**Name of journal:** ***World Journal of Gastroenterology***

**ESPS Manuscript NO: 30060**

**Manuscript type: Review**

**Less common etiologies of exocrine pancreatic insufficiency**

Singh VK *et al*.Causes of exocrine pancreatic insufficiency

Vikesh K Singh, Mark E Haupt, David E Geller, Jerry A Hall, Pedro M Quintana Diez

**Vikesh K Singh,** Division of Gastroenterology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, United States

**Mark E Haupt,** Medical Affairs, AbbVie Inc., North Chicago, IL 60064, United States

**David E Geller,** Cystic Fibrosis Clinical Development, AbbVie Inc., North Chicago, IL 60064, United States

**Jerry A Hall,** CREON® Clinical Development, AbbVie Inc., North Chicago, IL 60064, United States

**Pedro M Quintana Diez,** CREON® Development, AbbVie Inc., North Chicago, IL 60064, United States

**Author contributions:** Haupt ME, Geller DE, Hall JA and Quintana Diez PM designed the “search terms” of the literature review, analyzed the data, and summarized the findings; all authors critically reviewed and revised the manuscript, and approved the final version of the article, including the authorship list.

**Conflict-of-interest statement:** Singh VK is a consultant for Ariel, Kowa, Novo Nordisk, and AbbVie; he has been an advisory board participant for Akcea and Nordmark; Geller DE and Hall JA are employees of AbbVie and may own AbbVie stock and/or options; Haupt ME and Quintana Diez PM are former employees of AbbVie and may own AbbVie stock and/or options.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Correspondence to:** **Vikesh K Singh, MD, MSc, Associate Professor** of Medicine, Division of Gastroenterology, Johns Hopkins University School of Medicine, 1830 E Monument Street, Room 436, Baltimore, MD 21287, USA. vsingh1@jhmi.edu

**Telephone:** +1-410-6146708

**Fax:** +1-410-6147631

**Received:** September 7, 2016

**Peer-review started:** September 10, 2016

**First decision:** October 10, 2017

**Revised:** May 27, 2017

**Accepted:** June 1, 2017

**Article in press:**

**Published online:**

**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; exocrine pancreatic insufficiency; epidemiology; inflammatory bowel disease; malabsorption; pancreas; pancreatic cancer; secretion/absorption; surgery

**© The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tips:** 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.

Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM.Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol* 2017; In press

**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](#_ENREF_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](#_ENREF_1),[2](#_ENREF_2)]. The incidence of EPI in chronic pancreatitis ranges from 30% of patients with mild disease to 85% with severe disease[[3](#_ENREF_3)]. Approximately 85% of infants with cystic fibrosis have EPI at birth[[4](#_ENREF_4)]. However, EPI is also observed in other conditions that include unresectable pancreatic cancer; metabolic diseases (diabetes mellitus)[[1](#_ENREF_1),[2](#_ENREF_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](#_ENREF_1),[2](#_ENREF_2)]; small intestinal bacterial overgrowth[[5](#_ENREF_5),[6](#_ENREF_6)], although not all investigators have found a clear association[[7](#_ENREF_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](#_ENREF_8),[9](#_ENREF_9)] (Tables 1 and 2)[[1](#_ENREF_1),[2](#_ENREF_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\*” 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](#_ENREF_10),[11](#_ENREF_11)]. Furthermore, the deficiency in pancreatic lipase cannot be compensated by gastric lipase, the only other lipolytic enzyme in adult humans[[12](#_ENREF_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](#_ENREF_13)]. Untreated malabsorption places patients at high risk for developing nutritional deficiencies[[14](#_ENREF_14)], which can manifest as other health problems, including decreased bone mineral density resulting in osteoporosis or osteomalacia[[15-17](#_ENREF_15)]; bone metabolism deficiencies and muscle spasms; impaired night vision and decreased immune competence[[16](#_ENREF_16),[18](#_ENREF_18),[19](#_ENREF_19)]; coagulation problems[[16](#_ENREF_16)]; and ataxia and peripheral neuropathy[[16](#_ENREF_16)]. Additionally, EPI has been associated with high morbidity and mortality secondary to malnutrition-related complications and an increased risk of cardiovascular events[[20](#_ENREF_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](#_ENREF_21)]. Severe symptomatic EPI can be diagnosed by the presence of steatorrhea, diarrhea, flatulence, or weight loss[[22](#_ENREF_22)], which often manifest when fecal fat excretion is > 7 g/d (Table 4). Early diagnostic studies relied on direct pancreatic function tests (ie, those involving collection and analysis of secretions directly from the duodenum or pancreatic duct, including the secretin-pancreozymin and Lundh tests[[2](#_ENREF_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](#_ENREF_2),[23](#_ENREF_23),[24](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_25)] or 84 μg/g stool[[26](#_ENREF_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](#_ENREF_16),[24](#_ENREF_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](#_ENREF_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](#_ENREF_28)]. It is commonly accepted 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](#_ENREF_29)]. 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](#_ENREF_32)]. 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](#_ENREF_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](#_ENREF_3)].

Although not widely available, other tests for the diagnosis of EPI include the 13C-mixed triglyceride (13C-MTG) breath test and secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imaging (MRCP). In the 13C-MTG test, the patient ingests a small amount of 13C-marked triglycerides which are degraded by lipases in the intestine to 13C-marked fatty acids. The absorbed 13C fatty acids are metabolized by the liver, and 13CO2 is exhaled[[36](#_ENREF_36)]. Lower lipase activity is associated with less 13CO2 in the exhaled breath. This test can also be used to assess the effects of PERT[[37](#_ENREF_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](#_ENREF_38),[39](#_ENREF_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](#_ENREF_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](#_ENREF_21)]. A main goal of PERT is to restore sufficient intestinal lipase levels[[11](#_ENREF_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](#_ENREF_40)]. A number of porcine lipase preparations are approved for PERT[[41](#_ENREF_41)], and the reader is referred to publications from national and professional organizations for recommended dosages[[16](#_ENREF_16),[42-44](#_ENREF_42)] 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, and quality of life (QoL) of patients with EPI and significantly slowed gastric emptying[[45-48](#_ENREF_45)]. Patients with EPI experienced a reduction in stool frequency and fat/water content, as well as abdominal pain and flatulence[[47](#_ENREF_47)]. PERT is generally well tolerated; treatment-emergent adverse events include headache, infection, abdominal pain, flatulence, diarrhea, and dyspepsia[[45-47](#_ENREF_45),[49](#_ENREF_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](#_ENREF_50)] and adults[[51](#_ENREF_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](#_ENREF_52),[53](#_ENREF_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](#_ENREF_1),[16](#_ENREF_16),[54](#_ENREF_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](#_ENREF_1),[54](#_ENREF_54),[55](#_ENREF_55)].

The reported occurrence of malabsorption and exocrine dysfunction varies between 66% and 92% of patients with pancreatic cancer[[30](#_ENREF_30),[56-59](#_ENREF_56)], with 65% to 75% of patients experiencing fat malabsorption and 50% of patients experiencing some degree of protein malabsorption[[60](#_ENREF_60),[61](#_ENREF_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-month follow-up; 77% of patients were being treated with PERT[[59](#_ENREF_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](#_ENREF_62)]. Although EPI is usually moderate in severity[[61](#_ENREF_61)], in a prospective study, Partelli et al 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](#_ENREF_31)]. Pancreatic function abnormality seems to be higher in patients with tumors located in the pancreatic head versus in the body or tail[[31](#_ENREF_31),[63](#_ENREF_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[[31](#_ENREF_31)].

Several studies have also reported inadequate enzyme secretion (trypsin, lipase, amylase, elastase, and chymotrypsin) in patients with pancreatic cancer compared with healthy controls[[55](#_ENREF_55),[58](#_ENREF_58),[64](#_ENREF_64)]. Elastase production may be reduced earlier and to a greater extent compared with the output of other enzymes, for unknown reasons[[64](#_ENREF_64)]. Additionally, fecal amylase activity was significantly decreased in pancreatic cancer patients compared with healthy controls[[65](#_ENREF_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](#_ENREF_66)]. Gastrointestinal and diet management problems negatively impact patients’ QoL[[67](#_ENREF_67)]; consequently, early treatment of EPI has been suggested to reduce symptoms[[59](#_ENREF_59)] and to improve weight gain and fat absorption in patients with pancreatic cancer[[60](#_ENREF_60),[66](#_ENREF_66)]. The National Comprehensive Cancer Network has advised that PERT be given to patients with pancreatic cancer who show symptoms of EPI[[68](#_ENREF_68)]. Other organizations have noted that PERT may help maintain weight and promote QoL in patients with pancreatic cancer[[40](#_ENREF_40),[69](#_ENREF_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 50,000 units of lipase/meal gained 1.2% in body weight in 8 weeks, while those receiving placebo lost 3.7%[[66](#_ENREF_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 weeks of PERT (-1.49%) was not significantly different compared with placebo (-2.99%)[[70](#_ENREF_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](#_ENREF_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](#_ENREF_71)]. Type 2 diabetes is a metabolic disorder characterized by hyperglycemia in the context of insulin resistance and a relative lack of insulin[[71](#_ENREF_71)]. A third type of diabetes, type 3c or pancreatogenic diabetes[[71-73](#_ENREF_71)], 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](#_ENREF_74),[75](#_ENREF_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](#_ENREF_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](#_ENREF_77),[78](#_ENREF_78)]. Atrophy is more pronounced in type 1 versus type 2 diabetes[[79](#_ENREF_79),[80](#_ENREF_80)]. Moreover, the pancreata of diabetic patients are significantly smaller and have higher lobulation compared with healthy controls[[79](#_ENREF_79),[80](#_ENREF_80)]. In a cadaveric study, the mean weight of pancreata in type 1 diabetic patients weighed about a half of that of controls[[81](#_ENREF_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](#_ENREF_82),[83](#_ENREF_83)]. Additionally, pancreatic volume in diabetic patients was significantly lower when elastase and/or chymotrypsin levels were low[[77](#_ENREF_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](#_ENREF_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](#_ENREF_85)] compared with type 2 diabetes (20%-36%)[[78](#_ENREF_78),[85](#_ENREF_85),[86](#_ENREF_86),[88](#_ENREF_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](#_ENREF_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](#_ENREF_85),[90](#_ENREF_90)] and 3% to 20% of patients with type 2 diabetes[[85](#_ENREF_85),[86](#_ENREF_86),[88](#_ENREF_88),[91](#_ENREF_91),[92](#_ENREF_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](#_ENREF_86)]. Fecal elastase levels have also been found to correlate with worse glycemic control, less residual β-cell function, and higher BMI[[93](#_ENREF_93),[94](#_ENREF_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](#_ENREF_87)]. In a cohort of diabetics with fecal elastase levels < 100 µg/g, 59% of patients excreted ≥ 7 g of fat per day[[86](#_ENREF_86)]. Interestingly, 45% of type 1 diabetics with pathological fat excretion were asymptomatic in one prospective study[[89](#_ENREF_89)]. Fecal fat excretion did not correlate with the type or duration of diabetes, age at onset, glycemic control, or BMI[[89](#_ENREF_89),[95](#_ENREF_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 <10% of normal, which is typically when steatorrhea manifests[[89](#_ENREF_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](#_ENREF_96)]. Frier *et al*[[96](#_ENREF_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](#_ENREF_97)]. Increased somatostatin, also found in some diabetic patients, dose-dependently inhibits secretion of pancreatic bicarbonate, amylase, and trypsin[[98-100](#_ENREF_98)].

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](#_ENREF_79),[80](#_ENREF_80),[84](#_ENREF_84),[101](#_ENREF_101),[102](#_ENREF_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](#_ENREF_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](#_ENREF_101),[103](#_ENREF_103)]; insulin deficiency in diabetic patients may lead to pancreatic atrophy[[79](#_ENREF_79),[80](#_ENREF_80),[84](#_ENREF_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](#_ENREF_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](#_ENREF_75),[101](#_ENREF_101),[104](#_ENREF_104)]. Diabetic microangiopathy can reduce pancreatic perfusion and cause arterial lesions that can lead to pancreatic fibrosis[[105](#_ENREF_105),[106](#_ENREF_106)]. Patients with type 2 diabetes are also at an increased risk for biliary disease, which can diminish secretions from the pancreas[[107](#_ENREF_107)]. Finally, autoimmune diseases can involve both the exocrine and endocrine glands, as antibodies against islet cells can cross-react with acinar cells[[34](#_ENREF_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](#_ENREF_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](#_ENREF_8),[9](#_ENREF_9),[109](#_ENREF_109),[110](#_ENREF_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](#_ENREF_73)]. The etiologies of type 3c diabetes include chronic pancreatitis (76%-79%), pancreatic cancer (8%-9%), hereditary hemochromatosis (7%-8%), cystic fibrosis (4%), and postpancreatic resection (2%-3%)[[8](#_ENREF_8),[9](#_ENREF_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](#_ENREF_111)]. Per diagnostic criteria, all patients with type 3c diabetes display signs of EPI[[112](#_ENREF_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](#_ENREF_96)] and lower fecal elastase levels[[94](#_ENREF_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](#_ENREF_111),[113](#_ENREF_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](#_ENREF_111),[114](#_ENREF_114),[115](#_ENREF_115)]. Additionally, α- and β-cell responses were reduced in patients with autoimmune pancreatitis[[115](#_ENREF_115)]. Mechanisms besides simple islet cell destruction may also be involved, as even small adenocarcinomas are associated with type 3c diabetes[[116](#_ENREF_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](#_ENREF_16),[117](#_ENREF_117)] but should be carefully monitored because of the risk of disturbances in glucose homeostasis[[118](#_ENREF_118)]. Of course, increased glucose uptake may reduce the risk of hypoglycemia[[34](#_ENREF_34)]. There is some evidence that PERT can improve glucose metabolism by augmenting the effects of incretins and increasing postprandial insulin secretion[[48](#_ENREF_48),[119](#_ENREF_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](#_ENREF_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](#_ENREF_120)] but not all studies[[123](#_ENREF_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](#_ENREF_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](#_ENREF_124),[125](#_ENREF_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](#_ENREF_126),[127](#_ENREF_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](#_ENREF_126),[128](#_ENREF_128)].

Pancreatic dysfunction occurs in some patients with celiac disease but is typically transient and normalizes with a gluten-free diet[[129](#_ENREF_129),[130](#_ENREF_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](#_ENREF_131),[132](#_ENREF_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](#_ENREF_133)]. Subnormal secretion of at least 1 pancreatic enzyme was observed in 22% to 33% of patients with untreated celiac disease[[130](#_ENREF_130),[139](#_ENREF_139),[140](#_ENREF_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](#_ENREF_133)]. Carroccio et al. reported normalization of fecal chymotrypsin in almost all patients with celiac disease on a strict gluten-free diet[[140](#_ENREF_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](#_ENREF_129),[133](#_ENREF_133)], and thus can improve when mucosal regeneration occurs with a gluten-free diet and other treatments[[137](#_ENREF_137),[141](#_ENREF_141)].

In a single-center study by Rana et al[[142](#_ENREF_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 months 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](#_ENREF_133)]. Impaired CCK release leads to reduced pancreatic stimulation and secretion, postcibal asynchrony between gastric emptying and gallbladder contraction, and fat maldigestion[[143](#_ENREF_143),[144](#_ENREF_144)]. Decreased secretin release by the extensively damaged jejunal mucosa has also been reported[[145](#_ENREF_145)]. General malnutrition is associated with defects in pancreatic secretion[[146](#_ENREF_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](#_ENREF_147),[148](#_ENREF_148)]. One study, however, reported that EPI in celiac disease may be independent of nutritional status[[139](#_ENREF_139)]. There is some evidence for malabsorption of amino acids in patients with untreated celiac disease[[149](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_135),[141](#_ENREF_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 ≥ 3 daily bowel movements (BMs), loose stools, and a history of surgery[[34](#_ENREF_34),[151](#_ENREF_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](#_ENREF_152)]. Although still widely used, the fecal elastase test has poor diagnostic accuracy in patients with diarrhea[[12](#_ENREF_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](#_ENREF_153)]. Furthermore, 8.4% of patients had a pancreatic duct abnormality[[153](#_ENREF_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](#_ENREF_154),[155](#_ENREF_155)]. Factors related to impaired pancreatic function were disease activity, localization, and extent of bowel involvement[[154](#_ENREF_154)]. The prevalence of EPI based on low fecal elastase levels varies between 14% and 30% of patients with CD[[151](#_ENREF_151),[156](#_ENREF_156)]. Angelini et al determined that 35% of patients with CD have impaired bicarbonate and/or enzyme secretion[[157](#_ENREF_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[[157](#_ENREF_157),[158](#_ENREF_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](#_ENREF_159)], 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](#_ENREF_159),[160](#_ENREF_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](#_ENREF_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](#_ENREF_153)]. Finally, scarring or inflammation may reduce intestinal hormone secretion, thus insufficiently stimulating the pancreas[[154](#_ENREF_154)].

***UC***

In unselected patients with IBD, 22% of patients with UC had fecal elastase levels ≤ 200 µg/g, and 9% had severe EPI (fecal elastase ≤ 100 µg/g)[[151](#_ENREF_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](#_ENREF_153),[157](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_165)]. In one study, all patients (*n* = 15) developed severe EPI 3 months after total gastrectomy[[168](#_ENREF_168)]. Steatorrhea was also observed in all patients (*n* = 30) who underwent a partial gastrectomy[[166](#_ENREF_166)]. Two additional studies reported pathological fecal fat excretion in 92% and 67% of patients after total gastrectomy[[167](#_ENREF_167),[169](#_ENREF_169)]. Additionally, using the 13C-mixed triglyceride breath test, 82% of patients exhibited fat maldigestion after a Whipple procedure[[164](#_ENREF_164)]. Finally, using the same diagnostic test, Perez Aisa et al recently reported that 38% of patients developed fat malabsorption following partial or total gastrectomy[[170](#_ENREF_170)].

EPI and altered pancreatic enzymes and gastrointestinal hormone levels were reported after both total and partial gastrectomies[[168](#_ENREF_168),[171-173](#_ENREF_171)]. Luminal pancreatic enzyme and bile salt concentrations were markedly reduced after subtotal gastrectomies[[173](#_ENREF_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](#_ENREF_168)]. In another study, total gastrectomy significantly decreased bicarbonate (48%), lipase (39%), and chymotrypsin (24%) output in comparison with non-operated controls[[167](#_ENREF_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](#_ENREF_171)]. Low levels of gastrin and pancreatic polypeptide and high levels of postprandial plasma CCK have also been reported following total gastrectomy[[168](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_176)]. In 2 studies, patients had decreased pancreatic juice, lipase, trypsin, and bicarbonate secretion following vagotomy[[177](#_ENREF_177),[178](#_ENREF_178)]. In a similar study, fecal fat excretion was significantly increased after vagotomy and 45% of patients developed steatorrhea[[179](#_ENREF_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](#_ENREF_1),[180](#_ENREF_180)]. Additionally, total parenteral nutrition and anti-diarrheal agents used to treat short bowel syndrome are associated with pancreatic and gastric hyposecretion[[180](#_ENREF_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](#_ENREF_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](#_ENREF_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](#_ENREF_164),[182](#_ENREF_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](#_ENREF_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](#_ENREF_164),[182](#_ENREF_182)]. It has been suggested that PERT in combination with a high-energy diet over 6 to 8 meals/day may improve nutritional status and symptoms in these patients[[11](#_ENREF_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](#_ENREF_183)], weight gain[[166](#_ENREF_166)], quality of life[[184](#_ENREF_184)], and reduced steatorrhea and fecal fat excretion[[166](#_ENREF_166),[185](#_ENREF_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](#_ENREF_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.

**Acknowledgments**

This review was sponsored by AbbVie Inc., which participated in writing, review, and approval of the manuscript. Katherine Groschwitz, PhD, and Michael J. Theisen, PhD, of Complete Publication Solutions, LLC, provided medical writing support, which was funded by AbbVie.

**REFERENCES**

1 **Keller J**, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005; **54 Suppl 6**: vi1-v28 [PMID: 15951527 DOI: 10.1136/gut.2005.065946]

2 **Lindkvist B**. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol* 2013; **19**: 7258-7266 [PMID: 24259956 DOI: 10.3748/wjg.v19.i42.7258]

3 **Hart PA**, Conwell DL. Diagnosis of Exocrine Pancreatic Insufficiency. *Curr Treat Options Gastroenterol* 2015; **13**: 347-353 [PMID: 26077487 DOI: 10.1007/s11938-015-0057-8]

4 **Van de Vijver E**, Desager K, Mulberg AE, Staelens S, Verkade HJ, Bodewes FA, Malfroot A, Hauser B, Sinaasappel M, Van Biervliet S, Behm M, Pelckmans P, Callens D, Veereman-Wauters G. Treatment of infants and toddlers with cystic fibrosis-related pancreatic insufficiency and fat malabsorption with pancrelipase MT. *J Pediatr Gastroenterol Nutr* 2011; **53**: 61-64 [PMID: 21694537 DOI: 10.1097/MPG.0b013e31820e208e]

5 **Bordin D**, Osipenko Y, Drozdov V, Silvestrova S, Varvanina G. Importance of small intestinal bacterial overgrowth in chronic pancreatitis. Pancreatology 2013; 13: S70 [DOI: 10.1016/j.pan.2013.04.245]

6 **Bures J**, Cyrany J, Kohoutova D, Förstl M, Rejchrt S, Kvetina J, Vorisek V, Kopacova M. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010; **16**: 2978-2990 [PMID: 20572300 DOI: 10.3748/wjg.v16.i24.2978]

7 **Madsen JL**, Graff J, Philipsen EK, Scharff O, Rumessen JJ. Bile acid malabsorption or disturbed intestinal permeability in patients treated with enzyme substitution for exocrine pancreatic insufficiency is not caused by bacterial overgrowth. *Pancreas* 2003; **26**: 130-133 [PMID: 12604909]

8 **Ewald N**, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev* 2012; **28**: 338-342 [PMID: 22121010 DOI: 10.1002/dmrr.2260]

9 **Cui Y**, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology* 2011; **11**: 279-294 [PMID: 21757968 DOI: 10.1159/000329188]

10 **DiMagno EP**, Malagelada JR, Go VL. Relationship between alcoholism and pancreatic insufficiency. *Ann N Y Acad Sci* 1975; **252**: 200-207 [PMID: 1056723 DOI: 10.1111/j.1749-6632.1975.tb19157.x]

11 Friess H, Tempia-Caliera AA, Cammerer G, Buchler MW. Indication for pancreatic enzyme substitution following gastric resection. Pancreatology 2001; 1: 41-48 [DOI: 10.1159/000055891]

12 **Keller J**, Aghdassi AA, Lerch MM, Mayerle JV, Layer P. Tests of pancreatic exocrine function - clinical significance in pancreatic and non-pancreatic disorders. *Best Pract Res Clin Gastroenterol* 2009; **23**: 425-439 [PMID: 19505669 DOI: 10.1016/j.bpg.2009.02.013]

13 **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 [PMID: 4693931 DOI: 10.1056/NEJM197304192881603]

14 **Sikkens EC**, Cahen DL, Koch AD, Braat H, Poley JW, Kuipers EJ, Bruno MJ. The prevalence of fat-soluble vitamin deficiencies and a decreased bone mass in patients with chronic pancreatitis. *Pancreatology* 2013; **13**: 238-242 [PMID: 23719594 DOI: 10.1016/j.pan.2013.02.008]

15 **Vermeer C**. Vitamin K: the effect on health beyond coagulation - an overview. *Food Nutr Res* 2012; **56**: [PMID: 22489224 DOI: 10.3402/fnr.v56i0.5329]

16 **Pezzilli R**, Andriulli A, Bassi C, Balzano G, Cantore M, Delle Fave G, Falconi M, Exocrine Pancreatic Insufficiency collaborative G. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. *World J Gastroenterol* 2013; **19**: 7930-7946 [PMID: 24307787 DOI: 10.3748/wjg.v19.i44.7930]

17 **Bendik I**, Friedel A, Roos FF, Weber P, Eggersdorfer M. Vitamin D: a critical and essential micronutrient for human health. *Front Physiol* 2014; **5**: 248 [PMID: 25071593 DOI: 10.3389/fphys.2014.00248]

18 **Tanumihardjo SA**. Vitamin A: biomarkers of nutrition for development. *Am J Clin Nutr* 2011; **94**: 658S-665S [PMID: 21715511 DOI: 10.3945/ajcn.110.005777]

19 **Field CJ**, Johnson IR, Schley PD. Nutrients and their role in host resistance to infection. *J Leukoc Biol* 2002; **71**: 16-32 [PMID: 11781377]

20 **Domínguez-Muñoz JE**. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011; **26 Suppl 2**: 12-16 [PMID: 21323992 DOI: 10.1111/j.1440-1746.2010.06600.x]

21 **Gheorghe C**, Seicean A, Saftoiu A, Tantau M, Dumitru E, Jinga M, Negreanu L, Mateescu B, Gheorghe L, Ciocirlan M, Cijevschi C, Constantinescu G, Dima S, Diculescu M. Romanian guidelines on the diagnosis and treatment of exocrine pancreatic insufficiency. *J Gastrointestin Liver Dis* 2015; **24**: 117-123 [PMID: 25822444 DOI: 10.15403/jgld.2014.1121.app]

22 **Pongprasobchai S**. Maldigestion from pancreatic exocrine insufficiency. *J Gastroenterol Hepatol* 2013; **28 Suppl 4**: 99-102 [PMID: 24251713 DOI: 10.1111/jgh.12406]

23 **Keller J**, Layer P. Diagnosis of pancreatic exocrine insufficiency in chronic pancreatitis. Pancreapedia: Exocrine Pancreas Knowledge Base. Accessed 2017-04-24, Available from: URL: <http://www.pancreapedia.org/reviews/diagnosis-of-pancreatic-exocrine-insufficiency-in-chronic-pancreatitis>

24 **Hart PA**, Conwell DL. Challenges and Updates in the Management of Exocrine Pancreatic Insufficiency. *Pancreas* 2016; **45**: 1-4 [PMID: 26658035 DOI: 10.1097/MPA.0000000000000457]

25 **Halloran CM**, Cox TF, Chauhan S, Raraty MG, Sutton R, Neoptolemos JP, Ghaneh P. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. *Pancreatology* 2011; **11**: 535-545 [PMID: 22094930 DOI: 10.1159/000333308]

26 **González-Sánchez V**, Amrani R, González V, Trigo C, Picó A, de-Madaria E. Diagnosis of exocrine pancreatic insufficiency in chronic pancreatitis: (13)C-Mixed Triglyceride Breath Test versus Fecal Elastase. *Pancreatology* 2017; Epub ahead of print [PMID: 28291656 DOI: 10.1016/j.pan.2017.03.002]

27 **Hoffmeister A**, Mayerle J, Beglinger C, Büchler MW, Bufler P, Dathe K, Fölsch UR, Friess H, Izbicki J, Kahl S, Klar E, Keller J, Knoefel WT, Layer P, Loehr M, Meier R, Riemann JF, Rünzi M, Schmid RM, Schreyer A, Tribl B, Werner J, Witt H, Mössner J, Lerch MM. [S3-Consensus guidelines on definition, etiology, diagnosis and medical, endoscopic and surgical management of chronic pancreatitis German Society of Digestive and Metabolic Diseases (DGVS)]. *Z Gastroenterol* 2012; **50**: 1176-1224 [PMID: 23150111 DOI: 10.1055/s-0032-1325479]

28 **Leeds JS**, Oppong K, Sanders DS. The role of fecal elastase-1 in detecting exocrine pancreatic disease. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 405-415 [PMID: 21629239 DOI: 10.1038/nrgastro.2011.91]

29 **Löser C**, Möllgaard A, Fölsch UR. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut* 1996; **39**: 580-586 [PMID: 8944569 DOI: 10.1136/gut.39.4.580]

30 **Matsumoto J**, Traverso LW. Exocrine function following the whipple operation as assessed by stool elastase. *J Gastrointest Surg* 2006; **10**: 1225-1229 [PMID: 17114009 DOI: 10.1016/j.gassur.2006.08.001]

31 **Partelli S**, Frulloni L, Minniti C, Bassi C, Barugola G, D'Onofrio M, Crippa S, Falconi M. Faecal elastase-1 is an independent predictor of survival in advanced pancreatic cancer. *Dig Liver Dis* 2012; **44**: 945-951 [PMID: 22749648 DOI: 10.1016/j.dld.2012.05.017]

32 **Walkowiak J**, Herzig KH, Strzykala K, Przyslawski J, Krawczynski M. Fecal elastase-1 is superior to fecal chymotrypsin in the assessment of pancreatic involvement in cystic fibrosis. *Pediatrics* 2002; **110**: e7 [PMID: 12093988 DOI: 10.1542/peds.110.1.e7]

33 **Sonwalkar SA**, Holbrook IB, Phillips I, Kelly SM. A prospective, comparative study of the para-aminobenzoic acid test and faecal elastase 1 in the assessment of exocrine pancreatic function. *Aliment Pharmacol Ther* 2003; **17**: 467-471 [PMID: 12562462 DOI: 10.1046/j.1365-2036.2003.01451.x]

34 **Nakajima K**, Oshida H, Muneyuki T, Kakei M. Pancrelipase: an evidence-based review of its use for treating pancreatic exocrine insufficiency. *Core Evid* 2012; **7**: 77-91 [PMID: 22936895 DOI: 10.2147/CE.S26705]

35 **Weintraub A**, Blau H, Mussaffi H, Picard E, Bentur L, Kerem E, Stankiewicz H, Wilschanski M. Exocrine pancreatic function testing in patients with cystic fibrosis and pancreatic sufficiency: a correlation study. *J Pediatr Gastroenterol Nutr* 2009; **48**: 306-310 [PMID: 19274786 DOI: 10.1097/MPG.0b013e318180af4f]

36 **Lindkvist B**, Domínguez-Muñoz JE, Luaces-Regueira M, Castiñeiras-Alvariño M, Nieto-Garcia L, Iglesias-Garcia J. Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology* 2012; **12**: 305-310 [PMID: 22898630 DOI: 10.1016/j.pan.2012.04.006]

37 **Domínguez-Muñoz JE**, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. 13C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol* 2007; **5**: 484-488 [PMID: 17445754 DOI: 10.1016/j.cgh.2007.01.004]

38 **Akisik MF**, Aisen AM, Sandrasegaran K, Jennings SG, Lin C, Sherman S, Lin JA, Rydberg M. Assessment of chronic pancreatitis: utility of diffusion-weighted MR imaging with secretin enhancement. *Radiology* 2009; **250**: 103-109 [PMID: 19001148 DOI: 10.1148/radiol.2493080160]

39 **Hansen TM**, Nilsson M, Gram M, Frøkjær JB. Morphological and functional evaluation of chronic pancreatitis with magnetic resonance imaging. *World J Gastroenterol* 2013; **19**: 7241-7246 [PMID: 24259954 DOI: 10.3748/wjg.v19.i42.7241]

40 **Toouli J**, Biankin AV, Oliver MR, Pearce CB, Wilson JS, Wray NH. Management of pancreatic exocrine insufficiency: Australasian Pancreatic Club recommendations. *Med J Aust* 2010; **193**: 461-467 [PMID: 20955123]

41 **Struyvenberg MR**, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency - Breaking the myths. *BMC Med* 2017; **15**: 29 [PMID: 28183317 DOI: 10.1186/s12916-017-0783-y]

42 **Löhr JM**, Oliver MR, Frulloni L. Synopsis of recent guidelines on pancreatic exocrine insufficiency. *United European Gastroenterol J* 2013; **1**: 79-83 [PMID: 24917944 DOI: 10.1177/2050640613476500]

43 **Smith RC**, Smith SF, Wilson J, Pearce C, Wray N, Vo R, Chen J, Ooi CY, Oliver M, Katz T, Turner R, Nikfarjam M, Rayner C, Horowitz M, Holtmann G, Talley N, Windsor J, Pirola R, Neale R. Summary and recommendations from the Australasian guidelines for the management of pancreatic exocrine insufficiency. *Pancreatology* 2016; **16**: 164-180 [PMID: 26775768 DOI: 10.1016/j.pan.2015.12.006]

44 **de-Madaria E,** Abad-González A, Aparicio JR, Aparisi L, Boadas J, Boix E, de-Las-Heras G, Domínguez-Muñoz E, Farré A, Fernández-Cruz L, Gómez L, Iglesias-García J, García-Malpartida K, Guarner L, Lariño-Noia J, Lluís F, López A, Molero X, Moreno-Pérez O, Navarro S, Palazón JM, Pérez-Mateo M, Sabater L, Sastre Y, Vaquero EC, Martínez J. The Spanish Pancreatic Club's recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). *Pancreatology* 2013; **13**: 18-28 [PMID: 23395565 DOI: 10.1016/j.pan.2012.11.310]

45 **D'Haese JG**, Ceyhan GO, Demir IE, Layer P, Uhl W, Löhr M, Rychlik R, Pirilis K, Zöllner Y, Gradl B, Foerster D, Möbius J, Henniges F, Friess H. Pancreatic enzyme replacement therapy in patients with exocrine pancreatic insufficiency due to chronic pancreatitis: a 1-year disease management study on symptom control and quality of life. *Pancreas* 2014; **43**: 834-841 [PMID: 24717829 DOI: 10.1097/MPA.0000000000000131]

46 **Seiler CM**, Izbicki J, Varga-Szabó L, Czakó L, Fiók J, Sperti C, Lerch MM, Pezzilli R, Vasileva G, Pap A, Varga M, Friess H. Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. *Aliment Pharmacol Ther* 2013; **37**: 691-702 [PMID: 23383603 DOI: 10.1111/apt.12236]

47 **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 [PMID: 19815466 DOI: 10.1016/j.jcf.2009.08.008]

48 **Kuo P**, Stevens JE, Russo A, Maddox A, Wishart JM, Jones KL, Greville H, Hetzel D, Chapman I, Horowitz M, Rayner CK. Gastric emptying, incretin hormone secretion, and postprandial glycemia in cystic fibrosis--effects of pancreatic enzyme supplementation. *J Clin Endocrinol Metab* 2011; **96**: E851-E855 [PMID: 21389144 DOI: 10.1210/jc.2010-2460]

49 **Ewald N**, Bretzel RG, Fantus IG, Hollenhorst M, Kloer HU, Hardt PD. Pancreatin therapy in patients with insulin-treated 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 [PMID: 17103488 DOI: 10.1002/dmrr.708]

50 **FitzSimmons SC**, Burkhart GA, Borowitz D, Grand RJ, Hammerstrom T, Durie PR, Lloyd-Still JD, Lowenfels AB. High-dose pancreatic-enzyme supplements and fibrosing colonopathy in children with cystic fibrosis. *N Engl J Med* 1997; **336**: 1283-1289 [PMID: 9113931 DOI: 10.1056/NEJM199705013361803]

51 **Terheggen G**, Dieninghoff D, Rietschel E, Drebber U, Kruis W, Leifeld L. Successful non-invasive treatment of stricturing fibrosing colonopathy in an adult patient. *Eur J Med Res* 2011; **16**: 411-414 [PMID: 22024442 DOI: 10.1186/2047-783X-16-9-411]

52 **Hidalgo M**. Pancreatic cancer. *N Engl J Med* 2010; **362**: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]

53 **National Cancer Institute**. SEER Stat Fact Sheets: Pancreas Cancer. Available from: URL: <http://seer.cancer.gov/statfacts/html/pancreas.html>

54 **DiMagno EP**. Medical treatment of pancreatic insufficiency. *Mayo Clin Proc* 1979; **54**: 435-442 [PMID: 36518]

55 **DiMagno EP**, Malagelada JR, Go VL. The relationships between pancreatic ductal obstruction and pancreatic secretion in man. *Mayo Clin Proc* 1979; **54**: 157-162 [PMID: 431121]

56 **Dreiling DA**. The early diagnosis of pancreatic cancer. *Scand J Gastroenterol Suppl* 1970; **6**: 115-122 [PMID: 4917492]

57 **Reber HA**, Tweedie JH, Maslin SC, Austin JL. Pancreatic cancer: diagnostic value of pancreatic function tests. *Cancer Detect Prev* 1981; **4**: 443-448 [PMID: 7349807]

58 **Ihse I**, Arnesjö B, Kugelberg C, Lilja P. Intestinal activities of trypsin, lipase, and phospholipase after a test meal. An evaluation of 474 examinations. *Scand J Gastroenterol* 1977; **12**: 663-668 [PMID: 929105 DOI: 10.3109/00365527709181700]

59 **Sikkens EC**, Cahen DL, de Wit J, Looman CW, van Eijck C, Bruno MJ. A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *J Clin Gastroenterol* 2014; **48**: e43-e46 [PMID: 24717227 DOI: 10.1097/MCG.0b013e31829f56e7]

60 **Perez MM**, Newcomer AD, Moertel CG, Go VL, Dimagno EP. Assessment of weight loss, food intake, fat metabolism, malabsorption, and treatment of pancreatic insufficiency in pancreatic cancer. *Cancer* 1983; **52**: 346-352 [PMID: 6305473 DOI: 10.1002/1097-0142(19830715)52: 2<346: : AID-CNCR2820520228>3.0.CO; 2-Z]

61 **el-Kamar FG**, Grossbard ML, Kozuch PS. Metastatic pancreatic cancer: emerging strategies in chemotherapy and palliative care. *Oncologist* 2003; **8**: 18-34 [PMID: 12604729 DOI: 10.1634/theoncologist.8-1-18]

62 **Tseng DS**, Molenaar IQ, Besselink MG, van Eijck CH, Borel Rinkes IH, van Santvoort HC. Pancreatic Exocrine Insufficiency in Patients With Pancreatic or Periampullary Cancer: A Systematic Review. *Pancreas* 2016; **45**: 325-330 [PMID: 26495777 DOI: 10.1097/MPA.0000000000000473]

63 **Wakasugi H**, Hara Y, Abe M. A study of malabsorption in pancreatic cancer. *J Gastroenterol* 1996; **31**: 81-85 [PMID: 8808433 DOI: 10.1007/BF01211191]

64 **Mizuno R**, Hayakawa T, Noda A. Elastase secretion in pancreatic disease. *Am J Gastroenterol* 1985; **80**: 113-117 [PMID: 3844284]

65 **Moriyoshi Y**, Takeuchi T, Shiratori K, Watanabe S. Fecal isoamylase activity in patients with pancreatic diseases. *Pancreas* 1991; **6**: 70-76 [PMID: 1704633]

66 **Bruno MJ**, Haverkort EB, Tijssen GP, Tytgat GN, 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 [PMID: 9505892 DOI: 10.1136/gut.42.1.92]

67 **Gooden HM**, White KJ. Pancreatic cancer and supportive care--pancreatic exocrine insufficiency negatively impacts on quality of life. *Support Care Cancer* 2013; **21**: 1835-1841 [PMID: 23397095 DOI: 10.1007/s00520-013-1729-3]

68 **National Comprehensive Cancer Network**. NCCN Clinical Practice Guideline in Oncology: Pancreatic Adenocarcinoma. 2017

69 **Pancreatric Section, British Society of Gastroenterology**; Pancreatic Society of Great Britain and Ireland; Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland; Royal College of Pathologists; Special Interest Group for Gastro-Intestinal Radiology. Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut* 2005; **54 Suppl 5**: v1-v16 [PMID: 15888770 DOI: 10.1136/gut.2004.057059]

70 **Woo SM**, Joo J, Kim SY, Park SJ, Han SS, Kim TH, Koh YH, Chung SH, Kim YH, Moon H, Hong EK, Lee WJ. Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. *Pancreatology* 2016; **16**: 1099-1105 [PMID: 27618657 DOI: 10.1016/j.pan.2016.09.001]

71 **American Diabetes Association**. (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015; **38 Suppl**: S8-S16 [PMID: 25537714 DOI: 10.2337/dc15-S005]

72 **World Health Organization**. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: 1999

73 **Handelsman Y**, Bloomgarden ZT, Grunberger G, Umpierrez G, Zimmerman RS, Bailey TS, Blonde L, Bray GA, Cohen AJ, Dagogo-Jack S, Davidson JA, Einhorn D, Ganda OP, Garber AJ, Garvey WT, Henry RR, Hirsch IB, Horton ES, Hurley DL, Jellinger PS, Jovanovič L, Lebovitz HE, LeRoith D, Levy P, McGill JB, Mechanick JI, Mestman JH, Moghissi ES, Orzeck EA, Pessah-Pollack R, Rosenblit PD, Vinik AI, Wyne K, Zangeneh F. American association of clinical endocrinologists and american college of endocrinology - clinical practice guidelines for developing a diabetes mellitus comprehensive care plan - 2015. *Endocr Pract* 2015; **21 Suppl 1**: 1-87 [PMID: 25869408 DOI: 10.4158/EP15672.GL]

74 **Rickels MR**, Bellin M, Toledo FG, Robertson RP, Andersen DK, Chari ST, Brand R, Frulloni L, Anderson MA, Whitcomb DC. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatology* 2013; **13**: 336-342 [PMID: 23890130 DOI: 10.1016/j.pan.2013.05.002]

75 **Piciucchi M**, Capurso G, Archibugi L, Delle Fave MM, Capasso M, Delle Fave G. Exocrine pancreatic insufficiency in diabetic patients: prevalence, mechanisms, and treatment. *Int J Endocrinol* 2015; **2015**: 595649 [PMID: 25892991 DOI: 10.1155/2015/595649]

76 **Mohapatra S**, Majumder S, Smyrk TC, Zhang L, Matveyenko A, Kudva YC, Chari ST. Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy: Conclusions From a Review of Literature. *Pancreas* 2016; **45**: 1104-1110 [PMID: 26918874 DOI: 10.1097/MPA.0000000000000609]

77 **Philippe MF**, Benabadji S, Barbot-Trystram L, Vadrot D, Boitard C, Larger E. Pancreatic volume and endocrine and exocrine functions in patients with diabetes. *Pancreas* 2011; **40**: 359-363 [PMID: 21283038 DOI: 10.1097/MPA.0b013e3182072032]

78 **Nunes AC**, Pontes JM, Rosa A, Gomes L, Carvalheiro M, Freitas D. Screening for pancreatic exocrine insufficiency in patients with diabetes mellitus. *Am J Gastroenterol* 2003; **98**: 2672-2675 [PMID: 14687815 DOI: 10.1111/j.1572-0241.2003.08730.x]

79 **Fonseca V**, Berger LA, Beckett AG, Dandona P. Size of pancreas in diabetes mellitus: a study based on ultrasound. *Br Med J (Clin Res Ed)* 1985; **291**: 1240-1241 [PMID: 3933616 DOI: 10.1136/bmj.291.6504.1240]

80 **Gilbeau JP**, Poncelet V, Libon E, Derue G, Heller FR. The density, contour, and thickness of the pancreas in diabetics: CT findings in 57 patients. *AJR Am J Roentgenol* 1992; **159**: 527-531 [PMID: 1503017 DOI: 10.2214/ajr.159.3.1503017]

81 **Campbell-Thompson M**, Wasserfall C, Montgomery EL, Atkinson MA, Kaddis JS. Pancreas organ weight in individuals with disease-associated autoantibodies at risk for type 1 diabetes. *JAMA* 2012; **308**: 2337-2339 [PMID: 23232891 DOI: 10.1001/jama.2012.15008]

82 **Gaglia JL**, Guimaraes AR, Harisinghani M, Turvey SE, Jackson R, Benoist C, Mathis D, Weissleder R. Noninvasive imaging of pancreatic islet inflammation in type 1A diabetes patients. *J Clin Invest* 2011; **121**: 442-445 [PMID: 21123946 DOI: 10.1172/JCI44339]

83 **Williams AJ**, Thrower SL, Sequeiros IM, Ward A, Bickerton AS, Triay JM, Callaway MP, Dayan CM. Pancreatic volume is reduced in adult patients with recently diagnosed type 1 diabetes. *J Clin Endocrinol Metab* 2012; **97**: E2109-E2113 [PMID: 22879632 DOI: 10.1210/jc.2012-1815]

84 **Waguri M**, Hanafusa T, Itoh N, Miyagawa J, Imagawa A, Kuwajima M, Kono N, Matsuzawa Y. Histopathologic study of the pancreas shows a characteristic lymphocytic infiltration in Japanese patients with IDDM. *Endocr J* 1997; **44**: 23-33 [PMID: 9152611 DOI: 10.1507/endocrj.44.23]

85 **Hardt PD**, Krauss A, Bretz L, Porsch-Ozcürümez M, Schnell-Kretschmer H, Mäser E, Bretzel RG, Zekhorn T, Klör HU. Pancreatic exocrine function in patients with type 1 and type 2 diabetes mellitus. *Acta Diabetol* 2000; **37**: 105-110 [PMID: 11277309 DOI: 10.1007/s005920070011]

86 **Hardt PD**, Hauenschild A, Nalop J, Marzeion AM, Jaeger C, Teichmann J, Bretzel RG, Hollenhorst M, Kloer HU. 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 [PMID: 14526149 DOI: 10.1159/000073655]

87 **Cavalot F**, Bonomo K, Fiora E, Bacillo E, Salacone P, Chirio M, Gaia E, Trovati M. Does pancreatic elastase-1 in stools predict steatorrhea in type 1 diabetes? *Diabetes Care* 2006; **29**: 719-721 [PMID: 16505538 DOI: 10.2337/diacare.29.03.06.dc05-1389]

88 **Larger E**, Philippe MF, Barbot-Trystram L, Radu A, Rotariu M, Nobécourt E, Boitard C. Pancreatic exocrine function in patients with diabetes. *Diabet Med* 2012; **29**: 1047-1054 [PMID: 22273174 DOI: 10.1111/j.1464-5491.2012.03597.x]

89 **Hahn JU**, Kerner W, Maisonneuve P, Lowenfels AB, Lankisch PG. Low fecal elastase 1 levels do not indicate exocrine pancreatic insufficiency in type-1 diabetes mellitus. *Pancreas* 2008; **36**: 274-278 [PMID: 18362841 DOI: 10.1097/MPA.0b013e3181656f8]

90 **Icks A**, Haastert B, Giani G, Rathmann W. Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol* 2001; **39**: 823-830 [PMID: 11605150 DOI: 10.1055/s-2001-17867]

91 **Yilmaztepe A**, Ulukaya E, Ersoy C, Yilmaz M, Tokullugil HA. Investigation of fecal pancreatic elastase-1 levels in type 2 diabetic patients. *Turk J Gastroenterol* 2005; **16**: 75-80 [PMID: 16252196]

92 **Rathmann W**, Haastert B, Icks A, Giani G, Hennings S, Mitchell J, Curran S, Wareham NJ. Low faecal elastase 1 concentrations in type 2 diabetes mellitus. *Scand J Gastroenterol* 2001; **36**: 1056-1061 [PMID: 11589378 DOI: 10.1080/003655201750422657]

93 **Cavalot F**, Bonomo K, Perna P, Bacillo E, Salacone P, Gallo M, Mattiello L, Trovati M, Gaia E. Pancreatic elastase-1 in stools, a marker of exocrine pancreas function, correlates with both residual beta-cell secretion and metabolic control in type 1 diabetic subjects. *Diabetes Care* 2004; **27**: 2052-2054 [PMID: 15277440 DOI: 10.2337/diacare.27.8.2052]

94 **Ewald N**, Raspe A, Kaufmann C, Bretzel RG, Kloer HU, Hardt PD. Determinants of Exocrine Pancreatic Function as Measured by Fecal Elastase-1 Concentrations (FEC) in Patients with Diabetes mellitus. *Eur J Med Res* 2009; **14**: 118-122 [PMID: 19380282 DOI: 10.1186/2047-783X-14-3-118]

95 **Hardt PD**, Hauenschild A, Jaeger C, Teichmann J, Bretzel RG, Kloer HU. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: a prospective multicenter study. *Dig Dis Sci* 2003; **48**: 1688-1692 [PMID: 14560984 DOI: 10.1023/A: 1025422423435]

96 **Frier BM**, Saunders JH, Wormsley KG, Bouchier IA. Exocrine pancreatic function in juvenile-onset diabetes mellitus. *Gut* 1976; **17**: 685-691 [PMID: 976808 DOI: 10.1136/gut.17.9.685]

97 **Ferrer R**, Medrano J, Diego M, Calpena R, Graells L, Moltó M, Pérez T, Pérez F, Salido G. Effect of exogenous insulin and glucagon on exocrine pancreatic secretion in rats in vivo. *Int J Pancreatol* 2000; **28**: 67-75 [PMID: 11185712 DOI: 10.1385/IJGC: 28: 1: 67]

98 **Unger RH**, Aguilar-Parada E, Müller WA, Eisentraut AM. Studies of pancreatic alpha cell function in normal and diabetic subjects. *J Clin Invest* 1970; **49**: 837-848 [PMID: 4986215 DOI: 10.1172/JCI106297]

99 **Liu Z**, Kim W, Chen Z, Shin YK, Carlson OD, Fiori JL, Xin L, Napora JK, Short R, Odetunde JO, Lao Q, Egan JM. Insulin and glucagon regulate pancreatic α-cell proliferation. *PLoS One* 2011; **6**: e16096 [PMID: 21283589 DOI: 10.1371/journal.pone.0016096]

100 **Gyr K**, Beglinger C, Köhler E, Trautzl U, Keller U, Bloom SR. Circulating somatostatin. Physiological regulator of pancreatic function? *J Clin Invest* 1987; **79**: 1595-1600 [PMID: 2884233 DOI: 10.1172/JCI112994]

101 **Hardt PD**, Ewald N. Exocrine pancreatic insufficiency in diabetes mellitus: a complication of diabetic neuropathy or a different type of diabetes? *Exp Diabetes Res* 2011; **2011**: 761950 [PMID: 21822421 DOI: 10.1155/2011/761950]

102 **Folli F**, Okada T, Perego C, Gunton J, Liew CW, Akiyama M, D'Amico A, La Rosa S, Placidi C, Lupi R, Marchetti P, Sesti G, Hellerstein M, Perego L, Kulkarni RN. Altered insulin receptor signalling and β-cell cycle dynamics in type 2 diabetes mellitus. *PLoS One* 2011; **6**: e28050 [PMID: 22140505 DOI: 10.1371/journal.pone.0028050]

103 **Parsa I**, Marsh WH. Long-term organ culture of embryonic rat pancreas in a chemically defined medium. *Am J Pathol* 1976; **82**: 119-128 [PMID: 1247081]

104 **Fried GM**, Ogden WD, Sakamoto T, Greeley GH, Thompson JC. Experimental evidence for a vagally mediated and cholecystokinin-independent enteropancreatic reflex. *Ann Surg* 1985; **202**: 69-74 [PMID: 4015214]

105 **Czakó L**, Hegyi P, Rakonczay Z, Wittmann T, Otsuki M. Interactions between the endocrine and exocrine pancreas and their clinical relevance. *Pancreatology* 2009; **9**: 351-359 [PMID: 19454837 DOI: 10.1159/000181169]

106 **Vesterhus M**, Raeder H, Johansson S, Molven A, Njølstad PR. Pancreatic exocrine dysfunction in maturity-onset diabetes of the young type 3. *Diabetes Care* 2008; **31**: 306-310 [PMID: 17989309 DOI: 10.2337/dc07-1002]

107 **Noel RA**, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2009; **32**: 834-838 [PMID: 19208917 DOI: 10.2337/dc08-1755]

108 **Taniguchi T**, Okazaki K, Okamoto M, Seko S, Tanaka J, Uchida K, Nagashima K, Kurose T, Yamada Y, Chiba T, Seino Y. High prevalence of autoantibodies against carbonic anhydrase II and lactoferrin in type 1 diabetes: concept of autoimmune exocrinopathy and endocrinopathy of the pancreas. *Pancreas* 2003; **27**: 26-30 [PMID: 12826902]

109 **Hardt PD**, Brendel MD, Kloer HU, Bretzel RG. Is pancreatic diabetes (type 3c diabetes) underdiagnosed and misdiagnosed? *Diabetes Care* 2008; **31 Suppl 2**: S165-S169 [PMID: 18227480 DOI: 10.2337/dc08-s244]

110 **Hart PA**, Bellin MD, Andersen DK, Bradley D, Cruz-Monserrate Z, Forsmark CE, Goodarzi MO, Habtezion A, Korc M, Kudva YC, Pandol SJ, Yadav D, Chari ST. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol* 2016; **1**: 226-237 [PMID: 28404095 DOI: 10.1016/S2468-1253(16)30106-6]

111 **Kawabe K**, Ito T, Igarashi H, Takayanagi R. The current managements of pancreatic diabetes in Japan. *Clin J Gastroenterol* 2009; **2**: 1-8 [PMID: 26191800 DOI: 10.1007/s12328-008-0052-x]

112 **Andersen DK**, Andren-Sandberg Å, Duell EJ, Goggins M, Korc M, Petersen GM, Smith JP, Whitcomb DC. Pancreatitis-diabetes-pancreatic cancer: summary of an NIDDK-NCI workshop. *Pancreas* 2013; **42**: 1227-1237 [PMID: 24152948 DOI: 10.1097/MPA.0b013e3182a9ad9d]

113 **Ewald N**, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol* 2013; **19**: 7276-7281 [PMID: 24259958 DOI: 10.3748/wjg.v19.i42.7276]

114 **Vonlaufen A**, Wilson JS, Apte MV. Molecular mechanisms of pancreatitis: current opinion. *J Gastroenterol Hepatol* 2008; **23**: 1339-1348 [PMID: 18853993 DOI: 10.1111/j.1440-1746.2008.05520.x]

115 **Ito T**, Kawabe K, Arita Y, Hisano T, Igarashi H, Funakoshi A, Sumii T, Yamanaka T, Takayanagi R. Evaluation of pancreatic endocrine and exocrine function in patients with autoimmune pancreatitis. *Pancreas* 2007; **34**: 254-259 [PMID: 17312466 DOI: 10.1097/01.mpa.0000250127.18908.38]

116 . Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2012; **35 Suppl 1**: S64-S71 [PMID: 22187472 DOI: 10.2337/dc12-s064]

117 **Weitgasser R**, Abrahamian H, Clodi M, Fortunat W, Hammer H. [Position paper: Exocrine pancreatic insufficiency and diabetes mellitus]. *Wien Klin Wochenschr* 2012; **124 Suppl 2**: 100-103 [PMID: 23250472 DOI: 10.1007/s00508-012-0290-2]

118 **O'Keefe SJ**, Cariem AK, Levy M. The exacerbation of pancreatic endocrine dysfunction by potent pancreatic exocrine supplements in patients with chronic pancreatitis. *J Clin Gastroenterol* 2001; **32**: 319-323 [PMID: 11276275]

119 **Knop FK**, Vilsbøll T, Larsen S, Højberg PV, Vølund A, Madsbad S, Holst JJ, Krarup T. Increased postprandial responses of GLP-1 and GIP in patients with chronic pancreatitis and steatorrhea following pancreatic enzyme substitution. *Am J Physiol Endocrinol Metab* 2007; **292**: E324-E330 [PMID: 16954337 DOI: 10.1152/ajpendo.00059.2006]

120 **Laugier R**, Bernard JP, Berthezene P, Dupuy P. Changes in pancreatic exocrine secretion with age: pancreatic exocrine secretion does decrease in the elderly. *Digestion* 1991; **50**: 202-211 [PMID: 1812045 DOI: 10.1159/000200762]

121 **Rothenbacher D**, Löw M, Hardt PD, Klör HU, Ziegler H, Brenner H. Prevalence and determinants of exocrine pancreatic insufficiency among older adults: results of a population-based study. *Scand J Gastroenterol* 2005; **40**: 697-704 [PMID: 16036530 DOI: 10.1080/00365520510023116]

122 **Herzig KH**, Purhonen AK, Räsänen KM, Idziak J, Juvonen P, Phillps R, Walkowiak J. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC Geriatr* 2011; **11**: 4 [PMID: 21266058 DOI: 10.1186/1471-2318-11-4]

123 **Gullo L**, Simoni P, Migliori M, Lucrezio L, Bassi M, Frau F, Costa PL, Nesticò V. A study of pancreatic function among subjects over ninety years of age. *Pancreatology* 2009; **9**: 240-244 [PMID: 19407477 DOI: 10.1159/000212090]

124 **Fasano A**, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003; **163**: 286-292 [PMID: 12578508 DOI: 10.1001/archinte.163.3.286]

125 **Walker MM**, Murray JA, Ronkainen J, Aro P, Storskrubb T, D'Amato M, Lahr B, Talley NJ, Agreus L. Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. *Gastroenterology* 2010; **139**: 112-119 [PMID: 20398668 DOI: 10.1053/j.gastro.2010.04.007]

126 **Fine KD**, Meyer RL, Lee EL. The prevalence and causes of chronic diarrhea in patients with celiac sprue treated with a gluten-free diet. *Gastroenterology* 1997; **112**: 1830-1838 [PMID: 9178673 DOI: 10.1053/gast.1997.v112.pm9178673]

127 **Wahnschaffe U**, Schulzke JD, Zeitz M, Ullrich R. Predictors of clinical response to gluten-free diet in patients diagnosed with diarrhea-predominant irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2007; **5**: 844-850; quiz 769 [PMID: 17553753 DOI: 10.1016/j.cgh.2007.03.021]

128 **Abdulkarim AS**, Burgart LJ, See J, Murray JA. Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002; **97**: 2016-2021 [PMID: 12190170 DOI: 10.1111/j.1572-0241.2002.05917.x]

129 **Nousia-Arvanitakis S**, Karagiozoglou-Lamboudes T, Aggouridaki C, Malaka-Lambrellis E, Galli-Tsinopoulou A, Xefteri M. Influence of jejunal morphology changes on exocrine pancreatic function in celiac disease. *J Pediatr Gastroenterol Nutr* 1999; **29**: 81-85 [PMID: 10400109]

130 **Carroccio A**, Iacono G, Montalto G, Cavataio F, Di Marco C, Balsamo V, Notarbartolo A. Exocrine pancreatic function in children with coeliac disease before and after a gluten free diet. *Gut* 1991; **32**: 796-799 [PMID: 1855688 DOI: 10.1136/gut.32.7.796]

131 **Sadr-Azodi O**, Sanders DS, Murray JA, Ludvigsson JF. Patients with celiac disease have an increased risk for pancreatitis. *Clin Gastroenterol Hepatol* 2012; **10**: 1136-1142.e3 [PMID: 22801059 DOI: 10.1016/j.cgh.2012.06.023]

132 **Ludvigsson JF**, Montgomery SM, Ekbom A. Risk of pancreatitis in 14,000 individuals with celiac disease. *Clin Gastroenterol Hepatol* 2007; **5**: 1347-1353 [PMID: 17702659 DOI: 10.1016/j.cgh.2007.06.002]

133 **Nousia-Arvanitakis S**, Fotoulaki M, Tendzidou K, Vassilaki C, Agguridaki C, Karamouzis M. Subclinical exocrine pancreatic dysfunction resulting from decreased cholecystokinin secretion in the presence of intestinal villous atrophy. *J Pediatr Gastroenterol Nutr* 2006; **43**: 307-312 [PMID: 16954951 DOI: 10.1097/01.mpg.0000228098.66583.85]

134 **Vujasinovic M**, Tepes B, Volfand J, Rudolf S. Exocrine pancreatic insufficiency, MRI of the pancreas and serum nutritional markers in patients with coeliac disease. *Postgrad Med J* 2015; **91**: 497-500 [PMID: 26253920 DOI: 10.1136/postgradmedj-2015-133262]

135 **Leeds JS**, Hopper AD, Hurlstone DP, Edwards SJ, McAlindon ME, Lobo AJ, Donnelly MT, Morley S, Sanders DS. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Ther* 2007; **25**: 265-271 [PMID: 17269988 DOI: 10.1111/j.1365-2036.2006.03206.x]

136 **Licul V**, Cizmarević NS, Ristić S, Mikolasević I, Mijandrusić BS. CTLA-4 +49 and TNF-alpha-308 gene polymorphisms in celiac patients with exocrine pancreatic insufficiency. *Coll Antropol* 2013; **37**: 1191-1194 [PMID: 24611333]

137 **Walkowiak J**, Herzig KH. Fecal elastase-1 is decreased in villous atrophy regardless of the underlying disease. *Eur J Clin Invest* 2001; **31**: 425-430 [PMID: 11380594 DOI: 10.1046/j.1365-2362.2001.00822.x]

138 **Gomez JC**, Morán CE, Mauriño EC, Bai JC. Exocrine pancreatic insufficiency in celiac disease. *Gastroenterology* 1998; **114**: 621-623 [PMID: 9496962]

139 **Carroccio A**, Iacono G, Montalto G, Cavataio F, Lorello D, Soresi M, Di Martino D, Notarbartolo A. Pancreatic insufficiency in celiac disease is not dependent on nutritional status. *Dig Dis Sci* 1994; **39**: 2235-2242 [PMID: 7924748 DOI: 10.1007/BF02090377]

140 **Carroccio A**, Iacono G, Lerro P, Cavataio F, Malorgio E, Soresi M, Baldassarre M, Notarbartolo A, Ansaldi N, Montalto G. Role of pancreatic impairment in growth recovery during gluten-free diet in childhood celiac disease. *Gastroenterology* 1997; **112**: 1839-1844 [PMID: 9178674 DOI: 10.1053/gast.1997.v112.pm9178674]

141 **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 [PMID: 20458623 DOI: 10.1007/s10620-010-1261-y]

142 **Rana SS**, Dambalkar A, Chhabra P, Sharma R, Nada R, Sharma V, Rana S, Bhasin DK. Is pancreatic exocrine insufficiency in celiac disease related to structural alterations in pancreatic parenchyma? *Ann Gastroenterol* 2016; **29**: 363-366 [PMID: 27366039 DOI: 10.20524/aog.2016.0042]

143 **Deprez P**, Sempoux C, Van Beers BE, Jouret A, Robert A, Rahier J, Geubel A, Pauwels S, Mainguet P. Persistent decreased plasma cholecystokinin levels in celiac patients under gluten-free diet: respective roles of histological changes and nutrient hydrolysis. *Regul Pept* 2002; **110**: 55-63 [PMID: 12468110 DOI: 10.1016/S0167-0115(02)00162-3]

144 **DiMagno EP**, Go WL, Summerskill WH. Impaired cholecystokinin-pancreozymin secretion, intraluminal dilution, and maldigestion of fat in sprue. *Gastroenterology* 1972; **63**: 25-32 [PMID: 5055745]

145 **Polak JM**, Pearse AG, Van Noorden S, Bloom SR, Rossiter MA. Secretin cells in coeliac disease. *Gut* 1973; **14**: 870-874 [PMID: 4586733 DOI: 10.1136/gut.14.11.870]

146 **Barbezat GO**, Hansen JD. The exocrine pancreas and protein-calorie malnutrition. *Pediatrics* 1968; **42**: 77-92 [PMID: 5657699]

147 **DAVIES JN**. The essential pathology of kwashiorkor. *Lancet* 1948; **1**: 317-320 [PMID: 18905394]

148 **El-Hodhod MA**, Nassar MF, Hetta OA, Gomaa SM. Pancreatic size in protein energy malnutrition: a predictor of nutritional recovery. *Eur J Clin Nutr* 2005; **59**: 467-473 [PMID: 15536474 DOI: 10.1016/S0140-6736(48)92087-X]

149 **Silk DB**, Kumar PJ, Perrett D, Clark ML, Dawson AM. Amino acid and peptide absorption in patients with coeliac disease and dermatitis herpetiformis. *Gut* 1974; **15**: 1-8 [PMID: 4820629 DOI: 10.1136/gut.15.1.1]

150 **Carroccio A**, Iacono G, Montalto G, Cavataio F, Lorello D, Greco L, Soresi M, Notarbartolo A. Pancreatic enzyme therapy in childhood celiac disease. A double-blind prospective randomized study. *Dig Dis Sci* 1995; **40**: 2555-2560 [PMID: 8536512 DOI: 10.1007/BF02220441]

151 **Maconi G**, Dominici R, Molteni M, Ardizzone S, Bosani M, Ferrara E, Gallus S, Panteghini M, Bianchi Porro G. Prevalence of pancreatic insufficiency in inflammatory bowel diseases. Assessment by fecal elastase-1. *Dig Dis Sci* 2008; **53**: 262-270 [PMID: 17530399 DOI: 10.1007/s10620-007-9852-y]

152 **Pitchumoni CS**, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. *J Clin Gastroenterol* 2010; **44**: 246-253 [PMID: 20087199 DOI: 10.1097/MCG.0b013e3181cadbe1]

153 **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 [PMID: 8734352 DOI: 10.3109/00365529609006775]

154 **Hegnhøj J**, Hansen CP, Rannem T, Søbirk H, Andersen LB, Andersen JR. Pancreatic function in Crohn's disease. *Gut* 1990; **31**: 1076-1079 [PMID: 1698692 DOI: 10.1136/gut.31.9.1076]

155 **Winter TA**, O'keefe SJ, Callanan M, Marks T. Impaired gastric acid and pancreatic enzyme secretion in patients with Crohn's disease may be a consequenece of a poor nutritional state. *Inflamm Bowel Dis* 2004; **10**: 618-625 [PMID: 15472524]

156 **Barthet M**, Lesavre N, Desplats S, Panuel M, Gasmi M, Bernard JP, Dagorn JC, Grimaud JC. Frequency and characteristics of pancreatitis in patients with inflammatory bowel disease. *Pancreatology* 2006; **6**: 464-471 [PMID: 16847384 DOI: 10.1159/000094564]

157 **Angelini G**, Cavallini G, Bovo P, Brocco G, Castagnini A, Lavarini E, Merigo F, Tallon N, Scuro LA. Pancreatic function in chronic inflammatory bowel disease. *Int J Pancreatol* 1988; **3**: 185-193 [PMID: 3361159 DOI: 10.1007/BF02798930]

158 **Filipsson S**, Hultén L, Lindstedt G. Malabsorption of fat and vitamin B12 before and after intestinal resection for Crohn's disease. *Scand J Gastroenterol* 1978; **13**: 529-536 [PMID: 705247 DOI: 10.3109/00365527809181760]

159 **Seibold F**, Weber P, Jenss H, Wiedmann KH. Antibodies to a trypsin sensitive pancreatic antigen in chronic inflammatory bowel disease: specific markers for a subgroup of patients with Crohn's disease. *Gut* 1991; **32**: 1192-1197 [PMID: 1955175 DOI: 10.1136/gut.32.10.1192]

160 **Seibold F**, Mörk H, Tanza S, Müller A, Holzhüter C, Weber P, Scheurlen M. Pancreatic autoantibodies in Crohn's disease: a family study. *Gut* 1997; **40**: 481-484 [PMID: 9176075 DOI: 10.1136/gut.40.4.481]

161 **Kovacs M**, Lakatos PL, Papp M, Jacobsen S, Nemes E, Polgar M, Solyom E, Bodi P, Horvath A, Muller KE, Molnar K, Szabo D, Cseh A, Dezsofi A, Arato A, Veres G. Pancreatic autoantibodies and autoantibodies against goblet cells in pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2012; **55**: 429-435 [PMID: 22465933 DOI: 10.1097/MPG.0b013e318256b516]

162 **Piontek M**, Hengels KJ, Strohmeyer G. Crohn's disease: what about the pancreas? *J Clin Gastroenterol* 1990; **12**: 491-493 [PMID: 2229990]

163 **Toda N**, Akahane M, Kiryu S, Matsubara Y, Yamaji Y, Okamoto M, Minagawa N, Ohgi K, Komatsu Y, Yahagi N, Yoshida H, Kawabe T, Ohtomo K, Omata M. Pancreas duct abnormalities in patients with ulcerative colitis: a magnetic resonance pancreatography study. *Inflamm Bowel Dis* 2005; **11**: 903-908 [PMID: 16189420 DOI: 10.1097/01.MIB.0000183419.17563.17]

164 **Domínguez-Muñoz JE**. Pancreatic enzyme replacement therapy: exocrine pancreatic insufficiency after gastrointestinal surgery. *HPB (Oxford)* 2009; **11 Suppl 3**: 3-6 [PMID: 20495625 DOI: 10.1111/j.1477-2574.2009.00132.x]

165 **Olbe L**, Lundell L. Intestinal function after total gastrectomy and possible consequences of gastric replacement. *World J Surg* 1987; **11**: 713-719 [PMID: 3433789 DOI: 10.1007/BF01656593]

166 **Hillman HS**. Postgastrectomy malnutrition. *Gut* 1968; **9**: 576-584 [PMID: 5717108 DOI: 10.1136/gut.9.5.576]

167 **Gullo L**, Costa PL, Ventrucci M, Mattioli S, Viti G, Labò G. Exocrine pancreatic function after total gastrectomy. *Scand J Gastroenterol* 1979; **14**: 401-407 [PMID: 482852]

168 **Friess H**, Böhm J, Müller MW, Glasbrenner B, Riepl RL, Malfertheiner P, Büchler MW. Maldigestion after total gastrectomy is associated with pancreatic insufficiency. *Am J Gastroenterol* 1996; **91**: 341-347 [PMID: 8607504]

169 **Armbrecht U**, Lundell L, Stockbruegger RW. Nutrient malassimilation after total gastrectomy and possible intervention. *Digestion* 1987; **37 Suppl 1**: 56-60 [PMID: 3305116 DOI: 10.1159/000199542]

170 **Perez Aisa A**, Alcaide J, Garcia Gavilan MC, Fernández Cano FM, Mendez I, Navarro Jarabo JM, Rivera R, Rivas F. Preliminary data indicating the prevalence of secondary exocrine pancreatic insufficiency and impact of nutritional condition in gastrectomised patients. *Pancreatology* 2015; **15**: S130 [DOI: 10.1016/j.pan.2015.05.455]

171 **Heptner G**, Domschke S, Domschke W. Exocrine pancreatic function after gastrectomy. Specificity of indirect tests. *Gastroenterology* 1989; **97**: 147-153 [PMID: 2656361]

172 **Suda Y**, Shiraso M, Sato T. Exocrine pancreatic function after upper abdominal surgery. *Tohoku J Exp Med* 1975; **115**: 307-317 [PMID: 1145614 DOI: 10.1620/tjem.115.307]

173 **MacGregor I**, Parent J, Meyer JH. Gastric emptying of liquid meals and pancreatic and biliary secretion after subtotal gastrectomy or truncal vagotomy and pyloroplasty in man. *Gastroenterology* 1977; **72**: 195-205 [PMID: 830568]

174 **Borbély Y**, Plebani A, Kröll D, Ghisla S, Nett PC. Exocrine Pancreatic Insufficiency after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2016; **12**: 790-794 [PMID: 26965152 DOI: 10.1016/j.soard.2015.10.084]

175 **Pandiri AR**. Overview of exocrine pancreatic pathobiology. *Toxicol Pathol* 2014; **42**: 207-216 [PMID: 24190915 DOI: 10.1177/0192623313509907]

176 **Mikhailidis DP**, Foo Y, Ramdial L, Kirk RM, Rosalki SB, Dandona P. Pancreatic exocrine function after truncal and highly selective vagotomy. *J Clin Pathol* 1981; **34**: 963-964 [PMID: 6168662 DOI: 10.1136/jcp.34.9.963]

177 **Malagelada JR**, Go VL, Summerskill WH. Altered pancreatic and biliary function after vagotomy and pyloroplasty. *Gastroenterology* 1974; **66**: 22-27 [PMID: 4809496]

178 **Wormsley KG**. The effect of vagotomy on the human pancreatic response to direct and indirect stimulation. *Scand J Gastroenterol* 1972; **7**: 85-91 [PMID: 5010511 DOI: 10.3109/00365527209180742]

179 **Edwards JP**, Lyndon PJ, Smith RB, Johnston D. Faecal fat excretion after truncal, selective, and highly selective vagotomy for duodenal ulcer. *Gut* 1974; **15**: 521-525 [PMID: 4430470 DOI: 10.1136/gut.15.7.521]

180 **Layer P**, Melle U. Indication for pancreatic enzyme substitution following small intestinal resection (short bowel syndrome). *Pancreatology* 2001; **1**: 49-54 [DOI: 10.1159/000055892]

181 **Huddy JR**, Macharg FM, Lawn AM, Preston SR. Exocrine pancreatic insufficiency following esophagectomy. *Dis Esophagus* 2013; **26**: 594-597 [PMID: 23199208 DOI: 10.1111/dote.12004]

182 **Lankisch PG**. Appropriate pancreatic function tests and indication for pancreatic enzyme therapy following surgical procedures on the pancreas. *Pancreatology* 2001; **1**: 14-26 [DOI: 10.1159/000055888]

183 **Armbrecht U**, Lundell L, Stockbrügger RW. The benefit of pancreatic enzyme substitution after total gastrectomy. *Aliment Pharmacol Ther* 1988; **2**: 493-500 [PMID: 2979271 DOI: 10.1111/j.1365-2036.1988.tb00722.x]

184 **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 [PMID: 10333193]

185 **Wormsley KG**. Pancreatic exocrine function in patients with gastric ulceration before and after gastrectomy. *Lancet* 1972; **2**: 682-684 [PMID: 4115820 DOI: 10.1016/S0140-6736(72)92089-2]

**P-Reviewer:** Czakó L, Vujasinovic M **S-Editor:** Gong ZM

**L-Editor:** **E-Editor:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** United States

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): 0

Grade C (Good): C, C

Grade D (Fair): 0

Grade E (Poor): 0

**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.

**Table 2 Factors involved with exocrine pancreatic insufficiency in different medical conditions[**[**1**](#_ENREF_1)**,**[**16**](#_ENREF_16)**,**[**77**](#_ENREF_77)**,**[**78**](#_ENREF_78)**,**[**107**](#_ENREF_107)**,**[**129**](#_ENREF_129)**,**[**131**](#_ENREF_131)**,**[**133**](#_ENREF_133)**,**[**143**](#_ENREF_143)**,**[**144**](#_ENREF_144)**,**[**152-154**](#_ENREF_152)**,**[**164**](#_ENREF_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**](#_ENREF_1)**,**[**14-16**](#_ENREF_14)**,**[**18**](#_ENREF_18)**,**[**19**](#_ENREF_19)**,**[**22**](#_ENREF_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 |

**Table 4 Symptoms and tests used in the diagnosis of exocrine pancreatic insufficiency[**[**2**](#_ENREF_2)**,**[**16**](#_ENREF_16)**,**[**23**](#_ENREF_23)**,**[**24**](#_ENREF_24)**]**

|  |
| --- |
| Clinical symptoms |
| Steatorrhea |
| Diarrhea |
| Flatulence |
| Weight loss |
| Laboratory findings |
| Fecal fat >7 g/day on a 100-g fat/day dietInconvenient; special high-fat diet and prolonged collection of fecesConsidered gold standardAn abnormal coefficient of fat absorption is not specific for EPI |
| Fecal elastase-1 level ≤200 µg/g stool; <100 µg/g stool = severe EPISimple, convenient, and widely availableMeasured on a random stool sampleLiquid stools may lead to falsely low results due to dilutionLess accurate in mild stages of disease |
| Positive qualitative fecal fat (Sudan III) stainingSpecial high-fat dietLess accurate; semi-quantitative microscopic method Insensitive for mild disease |
| Fecal chymotrypsin ≤6 U/g stoolLess sensitive than fecal elastase for mild EPI |
| Fluorescein dilaurate (pancreolauryl test)Easy to performNot widely available |
| 13C-mixed triglyceride breath testWell establishedNot widely available |
| Imaging/endoscopy |
| Pancreatic duct dilatation |
| Main pancreatic duct calculi |
| Endosonographic criteria of chronic pancreatitis |
| Secretin-enhanced diffusion-weighted magnetic resonance cholangiopancreatography imagingNewNot widely available |

EPI: exocrine pancreatic insufficiency.

**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](#_ENREF_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](#_ENREF_70)] | DBRPC, 8 wk, 67 adults | Pancreatic cancer | The mean change in body weight at 8 weeks 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](#_ENREF_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](#_ENREF_49)] | DBRPC, 16 wk, 80 adults | Type 1 diabetes | No significant change in HbA1c, 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](#_ENREF_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](#_ENREF_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* ≤ 0.0001), but no weight increase (*P* = 0.3) | No descriptions regarding TEAEs |
| Leeds *et al*[[135](#_ENREF_135)] | Open-label, up to 2 years, 20 adults | Celiac disease | Significant improvement in chronic diarrhea with reduction in median stool frequency from 4/d to 1/d (*P* ≤ 0.0001), but no weight increase (*P* = 0.3) | No descriptions regarding TEAEs |
| Huddy *et al*[[181](#_ENREF_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](#_ENREF_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](#_ENREF_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 |
| Bragelmann *et al*[[184](#_ENREF_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; HbA1c: glycated hemoglobin A1c; PBO: placebo; PERT: pancreatic enzyme replacement therapy; PG-SGA: Patient-generated subjective global assessment; TEAE: treatment-emergent AE.