per day, and 25% of patients received $\leq$75,000 units per day [49]; thus, the dose of PERT used to treat many of these patients was considerably lower than the most recent recommendations for the treatment of PEI following GI surgery (75,000 units with meals and 50,000 units with snacks) [5].

Improvement of Malabsorption and Nutritional Status with PERT after GI Surgery

Although there are limited clinical trial data for PERT use in patients who have undergone GI surgery, several studies have demonstrated the efficacy of PERT in this patient population (Table 3) [50–58]. Following a 1-year open-label extension of a 1-week, double-blind, placebo-controlled, parallel-group study in 51 patients with severe PEI due to pancreatic resection, PERT led to significant improvements in the coefficient of fat absorption (CFA; $p < 0.001$), coefficient of nitrogen absorption (CNA; $p < 0.001$), body weight ($p < 0.05$), and body mass index (BMI; $p < 0.05$) [55].

The nutritional status and digestive function of 9 patients who had undergone pancreaticoduodenectomy with sclerosis of the residual pancreatic stump were as-

sessed 2 years after the surgery (baseline), and subsequently after administration of PERT for 6 months in a prospective study [50]. PERT was associated with normalization of nutritional status, as assessed by serum albumin levels, total iron binding capacity, and total lymphocyte count, and a significant increase in body weight ($p < 0.05$) [50].

In cases of local resection-longitudinal pancreaticojejunostomy, improvements in fat malabsorption were shown in a small placebo-controlled trial in 11 patients who had undergone surgery for chronic pancreatitis. All patients received PERT for 4 weeks postoperatively before they were randomized to receive either PERT or placebo for a further 4 weeks [51]. An additional 4 weeks of PERT was associated with significant improvements in CFA compared with placebo ($p < 0.02$) [51]. Although nutritional status, as assessed by levels of thiamine, folate, and vitamins A, B12, D, and E, was not significantly altered in this study, 4 patients randomized to receive PERT for a further 4 weeks had gained >3.6 kg of body weight at the end of the 8-week study period [51]. Similarly, a placebo-controlled, double-blind, parallel-group study in 54 patients with PEI due to chronic pancreatitis ($n = 40$) or pancreatic surgery ($n = 14$) found that treatment with PERT for 7 days was associated with improvements in CFA ($p < 0.0001$) and CNA ($p = 0.001$) compared with placebo [53]. In a 6-month open-label extension of this study, PERT resulted in significant improvements in body weight ($p < 0.0001$), in addition to a numerical but nonsignificant increase in BMI of 0.9 kg/m^2, indicating improvements in nutritional status [54].

The abovementioned data suggest that PERT is associated with improvements in fat and protein malabsorption, in addition to other nutritional parameters (serum albumin levels, total iron binding capacity, and total lymphocyte count), and may be an effective treatment for potential malnutrition following GI surgery.

PEI Symptom Control with PERT after Pancreatic Surgery

The use of PERT in patients following pancreatic surgery is also effective in reducing the common GI symptoms of PEI. A 6-month hospital-based study in patients who underwent pancreaticoduodenectomy found that fecal fat excretion was reduced from 32.8 to 16.7 g per day with PERT use [50]. A randomized, double-blind, crossover study comparing PERT administered in both standard and high-dose capsules in 37 patients who underwent pancreatectomy found these PERT formulations had similar efficacy in terms of fecal fat excretion, ab-

dominal pain, and global symptoms; however, 56% of patients still had fecal fat excretion of >7 g per day, suggesting that, with a mean overall dose of 155,000 units of lipase per day, this patient population was undertreated [52]. In a 7-day placebo-controlled trial, PERT was associated with significant improvements in flatulence ($p = 0.006$) and stool consistency ($p = 0.03$) [53], and with significant improvements in stool frequency ($p < 0.001$) in the 6-month open-label extension phase of this trial, designed as a parallel-group study of patients with PEI due to chronic pancreatitis or pancreatic surgery ($n = 48$) [54]. Significant reductions in stool frequency ($p < 0.001$) were reported following 1 year of PERT in 51 patients with severe PEI due to pancreatic resection [55]. Therefore, although the volume of data currently available is limited in patients following pancreatic surgery, PERT appears to be effective for the treatment of GI symptoms arising from PEI.

PEI Symptom Control with PERT after Gastric Surgery

Though PEI often arises because of gastric surgery, only a few studies have assessed the use of PERT to treat PEI in this patient population. A placebo-controlled, double-blind study in 52 patients with PEI who had undergone total gastrectomy for gastric cancer found no significant improvement in fat assimilation following administration of PERT compared with placebo [56]. Although there were no significant differences in body weight or GI symptoms between the PERT and the placebo group, PERT was associated with overall improvement in symptoms compared with placebo ($p = 0.006$) [56]. In addition, data from a small historical placebo-controlled, double-blind, crossover study in 15 patients who underwent total gastrectomy with Roux-en-Y anastomosis for stomach cancer found that administration of PERT was associated with a significant decrease in fecal fat excretion from 643 to 501 mmol/72 h ($p < 0.05$) in patients with severe steatorrhea ($n = 7$); however, fecal fat excretion was not significantly decreased overall [57]. Likewise, stool consistency was significantly improved in the PERT group (score of 7.6 [±0.5]) compared to placebo (score of 9.3 [±0.7], $p < 0.05$) [57]. A pilot study conducted in 22 patients with PEI arising after esophagectomy found that 64% of these patients had symptomatic improvement and that 41% of patients increased in weight after treatment with PERT [58]. Overall, the evidence for PERT use in patients with PEI following gastric surgery suggests that this treatment may be beneficial; however, there is a need for well-designed, large, controlled trials

for PERT, using modern enzyme preparations, in this patient population. Before new data are available, the possibility of PEI and the need for PERT should be considered in patients after gastric surgery, for both symptom and nutritional control.

National and International Guidelines on PERT Use after GI Surgery

Globally, various guidelines on the management of PEI are in agreement regarding the importance of PERT in addressing PEI after GI surgery (Table 4) [45, 59–61]. Proactive screening of all patients for PEI following pancreatic surgery is recommended [61] and administration of PERT should start as soon as PEI is diagnosed, or if there is a high clinical suspicion of PEI due to the presence of GI symptoms [45, 60]. Timely diagnosis and treatment of PEI is imperative in patients who have undergone GI surgery, since use of PERT can lead to increased QoL [45, 61], improvements in overall wellbeing [56], and reduced malnutrition-associated mortality post-surgery [60].

Spanish guidelines acknowledge that diagnosis of PEI in patients who have undergone pancreatic surgery can be difficult; therefore, the guidelines recommend the use of PERT in patients with high clinical suspicion of the condition due to their presenting symptoms, with retrospective diagnosis confirmed by improvement of symptoms, nutritional markers, and/or body weight after PERT [45]. Romanian guidelines suggest routine administration of PERT after surgery for chronic pancreatitis, even when no clinical signs of PEI are present [60]. This approach is mirrored in the Italian guidelines, in which algorithms are presented for monitoring and treating PEI following pancreatic or gastric surgery; PERT administration is recommended for patients with malignant disease (with the exception of cases of atypical resection), especially following pancreaticoduodenectomy [59]. For patients with benign disease, the assessment of PEI is suggested pre- and post-pancreaticoduodenectomy, and PERT should be administered if PEI is detected, particularly in cases in which typical resections extend beyond the right side of the portal vein [59]. There is no universal agreement on the need for routine testing for PEI in patients undergoing pancreatectomy, with the Italian guidelines suggesting that it is not necessary in patients undergoing typical or atypical pancreatectomies (except in cases where typical resections extend beyond the right side of the portal vein) [59]. Therefore, the consensus from various guidelines on the management of PEI is that the

Table 3. Improvements in fat absorption and body weight associated with PERT in patients undergoing GI surgery

Type of surgery	Study	Study population	Treatment	Outcome with PERT treatment Fat absorption or fecal fat excretion (±SD, if applicable)	Other outcomes (±SD, if applicable)	Key conclusion
Pancreatic surgery	[50]	9 Patients treated by pancreaticoduodenectomy and sclerosis of the residual pancreatic stump with neoprene	6 Months; 18,000 lipase units per meal	Fecal fat excretion: 16.7 g/day with PERT versus 32.8 g/day at baseline	Body weight: 58.0 kg (±11.1, $p < 0.05$) with PERT versus 52.8 kg (±9.7) at baseline	Patients receiving PERT for 6 months recovered much of their body weight and their nutritional status was normalized
	[51]	11 Patients treated by local resection–longitudinal pancreaticojejunostomy for chronic pancreatitis	4 Weeks of PERT followed by a further 4 weeks of PERT compared with placebo; pancreatin 32,000–96,000 units of lipase per day	CFA: 83.3% (±2.9, $p < 0.02$) with PERT versus 52.7% (±9.1) with placebo	Body weight: 4 patients receiving PERT gained >3.6 kg body weight over the 8-week study period	Data suggest that postoperative PERT is efficacious and necessary in patients with chronic pancreatitis after local resection–longitudinal pancreaticojejunostomy
	[52]	37 Patients treated by pancreatectomy	4 Weeks after a 2-week run-in period; mean dose of 155,000 units of lipase per day	Fecal fat excretion: no significant difference between high- and standard-dose PERT; 56% of patients still had fecal fat excretion of >7 g/day		High-dose PERT can reduce capsule intake and increase convenience and compliance rate; however, further progress is needed to resolve steatorrhea following pancreatic resection
	[53]	54 Patients with PEI due to chronic pancreatitis ($n = 40$) or pancreatic surgery ($n = 14$)	7 Days; 72,000 units of lipase per meal; 36,000 units per snack	CFA: 85.6% (±6.3, $p < 0.0001$) with PERT versus 66.3% (±20.4) with placebo	CNA: 13.0% (±45.4, $p = 0.001$) with PERT versus −64.0% (±101.5) with placebo Other symptoms: improvements in flatulence ($p = 0.006$) and stool consistency ($p = 0.03$) with PERT versus placebo	PERT was effective in treating fat and protein malabsorption in patients with PEI due to chronic pancreatitis or pancreatic surgery
	[54]	48 Patients with PEI due to chronic pancreatitis ($n = 39$) or pancreatic surgery ($n = 12$)[1]	6 Months; mean dose of 186,960±74,640 units of lipase per day		Body weight: increased by +2.7 kg (±3.4, $p < 0.0001$) with PERT from a body weight of 67.2 kg (±14.6) at baseline Stool frequency per day: 1.8 (±0.9, $p < 0.001$) with PERT versus 2.8 (±1.3) at baseline	Treatment with PERT for 6 months led to significant weight gain and reduced stool frequency in patients with PEI
	[55]	51 Patients with severe PEI due to pancreatic resection	51 Weeks; pancreatin 75,000 lipase units per meal and 50,000 per snack; 3 meals per day and 2 snacks per day	CFA: 78.4% (±20.7, $p < 0.001$) with PERT for 1 year versus 53.6% (±20.6) at baseline	CNA: 74.6% (±14.0, $p < 0.001$) with PERT for 1 year versus 52.8% (±24.4) at baseline Body weight: 70.5 kg (±16.3, $p < 0.05$) with PERT versus 68.2 kg (±15.8) at baseline Stool frequency per day: 1.5 (±0.8, $p < 0.001$) with PERT versus 2.4 (±1.6) at baseline	Treatment with PERT was efficacious in improving CFA in patients after pancreatic surgery

Table 3. (continued)

Type of surgery	Study	Study population	Treatment	Outcome with PERT treatment: Fat absorption or fecal fat excretion (±SD, if applicable)	Other outcomes (±SD, if applicable)	Key conclusion
Total gastrectomy	[56]	52 Patients with PEI treated for gastric cancer by total gastrectomy	2 Weeks; 72,000 units of lipase per meal; 36,000 units per snack	Fat assimilation: 15.5% (IQR 9.2–24.9) with PERT compared to 20.8% (IQR 16.4–30.4) at baseline, versus 18.7% (IQR 11.7–29.1) in the placebo group compared to 19.4% (IQR 14.3–27.1) at baseline	Overall well-being significantly improved with PERT compared with placebo ($p = 0.006$)	High-dose PERT was associated with improvements in fat assimilation and overall well-being after total gastrectomy in these patients
	[57]	15 Patients treated for stomach cancer by total gastrectomy with Roux-en-Y anastomosis	7 Days; 120,000 units of lipase per day	Fecal fat excretion: not significantly decreased overall, but decreased from 643 to 501 mmol/72 h ($p < 0.05$) in patients with severe steatorrhea	Stool consistency: score of 7.6 (±0.5, $p < 0.05$)[2] with PERT versus 9.3 (±0.7)[2] with placebo	PERT reduces severe steatorrhea and improves stool consistency after total gastrectomy
Esophagectomy	[58]	22 Patients with PEI after esophagectomy	Duration not stated (Pilot study); 25,000 units of lipase per meal	–	64% of patients had symptomatic improvement; 41% of patients increased in body weight	PEI can contribute to post-surgical morbidity in patients undergoing esophagectomy, and these patients may benefit from PERT

[1] This study was a continuation of that reported in [53].
[2] Standard errors were given in this paper instead of SD.
PERT, pancreatic enzyme replacement therapy; GI, gastrointestinal; CFA, coefficient of fat absorption; PEI, pancreatic exocrine insufficiency; CNA, coefficient of nitrogen absorption; IQR, interquartile range.

use of PERT should be routinely considered in patients after GI surgery (Table 4) [45, 59–61], particularly after resections that are associated with higher risk of PEI [59] in order to reduce mortality associated with the condition [60].

Adequate PERT Dosing in Patients after GI Surgery

Recommendations for the dosing of PERT for the management of PEI vary [5, 26, 45, 59, 60, 62]. Guidelines suggest starting doses in adults ranging between 25,000 and 75,000 units of lipase per meal and 10,000–50,000 units per snack to treat PEI following GI surgery (Table 4) [45, 59–61]. Studies have found that the starting doses of 75,000 units of lipase with meals and 50,000 units with snacks achieved significant increases in CFA values [53, 55]; however, these CFA values were still lower than CFA values in healthy individuals which are usually >90% [63]. Due to the difficulties of normalizing an anatomically altered GI transit, a starting dose of 75,000 units of lipase with meals has been suggested for patients with PEI following GI surgery (Fig. 2) [5].

The dose of PERT administered should be monitored and progressively increased to the lowest effective dose until symptoms of steatorrhea are resolved [2, 4, 18, 26, 59, 60]. However, nutritional deficiencies can still persist even when the PERT dose is high enough to improve symptoms of PEI [64, 65]; therefore, dosages of PERT should also be tailored to ensure normalization of the levels of nutritional markers, such as retinol-binding protein, albumin, and prealbumin [66]. Previously, maximal doses of 75,000–80,000 units of lipase per meal [26] or 10,000 units of lipase/kg of body weight/day [60] have been recommended due to the risk of fibrosing colonopathy associated with very high doses of PERT in patients with cystic fibrosis [26]. However, it has also been argued that evidence of an association between fibrosing colonopathy and high doses of PERT is very limited in patients without cystic fibrosis, and as a result, dose escalation should not be hindered in symptomatic or malnourished patients [2].

PERT administration is recommended during meals rather than before, in order for enzyme release to coincide with gastric emptying [60]. This recommendation on timing of PERT administration was based on a prospective, randomized, open-label, crossover clinical study in patients with chronic pancreatitis, which showed higher fat digestion in patients receiving PERT with meals ($^{13}CO_2$ recovery of 61.4% ± 21.4) or just after meals ($^{13}CO_2$ recovery of 60.6% ± 21.8) compared to those receiving PERT before meals ($^{13}CO_2$ recovery of 53.9% ± 20.3) [67].

Table 4. Guidelines on PERT use in patients with PEI following GI surgery

Guideline	Study	Method of assessment	Type of GI surgery	Dosing recommendations	Level of evidence for dosing
Spanish Association of Pancreatology (2016)	[45]	GRADE	Pancreatic	72,000–75,000 units of lipase per meal; 36,000–50,000 per snack	2c, weak recommendation and low quality of evidence
Italian Association for the Study of the Pancreas (2013)	[59]	Not stated	Gastric or pancreatic	Not <40,000–50,000 units of lipase per meal; 25,000 per snack	NA
Romanian Association for Pancreatic Pathology (2015)	[60]	Oxford classification	Gastric or pancreatic	Initial dose: 40,000 units of lipase per meal; 10,000–25,000 per snack	1b, evidence from individual RCTs with narrow confidence interval
Australasian Pancreatic Club (2015)	[61]	Oxford classification[1]	Gastric or pancreatic	Generally:[2] 25,000–40,000 units of lipase per meal; 10,000 per snack	5, expert opinion[3]

[1] With the addition of level 3c: critical review of literature.
[2] For gastric surgery; specific dosing recommendations were not stated for pancreatic surgery, although the dose should generally be in the region of 25,000–50,000 units of lipase.
[3] Without explicit critical appraisal, bench research or "first principles".
PERT, pancreatic enzyme replacement therapy; PEI, pancreatic enzyme insufficiency; GI, gastrointestinal; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; NA, not applicable; RCT, randomized controlled trial.

Coadministration of proton pump inhibitors (PPIs) with PERT is recommended in cases where symptoms are not resolved with PERT alone [2, 26, 59, 68]; however, their use is controversial [60] due to limited evidence of their effectiveness in improving malabsorption [2], with a retrospective analysis of 34 trials (*n* = 1,142) suggesting that there is no significant difference in CFA in patients administered PERT with or without PPIs [69]. Additionally, it has been recommended that some patients may benefit from a PPI following pancreaticoduodenectomy in order to reduce ulceration at the gastrojejunostomy [2].

Ongoing Patient Management after GI Surgery
Continuous follow-up of patients treated with PERT is important to ensure optimal management of the symptoms of PEI and nutritional status [61, 70, 71]; a proposed algorithm for the management of PEI using PERT in patients who have undergone GI surgery is shown in Figure 2. Diagnostic tests used to confirm the presence of PEI, such as the ^{13}C-MTG-BT and the fecal fat test, can be used to monitor the response to PERT [1, 60, 70]. Nutritional evaluation of patients with PEI is necessary to ensure that malnutrition is avoided [4]; this could include evaluation of body weight and routine nutritional markers in the blood, such as fat-soluble vitamins, albumin, prealbumin, retinol-binding protein, zinc, and magnesium, among others [45, 66, 70, 71]. Additionally, the sometimes complex nutritional needs of patients with PEI [4] mean that regular assessment by an experienced dietitian can be beneficial [2, 4, 26, 71]. Supplementation of fat-soluble vitamins [59, 60] and other micronutrients, such as zinc and selenium, may be necessary if patients continue to have these micronutrient deficiencies [59].

Smaller, more frequent meals are recommended as these tend to be better tolerated [18, 26, 60] and may allow more efficient mixing of chyme with pancreatic enzymes than 3 large meals per day [26]. Restriction of fat intake should be avoided in patients with PEI; a normal fat-containing diet (30% of calories from fat) [60] is recommended along with administration of PERT [2, 18, 26, 59, 60]. Of note, the Italian guidelines recommend creation of a personalized diet for patients after major GI surgery to prevent weight loss and anorexia [59].

The Spanish guidelines recommend that the frequency of follow-up visits should depend on the clinical and nutritional status of patients and that further follow-up should probably be on-demand once optimal symptom and nutritional management is achieved [45]. Conversely, a UK expert opinion review recommends regular review of symptoms and dietary adequacy, and suggest that patients should be reassessed if symptoms return or worsen [2]. Importantly, patient education on PERT use is rec-
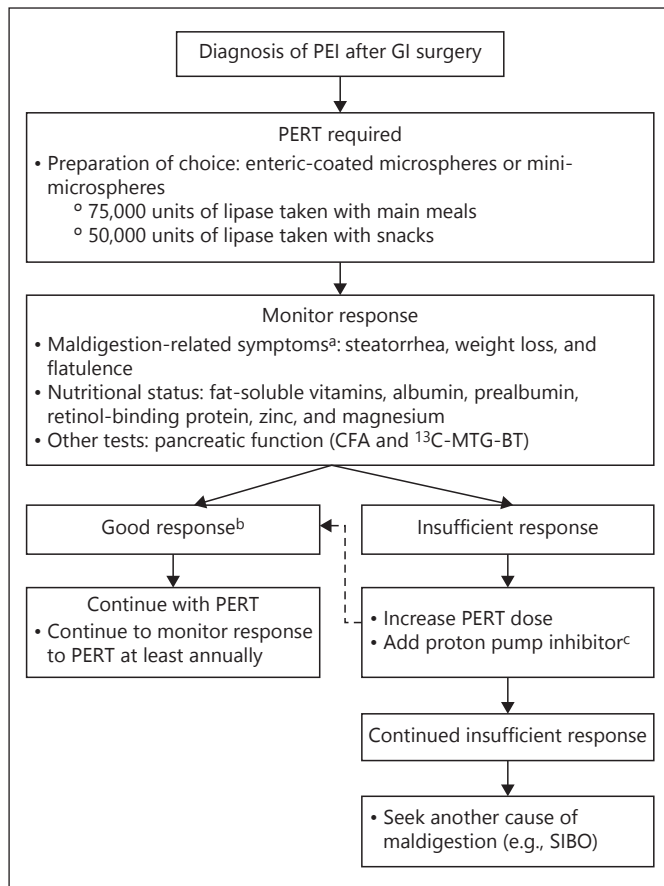
Fig. 2. Proposed algorithm for the management of PEI using PERT following GI surgery [5, 61, 70, 71]. [a] In clinical practice, the clinical and nutritional improvement of the patient is a sufficient enough criterion to evaluate response. [b] Improvement in symptoms, nutritional status, and QoL and improved results of pancreatic function tests. [c] In case of insufficient symptom relief and/or nutritional status not normalized; PPI therapy is not indicated after total gastrectomy. PEI, pancreatic exocrine insufficiency; GI, gastrointestinal; PERT, pancreatic enzyme replacement therapy; CFA, coefficient of fat absorption; ^{13}C-MTG-BT, ^{13}C-mixed triglyceride breath test; SIBO, small intestinal bacterial overgrowth.

ognized as key to ensuring optimal administration in all circumstances, including holidays, meals out, and hot weather [2]. Therefore, effective management of PEI requires regular monitoring of both symptoms and nutritional status to allow tailored PERT administration.

Conclusion

GI surgery can lead to removal of exocrine tissue and/or have effects on the passage of food particles and the processes involved in promoting their digestion by pan-

creatic enzymes [1, 2]. These changes in the anatomy and functioning of the GI tract can result in PEI, a common long-term complication following pancreatic or gastric surgery [1, 2]. PEI is associated with malnutrition and subsequent morbidities that may have detrimental effects on patient QoL and mortality [31, 36]. Therefore, the timely diagnosis and treatment of PEI is vital to prevent the development of a state of malnutrition and has the potential to improve the long-term outcomes of patients who have undergone GI surgery [5]. PERT is effective in improving malabsorption, nutritional status, and BMI [50–58], thereby minimizing the effects of PEI-associated malnutrition on patient morbidity and possibly mortality [5]. Multiple guidelines on the management of PEI recommend routine screening of patients following GI surgery, particularly for procedures associated with a higher likelihood of causing PEI, such as pancreaticoduodenectomies [18, 26, 59, 60, 71]. Management of PEI should go beyond symptom control and aim to bring significant improvement in nutritional parameters, since nutritional deficiencies substantially contribute to morbidity and mortality in patients' post-surgery [5]. Therefore, effective management of PEI encompasses adequate dose escalation until optimal dosage of PERT is reached, regular assessment of the nutritional status of patients, appropriate patient education on optimal administration of PERT, and reassessment if symptoms reappear.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

A.C. has participated in speaking activities for Abbott Laboratories Ltd. J.E.D.-M. has participated in consulting and speaking activities for Abbott Laboratories Ltd., Mylan N.V., and Allergan plc. P.L. has participated in consulting and speaking activities for Abbott Laboratories Ltd., Allergan, Almirall, Dr. Falk Pharma GmbH, Nordmark Arzneimittel GmbH and Co. KG, and Shire. M.M.L. has participated in consulting and speaking activities for AbbVie Ltd., Abbott Laboratories Ltd., Dr. Falk Pharma GmbH, AstraZeneca plc, Nordmark Arzneimittel GmbH and Co. KG, Centogene AG, and KMG.

Author Contributions

All authors contributed to the interpretation of data and to manuscript conception, design and drafting, approved the final manuscript for submission, and agree to be accountable for all aspects of the work.

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