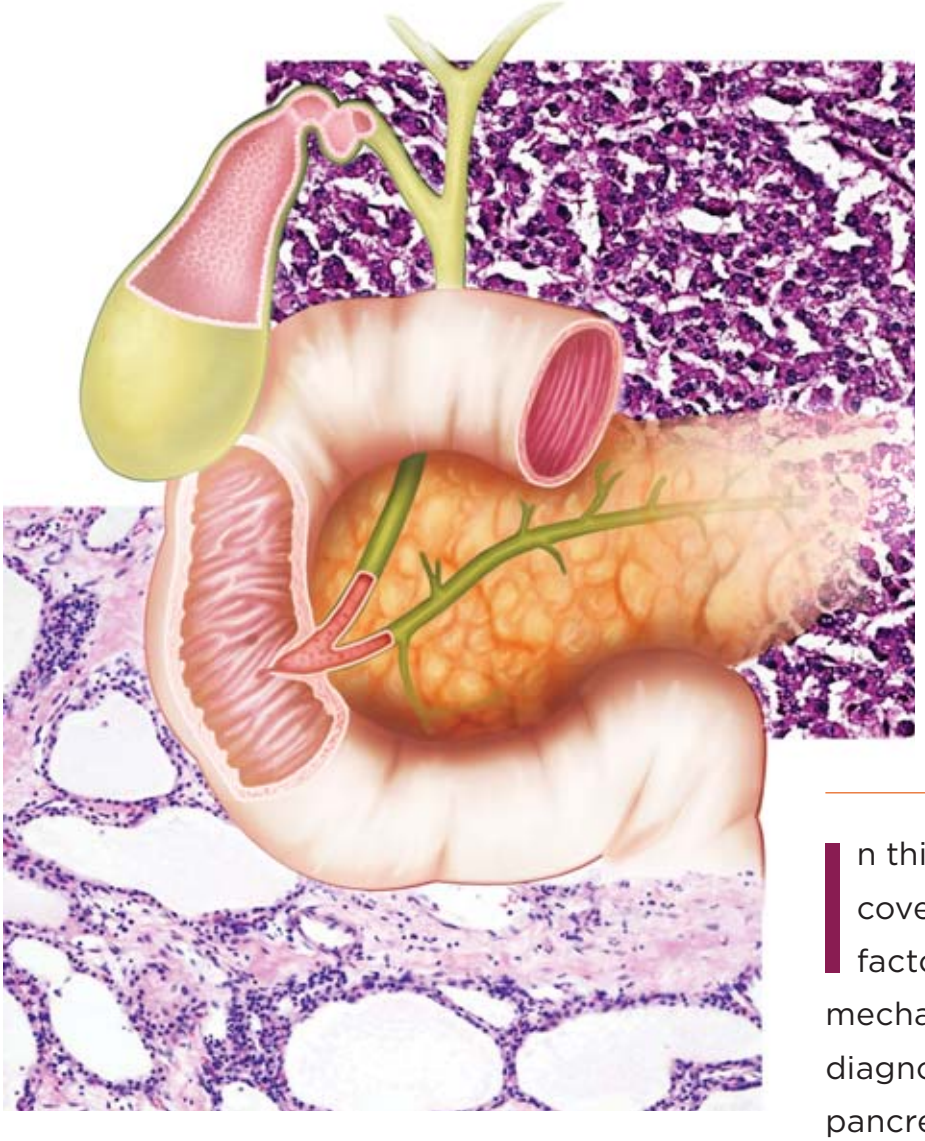
Pancreatic Exocrine Insufficiency

Part 1 of 2: Pathogenic and Diagnostic Considerations



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In this 2-part review, Part 1 covers the epidemiologic factors, pathogenic mechanisms, and current diagnostic strategies of pancreatic exocrine insufficiency (PEI); Part 2 covers treatment approaches for patients with PEI, including the proper use of currently FDA-approved pancrelipase preparations.

The exocrine pancreas plays an essential physiologic role in maintaining digestive health, nutrition, and proper patterns of growth. Pancreatic exocrine secretion of digestive enzymes breaks down ingested food into micronutrients for absorption into the circulatory system. A disruption of this process by pancreatic ductal blockage, parenchymal destruction, or surgical resection may lead to PEI. Vulnerable patients who have lost more than 90% of pancreatic function exhibit steatorrhea and are at risk for short- and long-term nutritional deficiencies and complications that compromise clinical outcomes.[1]

Utilization of pancreas function tests in at-risk patients allows for accurate diagnosis of PEI, which is critical to initiating effective disease management and limiting complications of maldigestion. Although dietary modifications are helpful, most patients with PEI require individualized, lifelong support with pancreatic enzyme replacement therapy (PERT). Proper dosage, timing, and adherence to exogenous pancreatic enzyme replacements are essential to optimize efficacy and minimize adverse effects that may impact life expectancy and patient quality of life. Improper use of PERT by clinicians or patients may also exacerbate disease complications, increasing healthcare expenditures and the overall economic burden of PEI.

Epidemiology and Burden of PEI

PEI develops most commonly in children with cystic fibrosis (CF) or adults with advanced-stage chronic pancreatitis (CP).[2] As shown in the Table, other causes of pancreatic exocrine dysfunction include pancreatic diseases such as hereditary pancreatitis, tropical pancreatitis, severe acute necrotizing pancreatitis, acute recurrent pancreatitis, and chronic main pancreatic duct obstruction, including pancreatic cancer. Metabolic disorders, such as hypercalcemia and hyperlipoproteinemia;[2] extrapancreatic illnesses, such as celiac disease, Crohn's disease, primary biliary cirrhosis, and sclerosing cholangitis; and, rarely, isolated enzyme deficiencies observed in pediatric patients have been associated with PEI.[3,4] PEI is also common after pancreatic and gastric surgical procedures, notably including pancreatic resection. The clinical and economic burden attributable to PEI is difficult to determine and has not been clearly established in medical literature. However, since individuals with CF and CP require PERT to remedy enzyme insufficiencies,[5-7] PEI prevalence and costs can be extrapolated from epidemiologic data available for CF and CP patient populations.

Cystic Fibrosis

CF is the most common lethal genetic defect occurring in the Caucasian population.[8] The global incidence of CF varies among races, and in the United States ranges from 1 in 2,500 to 1 in 3,500 live births in the Caucasian population.[8,9] CF currently affects approximately 30,000 adults and children in the United States.[10] Although the cost of care is variable, the mean annual cost of care for a patient with CF has been estimated at $7,524.[9]

CF is inherited in an autosomal recessive pattern localized to chromosome 7, which encodes the cystic fibrosis transmembrane conductance regulator (CFTR). Dysfunction of CFTR leads to the clinical manifestations of CF.[11] Although the pulmonary complications are more evident, in the pancreas this mutation alters chloride transport from pancreatic ductal cells causing viscous proteinaceous secretions which block the pancreas ducts. This eventually leads to scarring and progressive pancreatic insufficiency.[11,12] Other common gastrointestinal manifestations of CF include gastroesophageal reflux disease, small bowel overgrowth, rectal prolapse, hepatobiliary disease, intussusception, meconium ileus, and distal intestinal obstructive syndrome (DIOS).[13]

Approximately 50% of children with CF exhibit pancreatic insufficiency at birth, and another 25% develop pancreatic dysfunction within the first 6 months of life.[14,15] Of the remaining 25% of children with CF, at least 15% will develop PEI later in childhood or young adulthood, leaving up to only 10% of children with CF who will have sufficient pancreatic activity for the duration of their lives.[15] Although pancreatic sufficiency in CF patients is generally associated with better clinical outcomes, it does not imply normal pancreatic function and is still associated with a risk for developing DIOS or CF-related diabetes.[13,16] It is estimated that more than 90% of children with CF require PERT as a life-sustaining intervention for PEI.[17] Expected survival rates for individuals with CF has improved with the use of PERT, as well as advances in pulmonary care and recognition of early signs of malnutrition.[18] The median age of survival for people with CF has risen to 37 years, with more than 40% of individuals with CF being 18 years of age or older.[10] The rising life expectancy of individuals with CF augments the opportunity to effectively treat the disease and manage gastrointestinal symptoms as well as other associated sequelae (ie, metabolic bone disease).

Chronic Pancreatitis

CP is caused by chronic inflammation of the pancreas associated with genetic, autoimmune, and environmental factors and occurs more frequently in male adults.[2] The incidence ranges from 3 to 9 cases per 100,000 individuals and increases with age.[19,20] The data on prevalence is scarce but is estimated at 28.5 to 41.8 cases per 100,000 persons. The gradual rise in incidence observed in some countries may be attributed to earlier diagnosis and/or increasing alcohol consumption.[19,21-23] Alcohol abuse accounts for 70% to 80% of CP cases.[24] PEI and symptoms of maldigestion usually develop after approximately 10 to 15 years of chronic alcoholic abuse[25] and vary according to CP disease

Table. Etiologies of Pancreatic Exocrine Insufficiency[69]

Mechanism	Etiology
Decreased lipase production and delivery, increased lipase destruction	Chronic pancreatitis, cystic fibrosis, diabetes
Pancreatic duct obstruction	Periampullary tumor, pancreatic head cancer, IPMN, benign tumors
Decreased endogenous lipase stimulation and production	Celiac disease, Crohn's disease, Shwachman–Diamond syndrome
Motility disorders (decreased contact time, interaction with chyme, and stimulation of pancreatic enzymes)	Gastrectomy, gastric bypass, extensive small bowel resection

IPMN, intraductal papillary mucinous neoplasm

severity and duration; prevalence of PEI is estimated at 30% for mild CP and up to 85% for severe CP.[26] Idiopathic PEI accounts for 10% of adult CP cases.[25] Management of patients with CP involves significant annual healthcare expenditures, accounting for more than 122,000 outpatient visits and over 56,000 hospitalizations in the United States, with total treatment costs estimated at $2.1 billion in 1998.[27,28] Emerging epidemiological data from the North American Pancreatitis Study Group has improved our understanding of the etiologic factors at play in CP in the United States, implicating smoking as a dose-dependent, causal co-factor for CP. The combined effect of smoking and alcohol is synergistic and contributes profoundly to development and progression of the disease.

Pathogenesis of PEI

Loss of exocrine function in patients with CF and CP results from the inflammatory destruction of pancreatic ductal and acinar cells, causing a reduction in the quantity of enzymes available to digest carbohydrates, proteins, and fats and consequently resulting in maldigestion and malabsorption.

The Digestive Process and Fat Malabsorption

Suboptimal carbohydrate, protein, and fat digestion processes underlie the clinical symptoms of PEI and are among the diagnostic criteria for the condition. Carbohydrate digestion starts in the mouth with salivary amylase and continues at the brush border of the small intestine with both intestinal oligosaccharidases and pancreatic amylase secretions.[29] Protein digestion begins in the stomach with hydrochloric acid activation of pepsin and continues at the brush border with pancreatic and intestinal proteolytic enzymes.[29] Despite loss of pancreatic function, carbohydrate and protein digestion are well maintained in individuals with PEI, as the digestive system is capable of compensating for PEI. In contrast, lipid digestion involves a more complex, multistep process of emulsification and ultimately fatty acid hydrolysis, the latter process being highly dependent on pancreatic lipase. Thus, exogenous therapeutic intervention is necessary to rescue the functional deficiency.[29]

In healthy individuals, dietary fat is first modified by lingual and gastric lipase in the stomach. Bile salts subsequently solubilize the lipolytic products through the formation of micelles for further hydrolysis in the small intestine by pancreatic lipase. Lipase then breaks down the lipids into long-chain fatty acids and monoglycerides in a neutralized chymal environment maintained by duct cell bicarbonate secretion.[29] Following absorption across the intestinal barrier, micelles are converted back into chylomicrons (lipoprotein particles), which circulate in the lymphatic system and return to the circulatory system for delivery to the body.[29]

Fat absorption is particularly affected in individuals with PEI for several reasons.[30] The functional ability of the pancreas to synthesize and secrete lipase is impaired earlier and more severely than its other enzymes, particularly in the course of CP.[30-32] The pancreas is the primary source of lipase secretion for the digestion of dietary fat, with intragastric lipase digestion accounting for approximately only 10% of total lipid digestion.[29] However, in patients with PEI, intragastric lipase digestion may account for more than 90% of total lipase activity but cannot compensate for loss of pancreatic lipase secretion.[33] Additionally, the insufficient pancreas does not secrete an adequate concentration of sodium bicarbonate, which protects pancreatic enzymes from denaturation by gastric acid and establishes an optimal pH (~8.0) for pancreatic enzyme activity. The resulting low duodenal pH impairs lipid solubilization by inactivating the bile acids, a complication further exacerbated by the denaturation of the pancreatic enzymes, notable at pH 5.0 or lower.[34,35] Lastly, lipase is more susceptible

to proteolytic degradation than other enzymes, including amylase.[36,37] Lipase activity declines rapidly during small intestinal transit and is active for relatively short periods of time in both healthy individuals and patients with PEI.[36-38] Thus, lipolysis is a complicated process for which pancreatic secretion of bicarbonate and lipolytic enzymes is essential and, once impaired, results in maldigestion and malabsorption, necessitating extrinsic pancreatic enzyme supplementation.

Signs and Symptoms of PEI

The primary clinical sign of PEI is steatorrhea—loose, fatty, pale, malodorous stool resulting from lipid maldigestion. Unabsorbed fat and oil droplets in stool that stick to the toilet bowl or that are difficult to flush are highly suggestive of PEI. This is a late manifestation of pancreas dysfunction, typically occurring after 90% of exocrine glandular function is lost.[1] Other clinical symptoms that may be suggestive of PEI include malnutrition, growth retardation, or delayed maturation related to nutritional failure; hyperproteinemia with severe edema; decreased muscle mass; and abdominal distension and pain. A small number of patients exhibit fat-soluble vitamin (A, D, E, and K) deficiencies.[39] Noticeable digression from weight and height curves plotted during routine pediatric well-visits should also be considered in the context of other symptoms of PEI.[40] Recent evidence also implicates PEI with associated metabolic bone disease and osteoporosis.[41]

Diagnostic Tests To Assess Pancreatic Function

Upon clinical suspicion of pancreatic dysfunction following a complete physical examination, family history, and differential diagnosis, accurate assessment of exocrine function with direct or indirect pancreas function tests is necessary to confirm pancreatic status and initiate appropriate therapy. Pancreas function tests assess pancreatic secretory reserve and are used to diagnose early disease, to monitor disease progression, and to assess the efficacy of PERT in order to tailor therapy.[42-44] Pancreatic function tests are similar in diagnostic utility across age groups.

Infrequently used in clinical practice, direct (invasive) pancreas function tests require placement of double-lumen gastroduodenal tubes for pancreatic fluid collection following intravenous cholecystokinin (CCK) or secretin stimulation.[45] The extracted fluid is analyzed quantitatively for enzyme and bicarbonate production. Direct tests are highly accurate for PEI, particularly in early CP, because they detect subtle changes in pancreatic function before the development of overt steatorrhea and morphologic changes observed on imaging tests. Direct tests have been reported to be more than 90% sensitive and specific for detection of PEI.[45] The major limitations of direct pancreatic function testing have been the cumbersome nature of the test and the difficulty of pancreatic fluid collection with the gastroduodenal tube method.[46] Thus, they have only been available at select research centers with dedicated gastroenterology laboratory personnel.[47]

Over the past several years, endoscopic collection methods have been developed which have simplified pancreatic fluid collection. These techniques have made the test more suitable for widespread clinical use, including screening patients with chronic pain syndromes for pancreatic disease.[48,49] With these newer approaches, the upper endoscope is used instead of the gastroduodenal tube to: 1) directly aspirate pancreas fluid (endoscopic pancreatic function testing [ePFT]);[48] 2) facilitate placement of a modified Dreiling tube (endoscopy-assisted);[49] or 3) facilitate placement of a Liguory tube.[50,51] Some centers also directly cannulate the pancreas duct during endoscopic retrograde cholangiopancreatography; this carries some risk for procedure-induced pancreatitis and may not be as accurate as other diagnostic methods.[52] Furthermore, these newer methods have promoted the use of a hospital autoanalyzer in place of back-titration methods to analyze fluids.[53,54] Both the application of an endoscopic collection method and the adoption of an autoanalyzer to systematize pancreatic fluid analysis have markedly increased the use of pancreas function testing in the United States.

The ePFT method of direct pancreas fluid aspiration from the duodenum is the most studied and validated endoscopic method of pancreatic function testing.[55,56] It causes minimal harm to the patient and does not induce pancreatitis. Secretin-, CCK-, and combined secretin-CCK-stimulated ePFT methods have been developed.[57] Additionally, a shortened "screening" method has been reported to rapidly assess patients with chronic pain syndromes who have a low likelihood of having pancreatic disease.[58] Aspirated pancreas fluid samples are kept on ice and transported to the hospital laboratory for autoanalyzer analysis of electrolyte and/or enzyme concentration. Peak pancreas fluid bicarbonate concentrations less than 80 meq/L in the secretin test and peak lipase concentrations less than 780,000 IU/L in CCK-stimulated ePFT are diagnostic of PEI.

In general, investigators have preferentially relied on indirect (noninvasive) methods to circumvent the challenges associated with direct pancreatic function tests. Clinically available indirect tests of pancreatic function include fecal fat analysis, fecal chymotrypsin analysis, acid steatocrit analysis, and fecal elastase analysis.[59-62] Most indirect tests are sensitive for moderate- and late-stage PEI but lack sensitivity for early disease detection. However, they are adequate for the assessment of steatorrhea, a manifestation of significant loss of pancreatic function.[49] The 72-hour fecal fat collection test with calculation of a coefficient of fat absorption is the gold standard for the assessment of fat malabsorption.[63] The test requires a 5-day diet of 100 g of fat per

day, with stool collections performed throughout the last 72 hours of the diet.[63] Fecal fat excretion exceeding 7 g per day is abnormal but not sensitive or specific for PEI, as other gastrointestinal diseases also may be associated with steatorrhea.[63] The fecal fat test is inconvenient, unpleasant for patients, and prone to laboratory error and sample loss; therefore, it is primarily used in research settings.[63]

The fecal elastase-1 test is emerging globally as the most commonly utilized noninvasive test for PEI assessment and also is gaining widespread recognition in the United States.[64] Elastase-1, a specific protease synthesized by pancreatic acinar cells, is a useful tool for the evaluation of insufficiency because it is stable in stool, unaffected by PERT, and correlates well with stimulated pancreas function tests.[64] The fecal elastase-1 test is an enzyme-linked immunosorbent assay that uses monoclonal antibodies against two different epitopes of human pancreatic elastase. It has a superior overall diagnostic accuracy when compared with chymotrypsin (92% vs 82%), and measurements may be reproduced for approximately 7 days post-collection.[64] As with other indirect pancreas function tests, stool dilution can cause false-positive results.[64] Fecal elastase-1 testing has gained popularity in CF clinics and is now commonly used as evidence of PEI in infants screened for CF to confirm the need for PERT.[65] Mild and severe PEI diagnoses are based on a fecal elastase-1 value of less than 200 mcg per gram of stool and 100 mcg per gram of stool, respectively.[61]

Despite radiologic and endoscopic advances, a diagnostic test that can detect early PEI prior to clinically evident symptoms of steatorrhea is currently unavailable.[1] Diagnostic methods sensitive for early disease are an active area of research and include recent advances in magnetic resonance imaging and secretin-stimulated magnetic resonance cholangiopancreatography as well as endoscopic ultrasound, which correlate pancreatic function with duct morphology in moderate to advanced disease.[66,67] Simplification of endoscopic direct function tests as well as further advances in radiologic imaging would potentially offer diagnostic possibilities less cumbersome and better tolerated by patients, thereby broadening the availability and clinical use of direct tests for the early detection of PEI.[47,68]

Conclusion

Ongoing epidemiologic study is establishing the incidence and prevalence of PEI in the United States and more clearly defining its etiologic risk factors. Despite recent advances in direct pancreas function testing, a point-of-care diagnostic test that can detect early PEI prior to clinically evident symptoms of steatorrhea is still lacking.[1] The patients identified may be started on pancreatic enzyme replacement therapy (PERT) early in the course of the disease in hopes of retarding the complications of long-term malnutrition.

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