REVIEW

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Pancreatic Enzyme Replacement Therapy: Not Only in Chronic Pancreatitis

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ABSTRACT

The therapeutic application of Pancrelipase spans several key gastroenterological conditions, ranging from chronic pancreatitis to genetic disorders such as cystic fibrosis. Consequently, pancreatic enzyme replacement therapy (PERT) is applicable in a variety of clinical settings, managing pancreatic insufficiency. Beyond chronic pancreatitis, PERT has also shown effectiveness in addressing malabsorption associated with pancreatic surgery, gastrointestinal malignancies, and various dysmetabolic conditions. This review aims to provide a comprehensive overview of the therapeutic applications of PERT and its clinical role in managing both surgical and non-surgical conditions, beyond chronic pancreatitis. PERT has proven crucial in improving patient outcomes, addressing gastrointestinal symptoms, and supporting long-term health in patients with pancreatic insufficiency. While more research, particularly from randomized controlled trials, is required to optimize dosing strategies and establish standardized PERT protocols, clinicians should consider tailoring PERT to individual patient needs based on the available evidence across various clinical scenarios.

Key words: pancreatic enzyme replacement therapy – PERT – pancrealipase – pancreatic disease.

Abbreviations: CF: cystic fibrosis; CP: chronic pancreatitis; EPI: exocrine pancreatic insufficiency; FE: fecal elastase; IBS-D: diarrhea-predominant irritable bowel syndrome; PERT: pancreatic enzyme replacement therapy; PL: pancrealipase; PPI: proton pump inhibitor; RCT: randomized controlled trial; T1d: type-1 diabetes; T2D: type-2 diabetes.

INTRODUCTION

Pancrelipase (PL) is a pancreatic enzyme supplement primarily used to aid the digestion of fats, proteins, and carbohydrates. It contains a combination of enzymes, including lipase, protease, and amylases that are naturally produced and secreted by the pancreas to break down food components in the small intestine [1].

The therapeutic use of PL spans several key gastroenterological conditions ranging from chronic pancreatitis (CP) to genetic disorders, such as cystic fibrosis (CF) [2], which is characterized by exocrine pancreatic insufficiency (EPI) requiring supplemental enzyme therapy to aid digestion and nutritional absorption. From an epidemiological perspective, exocrine EPI is frequently underdiagnosed, with an estimated prevalence in the general population ranging from 10% to 20%. The prevalence increases with age, and chronic pancreatitis remains the leading cause, with reported incidences as high as 90% in affected individuals [3]. However, EPI often presents with non-specific gastrointestinal symptoms, leading to missed or delayed diagnosis and, consequently, an underestimation of its true prevalence -particularly in specific conditions such as diabetes mellitus and diarrhea-predominant irritable bowel syndrome (IBS-D) [4]. Therefore, increasing clinical awareness and implementing appropriate screening strategies could enhance early diagnosis and timely treatment, especially in non–chronic pancreatitis-related cases. Symptoms of untreated EPI include difficulty in digesting fat and maldigestion and malnutrition-related symptoms such as essential fatty acids and fat-soluble vitamins deficiencies, weight loss, cramping, flatulence, bloating, and greasy, loose stools (steatorrhea) [5]. Exocrine pancreas has a large functional reserve capacity and, generally, symptoms linked to EPI occurred in cases of a 10%-lower residual

pancreatic function [6]. Considering its low cost and its minimal invasiveness, fecal elastase (FE) level is the more widely used test for EPI diagnosis [7], with good accuracy in the case of severe EPI and a sub-optimal sensitivity in moderate ones [8]. In a recent systematic review, the pooled sensitivity and specificity of FE were found to be 96% (79–99%) and 88% (59–97%), respectively, when compared to quantitative fecal fat estimation. Furthermore, in patients with a low pre-test probability of EPI, the fecal elastase-1 assay exhibited a false-negative rate of 1.1% and a false-positive rate of 11%. These findings suggest that while the test is highly effective in ruling out EPI, it may not be as reliable for detecting the condition [9]. Moreover, structural changes may result in a lack of synchronization between enzyme release and nutrient passage, as well as inadequate trituration of nutrients. As a result, FE values could remain within the normal range in such clinical contexts [10].

Several tests have been validated for EPI diagnosis in the last decades. However, the majority are invasive and not routinely used in clinical practice (^{13}C-mixed triglyceride breath test, secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imaging, endoscopic collection, and analysis of pancreatic secretion) [7].

The most accurate test for diagnosis of EPI consists of the evaluation of the coefficient fat absorption; however, its complexity restricts its use beyond the field of research [11].

As shown in a meta-analysis including four randomized controlled trials (RCTs) PL supplementation in patients with CP improves fat absorption coefficient compared with placebo [12].

Moreover, in a large retrospective real-world study involving 10,656 patients with CP or type-2 diabetes (T2D), the administration of PL resulted in a significant reduction in EPI symptoms such as abdominal pain, diarrhea, steatorrhea, and nausea [13]. Pancreatic enzyme replacement therapy (PERT) improves fat and protein absorption in patients with EPI due to chronic pancreatitis or after pancreatectomy [14]. Similar results have been shown in another study that included patients with or without T2D [15]. However, PERT did not seem to relieve abdominal pain in patients with CP and should not be prescribed for this purpose [16].

Additionally, PERT is prescribed to patients with pancreatic cancer and after pancreatectomy. Surgical removal of the pancreas or obstruction due to tumor growth impairs enzymatic secretion; in these cases, PERT improves the quality of life reducing symptoms such as steatorrhea, bloating, and malnutrition [7]. Although most evidence comes from retrospective studies or trials with small sample sizes, the use of PERT has successfully met its primary endpoint in both advanced pancreatic cancer and pancreatic surgery related to pancreatic cancer [17].

In clinical practice, PERT is also prescribed in non-pancreatic digestive conditions where EPI has not been diagnosed, such as short gut syndrome, celiac disease, Crohn's disease, post gastrectomy, and chronic diarrhea of unclear etiology. The rationale behind this indication is linked to the optimization of nutrient requirements in case of suboptimal absorption (Fig. 1).

In this review, we aim to provide a comprehensive overview of the therapeutic applications of PERT and its clinical role in managing various gastrointestinal conditions, different from chronic pancreatitis (Table I).

TYPE OF FORMULATIONS

To ensure clinical efficacy, pancreatic enzyme preparations must meet specific criteria, overcoming challenges posed by gastric acidity, gastrointestinal transit, and duodenal release. These formulations have shown significant effectiveness in reducing malabsorption-related symptoms [18] and are specifically engineered to withstand the acidic environment of the stomach and release enzymes in alkaline conditions of the small intestine, where their activity could be maximized [19]. Typically, these formulations consist of microspheres or micro-tablets encased in a protective coating, which enhances their ability to mix with ingested food and facilitate digestion. Porcine-derived PL is considered the most effective PERT preparations. However, alternative formulations containing microbial pancreatic-like enzymes have demonstrated efficacy in improving lipid absorption in animal models [20]. Innovative techniques, such as artificial cell encapsulation, could offer potential benefits by protecting enzymes from degradation within semi-permeable membranes and enabling controlled release [21].

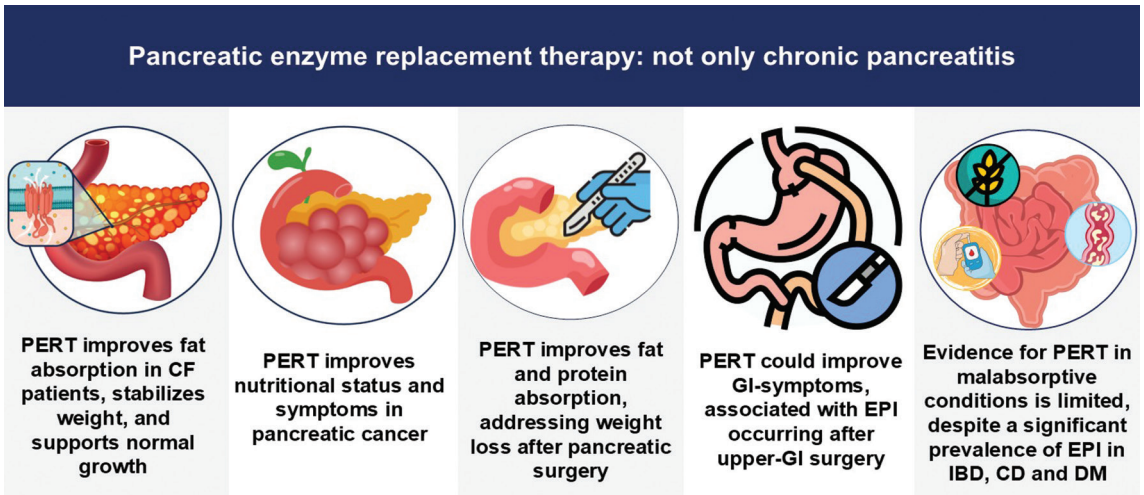

Fig. 1. Pancreatic enzyme replacement therapy

Table I. Summary of findings

Disease	Main Issue	Results	RCTs available
Cystic Fibrosis [36,37]	CF causes EPI in 85-90% of patients.	• PERT is a safe and effective treatment for malabsorption associated with EPI in CF • 25,000-40,000 lipase units per meal is the recommended dose.	Yes
Pancreatic Cancer [43,45,55]	Malnutrition significantly worsens outcomes in PC	• PERT significantly improves nutritional status. • PERT significantly improves body weight • longer survival in patients with >10% weight loss when PERT was combined with chemotherapy.	Yes
Pancreatic Surgery [60]	Pancreatic surgeries often lead to EPI.	• PERT results in significant weight gain and reduced stool frequency after pancreatic surgery	Yes
Upper-GI surgery [80,82,84,85,91]	More than one-third of gastrectomy patients develop EPI. Roux-en-Y gastric bypass and biliopancreatic diversion carry a higher EPI risk than sleeve gastrectomy or gastric banding.	• PERT improves nutritional status and quality of life after gastrectomy • PERT improves stool consistency after gastrectomy • PERT improves GI symptoms and increases weight after esophagectomy • PERT could improve symptoms after bariatric surgery	Yes
Celiac disease [90,91]	EPI is reported in 17-61% of celiac patients and in 18-80% of IBD.	• PERT leads to an increase in body weight in pediatric patients with celiac disease No improvement is observed in gastrointestinal symptoms	No
Diabetes Mellitus [75,76]	The prevalence of EPI in T1DM ranged from 14% to 77.5% and 16.8%-49.2% in T2DM	• PERT increases gastrointestinal symptoms in patients with DM and EPI.	Yes
IBS-D	The prevalence of EPI ranging between 1.8 and 6.1%	• PERT could increases gastrointestinal symptoms in patients with IBS-D and EPI.	No

CF: Cystic fibrosis; DM: Diabetes Mellitus; EPI: exocrine pancreatic insufficiency; IBS-D: Diarrhea Predominant - Irritable Bowel Syndrome PC: Pancreatic cancer; PERT: Pancreatic enzyme replacement therapy.

Currently, porcine pancreatic enzymes are the only ones approved for medical use in the EU. Nevertheless, biotechnological advancements have led to the development of biosimilar and synthetic enzyme formulations, which offer alternatives to animal-derived products, although they are not yet available in clinical practice [22]. These alternatives may be beneficial for patients with sensitivities or ethical concerns related to animal-derived products. However, their safety and efficacy require thorough comprehensive evaluation in clinical trials. In cases where standard PERT is insufficient, adjuvant therapy proton pump inhibitor (PPI)-based may be considered to enhance the effectiveness of enteric-coated enzyme preparations by reducing gastric acid secretion and preventing premature activation or degradation in the stomach [23]. However, PPI co-administration should be reserved for cases where standard PERT dosages fail to achieve satisfactory results, as routine use is not universally recommended [24, 25]. Despite the widespread use of these strategies, there is a notable lack of large-scale, randomized comparative studies to comprehensively evaluate the relative efficacy of different pancreatic enzyme preparations.

PANCREATIC ENZYME REPLACEMENT THERAPY IN CYSTIC FIBROSIS

Cystic fibrosis is a genetic disorder inherited in an autosomal recessive manner caused by a mutation in CFTR gene, leading to abnormal ion transport and accumulation of viscous mucus, impairing the function of multiple organs, including pancreas. This condition can result in EPI in approximately 85-90% of patients [26]. Cystic fibrosis related pancreatic insufficiency is not different from other EPI, and it is characterized by reduced pancreatic enzymes secretion, causing malabsorption of nutrients, particularly of fats and fat-soluble vitamins (A, D, E, K) [27]. The main clinical manifestation is steatorrhea, along with symptoms related to specific nutrient deficiencies.

In this context, PERT is crucial for improving nutrient absorption. Enteric-coated formulations protect enzymes from gastric acidity (high-buffered, with bicarbonate) and ensure release beyond the gastric barrier, reducing fat excretion [28-32].

The efficacy and tolerability of PERT have been widely proven [33-35]. The recommended dosage for adults is 25,000-

40,000 units of lipase per meal, while in children, the dosage is weight-based (1,000 units of lipase per kg for younger children less than 4 years of age and 500 units per kg for children older than 4 years of age [36].

Proper administration of PERT improves fat absorption in CF patients, stabilizes weight, and supports normal growth, which is particularly critical during childhood. The primary measure or PERF effectiveness is historically the coefficient of fat absorption, which demonstrated significant improvement in treated patients, resulting in notable reductions in gastrointestinal symptoms and bowel movement frequency [37].

The coefficient of fat absorption measurement involves a 72-hour stool collection, which can be unpleasant and inconvenient for patients. Some authors have suggested alternative methods, such as sparse stool sampling for percentage fat analysis [38], or more recently, plasma sterol evaluation, including phytosterols and cholesterol, to monitor lipid metabolism, optimize PERT dosage and therapeutic response [39]. Specifically, measuring campesterol and β-sitosterol concentrations in CF patients may serve as indicators of PERT efficacy and/or compliance [40]. These parameters can aid in personalizing enzyme therapy and optimizing fat absorption.

Lastly, recent studies have also explored the impacts of PERT on other aspects of digestive physiology in CF patients, particularly gastric emptying, and incretin hormone secretion. Pancreatic enzyme replacement therapy has been found to influence postprandial glycemic responses by slowing gastric emptying and increasing incretin hormone secretion, leading to improved glycemic control [41, 42].

Despite the efficacy of PERT, complete restoration of normal digestive function may not always be achievable due to factors such as duodenal pH variations or timing discrepancies between enzyme release and food transit [36]. Therefore, full normalization of fat absorption is not always achieved, highlighting the complexity of managing CF-related pancreatic insufficiency.

In conclusion, PERT is a cornerstone therapy for addressing malabsorption and pancreatic symptoms in CF-related pancreatic insufficiency, significantly improving quality of life and clinical outcomes. However, challenges remain in determining the optimal PERT dosage relative to pancreatic status and in optimizing its efficacy.

PANCREATIC ENZYME REPLACEMENT THERAPY IN PANCREATIC DISEASE AND PANCREATIC SURGERY

Pancreatic Cancer

Pancreatic cancer is one of the most aggressive malignancies, with a poor prognosis characterized by a five-year survival rate lower than 10%. Malnutrition plays a significant role in these patients and is directly linked to poorer outcomes, affecting their ability to tolerate cancer treatments, their quality of life, and, as expected, overall mortality [43, 44]. The primary cause of malnutrition is the development of PEI, which results from the loss of functional pancreatic tissue and obstruction of the main pancreatic duct with upstream atrophy [45] leading to malabsorption, particularly of fats, which manifests clinically as steatorrhea, weight loss, nutritional and vitamin deficiencies, and cachexia [46]. Exocrine pancreatic insufficiency is highly prevalent in patients with resectable, borderline resectable and unresectable pancreatic cancer [47] . Supportive care measures including oral or intravenous supplementation, physical exercise, pharmacologic interventions, and enzymatic therapy can help improve malabsorption. The administration of PERT at a recommended dose of 2,500 lipase units per kilogram of body weight is recognized as the standard treatment for improving nutritional status and alleviating symptoms [48]. Additionally, both international and national guidelines provide recommendations on PERT, including the minimum initial dose, timing of administration, and the necessity of patient follow-up for dose adjustments.

For conditions such as chronic pancreatitis, the recommended initial dose is 40,000 to 50,000 lipase units per meal, while for pancreatic cancer or post-pancreatic surgery, the recommended dose is 72,000 to 75,000 lipase units per meal [49]. The initial dose should be gradually increased until steatorrhea is adequately controlled, and this optimized dosage should be maintained over time [17].

Although the use of PERT is recommended in the latest ESMO guidelines [50], its implementation in clinical practice remains limited, leading to underdiagnosis and undertreatment [51]. Factors contributing to this discrepancy include lack of awareness among physicians or specialists and variable patient compliance, with only about 50% adherence to enzyme therapy [52]. Despite the low usage rate among pancreatic cancer, population-based studies have shown that patients receiving PERT have improved median survival [52, 53].

Patients with unresectable pancreatic cancer, whose prognosis depends on to chemotherapy response may benefit the most from PERT. Clinical studies, such as those conducted by Saito et al. [54], have demonstrated that PERT can help maintain body mass index and improve overall nutritional status in patients undergoing chemotherapy for advanced pancreatic cancer. Moreover, a RCT involving 21 patients with unresectable pancreatic head cancer demonstrated a 2.2% increase in mean body weight in patients treated with pancreatic enzymes, compared to a 3.7% weight loss in the control group [55]. In another randomized controlled trial, although no significant improvements in body mass index were observed after eight weeks of PL treatment, patients receiving PERT showed a trend toward longer overall survival [56]. Finally, a retrospective analysis found that unresectable pancreatic cancer patients receiving PERT alongside chemotherapy had significantly longer survival compared to those without PERT, particularly among patients with more than 10% weight loss [57].

In conclusion, EPI is a common and debilitating complication in pancreatic cancer, but PERT represents an effective strategy to improve digestion, body weight, and potentially survival. Patient education is essential to enhance therapy adherence and administration schedules, also emphasizing the importance of taking capsules at the beginning and throughout meals [48], despite the lack of standardized dosage and titration to oral intake [58]. However, there are still knowledge gaps, and not all clinical studies reached the same conclusions [43]. Further research is needed to establish optimal guidelines for the use of PERT in this clinical context.

Pancreatic Surgery

Pancreatic enzyme replacement therapy provides significant clinical benefits in patients undergoing pancreatic surgery, including pancreaticoduodenectomy and total pancreatectomy for various malignant pancreatic diseases such as pancreatic cancer, premalignant mucinous lesions, and other periampullary neoplasms. While these procedures are often lifesaving, they frequently lead to various degrees of EPI, resulting in nutrient malabsorption, weight loss, and deterioration of the patient's overall nutritional status.

Pancreatic enzyme replacement therapy, especially with newer delayed-release formulations, has become the cornerstone of managing post-surgical EPI [59]. In this setting, PERT has demonstrated efficacy in improving fat and protein absorption, reducing stool frequency, addressing weight loss, and alleviating symptoms related to malabsorption. For instance, Gubergrits et al. [60] showed that prolonged use of PL in post-surgical patients significantly increased body weight, improved stool consistency and quality of life [60]. The benefits of PERT are particularly pronounced in individuals with dilated pancreatic ducts, which could indicate a severe EPI [61].

A significant complication following pancreatic surgery is new onset steatotic liver disease, possibly resulting from impaired fat absorption [62]. In this context, PERT has shown superior efficacy compared to other enzyme supplements [63], although some authors support combining PERT with branched-chain amino acids (BCAA), efficacy in preventing steatotic liver disease [64]. Pancreatic enzyme replacement therapy has been found to improve mild liver dysfunction observed at 1, 3, and 6 months after pancreatic surgery [65], alongside improving nutritional parameters such as total protein, albumin, and total cholesterol levels [66].

Despite these well-established benefits, cultural challenges barriers persist among clinicians and patients. Although PERT is recommended for all post pancreatic surgery patients, a quality-of-life survey conducted after pancreaticoduodenectomy revealed that only half of the patients regularly adhered to PERT supplementation [67]. Compliance significantly impacted weight loss, prompting the introduction of high dose PERT-capsules which have been introduced to reduce the daily capsule count and improve adherence [68].

While the benefits of PERT are evident, its management in surgical patients requires continuous monitoring to optimize dosage and ensure a favorable clinical response. Future research should focus on optimizing enzyme therapy and understanding the pathophysiological mechanisms underlying post-surgical EPI to further improve clinical outcomes and quality of life.

Acute Pancreatitis

The relationship between acute pancreatitis and the development of EPI remains a subject of debate in the literature. A few years ago, a systematic review and meta-analysis sought to clarify the incidence of EPI following a first episode of acute pancreatitis and to identify high-risk patient characteristics. The analysis reported an overall prevalence of EPI of 62% during hospitalization and 35% after discharge. Independent risk factors included severe pancreatitis, necrotizing disease, and an alcoholic etiology [69]. Some uncertainty remains regarding the efficacy of PERT. A double-blind, placebo-controlled, randomized, parallel-group study involving 56 patients with acute pancreatitis evaluated the effectiveness of PL. The primary outcome was the recovery median time from EPI between the two groups. No significant difference was observed concerning the primary outcome. However, the median time to recover from pancreatic exocrine insufficiency was 14 and 23 days among the intervention and placebo groups, respectively (p=0.641). Pain scores also showed no significant difference between the two groups [70]. Nonetheless, as a pragmatic recommendation, all patients should be tested for exocrine pancreatic insufficiency prior to discharge to allow appropriate long-term therapeutic planning. Ongoing follow-up should be ensured by the managing clinicians.

PANCREATIC ENZYME REPLACEMENT THERAPY IN DIABETES MELLITUS

Type 1 diabetes (T1D) and T2DM have a higher prevalence of EPI compared to the general population. A systematic review found that the prevalence of EPI in T1DM ranged from 14% to 77.5%, with a median of 33%, while in T2DM, it ranged from 16.8% to 49.2%, with a median of 29% [71].

Several hypotheses have been proposed to explain these findings, including exocrine diseases leading to endocrine dysfunction, exocrine failure as a complication of diabetes, or a pathological process affecting the entire pancreas [72, 73].

A retrospective study assessing exocrine function through FE measurements found that among 1,015 patients, 59.3% had normal FE levels (>200 μg/g), 17.8% had reduced levels (100–200 μg/g), and 22.9% had markedly reduced levels (<100 μg/g) [74].

In a recent study including 96 patients with diabetes mellitus and EPI, PERT did not significantly affect glycemic control. However, gastrointestinal symptoms improved in 87% of patients who received the recommended dosage of PERT [75]. Moreover, in a RCT, 21.1% of patients with diabetes mellitus receiving insulin therapy had concomitant EPI, with FE levels <100 μg/g (normal cut-off >200 μg/g). A total of 80 patients were randomized to receive PERT (39 patients) or a placebo (41 patients) for 16 weeks. At the end of the follow-up period, no significant differences were observed in HbA_1c, fasting glucose levels, or 2-hour postprandial glucose levels between the groups. However, a reduction in mild and moderate hypoglycemia, as well as an increase in serum vitamin D levels, was observed in the PERT group [76].

This evidence suggests that a significant number of individuals with diabetes and EPI remain undiagnosed. People with diabetes (both T1DM and T2DM) who experience gastrointestinal symptoms (such as steatorrhea, changes in stool, bloating, or abdominal pain) should be screened for EPI.

PANCREATIC ENZYME REPLACEMENT THERAPY IN GASTROINTESTINAL SURGERY AND NON-PANCREATIC DISEASE

Data concerning the use of PERT in non-pancreatic disease remains lack and sparse. In a US population-based study, the prevalence of PERT use for non-pancreatic digestive conditions

was 60.2 per 100,000 persons with a higher prevalence in women, with a median dose of PL supplementation of 2,880 lipase units/day [77]. In this clinical setting, the most frequent post-surgical conditions were esophagectomy and gastrectomy and, as expected, diarrhea and abdominal pain being the main diagnoses. Other notable indications included Crohn's disease and ulcerative colitis with or without a history of previous intestinal resection and short gut syndrome [77]. Interestingly, also IBS-D patients could present mimicking symptoms, leading to EPI underdiagnosis.

Gastric and Esophageal Surgery

More than a third of patients who underwent gastrectomy for gastric carcinoma developed asymptomatic EPI based on FE evaluation. After gastric surgery, structural or functional changes in gastrointestinal could lead to inadequate production, insufficient secretion, and/or inactivation of pancreatic enzymes [78]. Additionally, structural changes can lead to non-synchronization between release of enzymes and passage of nutrients and to insufficient trituration of nutrients [10] Consequently, FE values may remain within the normal range in this clinical context [79]. Another potential mechanism involved in the pathophysiology of EPI after gastric surgery is linked to vagal nerve injury, which can contribute to dysfunction in the regulation of pancreatic exocrine secretions [10]. However, routine administration of PERT in patients who had undergone gastrectomy showed no benefit in a single study including 52 institutionalized patients [80] and did not reduce the number of bowel movements and the abdominal symptoms [81]. A randomized trial showed an improvement in nutritional assessment in patients treated with PERT after gastrectomy compared to control was observed. Nevertheless, there was no significant difference in terms of body mass index, quality of life, and pre-albumin levels between the two groups [82]. Thus, routine pancreatic supplementation after gastric resection surgery may not be necessary but monitoring for EPI symptoms in the long term could help identify the need for PERT [83]. Finally, an open-label study involving 10 patients after esophagectomy showed an improvement in gastrointestinal symptoms and a body weight increase after PERT [84].

Bariatric Surgery

A common clinical scenario associated with the development of EPI is post-bariatric surgery. Patients who underwent Roux-en-Y gastric bypass or a biliopancreatic diversion with a duodenal switch have a higher risk compared to sleeve gastrectomy or adjustable gastric banding. In a retrospective study including patients who underwent bariatric surgery, EPI was diagnosed in 41.6% of the population. Therapeutic PERT was administered to 65 out of 79 patients with EPI, and 56 (86.2%) reported improvement in symptoms [85]. Another study found that about 20% of post-operative bariatric surgery patients experienced steatorrhea, with 9.3% being diagnosed with EPI [86]. Another frequent complication is the severe protein malnutrition [87], associated with increased morbidity and mortality. However, an evidence-based therapeutics approach is not yet available. In a single-center case series, eleven patients with severe hypoalbuminemia were treated with 24 hours of nasal-jejunal tube feeding of a medium-chain triglyceride formulation in combination with pancreatic enzyme supplementation every 3 hours (supplemented for a median of 75 days). This approach was effective in all included patients without significant side effects [88].

Celiac disease and Inflammatory Bowel Disease

Celiac disease is chronic enteropathy triggered by gluten ingestion in genetically susceptible individuals. Exocrine pancreatic insufficiency has been reported in 17-61% of celiac patients, with some studies showing persistence of EPI despite adherence to a gluten-free diet (GFD). On the other hand, some studies have shown a relation between the severity of intestinal damage and FE levels suggesting a possible link between microstructural bowel damage and EPI unrelated to the pancreatic dysfunction [89].

Two published trials did not show an improvement in gastrointestinal symptoms in celiac patients treated with PERT [90], while an RCT in pediatric celiac patients demonstrated an increase in body weight compared to placebo [91].

Despite limited evidence, there are no recommendations indicating the use of PERT in celiac disease [92]. However, in celiac patients on GFD with persistent diarrhea the possible onset of EPI should be appropriately considered [93].

Inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, are chronic diseases, mediated by the immune system affecting the gastrointestinal tract. Malnutrition and undernutrition are often observed in these patients, and these conditions are variable during the disease course [94]. Malnutrition is common and can result from various factors such as inadequate nutrient intake, altered metabolism, malabsorption, excessive gastrointestinal losses, and medication effects. Pancreatic insufficiency has been reported in a significant proportion of patients with IBD, with prevalence rates ranging from 18% to 80% identified a reduced fecal elastase level in 18% of IBD patients [95, 96]. Heikius et al. [97] found signs of pancreatic insufficiency in 19% of non-selected IBD patients, based on tests such as the paraminobenzoic acid test or the secretin-cerulein test [97]. In a prospective observational study 35% of patients with Crohn's disease and 50% of patients with ulcerative colitis presented a decrease in plasma bicarbonate and serum enzymes during a secretin-cerulein test. A reduction in lipase levels was noted in 58% and 80% of Crohn's disease and ulcerative colitis patients, respectively [98]. Furthermore, a larger study by Hegnohj et al. [99] confirmed a significant reduction in amylase and lipase output through the Lundh meal test. Pancreatic insufficiency in IBD appears to be associated with the extent of Crohn's disease, particularly when there is ileal involvement and during active disease phases. However, there is no evidence supporting the use of PERT in IBD patients and recommendations for its use are lacking.

Diarrhea Predominant Irritable Bowel Syndrome

Diarrhea predominant irritable bowel syndrome is a functional disorder characterized by recurrent abdominal pain associated with an increased frequency of bowel movements and stool loose, based on Rome IV criteria, representing about 35% of all IBS cases [100, 101]. In this setting, some people

could present mimicking symptoms. In fact, in a non-negligible rate of patients, ranging between 1.8 and 6.1%, IBS-D related symptoms hides the diagnosis of EPI [102]. These findings are further supported by Olmos et al. [103], who demonstrated that dyspepsia was significantly more common in patients with EPI (OR=34.7). This condition was also associated with vitamin deficiencies, and endoscopic ultrasound revealed pancreatic steatosis in 71% of the cases. The clinical relevance of these data lies in the distinct therapeutic approach required for this population [103]. Indeed, in 95 % of patients with concurrent EPI and IBS-D, a 12-week course of PERT led to significant improvements in stool frequency, consistency, and abdominal pain, compared to only 7% of matched IBS-D control [104].

Although guidelines do not suggest excluding the presence of pancreatic insufficiency to formulate the diagnosis of IBS-D, clinicians should consider proper testing for non-responders patients.

CONCLUSIONS

Pancreatic enzyme replacement therapy has shown its effectiveness in various conditions beyond CP. One of the main applications, supported by strong evidence, is CF. Additionally, PERT could be beneficial in patients with pancreatic cancer and post-surgical states, as it may improve nutritional status, leading to better nutritional outcomes. Emerging evidence also suggests potential benefits of PERT in managing exocrine pancreatic insufficiency associated with diabetes mellitus and gastrointestinal surgeries.

Thus, PL is a cornerstone in the management of several complex gastroenterological conditions, promoting digestive health and improving the quality of life for affected individuals. In conclusion, PERT plays a crucial role in managing pancreatic insufficiency, improving nutritional status and quality of life across different clinical situations. While more research, particularly from RCTs, is needed to optimize dosing strategies and establish standardized PERT protocols, clinicians should consider tailoring PERT to individual patient needs based on the available evidence across various clinical scenarios.

Conflicts of interest: None to declare.

Authors' contribution: L.V., M.V. and M.C. conceived and designed the study. M.V. and M.C. collected the data. M.V. and M.C. designed the methodology and drafted the manuscript. L.V. F.A., L.B., and G.d.N critically revised the manuscript. All authors read and approved the final version of the manuscript.

REFERENCES

1. Mössner J, Keim V. Pancreatic Enzyme Therapy. Dtsch Arztebl Int 2011;108:578-582. doi:10.3238/arztebl.2011.0578
2. Venkatesh P, Kasi A. Pancrelipase Therapy. StatPearls. 2025. Venkatesh P, Kasi A. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
3. Capurso G, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. Clin Exp Gastroenterol 2019;12:129–139. doi:10.2147/CEG.S168266
4. Lewis D. An Updated Review of Exocrine Pancreatic Insufficiency Prevalence finds EPI to be More Common in General Population than Rates of Co-Conditions. J Gastrointestin Liver Dis 2024;33:123–130. doi:10.15403/jgld-5005
5. Kuhn RJ, Gelrud A, Munck A, Caras S. CREON (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency. Adv Ther 2010;27:895–916. doi:10.1007/s12325-010-0085-7
6. DiMagno EP, Go VL, Summerskill WH. Relations between Pancreatic Enzyme Outputs and Malabsorption in Severe Pancreatic Insufficiency. N Engl J Med 1973;288:813-815. doi:10.1056/NEJM197304192881603
7. Singh VK, Haupt ME, Geller DE, Hall JA, Diez PMQ. Less common etiologies of exocrine pancreatic insufficiency. World J Gastroenterol 2017;23:7059–7076. doi:10.3748/wjg.v23.i39.7059
8. González-Sánchez V, Amrani R, González V, Trigo C, Picó A, de-Madaria E. Diagnosis of exocrine pancreatic insufficiency in chronic pancreatitis: 13C-Mixed Triglyceride Breath Test versus Fecal Elastase. Pancreatology 2017;17:580–585. doi:10.1016/j.pan.2017.03.002
9. Vanga RR, Tansel A, Sidiq S, El-Serag HB, Othman MO. Diagnostic Performance of Measurement of Fecal Elastase-1 in Detection of Exocrine Pancreatic Insufficiency: Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol 2018;16:1220-1228.e4. doi:10.1016/j.cgh.2018.01.027
10. Chaudhary A, Domínguez-Muñoz JE, Layer P, Lerch MM. Pancreatic Exocrine Insufficiency as a Complication of Gastrointestinal Surgery and the Impact of Pancreatic Enzyme Replacement Therapy. Dig Dis 2020;38:53–68. doi:10.1159/000501675
11. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. World J Gastroenterol 2013;19:7258-66. doi:10.3748/wjg.v19.i42.7258
12. Waljee AK, Dimagno MJ, Wu BU, Schoenfeld PS, Conwell DL. Systematic review: pancreatic enzyme treatment of malabsorption associated with chronic pancreatitis. Aliment Pharmacol Ther 2009;29:235–246. doi:10.1111/j.1365-.2008.03885.x
13. Rosenberg J, Reddy MN, Seelam P, Li O, Twal 2036J, Pack J. A Retrospective Real-World Evidence Evaluation of the Characteristics of Exocrine Pancreatic Insufficiency in Patients With Chronic Pancreatitis and Type 2 Diabetes Treated With Pancrelipase in the United States. Pancreas 2022;51:1308–1314. doi:10.1097/MPA.0000000000002203
14. Barkin JA, Barkin JS. Effect of Pancrelipase Therapy on Exocrine Pancreatic Insufficiency Symptoms and Coefficient of Fat Absorption Associated with Chronic Pancreatitis. Pancreas 2021;50:176–182. doi:10.1097/MPA.0000000000001733
15. Whitcomb DC, Bodhani A, Beckmann K, et al. Efficacy and Safety of Pancrelipase/Pancreatin in Patients With Exocrine Pancreatic Insufficiency and a Medical History of Diabetes Mellitus. Pancreas 2016;45:679–686. doi:10.1097/MPA.0000000000000514
16. Yaghoobi M, McNabb-Baltar J, Bijarchi R, Cotton PB. Pancreatic Enzyme Supplements Are Not Effective for Relieving Abdominal Pain in Patients with Chronic Pancreatitis: Meta-Analysis and Systematic Review of Randomized Controlled Trials. Can J Gastroenterol Hepatol 2016;2016:8541839. doi:10.1155/2016/8541839
17. Pezzilli R, Caccialanza R, Capurso G, Brunetti O, Milella M, Falconi M. Pancreatic Enzyme Replacement Therapy in Pancreatic Cancer. Cancers (Basel) 2020;12:275. doi:10.3390/cancers12020275
18. Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The Effects of Oral Pancreatic Enzymes (Creon 10 Capsule) on Steatorrhea. Pancreas 2006;33:156–162. doi:10.1097/01.mpa.0000226884.32957.5e

19. Thomson M, Clague A, Cleghorn GJ, Shepherd RW. Comparative In Vitro and In Vivo Studies of Enteric-Coated Pancrelipase Preparations for Pancreatic Insufficiency. J Pediatr Gastroenterol Nutr 1993;17:407–413. doi:10.1097/00005176-199311000-00013
20. Pierzynowska K, Valverde-Piedra J, Szymanczyk S, et al. Pancreatic-like enzymes of microbial origin restore growth and normalize lipid absorption in a pig model with exocrine pancreatic insufficiency. Arch Med Sci 2018;14:407-414. doi:10.5114/aoms.2018.73471
21. Sadeghi S, Vallerinteavide Mavelli G, Vaidya SS, Drum CL. Gastrointestinal Tract Stabilized Protein Delivery Using Disulfide Thermostable Exoshell System. Int J Mol Sci 2022;23:9856. doi:10.3390/ijms23179856
22. Konstan MW, Wagener JS, Wilschanski M, et al. A comparison of liprotamase, a non-porcine pancreatic enzyme replacement therapy, to porcine extracted pancrelipase in a noninferiority randomized clinical trial in patients with cystic fibrosis. Clin Investig (Lond) 2018;8:147-154.
23. Sander-Struckmeier S, Beckmann K, Janssen-van Solingen G, Pollack P. Retrospective Analysis to Investigate the Effect of Concomitant Use of Gastric Acid–Suppressing Drugs on the Efficacy and Safety of Pancrelipase/Pancreatin (CREON®) in Patients with Pancreatic Exocrine Insufficiency. Pancreas 2013;42:983–989. doi:10.1097/MPA.0b013e31828784ef
24. Shimizu K, Ito T, Irisawa A, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2021. J Gastroenterol 2022;57:709–724. doi:10.1007/s00535-022-01911-6
25. Francisco MP, Wagner MH, Sherman JM, Theriaque D, Bowser E, Novak DA. Ranitidine and Omeprazole as Adjuvant Therapy to Pancrelipase to Improve Fat Absorption in Patients With Cystic Fibrosis. J Pediatr Gastroenterol Nutr 2002;35:79–83. doi:10.1097/00005176-200207000-00017
26. Singh VK, Schwarzenberg SJ. Pancreatic insufficiency in Cystic Fibrosis. J Cyst Fibros 2017;16 Suppl 2:S70-S78. doi:10.1016/j.jcf.2017.06.011
27. Freedman SD, Blanco PG, Zaman MM, et al. Association of Cystic Fibrosis with Abnormalities in Fatty Acid Metabolism. N Engl J Med 2004;350:560-569. doi:10.1056/NEJMoa021218
28. Brady MS, Garson JL, Krug SK, et al. An Enteric-Coated High-Buffered Pancrelipase Reduces Steatorrhea in Patients with Cystic Fibrosis: A Prospective, Randomized Study. J Am Diet Assoc 2006;106:1181–1186. doi:10.1016/j.jada.2006.05.011
29. Graff GR, McNamara J, Royall J, Caras S, Forssmann K. Safety and Tolerability of a New Formulation of Pancrelipase Delayed-Release Capsules (CREON®) in Children Under Seven Years of Age with Exocrine Pancreatic Insufficiency due to Cystic Fibrosis. Clin Drug Investig 2010;30:351–364. doi:10.2165/11533390-000000000-00000
30. Colombo C, Fredella C, Russo MC, et al. Efficacy and Tolerability of Creon for Children in Infants and Toddlers With Pancreatic Exocrine Insufficiency Caused by Cystic Fibrosis. Pancreas 2009;38:693–699. doi:10.1097/MPA.0b013e3181a85eaf
31. Graff GR, Maguiness K, McNamara J, et al. Efficacy and tolerability of a new formulation of pancrelipase delayed-release capsules in children aged 7 to 11 years with exocrine pancreatic insufficiency and cystic fibrosis: A multicenter, randomized, double-blind, placebo-controlled, two-period crossover, superiority study. Clin Ther 2010;32:89–103. doi:10.1016/j.clinthera.2010.01.012
32. Konstan MW, Accurso FJ, Nasr SZ, Ahrens RC, Graff GR. Efficacy and safety of a unique enteric-coated bicarbonate-buffered pancreatic enzyme replacement therapy in children and adults with cystic fibrosis. Clin Investig (Lond) 2013;3:723–729. doi:10.4155/cli.13.62
33. Wooldridge JL, Heubi JE, Amaro-Galvez R, et al. EUR-1008 pancreatic enzyme replacement is safe and effective in patients with cystic fibrosis and pancreatic insufficiency. J Cyst Fibros 2009;8:405–417. doi:10.1016/j.jcf.2009.07.006
34. Trapnell BC, Strausbaugh SD, Woo MS, et al. Efficacy and safety of PANCREAZE® for treatment of exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2011;10:350–356. doi:10.1016/j.jcf.2011.04.005
35. Trapnell BC, Maguiness K, Graff GR, Boyd D, Beckmann K, Caras S. Efficacy and safety of Creon® 24,000 in subjects with exocrine pancreatic insufficiency due to cystic fibrosis. J Cyst Fibros 2009;8:370–377. doi:10.1016/j.jcf.2009.08.008
36. Baker S. Delayed release pancrelipase for the treatment of pancreatic exocrine insufficiency associated with cystic fibrosis. Ther Clin Risk Manag 2008;4:1079–1084. doi:10.2147/tcrm.s3123
37. Konstan MW, Liou TG, Strausbaugh SD, et al. Efficacy and Safety of a New Formulation of Pancrelipase (Ultrase MT20) in the Treatment of Malabsorption in Exocrine Pancreatic Insufficiency in Cystic Fibrosis. Gastroenterol Res Pract 2010;2010:898193. doi:10.1155/2010/898193
38. Caras S, Boyd D, Zipfel L, Sander-Struckmeier S. Evaluation of Stool Collections to Measure Efficacy of PERT in Subjects With Exocrine Pancreatic Insufficiency. J Pediatr Gastroenterol Nutr 2011;53:634–640. doi:10.1097/MPG.0b013e3182281c38
39. Gelzo M, Iacotucci P, Sica C, et al. Influence of pancreatic status on circulating plasma sterols in patients with cystic fibrosis. Clin Chem Lab Med 2020;58:1725–1730. doi:10.1515/cclm-2019-1112
40. Drzymała-Czyż S, Krzyżanowska-Jankowska P, Dziedzic K, et al. Severe Genotype, Pancreatic Insufficiency and Low Dose of Pancreatic Enzymes Associate with Abnormal Serum Sterol Profile in Cystic Fibrosis. Biomolecules 2021;11:313. doi:10.3390/biom11020313
41. Perano SJ, Couper JJ, Horowitz M, et al. Pancreatic Enzyme Supplementation Improves the Incretin Hormone Response and Attenuates Postprandial Glycemia in Adolescents With Cystic Fibrosis: A Randomized Crossover Trial. J Clin Endocrinol Metab 2014;99:2486–2493. doi:10.1210/jc.2013-4417
42. Kuo P, Stevens JE, Russo A, et al. Gastric Emptying, Incretin Hormone Secretion, and Postprandial Glycemia in Cystic Fibrosis—Effects of Pancreatic Enzyme Supplementation. J Clin Endocrinol Metab 2011;96:E851–E855. doi:10.1210/jc.2010-2460
43. Woo SM, Joo J, Kim SY, et al. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. Pancreatology 2016;16:1099–1105. doi:10.1016/j.pan.2016.09.001
44. Lan X, Robin G, Kasnik J, Wong G, Abdel-Rahman O. Challenges in Diagnosis and Treatment of Pancreatic Exocrine Insufficiency among Patients with Pancreatic Ductal Adenocarcinoma. Cancers (Basel) 2023;15:1331. doi:10.3390/cancers15041331
45. Kroon VJ, Daamen LA, Tseng DSJ, et al. Pancreatic exocrine insufficiency following pancreatoduodenectomy: A prospective bi-center study. Pancreatology 2022;22:1020–1027. doi:10.1016/j.pan.2022.08.002
46. Imrie CW, Connett G, Hall RI, Charnley RM. Review article: enzyme supplementation in cystic fibrosis, chronic pancreatitis, pancreatic and periampullary cancer. Aliment Pharmacol Ther 2010;32 Suppl 1:1–25. doi:10.1111/j.1365-2036.2010.04437.x
47. Roeyen G, Berrevoet F, Borbath I, et al. Expert opinion on management of pancreatic exocrine insufficiency in pancreatic cancer. ESMO Open 2022;7:100386. doi:10.1016/j.esmoop.2022.100386

48. Hendifar AE, Petzel MQB, Zimmers TA, et al. Pancreas Cancer-Associated Weight Loss. Oncologist 2019;24:691–701. doi:10.1634/theoncologist.2018-0266
49. Barkin JA, Harb D, Kort J, Barkin JS. Real-World Patient Experience With Pancreatic Enzyme Replacement Therapy in the Treatment of Exocrine Pancreatic Insufficiency. Pancreas 2024;53:e16–e21. doi:10.1097/MPA.0000000000002273
50. Conroy T, Pfeiffer P, Vilgrain V, et al. Pancreatic cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2023;34:987–1002. doi:10.1016/j.annonc.2023.08.009
51. Landers A, Muircroft W, Brown H. Pancreatic enzyme therapy (PERT) for malabsorption in patients with metastatic pancreatic cancer. BMJ Support Palliat Care 2016;6:75–79. doi:10.1136/bmjspcare-2014-000694
52. Barkin JA, Westermann A, Hoos W, et al. Frequency of Appropriate Use of Pancreatic Enzyme Replacement Therapy and Symptomatic Response in Pancreatic Cancer Patients. Pancreas 2019;48:780–786. doi:10.1097/MPA.0000000000001330
53. Roberts KJ, Bannister CA, Schrem H. Enzyme replacement improves survival among patients with pancreatic cancer: Results of a population based study. Pancreatology 2019;19:114–121. doi:10.1016/j.pan.2018.10.010
54. Saito T, Hirano K, Isayama H, et al. The Role of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. Pancreas 2017;46:341–346. doi:10.1097/MPA.0000000000000767
55. Bruno MJ, Haverkort EB, Tijssen GP, Tytgat GNJ, van Leeuwen DJ. Placebo controlled trial of enteric coated pancreatin microsphere treatment in patients with unresectable cancer of the pancreatic head region. Gut 1998;42:92–96. doi:10.1136/gut.42.1.92
56. Saito T, Nakai Y, Isayama H, et al. A Multicenter Open-Label Randomized Controlled Trial of Pancreatic Enzyme Replacement Therapy in Unresectable Pancreatic Cancer. Pancreas 2018;47:800–806. doi:10.1097/MPA.0000000000001079
57. Domínguez-Muñoz JE, Nieto-Garcia L, López-Díaz J, Lariño-Noia J, Abdulkader I, Iglesias-Garcia J. Impact of the treatment of pancreatic exocrine insufficiency on survival of patients with unresectable pancreatic cancer: a retrospective analysis. BMC Cancer 2018;18:534. doi:10.1186/s12885-018-4439-x
58. Landers A, Donaldson F, Brown H, McKenzie C, Pendharkar S. The Impact of Pancreatic Enzyme Replacement Therapy on Patients With Advanced Pancreatic Adenocarcinoma. Pancreas 2022;51:405–414. doi:10.1097/MPA.0000000000002049
59. Whitcomb DC, Lehman GA, Vasileva G, et al. Pancrelipase Delayed-Release Capsules (CREON) for Exocrine Pancreatic Insufficiency due to Chronic Pancreatitis or Pancreatic Surgery: A Double-Blind Randomized Trial. Am J Gastroenterol 2010;105:2276–2286. doi:10.1038/ajg.2010.201
60. Gubergrits N, Malecka-Panas E, Lehman GA, et al. A 6-month, open-label clinical trial of pancrelipase delayed-release capsules (Creon) in patients with exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery. Aliment Pharmacol Ther 2011;33:1152–1161. doi:10.1111/j.1365-2036.2011.04631.x
61. Roberts KJ, Schrem H, Hodson J, et al. Pancreas exocrine replacement therapy is associated with increased survival following pancreatoduodenectomy for periampullary malignancy. HPB 2017;19:859–867. doi:10.1016/j.hpb.2017.05.009
62. Izumi H, Yoshii H, Fujino R, et al. Factors contributing to nonalcoholic fatty liver disease (NAFLD) and fat deposition after pancreaticoduodenectomy: A retrospective analysis. Ann Gastroenterol Sur 2023;7:793–799. doi:10.1002/ags3.12673
63. Kishi Y, Shimada K, Nara S, Esaki M, Kosuge T. Administration of Pancrelipase as Effective Treatment for Hepatic Steatosis After Pancreatectomy. Pancreas 2015;44:983–987. doi:10.1097/MPA.0000000000000356
64. Yamazaki S, Takayama T, Higaki T, et al. Pancrelipase with branched-chain amino acids for preventing nonalcoholic fatty liver disease after pancreaticoduodenectomy. J Gastroenterol 2016;51:55–62. doi:10.1007/s00535-015-1077-9
65. Nagai M, Sho M, Satoi S, et al. Effects of pancrelipase on nonalcoholic fatty liver disease after pancreaticoduodenectomy. J Hepatobiliary Pancreat Sci 2014;21:186–192. doi:10.1002/jhbp.14
66. Asano Y, Horiguchi A, Ito M, et al. Effect of pancrelipase in preventing pancreatic dysfunction after pancreaticoduodenectomy. Fujita Med J 2019;5:63-66. doi:10.20407/fmj.2018-016
67. Fong ZV, Alvino DM, Castillo CF, et al. Health-related Quality of Life and Functional Outcomes in 5-year Survivors After Pancreaticoduodenectomy. Ann Surg 2017;266:685–692. doi:10.1097/SLA.0000000000002380
68. Rompen IF, Merz DC, Alhalabi KT, et al. Perioperative Drug Treatment in Pancreatic Surgery—A Systematic Review and Meta-Analysis. J Clin Med 2023;12:1750. doi:10.3390/jcm12051750
69. Huang W, de la Iglesia-García D, Baston-Rey I, et al. Exocrine Pancreatic Insufficiency Following Acute Pancreatitis: Systematic Review and Meta-Analysis. Dig Dis Sci 2019;64:1985–2005. doi:10.1007/s10620-019-05568-9
70. Kahl S, Schütte K, Glasbrenner B, et al. The effect of oral pancreatic enzyme supplementation on the course and outcome of acute pancreatitis: a randomized, double-blind parallel-group study. JOP 2014;15:165-174. doi:10.6092/1590-8577/797
71. Lewis DM. A Systematic Review of Exocrine Pancreatic Insufficiency Prevalence and Treatment in Type 1 and Type 2 Diabetes. Diabetes Technol Ther 2023;25:659–672. doi:10.1089/dia.2023.0157
72. Nakamura T, Imamura K, Takebe K, et al. Correlation between pancreatic endocrine and exocrine function and characteristics of pancreatic endocrine function in patients with diabetes mellitus owing to chronic pancreatitis. Int J Pancreatol 1996;20:169–175. doi:10.1007/BF02803765
73. Korc M. Islet growth factors: curing diabetes and preventing chronic pancreatitis? Journal of Clinical Investigation 1993;92:1113–1114. doi:10.1172/JCI116677
74. Hardt PD, Hauenschild A, Nalop J, et al. High prevalence of exocrine pancreatic insufficiency in diabetes mellitus. A multicenter study screening fecal elastase 1 concentrations in 1,021 diabetic patients. Pancreatology 2003;3:395–402. doi:10.1159/000073655
75. Alexandre-Heymann L, Yaker F, Lassen PB, Dubois-Laforgue D, Larger E. Pancreatic enzyme replacement therapy in subjects with exocrine pancreatic insufficiency and diabetes mellitus: a real-life, case–control study. Diabetol Metab Syndr 2024;16:39. doi:10.1186/s13098-024-01265-4
76. Ewald N, Bretzel RG, Fantus IG, et al; S-2453110 Study Group. Pancreatin therapy in patients with insulin-treat ed diabetes mellitus and exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations. Results of a prospective multi-centre trial. Diabetes Metab Res Rev 2007;23:386–391. doi:10.1002/dmrr.708
77. Phillips AE, Tang G, Wang X, Forsmark CE, Yadav D. Pancreatic Enzyme Replacement Therapy in Patients with Non-pancreatic Digestive Conditions: A Nationwide Claims Analysis. Dig Dis Sci 2023;68:1754–1761. doi:10.1007/s10620-022-07750-y
78. Antonini F, Crippa S, Falconi M, Macarri G, Pezzilli R. Pancreatic enzyme replacement therapy after gastric resection: An update. Dig Liver Dis 2018;50:1–5. doi:10.1016/j.dld.2017.10.025

79. Domínguez-Muñoz JE. Pancreatic enzyme replacement therapy: exocrine pancreatic insufficiency after gastrointestinal surgery. HPB (Oxford) 2009;11 Suppl 3:3-6. doi: 10.1111/j.1477-2574.2009.00132.x
80. Brägelmann R, Armbrecht U, Rosemeyer D, Schneider B, Zilly W, Stockbrügger RW. The effect of pancreatic enzyme supplementation in patients with steatorrhoea after total gastrectomy. Eur J Gastroenterol Hepatol 1999;11:231–237. doi:10.1097/00042737-199903000-00004
81. Armbrecht U, Lundell L, Stockbrügger RW. The benefit of pancreatic enzyme substitution after total gastrectomy. Aliment Pharmacol Ther 1988;2:493–500. doi:10.1111/j.1365-2036.1988.tb00722.x
82. Catarci M, Berlanda M, Grassi GB, Masedu F, Guadagni S. Pancreatic enzyme supplementation after gastrectomy for gastric cancer: a randomized controlled trial. Gastric Cancer 2018;21:542–551. doi:10.1007/s10120-017-0757-y
83. Sridhar RP, Yacob M, Chowdhury SD, Balasubramanian KA, Samarasam I. Exocrine Pancreatic Insufficiency Following Gastric Resectional Surgery - is Routine Pancreatic Enzyme Replacement Therapy Necessary? Indian J Surg Oncol 2021;12:391–396. doi:10.1007/s13193-021-01315-7
84. Huddy JR, Macharg FMS, Lawn AM, Preston SR. Exocrine pancreatic insufficiency following esophagectomy. Dis Esophagus 2013;26:594-597. doi: 10.1111/dote.12004
85. Moore HN, Chirco AR, Plescia T, et al. Exocrine pancreatic insufficiency after bariatric surgery: a bariatric surgery center of excellence experience. Surg Endosc 2023;37:1466–1475. doi:10.1007/s00464-022-09388-3
86. Kwon JY, Nelson A, Salih A, et al. Exocrine pancreatic insufficiency after bariatric surgery. Pancreatology 2022;22:1041–1045. doi:10.1016/j.pan.2022.07.009
87. Ganipisetti VM, Naha S. Bariatric Surgery Malnutrition Complications. 2025. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025.
88. Kuin C, den Ouden F, Brandts H, et al. Treatment of Severe Protein Malnutrition After Bariatric Surgery. Obes Surg 2019;29:3095–3102. doi:10.1007/s11695-019-04035-8
89. Rana SS. Is pancreatic exocrine insufficiency in celiac disease related to structural alterations in pancreatic parenchyma? Ann Gastroenterol 2016;29:363-366. doi:10.20524/aog.2016.0042
90. Yoosuf S, Barrett CG, Papamichael K, et al. Pancreatic enzyme supplementation versus placebo for improvement of gastrointestinal symptoms in non-responsive celiac disease: A cross-over randomized controlled trial. Front Med (Lausanne) 2023;9:1001879. doi:10.3389/fmed.2022.1001879
91. Carroccio A, Iacono G, Montalto G, et al. Pancreatic enzyme therapy in childhood celiac disease. Dig Dis Sci 1995;40:2555–2560. doi:10.1007/BF02220441
92. Valvano M, Fabiani S, Monaco S, et al. Old and New Adjunctive Therapies in Celiac Disease and Refractory Celiac Disease: A Review. Int J Mol Sci 2023;24:12800. doi:10.3390/ijms241612800
93. Evans KE, Leeds JS, Morley S, Sanders DS. Pancreatic Insufficiency in Adult Celiac Disease: Do Patients Require Long-Term Enzyme Supplementation? Dig Dis Sci 2010;55:2999–3004. doi:10.1007/s10620-010-1261-y
94. Valvano M, Capannolo A, Cesaro N, et al. Nutrition, Nutritional Status, Micronutrients Deficiency, and Disease Course of Inflammatory Bowel Disease. Nutrients 2023;15:3824. doi:10.3390/nu15173824
95. Antonini F, Pezzilli R, Angelelli L, Macarri G. Pancreatic disorders in inflammatory bowel disease. World J Gastrointest Pathophysiol 2016;7:276-282. doi:10.4291/wjgp.v7.i3.276
96. Maconi G, Dominici R, Molteni M, et al. Pevalence of Pancreatic Insufficiency in Inflammatory Bowel Diseases. Assessment by Fecal Elastase-1. Dig Dis Sci 2008;53:262–270. doi:10.1007/s10620-007-9852-y
97. Heikius B, Niemelä S, Lehtola J, Karttunen T, Lähde S. Pancreatic Duct Abnormalities and Pancreatic Function in Patients with Chronic Inflammatory Bowel Disease. Scand J Gastroenterol 1996;31:517–523. doi:10.3109/00365529609006775
98. Angelini G, Cavallini G, Bovo P, et al. Pancreatic function in chronic inflammatory bowel disease. Int J Pancreatol 1988;3:185-193. doi:10.1007/BF02798930
99. Hegnhoj J, Hansen CP, Rannem T, Sobirk H, Andersen LB, Andersen JR. Pancreatic function in Crohn's disease. Gut 1990;31:1076–1079. doi:10.1136/gut.31.9.1076
100. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. Gastroenterology 2016;150:1262-1279.e2. doi:10.1053/j.gastro.2016.02.032
101. Moshiree B, Heidelbaugh JJ, Sayuk GS. A Narrative Review of Irritable Bowel Syndrome with Diarrhea: A Primer for Primary Care Providers. Adv Ther 2022;39:4003-4020. doi:10.1007/s12325-022-02224-z
102. Poon D, Law GR, Major G, Andreyev HJN. A systematic review and meta-analysis on the prevalence of non-malignant, organic gastrointestinal disorders misdiagnosed as irritable bowel syndrome. Sci Rep 2022;12:1949. doi:10.1038/s41598-022-05933-1
103. Olmos JI, Piskorz MM, Litwin N, et al. Exocrine Pancreatic Insufficiency is Undiagnosed in Some Patients with Diarrhea-Predominant Irritable Bowel Syndrome Using the Rome IV Criteria. Dig Dis Sci 2022;67:5666–5675. doi:10.1007/s10620-022-07568-8
104. Leeds JS, Hopper AD, Sidhu R, et al. Some Patients With Irritable Bowel Syndrome May Have Exocrine Pancreatic Insufficiency. Clin Gastroenterol Hepatol 2010;8:433-438. doi:10.1016/j.cgh.2009.09.032