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REVIEW

Less common etiologies of exocrine pancreatic insufficiency

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Abstract

Exocrine pancreatic insufficiency (EPI), an important cause of maldigestion and malabsorption, results from primary pancreatic diseases or secondarily impaired exocrine pancreatic function. Besides cystic fibrosis and chronic pancreatitis, the most common etiologies of EPI, other causes of EPI include unresectable pancreatic cancer, metabolic diseases (diabetes); impaired hormonal stimulation of exocrine pancreatic secretion by cholecystokinin (CCK); celiac or inflammatory bowel disease (IBD) due to loss of intestinal brush border proteins; and gastrointestinal surgery (asynchrony between motor and secretory functions, impaired enteropancreatic feedback, and inadequate mixing of pancreatic secretions with food). This paper reviews such conditions that have less straightforward associations with EPI and examines the role of pancreatic enzyme replacement therapy (PERT). Relevant literature was identified by database searches. Most patients with inoperable pancreatic cancer develop EPI (66%-92%). EPI occurs in patients with type 1 (26%-57%) or type 2 diabetes (20%-36%) and is typically mild to moderate; by definition, all patients with type 3c (pancreatogenic) diabetes have EPI. EPI occurs in untreated celiac disease (4%-80%), but typically resolves on a gluten-free diet. EPI manifests in patients with IBD (14%-74%) and up to 100% of gastrointestinal surgery patients (47%-100%; dependent on surgical site). With the paucity of published studies on PERT use for these

conditions, recommendations for or against PERT use remain ambiguous. The authors conclude that there is an urgent need to conduct robust clinical studies to understand the validity and nature of associations between EPI and medical conditions beyond those with proven mechanisms, and examine the potential role for PERT.

Key words: Celiac disease; Inflammatory bowel disease; Exocrine pancreatic insufficiency; Malabsorption; Epidemiology; Pancreas; Pancreatic cancer; Secretion/absorption; Surgery

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Core tip: Exocrine pancreatic insufficiency (EPI) results from primary pancreatic diseases or secondarily impaired exocrine pancreatic function. Pancreatic enzyme replacement therapy (PERT) may prevent serious nutritional complications when such patients have symptomatic EPI. However, EPI may be more prevalent in patients with non-pancreatic diseases, diabetes, and pancreatic cancer than has generally been appreciated. Scant published evidence on EPI in these less common etiologies precludes firm recommendations on management. Robust clinical studies are urgently needed to understand the relationships between EPI and medical conditions beyond those with proven mechanisms, and examine the potential role for PERT.

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INTRODUCTION

The pancreas is a dual function organ that possesses both exocrine and endocrine components that are critical for the digestion, absorption, and metabolism of nutrients. Normal digestion requires the exocrine function of the pancreas for macronutrient digestion. This occurs primarily *via* enzymatic hydrolysis by pancreatic enzymes, in particular lipase, amylase, and proteases (trypsin and chymotrypsin)[1]. Exocrine pancreatic insufficiency (EPI) refers to the presence of maldigestion and malabsorption of nutrients and is a consequence of primary loss of functional parenchyma and/or secondarily impaired exocrine pancreatic function and insufficient pancreatic enzyme activity. EPI is sometimes defined simply as an enzyme output less than 10% of that necessary to sustain normal digestion; however, there is no consensus in the literature on the definition of EPI. Furthermore, the clinical presentation of EPI can vary widely depending on the underlying cause, as well as disease stage, diet, and other factors.

EPI is most commonly caused by diseases that destroy the pancreatic parenchyma, such as chronic pancreatitis and cystic fibrosis, as well as pancreatic resection[1,2]. The incidence of EPI in chronic pancreatitis ranges from 30% of patients with mild disease to 85% with severe disease[3]. Approximately 85% of infants with cystic fibrosis have EPI at birth[4]. However, EPI is also observed in other conditions that include unresectable pancreatic cancer; metabolic diseases (diabetes mellitus)[1,2]; impaired hormonal stimulation of exocrine pancreatic secretion by cholecystokinin (CCK); celiac disease or inflammatory bowel disease (IBD) due to loss of intestinal brush border proteins[1,2]; small intestinal bacterial overgrowth[5,6], although not all investigators have found a clear association[7]; impaired coordination between motor and secretory functions (asynchrony); impaired enteropancreatic feedback, and/or inadequate mixing of pancreatic juices with ingested food after gastrointestinal surgery; and other diseases that affect the pancreas, such as hemochromatosis[8,9] (Tables 1 and 2)[1,2].

In this publication, we first briefly review the diagnosis of EPI and management with pancreatic enzyme replacement therapy (PERT). Most knowledge about EPI comes from studies in patients with chronic pancreatitis or cystic fibrosis, and has already been thoroughly explained in previous reviews. Therefore, our article focuses on several other disease states for which the association with EPI is less straightforward, such as inoperable pancreatic cancer, diabetes mellitus, celiac disease, IBD, and gastrointestinal surgery. Finally, we summarize the limited available data on PERT for the treatment of patients with EPI due to these less common etiologies.

LITERATURE SEARCHES

Searches of BIOSIS Previews, Derwent Drug File, Embase, Embase Alert, International Pharmaceutical Abstracts, MEDLINE, and SciSearch were performed to identify eligible literature from the earliest available date to December 5, 2016. The search terms for EPI were "EPI" or "exocrine pancreatic insufficiency" or "maldigestion" or "malabsorption" or "nutritional deficiency" or "steatorrhea" or "(fat* or oil* or elastase) pre/2 (stool* or fece* or fecal)" or "pancreatic near/3 (function or test)" with the terms NOT "chronic pancreatitis" or "cystic fibrosis". For pancreatic cancer, the search included the following terms: "pancreatic cancer" or "pancreatic adenocarcinoma" or "pancreatic tumor". For diabetes mellitus, the search strategy included "diabetes" and "type 1" or "IDDM" or "insulin-dependent" or "type 2" or "NIDDM" or "noninsulin-dependent" or "type 3" or "type 3c" or "type Ⅲ" or "pancreatogenic". For celiac disease, the search included "celiac disease" or "celiac*". For IBD, the search strategy included "inflammatory bowel disease" or "ibd" or "Ulcerative Colitis" or "Crohn*"

Table 1 Causes of exocrine pancreatic insufficiency

Definite association with EPI
Chronic pancreatitis
Pancreatic tumor/cancer
Cystic fibrosis
Pancreatic resection
Pancreatic hemochromatosis
Mechanisms associated with EPI not fully identified
Type 1 and 2 diabetes
Type 3c (pancreatogenic) diabetes
Gastrointestinal diseases
Celiac disease
Inflammatory bowel disease
Crohn's disease
Ulcerative colitis
Gastrointestinal surgery
Aging

EPI: Exocrine pancreatic insufficiency.

or "Crohn Disease". For gastrointestinal surgery, the search strategy included "gastrointestinal surgery" or "digestive system surgical procedures" or [(post or surg*) near/5 ("gastr*" or "bariatric" or "duodenal switch" or "biliopancreatic diversion")] or "bariatric surger*" or "gastrectom*" or "gastric bypass" or "stomach bypass". Reviews, practical guidelines, letters, editorials, and articles were evaluated. The searches returned 582 hits, from which 163 published articles were initially selected. Subsequently, articles were selected based on their clinical relevance, and additional papers were found after a review of the reference lists of these articles. Only a few were designed as prospective controlled studies with clearly defined methodology; this underscores the lack of data to support associations and mechanisms relevant to the conditions explored.

DIAGNOSIS OF EPI

Patients with EPI may exhibit a wide variety of clinical symptoms and nutritional deficiencies (Table 3). Clinical symptoms associated with EPI include steatorrhea (large-volume, foul-smelling stools), diarrhea, weight loss, flatulence, and abdominal pain. EPI may be diagnosed when fecal fat excretion is > 7 g/d on a 100-g fat/d diet. In EPI, fat malabsorption often develops prior to protein and carbohydrate malabsorption because lipase has a higher susceptibility to intraluminal denaturation and proteolytic destruction compared with other enzymes[10,11]. Furthermore, the deficiency in pancreatic lipase cannot be compensated by gastric lipase, the only other lipolytic enzyme in adult humans[12]. Because the exocrine pancreas has a large functional reserve capacity, clinical symptoms may not manifest until exocrine pancreatic function is < 10% of normal[13]. Untreated malabsorption places patients at high risk for developing nutritional deficiencies[14], which can manifest as other health problems, including decreased bone mineral density resulting in osteoporosis or osteomalacia[15-17]; bone metabolism deficiencies and muscle spasms; impaired night vision and decreased immune competence[16,18,19]; coagulation problems[16]; and ataxia and peripheral neuropathy[16]. Additionally, EPI has been associated with high morbidity and mortality secondary to malnutrition-related complications and an increased risk of cardiovascular events[20].

In routine clinical practice, EPI may be difficult to diagnose, particularly in the early stages when patients are less symptomatic. Often patients make dietary modifications to reduce symptoms. Patients may have low serum levels of fat-soluble vitamins, micronutrients, and lipoproteins[21]. Severe symptomatic EPI can be diagnosed by the presence of steatorrhea, diarrhea, flatulence, or weight loss[22], which often manifest when fecal fat excretion is > 7 g/d (Table 4). Early diagnostic studies relied on direct pancreatic function tests (*i.e.*, those involving collection and analysis of secretions directly from the duodenum or pancreatic duct, including the secretin-pancreozymin and Lundh tests[2]), which remain the most sensitive and specific methods for assessing exocrine pancreatic function. Direct tests, however, are limited by their cost, duration, and invasive nature, which involve endoscopic aspiration or tube aspiration of secretions from the duodenum for several hours. During the past 20 years, the use of non-invasive indirect methods has become more common. These tests are more readily performed in multiple settings and are based on the measurement of fecal elastase and fecal fat[2,23,24].

The coefficient of fat absorption is the gold standard for diagnosing fat maldigestion; however, it is poorly accepted by patients and laboratory personnel because it requires a strict diet containing 100 g of fat daily for 5 d and collection of all feces for the last 3 d (classical Van de Kamer test)[2]. In addition, fat excretion > 7 g/d indicates steatorrhea but is not informative about whether this is due to EPI or extrapancreatic causes. Fecal elastase is a pancreatic enzyme that is stable during passage through the gastrointestinal tract; some consider its measurement as the new gold standard for EPI diagnosis[2]. However, the current cutoffs that are used to define EPI might be improved if the cutoff were reduced to 128 μg/g stool[25] or 84 μg/g stool[26]. For better sensitivity, formed stool samples are best, as loose samples may spuriously dilute and lower the elastase levels and give a false positive result[16,24]. Fecal elastase, measured by enzyme-linked immunosorbent assay, has a good sensitivity for moderate EPI (75%) and high sensitivity for severe EPI (95%), and has a higher specificity (79%-96%) compared with the direct tests[27]. It should be noted that decreased fecal elastase values have been reported in patients with conditions not typically associated with EPI, such as HIV infection (23%-54%), advanced renal disease (10%-48%), and irritable bowel syndrome (6%)[28]. It is commonly accepted

Table 2 Factors involved with exocrine pancreatic insufficiency in different medical conditions[1,16,77,78,107,129,131,133,143,144,152-154,164]

Mechanism involved	Pancreatic cancer	Diabetes mellitus	Celiac disease	IBD	GI surgery
Normal pancreas		√	√	√	√
Abnormal pancreas	√	√	√	√	
Low or absent pancreatic enzyme production	√	√	√	√	√
Lack of stimulus for pancreatic enzyme production			√	√	√
Postcibal asynchrony	√	√	√	√	√
Pancreatic or biliary tract abnormalities	√	√		√	
GI malabsorption			√	√	√

EPI: Exocrine pancreatic insufficiency; GI: Gastrointestinal; IBD: Inflammatory bowel disease.

Table 3 Common signs and symptoms of exocrine pancreatic insufficiency[1,14-16,18,19,22]

Sign/symptom	Associated findings
Excessive flatulence	Abdominal bloating or distension, cramps, belching
Steatorrhea	Fatty, bulky stools; increased bowel movements
Malnutrition	Weight loss, anorexia, fatigue
Vitamin D deficiency	Deficient bone mineralization, osteomalacia, osteoporosis
Vitamin K deficiency	Coagulation abnormalities, ecchymoses, bone metabolism deficiencies
Vitamin A deficiency	Night blindness, decreased immune competence
Vitamin E deficiency	Ataxia and peripheral neuropathy
Hypocalcemia	Muscle spasms, osteomalacia, osteoporosis
Hypoalbuminemia	Nail leukonychia

that a fecal elastase-1 level ⩽ 200 μg/g stool indicates EPI, with levels of 100 to 200 μg/g typically indicating mild to moderate impairment and levels < 100 μg/g reflecting severe impairment[29-31]. Fecal elastase testing is considerably more sensitive than the fecal chymotrypsin or PABA test and is the standard clinical marker for moderate to severe EPI[32-34]. However, there is poor correlation between fecal elastase levels and coefficient of fat absorption, making fecal elastase less attractive for clinical research and regulatory purposes[35]. Additionally, because fecal elastase values are unaffected by PERT, enzymes do not need to be stopped before testing; unfortunately, this also means that fecal elastase testing is ineffective for monitoring response to PERT, unlike direct measurement of fat absorption[3].

Although not widely available, other tests for the diagnosis of EPI include the ^{13}C-mixed triglyceride (^{13}C-MTG) breath test and secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imaging (MRCP). In the ^{13}C-MTG test, the patient ingests a small amount of ^{13}C-marked triglycerides which are degraded by lipases in the intestine to ^{13}C-marked fatty acids. The absorbed ^{13}C fatty acids are metabolized by the liver, and $^{13}CO_2$ is exhaled[36]. Lower lipase activity is associated with less $^{13}CO_2$ in the exhaled breath. This test can also be used to assess the effects of PERT[37]. Pancreatic exocrine function can also be assessed by changes in duodenal filling, pancreatic duct caliber, and accumulation of fluid in the pancreatic parenchyma, as monitored by MRCP following stimulation with exogenous secretin[38,39].

PERT

PERT is the backbone of EPI treatment. Patients with abnormal fecal fat excretion, steatorrhea, and/or weight loss are generally considered candidates for PERT[20]. The aims of PERT are to compensate for deficiencies in endogenous enzyme secretion, correct maldigestion and malabsorption, and ameliorate symptoms resulting from a loss of exocrine function. To achieve this, the enzymatic activity delivered into the duodenum in conjunction with gastric emptying must be sufficient to optimize digestion and nutrient absorption[21]. A main goal of PERT is to restore sufficient intestinal lipase levels[11]. Unprotected lipase is irreversibly inactivated in the acidic environment of the stomach (pH ⩽ 4). Consequently, inhibition of gastric acid secretion has been used to prevent lipase inactivation. Modern preparations consist of pancreatic enzymes encapsulated in microspheres or microgranules, with an enteric coating designed to release the enzymes into the pH-neutral environment of the intestinal lumen[40]. A number of porcine lipase preparations are approved for PERT[41], and the reader is referred to publications from national and professional organizations for recommended dosages[16,42-44] Replacement of protease and amylase is also important in EPI, where some of its symptoms relate to deficiency of these two enzymes, as well. Pancrelipase of porcine origin contains the three enzymes (lipase, protease, and amylase) in adequate ratios to treat EPI.

In randomized controlled trials, PERT improved the coefficient of fat absorption, clinical symptoms,

Table 4 Symptoms and tests used in the diagnosis of exocrine pancreatic insufficiency[2,16,23,24]

Clinical symptoms
Steatorrhea
Diarrhea
Flatulence
Weight loss
Laboratory findings
Fecal fat > 7 g/d on a 100-g fat/d diet
Inconvenient; special high-fat diet and prolonged collection of feces
Considered gold standard
An abnormal coefficient of fat absorption is not specific for EPI
Fecal elastase-1 level ⩽ 200 μg/g stool; < 100 μg/g stool = severe EPI
Simple, convenient, and widely available
Measured on a random stool sample
Liquid stools may lead to falsely low results due to dilution
Less accurate in mild stages of disease
Positive qualitative fecal fat (Sudan Ⅲ) staining
Special high-fat diet
Less accurate; semi-quantitative microscopic method
Insensitive for mild disease
Fecal chymotrypsin ⩽ 6 U/g stool
Less sensitive than fecal elastase for mild EPI
Fluorescein dilaurate (pancreolauryl test)
Easy to perform
Not widely available
^{13}C-mixed triglyceride breath test
Well established
Not widely available
Imaging/endoscopy
Pancreatic duct dilatation
Main pancreatic duct calculi
Endosonographic criteria of chronic pancreatitis
Secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imaging
New
Not widely available

EPI: Exocrine pancreatic insufficiency.

and quality of life (QoL) of patients with EPI and significantly slowed gastric emptying[45-48]. Patients with EPI experienced a reduction in stool frequency and fat/water content, as well as abdominal pain and flatulence[47]. PERT is generally well tolerated; treatment-emergent adverse events include headache, infection, abdominal pain, flatulence, diarrhea, and dyspepsia[45-47,49]. However, because only porcine PERT products are currently available, allergic reactions, including anaphylactic shock, could potentially occur. Furthermore, fibrosing colonopathy, a rare but serious complication, has been reported in children[50] and adults[51] with cystic fibrosis receiving high-dose PERT, but there have been no reports in subjects with chronic pancreatitis.

PANCREATIC CANCER AND EPI

Pancreatic cancer ranks fourth among cancer-related deaths in the United States and has a 5-year survival rate of 7.2%[52,53]. This review focuses on inoperable pancreatic cancer, as the relationship between pancreatectomy and EPI is already well-recognized. EPI in patients with pancreatic cancer is related to the loss of pancreatic parenchyma and/or obstruction of the main duct, which impedes the production of pancreatic enzymes or their transportation into the duodenum. The most important predictors for EPI are localization of the tumor to the pancreatic head, ⩾ 90% destruction of normal tissue, degree of ductal obstruction, and surgical loss of pancreatic tissue[1,16,54]. The severity of ductal obstruction is proportional to the length of the obstructed duct; hence, enzyme secretion decreases as the cancer spreads distally, from head to body to tail[1,54,55].

The reported occurrence of malabsorption and exocrine dysfunction varies between 66% and 92% of patients with pancreatic cancer[30,56-59], with 65% to 75% of patients experiencing fat malabsorption and 50% of patients experiencing some degree of protein malabsorption[60,61]. In a prospective study of patients with an inoperable tumor of the pancreatic head region, 66% had EPI at diagnosis and 92% had a fecal elastase level < 200 μg/g by the 6-mo follow-up; 77% of patients were being treated with PERT[59]. In a systematic review, the prevalence of EPI was 25% to 50% in patients with advanced pancreatic cancer who did not undergo resection[62]. Although EPI is usually moderate in severity[61], in a prospective study, Partelli *et al*[31] detected extremely reduced (fecal elastase ⩽ 20 μg/g) in 25%, severely reduced (> 20 to < 100 μg/g) in 14%, and moderately reduced exocrine pancreatic secretion (⩾ 100-200 μg/g) in 11% of patients with advanced pancreatic cancer[31]. Pancreatic function abnormality seems to be higher in patients with tumors located in the pancreatic head versus in the body or tail[31,63]. Furthermore, in a prospective study, significantly more patients with a pancreatic head tumor had extremely reduced exocrine pancreatic secretion (fecal elastase ⩽ 20 μg/g) versus patients with a body or tail tumor; notably, a significant correlation was found between extremely reduced exocrine pancreatic secretion and poor survival.

Several studies have also reported inadequate enzyme secretion (trypsin, lipase, amylase, elastase, and chymotrypsin) in patients with pancreatic cancer compared with healthy controls[55,58,64]. Elastase production may be reduced earlier and to a greater extent compared with the output of other enzymes, for unknown reasons[64]. Additionally, fecal amylase activity was significantly decreased in pancreatic cancer patients compared with healthy controls[65].

PANCREATIC CANCER AND PERT

Approximately 80% to 90% of patients with pancreatic cancer have unresectable or advanced metastatic disease, leaving only palliative treatment options to manage symptoms[66]. Gastrointestinal and diet management problems negatively impact patients' QoL[67]; consequently, early treatment of EPI has been suggested to reduce symptoms[59] and to improve weight gain and fat absorption in patients with

pancreatic cancer[60,66]. The National Comprehensive Cancer Network has advised that PERT be given to patients with pancreatic cancer who show symptoms of EPI[68]. Other organizations have noted that PERT may help maintain weight and promote QoL in patients with pancreatic cancer[40,69].

The recommendations for PERT use in pancreatic cancer patients were made despite a paucity of data to support them. Only two randomized placebo-controlled trials have investigated the use of PERT in pancreatic cancer (Table 5). In a double-blind trial of 21 patients with unresectable cancer of the pancreatic head, patients treated with 50000 units of lipase/meal gained 1.2% in body weight in 8 wk, while those receiving placebo lost 3.7%[66]. Fat absorption also improved by 25% with PERT, whereas it dropped by 25% with placebo. Steatorrhea did not significantly differ between groups; however, there was a trend for lower stool frequency in patients receiving PERT. When patients receiving placebo were switched to open-label PERT, they demonstrated weight stabilization and improvements in steatorrhea-related symptoms. In a double-blind, placebo-controlled study in patients with unresectable pancreatic cancer (43% had severe EPI, defined as fecal elastase-1 < 100 μg/g stool), mean weight loss after 8 wk of PERT (-1.49%) was not significantly different compared with placebo (-2.99%)[70]. However, PERT did improve nutritional status in a subset of patients with unresectable cancer of the pancreatic head region. Additionally, in an uncontrolled study of patients with unresectable pancreatic cancer, patients with moderate to severe fat or protein malabsorption showed improved nutrient absorption with PERT[60].

DIABETES MELLITUS AND EPI

Type 1 diabetes is considered a primary autoimmune process characterized by typically early onset, an eventual absolute lack of insulin, and islet cell antibodies[71]. Type 2 diabetes is a metabolic disorder characterized by hyperglycemia in the context of insulin resistance and a relative lack of insulin[71]. A third type of diabetes, type 3c or pancreatogenic diabetes[71-73], occurs secondary to parenchymal pancreatic disease and is characterized by an absent pancreatic polypeptide response to nutrients and loss of islet cells by inflammatory destruction and fibrosis[74,75]. The relationship between EPI and diabetes is complex due to the close anatomic and physiologic linkages between the exocrine and endocrine pancreas; pathological conditions of the endocrine tissue can cause impairment of exocrine function and vice versa. Furthermore, depending on the particular diagnostic tests that are used, there is the chance of inadvertently classifying type 3c diabetes as type 1 or 2, confounding understanding of their relative prevalence and relationship to EPI.

Type 1 and type 2 diabetes

Marked alterations in the exocrine pancreas are observed in patients with diabetes, including changes in size, morphology, and histology[76]. No studies have examined at what point during the course of diabetes these pancreatic abnormalities develop. Diabetic pancreata are often atrophic and can have prominent fatty involutions and calcification[77,78]. Atrophy is more pronounced in type 1 *vs* type 2 diabetes[79,80]. Moreover, the pancreata of diabetic patients are significantly smaller and have higher lobulation compared with healthy controls[79,80]. In a cadaveric study, the mean weight of pancreata in type 1 diabetic patients weighed about a half of that of controls[81], while magnetic resonance imaging studies in adults with recent-onset diabetes found only a 26% to 31% reduction in pancreatic volume index after adjustment for body weight compared with healthy controls[82,83]. Additionally, pancreatic volume in diabetic patients was significantly lower when elastase and/or chymotrypsin levels were low[77]. Atrophy of the gland and acini, lymphocytic infiltration, moderate to severe fibrosis, and fatty changes were noted on autopsy in the exocrine pancreas of Japanese patients with diabetes[84].

EPI associated with diabetes is typically mild to moderate and not associated with overt steatorrhea. The prevalence of EPI is higher in type 1 diabetes (26%-57%)[85-89] compared with type 2 diabetes (20%-36%)[78,85,86,88], significantly so in a pooled literature analysis of 3662 patients with diabetes (39% *vs* 28%, respectively, using a cutoff of fecal elastase 200 μg/g stool; $P < 0.00001$)[76]. Severe reductions in fecal elastase levels (< 100 μg/g) have been observed in 11% to 30% of patients with type 1 diabetes[85-88,90] and 3% to 20% of patients with type 2 diabetes[85,86,88,91,92]. Notably, in a large screening study of diabetic patients, correlations between exocrine insufficiency and early onset/longer duration of diabetes, insulin use, and lower body mass index (BMI) have been demonstrated[86]. Fecal elastase levels have also been found to correlate with worse glycemic control, less residual β-cell function, and higher BMI[93,94].

Fecal fat excretion inversely correlates with fecal elastase levels in type 1 diabetes; however, excessive fecal fat excretion occurred in 22% of patients with normal fecal elastase levels[87]. In a cohort of diabetics with fecal elastase levels < 100 μg/g, 59% of patients excreted ⩾ 7 g of fat per day[86]. Interestingly, 45% of type 1 diabetics with pathological fat excretion were asymptomatic in one prospective study[89]. Fecal fat excretion did not correlate with the type or duration of diabetes, age at onset, glycemic control, or BMI[89,95]. The prevalence of EPI was 33% using the direct secretin-cerulein test in patients with type 1 diabetes; among patients with an abnormal secretin-cerulein test result and steatorrhea ($n = 8$), 50% had decreased lipase but none had an enzyme secretion level

Table 5 Pancreatic enzyme replacement therapy clinical trials

Study	Study design, duration (when given), and number of patients	Disease	Results	Adverse effects
Bruno *et al*[66]	DBRPC, 8 wk, 24 adults (21 analyzed)	Pancreatic cancer	The mean absolute difference for PERT *vs* placebo in percentage change in body weight was 4.9% (P = 0.02); other outcomes were numerically improved with PERT *vs* placebo [fat absorption coefficient, 12% increase *vs* 8% decrease (P = 0.13); stool frequency, decrease of 1/d *vs* increase of 2/d (P = 0.07)]	No treatment-related AEs
Woo *et al*[70]	DBRPC, 8 wk, 67 adults	Pancreatic cancer	The mean change in body weight at 8 wk was similar with PERT *vs* placebo (-1.49% *vs* -2.99%; P = 0.381), but the mean change in nutritional status was superior with PERT *vs* placebo in the subset of patients with cancer of the pancreatic head (PG-SGA score, -42.65% *vs* 32.93%; P = 0.039)	Three patients died [PERT group, 2/34 (6%); placebo group, 1/33 (3%)] There were no PERT-related serious AEs
Perez *et al*[60]	Open-label, 12 adults	Pancreatic cancer	Most patients with moderate to severe fat (6/7) or protein (3/3) malabsorption improved, but no patients with mild fat or protein (0/8) malabsorption improved	No descriptions regarding TEAEs
Ewald *et al*[49]	DBRPC, 16 wk, 80 adults	Type 1 diabetes	No significant change in HbA_{1c}, fasting glucose, or postprandial glucose; increase in mean vitamin D from baseline to week 16 (PERT, from 54.1 to 59.4 nmol/L; placebo, 60.2 to 62.7 nmol/L)	TEAEs occurred in 33 patients (84.6%) in PERT group and in 35 (85.4%) in PBO group; most frequent AEs were headache, infection, pain, diarrhea, and dyspepsia
Carroccio *et al*[150]	DBRPC, 2 mo, 40 children	Celiac disease	Significant mean ± SD weight gain in first 30 d (1131 ± 461 g with PERT *vs* 732 ± 399 g with placebo; P < 0.006), not significant at 60 d	No undesired side effects were reported
Evans *et al*[141]	Open-label, up to 4 yr, 20 adults	Celiac disease	Significant increase in fecal elastase from median of 90 μg/g to 365 μg/g (P < 0.0001) and improvement in chronic diarrhea with reduction in median stool frequency from 4/d to 1/d ($P \leqslant 0.0001$), but no weight increase (P = 0.3)	No descriptions regarding TEAEs
Leeds *et al*[135]	Open-label, up to 2 yr, 20 adults	Celiac disease	Significant improvement in chronic diarrhea with reduction in median stool frequency from 4/d to 1/d ($P \leqslant 0.0001$), but no weight increase (P = 0.3)	No descriptions regarding TEAEs
Huddy *et al*[181]	Open-label, 10 adults	Esophagectomy	Improvement in diarrhea and steatorrhea (9/10), increased weight (7/10)	Nausea in 1 patient
Armbrecht *et al*[183]	DBRPC crossover trial, 2 wk (plus 1-wk washout), 15 adults	Total gastrectomy	Improved stool consistency (score, 7.6 with PERT *vs* 9.3 with placebo; P < 0.05), but not the number of bowel movements or abdominal symptoms	No descriptions regarding TEAEs
Hillman *et al*[166]	Open-label, 6 mo, 30 adults	Partial gastrectomy	Mean ± SE weight gain of 6.73 ± 0.77 (P < 0.001), mean ± SE decrease in steatorrhea of 49.7% ± 7.7% (P < 0.001)	No descriptions regarding TEAEs
Brägelmann *et al*[184]	DBRPC, 14 d, 52 adults	Total gastrectomy	Improvement of overall well-being (15/23 with PERT *vs* 6/24 with placebo; P = 0.006), but no improvement of specific symptom	No descriptions regarding TEAEs

AE: Adverse event; DBRPC: Double-blind, randomized, placebo-controlled; GIP: Gastric inhibitory polypeptide; GLP-1: Glucagon-like peptide-1; HbA_{1c}: Glycated hemoglobin A_{1c}; PBO: Placebo; PERT: Pancreatic enzyme replacement therapy; PG-SGA: Patient-generated subjective global assessment; TEAE: Treatment-emergent AE.

< 10% of normal, which is typically when steatorrhea manifests[89]. In the same study, the fecal elastase test had low sensitivity (36%-55%) and specificity (59%-77%) to reproduce the secretin-cerulein test results; the authors concluded that low fecal elastase levels do not reliably indicate EPI in type 1 diabetes.

Secretory abnormalities have been noted in diabetics[96-100]. Frier *et al*[96] observed reductions in exogenously stimulated secretion of amylase (66%) and trypsin (54%) in type 1 diabetics, and the degree of dysfunction correlated with disease duration in a small controlled study. Bicarbonate output was also significantly reduced and showed a significant inverse correlation with the daily insulin dosage in patients with a disease duration < 10 years. Furthermore, hyperglucagonemia, which is observed in some type 2 diabetic patients, is associated with a marked inhibition of pancreatic enzyme output, including lipase, amylase, and trypsin[97]. Increased somatostatin, also found in some diabetic patients, dose-dependently inhibits secretion of pancreatic bicarbonate, amylase, and trypsin[98-100].

Several theories have been proposed to explain the reduced exocrine function in diabetes, including

imbalances between stimulatory and inhibitory islet hormones, pancreatic atrophy or fibrosis, autonomic neuropathy, altered release of gastrointestinal regulatory mediators, and autoimmunity[79,80,84,101,102]. Disturbances in acinar-islet interactions with imbalances between stimulatory (insulin) and inhibitory (glucagon, somatostatin) islet hormones are linked to EPI in some diabetic patients[101]. Insulin has a trophic effect on the acinar cells and a stimulatory effect on exocrine enzyme secretion in animal models and cell cultures, suggesting that insulin deficiency may play a role in pancreatic atrophy[101,103]; insulin deficiency in diabetic patients may lead to pancreatic atrophy[79,80,84]. If insulin deficiency were the primary reason for exocrine dysfunction, however, then all patients with type 1 diabetes would be expected to have EPI.

Regulation of pancreatic enzyme elaboration and secretion depends on gastrointestinal hormones and local neuronal signals[101]. Unsurprisingly, therefore, autonomic diabetic neuropathy and secondary gastroparesis can impair enteropancreatic reflexes, such as changes in gut peptides, that may mediate as much as 50% of the postprandial exocrine pancreatic response[75,101,104]. Diabetic microangiopathy can reduce pancreatic perfusion and cause arterial lesions that can lead to pancreatic fibrosis[105,106]. Patients with type 2 diabetes are also at an increased risk for biliary disease, which can diminish secretions from the pancreas[107]. Finally, autoimmune diseases can involve both the exocrine and endocrine glands, as antibodies against islet cells can cross-react with acinar cells[34]. Autoantibodies against exocrine pancreatic antigens were detected in 77% of patients with type 1 diabetes, but were not detected in any patients with type 2 diabetes[108]. In summary, screening for EPI in patients with type 1 or type 2 diabetes is appropriate when symptoms suggest pancreatic insufficiency.

Type 3c diabetes

Pancreatogenic or type 3c diabetes occurs secondary to pancreatic disease, injury, or resection and accounts for 5% to 10% of the Western diabetic population[8,9,109,110]. Despite the prevalence of type 3c diabetes, the American Association of Clinical Endocrinologists and American College of Endocrinology have not formally included it in their guidelines[73]. The etiologies of type 3c diabetes include chronic pancreatitis (76%-79%), pancreatic cancer (8%-9%), hereditary hemochromatosis (7%-8%), cystic fibrosis (4%), and post-pancreatic resection (2%-3%)[8,9]. Furthermore, the prevalence of type 3c diabetes in chronic pancreatitis is correlated with the degree of exocrine dysfunction (with a prevalence of 63%, 32%, and 13% with severe, moderate, and mild dysfunction, respectively)[111]. Per diagnostic criteria, all patients with type 3c diabetes display signs of EPI[112], and this EPI is more severe compared with that of patients with type 1 and type 2 diabetes, as demonstrated by lower stimulated bicarbonate and trypsin output[96] and lower fecal elastase levels[94].

Because of the close anatomical relationship between exocrine and endocrine cells, type 3c diabetes may result from progression of the primary pancreatic exocrine disease that destroys islet cells by pancreatic inflammation or fibrosis[111,113]. Indeed, the impairment of pancreatic endocrine function in chronic pancreatitis proceeds in parallel with the destruction and spread of fibrosis inside islet cells[111,114,115]. Additionally, α- and β-cell responses were reduced in patients with autoimmune pancreatitis[115]. Mechanisms besides simple islet cell destruction may also be involved, as even small adenocarcinomas are associated with type 3c diabetes[116].

DIABETES MELLITUS AND PERT

Despite a paucity of clinical data for PERT use in patients with diabetes, position statements have stated that symptomatic patients with fecal elastase levels <100 μg/g may be treated with PERT[16,117] but should be carefully monitored because of the risk of disturbances in glucose homeostasis[118]. Of course, increased glucose uptake may reduce the risk of hypoglycemia[34]. There is some evidence that PERT can improve glucose metabolism by augmenting the effects of incretins and increasing postprandial insulin secretion[48,119]; however, no significant differences in hemoglobin A1c, fasting glucose, or oral glucose tolerance test results were observed between patients with type 1 diabetes treated with PERT and placebo (Table 5)[49].

In summary, there are different gastrointestinal motility and comorbid conditions in patients with diabetes mellitus that may result in EPI or decreased digestion or absorption of fat and protein. Early EPI is very difficult to diagnose in diabetic patients, where the condition appears and progresses insidiously across years. Although endocrinologists have not formally recognized type 3c diabetes, most of the conditions that lead to type 3c diabetes have a well-known association with EPI and the need for PERT. An interdisciplinary approach is needed to better define the possible association of EPI with diabetes and potential mechanisms, and to separate them from pancreatic processes that may or may not be related to diabetes. Furthermore, guidelines are needed to help clinicians decide when to test diabetic patients for EPI, and when use of PERT is beneficial.

AGING AND EPI

There are few studies on the effects of aging on exocrine pancreas function, and most[120-122] but not all studies[123] have found that EPI appears to increase with age. For example, in a study of older individuals (age 60 to > 79 years) without gastrointestinal

diseases or diabetes, fecal elastase-1 levels correlated negatively with age and were significantly lower in individuals > 70 years of age compared with a control group (age 20-28 years)[122]. Among subjects over 60 years of age, 21.7% had fecal elastase-1 levels below 200 μg/g stool.

CELIAC DISEASE AND EPI

Celiac disease is an inappropriate T-cell–mediated reaction to gluten that causes inflammatory injury to the small intestine; the estimated worldwide prevalence is 1% to 2%[124,125]. Diarrhea is common with celiac disease and is typically attributed to gluten-related indigestion, malabsorption, and fluid secretion. The primary treatment is a gluten-free diet, which usually improves gastrointestinal function, diarrhea, and weight gain. Nonetheless, 17% to 61% of patients with treated celiac disease have persistent diarrhea[126,127]. Diagnostic testing of celiac patients with chronic diarrhea on a gluten-free diet determined that EPI was present in 12% (based on pancreatic test or trial of PERT) to 18% (based on steatorrhea and trial of PERT)[126,128].

Pancreatic dysfunction occurs in some patients with celiac disease but is typically transient and normalizes with a gluten-free diet[129,130]. However, some patients do have substantially impaired exocrine pancreatic function, leading to maldigestion, malabsorption, and malnutrition. Comorbid chronic pancreatitis has been one possible explanation for these severe cases, with several publications reporting a higher incidence of chronic pancreatitis in patients with celiac disease[131,132]. In patients with untreated celiac disease, the prevalence of EPI (measured and defined by the fecal elastase test) ranges from 4% to 80%[133-138]. Subnormal secretion of at least 1 pancreatic enzyme was observed in 22% to 33% of patients with untreated celiac disease[130,139,140]. In a small controlled study, a significant inverse correlation was demonstrated between the severity of intestinal damage and fecal elastase levels in patients with celiac disease[133]. Carroccio *et al*[140]. reported normalization of fecal chymotrypsin in almost all patients with celiac disease on a strict gluten-free diet[140],which speaks to the functional aspect of EPI due to lack of stimulus rather than to structural damage. It has been suggested that impairment of exocrine pancreatic dysfunction is related to mucosal villous atrophy[129,133], and thus can improve when mucosal regeneration occurs with a gluten-free diet and other treatments[137,141].

In a single-center study by Rana *et al*[142], 36 patients with celiac disease serologically and histopathologically diagnosed were studied with fecal elastase, endoscopic ultrasound (EUS), and elastography. At study entry, 10 of the patients (28%) were diagnosed with EPI based on abnormal fecal elastase levels; 9 (90%) of these patients had villous atrophy of the duodenum, and 1 patient had a history of several episodes of acute pancreatitis. The 10 patients were subjected to a gluten-free diet, and after 3 mo 7 patients had a repeat fecal elastase test that had normalized in all cases, except for the patient with prior acute pancreatitis events. Elastography results were normal in all 8 patients who consented to EUS, except for the patient with prior acute pancreatitis events. The authors concluded that EPI, identified based on fecal elastase levels in adult patients with celiac disease, may be unrelated to structural changes in the pancreatic parenchyma and might be reversible by a gluten-free diet in most patients.

The pathophysiological mechanisms of EPI in celiac disease may be multifactorial. A primary mechanism could be a defective postprandial response to intraluminal contents by an atrophic upper intestinal mucosa with altered synthesis, storage, and/or secretion of secretin and CCK, which are potent stimulators of pancreatic secretion. Postprandial plasma CCK levels were significantly lower in patients with untreated celiac disease compared with controls and were significantly correlated with fecal elastase levels[133]. Impaired CCK release leads to reduced pancreatic stimulation and secretion, postcibal asynchrony between gastric emptying and gallbladder contraction, and fat maldigestion[143,144]. Decreased secretin release by the extensively damaged jejunal mucosa has also been reported[145]. General malnutrition is associated with defects in pancreatic secretion[146]; consequently, it is not unexpected that protein malnutrition in celiac disease is associated with a decrease in pancreatic enzyme output, as well as structural changes in the pancreas, including atrophy of acinar cells with fewer secretory granules, pancreatic fibrosis, and a smaller pancreatic head[147,148]. One study, however, reported that EPI in celiac disease may be independent of nutritional status[139]. There is some evidence for malabsorption of amino acids in patients with untreated celiac disease[149], which might contribute to EPI by restricting the substrates for synthesis of digestive enzymes.

CELIAC DISEASE AND PERT

Pancreatic function tests are usually not performed on newly diagnosed patients or patients with uncomplicated celiac disease; these tests should be considered if there is persistent diarrhea or steatorrhea despite a gluten-free diet or if there are signs of overt malnutrition. Patients on a gluten-free diet with low fecal elastase levels should receive PERT[16]. Data from a double-blind randomized trial of children with celiac disease on a gluten-free diet demonstrated that PERT increased body weight versus placebo during the first 30 days after diagnosis (Table 5)[150]. Similarly, PERT reduced chronic diarrhea from 4 to 1 stools/day in 90% of patients with celiac disease in 2 other uncontrolled studies[135,141].

Gastroenterologists specializing in celiac disease have not recognized a definite association between

celiac disease and EPI and are silent on the possible association and the need for treatment with PERT. Further studies are required to demonstrate whether there is any direct association between celiac disease and EPI.

IBD AND EPI

Crohn's disease (CD) and ulcerative colitis (UC) are chronic relapsing immune-mediated disorders of the gastrointestinal tract, characterized by chronic gastrointestinal inflammation. It is suggested that these disorders result from an aberrant immune response and loss of tolerance to the normal intestinal flora. Patients with IBD are at an increased risk for developing EPI, particularly if they have $\geqslant$ 3 daily bowel movements (BMs), loose stools, and a history of surgery[34,151]. Autopsy studies have found pancreatic lesions in 38% of patients with CD and 53% of patients with UC without prior evidence of pancreatitis[152]. Although still widely used, the fecal elastase test has poor diagnostic accuracy in patients with diarrhea[12]. In a cross-sectional study of 237 unselected patients with IBD, 21% demonstrated exocrine dysfunction as measured by the PABA test, and 19% exhibited abnormally low bicarbonate secretion in response to a secretin test; the frequency of abnormal results was similar in patients with CD and UC[153]. Furthermore, 8.4% of patients had a pancreatic duct abnormality[153].

CD

As a group, patients with CD have significantly decreased lipase, amylase, and trypsin activity compared with controls; these changes are not correlated with disease duration or location or extent of a previous bowel resection[154,155]. Factors related to impaired pancreatic function were disease activity, localization, and extent of bowel involvement[154]. The prevalence of EPI based on low fecal elastase levels varies between 14% and 30% of patients with CD[151,156]. Angelini *et al*[157] determined that 35% of patients with CD have impaired bicarbonate and/or enzyme secretion[157]. Depending on the involvement of the gastrointestinal tract (ileum, colon, or both), abnormal fat excretion varies between 17% and 35% in patients with CD[158].

Possible mechanisms for the development of EPI in CD include pancreatic autoantibodies, duodenal reflux, and reduced secretory hormone secretion. About one third of patients with CD have autoantibodies against pancreatic components[159-161], suggesting that EPI could result from immunologic induction of pathways that impair exocrine function. These antibodies appear specific for CD, as opposed to an individual with UC or without IBD[159,160]. Other possible mechanisms for pancreatitis in patients with CD include duodenal reflux into the pancreatic duct through an inflamed and incompetent ampulla of Vater and fistula formation between the pancreatic duct and the duodenum[162]. These processes could play a role in CD-associated EPI by damaging the pancreatic duct. Indeed, pathological changes in the pancreatic duct that may impede flow have been reported in patients with CD and UC[153]. Finally, scarring or inflammation may reduce intestinal hormone secretion, thus insufficiently stimulating the pancreas[154].

UC

In unselected patients with IBD, 22% of patients with UC had fecal elastase levels $\leqslant$ 200 μg/g, and 9% had severe EPI (fecal elastase $\leqslant$ 100 μg/g)[151]. Additionally, using a secretin-cerulein test, 50% of patients with UC demonstrated bicarbonate and/or enzyme insufficiency, while 74% had an abnormal PABA test[153,157]. By magnetic resonance cholangiopancreatography, 16.5% of patients with UC had a pancreatic duct abnormality, compared with no individuals in the control group[163].

IBD AND PERT

Despite the high prevalence of EPI in patients with IBD, we identified no studies that assessed whether PERT can improve maldigestion or malabsorption in patients with either CD or UC, nor any guidelines for the use of PERT in these populations.

GASTROINTESTINAL SURGERY AND EPI

Upper gastrointestinal surgery can distort the normal anatomy and physiology of digestion, thus disrupting the intricate sequence of events that control normal digestion and absorption. Maldigestion occurs in as many as 80% of patients following such procedures, and EPI may contribute to the pathogenesis[164]. Pancreatectomy results in bulk loss of enzyme-producing cells and is already an indication for PERT, so it will not be discussed here.

Post-gastrectomy diarrhea and/or steatorrhea occur in > 47% of gastrectomy patients, and significant weight loss is common[165-167]. In one study, all patients (n = 15) developed severe EPI 3 mo after total gastrectomy[168]. Steatorrhea was also observed in all patients (n = 30) who underwent a partial gastrectomy[166]. Two additional studies reported pathological fecal fat excretion in 92% and 67% of patients after total gastrectomy[167,169]. Additionally, using the ^{13}C-mixed triglyceride breath test, 82% of patients exhibited fat maldigestion after a Whipple procedure[164]. Finally, using the same diagnostic test, Perez Aisa *et al*[170] recently reported that 38% of patients developed fat malabsorption following partial or total gastrectomy.

EPI and altered pancreatic enzymes and gastrointestinal hormone levels were reported after both total and partial gastrectomies[168,171-173]. Luminal pancreatic enzyme and bile salt concentrations were

markedly reduced after subtotal gastrectomies[173], and significant reductions in the stimulated secretion of pancreatic juice (76%), trypsin (89%), chymotrypsin (91%), and amylase (72%) were observed after total gastrectomy compared with preoperative levels[168]. In another study, total gastrectomy significantly decreased bicarbonate (48%), lipase (39%), and chymotrypsin (24%) output in comparison with non-operated controls[167]. In a third study, only 30% of patients had EPI following subtotal or total gastric resection as measured by the fecal chymotrypsin test[171]. Low levels of gastrin and pancreatic polypeptide and high levels of postprandial plasma CCK have also been reported following total gastrectomy[168].

Gastrectomy disrupts several of the normal digestive processes; different factors may contribute to the postoperative changes, including deficient trituration of nutrients, altered gastric emptying, pancreatic denervation, postcibal asynchrony between gastric emptying and gallbladder contraction, and/or decreased absorptive surface and enzyme contact[16]. When the duodenum is also resected (gastroduodenal resection), a reduction in CCK secretion from the duodenum decreases pancreatic stimulation and contributes to EPI[164]. Likewise, Roux-en-Y gastric bypass surgery to treat obesity disrupts the normal digestive process, and almost a third of patients develop EPI post-operatively[174]. However, since the purpose of the procedure is to effect weight loss, it is unlikely that EPI in this situation would be treated.

The vagus nerve plays an important role in the regulation of exocrine pancreatic secretions, as vago-vagal enteropancreatic reflexes mediate responses in the intestinal phase of exocrine pancreatic secretion[175]. Vagotomies, which reduce gastric acid secretion by severing the vagal nerve supply to the stomach, also cause dysfunction of the exocrine pancreas; during extensive gastric surgery, severing of the vagus nerve (truncal vagotomy) can contribute to postoperative EPI, and a vagotomy by itself is sufficient to cause EPI[176]. In 2 studies, patients had decreased pancreatic juice, lipase, trypsin, and bicarbonate secretion following vagotomy[177,178]. In a similar study, fecal fat excretion was significantly increased after vagotomy and 45% of patients developed steatorrhea[179].

Extensive small bowel resections leading to short bowel syndrome can also reduce endogenous exocrine pancreatic secretion. Short bowel syndrome is characterized by malabsorption, with contributing factors including a reduction in gastrointestinal hormones (particularly CCK), postcibal asynchrony, gastric acid hypersecretion, loss of intestinal regulatory feedback, massive loss of absorptive surface, and rapid transit through the small intestine[1,180]. Additionally, total parenteral nutrition and anti-diarrheal agents used to treat short bowel syndrome are associated with pancreatic and gastric hyposecretion[180]. Some of these mechanisms, though not all, involve the pancreas, suggesting a role for EPI. There is wide variability depending upon the individual and the specific region resected. In patients undergoing ileal resection for CD, fecal fat excretion showed a highly significant correlation to the ileal length resected; for patients with only a 30-cm resection or less, the prevalence of abnormal fat excretion was 37%, whereas 100% of patients who underwent a 90-cm resection or greater displayed abnormal fecal fat excretion[158].

Esophagectomy has also been associated with EPI in one study (n = 63); 10 patients (16%) who underwent an esophagectomy had weight loss and fecal elastase levels < 200 μg/g stool and had symptomatic EPI with diarrhea and/or steatorrhea[181]. Potential mechanisms include decreased gastric reservoir, vagal denervation, and the presence of pyloroplasty that may be part of the procedure and cause dumping syndrome.

GASTROINTESTINAL SURGERY AND PERT

Despite a paucity of evidence regarding PERT use following gastrointestinal surgery, PERT is often recommended for post-surgical patients with steatorrhea, diarrhea, weight loss, or maldigestion-related symptoms[164,182]. In patients with EPI post-esophagectomy, 9 of 10 patients with fecal elastase levels < 200 μg/g stool had symptomatic improvement (no diarrhea or steatorrhea) with PERT and 70% experienced weight gain (Table 5)[181]. PERT may also be appropriate for asymptomatic patients with fat excretion > 15 g/d, as these patients are at high risk for developing nutritional deficiencies[164,182]. It has been suggested that PERT in combination with a high-energy diet over 6 to 8 meals/d may improve nutritional status and symptoms in these patients[11]. Because each patient and surgery is unique and patients have different degrees of EPI, PERT dosing must be tailored to the individual symptoms of a patient.

Data regarding the overall benefits of PERT in total or partial gastrectomy patients are conflicting; while some evidence suggests improved stool consistency[183], weight gain[166], quality of life[184], and reduced steatorrhea and fecal fat excretion[166,185], the same benefits were not observed in all studies. For example, in the double-blind crossover study that showed improvements in stool consistency following a total gastrectomy, there were no beneficial effects of PERT on fecal fat output; however, in the subset of patients with massive steatorrhea, there was a significant reduction in fecal fat excretion following treatment with PERT[183]. The variable trial results

prevent definitive conclusions about the benefits of PERT in fecal fat excretion and steatorrhea following gastric surgery.

CONCLUSION

The prevalence of EPI may be higher in patients with diverse non-pancreatic diseases or pancreatic cancer (Table 2) than has generally been appreciated. EPI should be considered as a possible etiology for any patient with diabetes, celiac disease, IBD, gastrointestinal surgery, or pancreatic cancer who presents with malnutrition, weight loss, and/or abnormal fatty stools (Table 4). In patients with symptomatic EPI, dietary modifications should be implemented and PERT may be initiated and doses should be titrated to achieve the optimal response.

Evidence from clinical research on EPI in less common etiologies is scanty and precludes firm recommendations on management. The lack of studies and evidence-based practices on the association of EPI with the medical conditions discussed herein makes conclusions difficult and needs to be substituted with consensus and clinical practice guidelines derived from future prospective, controlled studies, to confirm or refute these associations. EPI is a serious condition that, once confirmed and regardless of the cause, requires PERT treatment to prevent devastating, sometimes fatal, nutritional complications associated with untreated maldigestion and malabsorption. Further studies are needed to define the association of EPI with these conditions and to support recommendations on the timing of diagnostic testing and initiation of PERT.

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