Disruption of exocrine pancreatic function may lead to pancreatic exocrine insufficiency (PEI) and to the inability to process and absorb vital nutrients. Supplementation with oral pancreatic enzyme replacement therapy (PERT) can improve nutritional status and quality of life (QoL). This review will outline the major causes and diagnosis of PEI and the approach to treatment and monitoring of patients who require PERT.

Normal exocrine pancreatic function involves the secretion of enzyme-rich fluid that is responsible for the breakdown of fats, starches, and proteins, the vital nutrients that are absorbed during the transit of food through the intestinal lumen. A disruption in this process by pancreatic ductal blockage, parenchymal destruction, or surgical removal of a significant portion of pancreatic tissue may lead to PEI and to the inability to process and absorb these nutrients. If a majority of the enzymatic secretion is lost, symptoms of
progressive weight loss and steatorrhea may develop, leading to decreased QoL, malnutrition, and morbidity. Supplementation with PERT can improve nutritional status, relieve steatorrhea, and improve QoL.

**Causes of PEI**

Any disruption in the production or secretion of pancreatic enzymes can lead to PEI. Most commonly, this clinical situation results from destruction of glandular tissue (eg, chronic pancreatitis [CP]), obstruction of pancreatic ducts (eg, trauma, calcifications, tumors), surgical removal of a significant portion of the pancreas, or small bowel mucosal disease. Whatever the cause, significant malabsorption requiring enzyme supplementation does not develop until 90% of exocrine function has been lost.

**CHRONIC PANCREATITIS**

CP is a progressive inflammatory disease that leads to destruction of glandular tissue and permanent structural damage. The end result is the inability to produce enzymes and hormones necessary for normal digestion. There are many etiologies of CP, which is the most common cause of PEI.

**ALCOHOLISM AND SMOKING**

In Western countries, high alcohol consumption is responsible for 60% to 80% of documented cases of CP; however, only 5% to 15% of alcoholics develop CP. This suggests that a genetic susceptibility must coexist with alcohol consumption in order for pancreatic damage to develop. Smoking tobacco also has been shown to be a dose-dependent risk factor for development of CP.

**GENETIC DISORDERS**

Certain genetic disorders have been identified that lead to pancreatic insufficiency. For example, more than 1,500 mutations have been identified in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is responsible for cystic fibrosis (CF). Any number of these genetic abnormalities may lead to abnormal cellular chloride transportation across epithelial membranes and the production of particularly thick mucus and proteinaceous secretions. The resulting viscous fluid inhibits the normal flow of pancreatic juices, causing obstruction of the proximal pancreatic ducts. Over time, secondary acinar cell destruction, fibrosis, and PEI develop in up to 85% of individuals with CF. However, CP occurs in only a minority of patients with CF and is usually found in those with pancreas sufficiency who have less severe mutations in the CFTR gene. Conversely, CFTR mutations have been found in up to 45% of patients with idiopathic chronic pancreatitis who have no other clinical manifestations or diagnostic evidence of CF. This suggests that the importance of CFTR mutations is underestimated in certain patients with CP.

Autosomal dominant (hereditary) CP is another familial form of pancreatic disease that is usually the result of mutations in the serine protease 1 (PRSSI) gene on chromosome 7q35. PRSSI encodes a protein, cationic trypsinogen, which is responsible for regulation of pancreatic enzymatic activity. Mutations in this protein alter the regulatory mechanisms necessary to protect the pancreas from autodigestion, resulting in recurrent episodes of acute pancreatitis, and eventually, CP. These patients have up to a 54% cumulative risk for developing pancreatic cancer, which is further increased in those who smoke and who are diabetic.

Mutations in the serine protease inhibitor Kazal type 1 (SPINK1) gene (also called the pancreatic secretory trypsin inhibitor [PSTI] gene) are associated with an autosomal recessive form of CP. Mutations in this protein lead to the inability to protect the pancreas from damage due to activated trypsin. Similar to mutations in the CFTR gene, studies have shown mutations in SPINK1 in patients who were previously diagnosed with idiopathic CP.

Another autosomal recessive disorder, Shwachman-Diamond syndrome, is a rare cause of PEI due to pancreatic hypoplasia that typically presents during infancy or early childhood. Patients affected by this disorder usually have symptoms of pancreatic insufficiency (eg, steatorrhea, growth failure), along with bone marrow failure. Other skeletal abnormalities also have been identified as a part of this clinical syndrome.

**DUCTAL OBSTRUCTION**

Any clinical situation that leads to obstruction and prevention of release of pancreatic fluid into the duodenum can lead to CP. Trauma, calcifications from recurrent pancreatitis, cystic lesions of the pancreas, tumors, pancreas divisum, and sphincter of Oddi dysfunction all have been implicated as possible causes of ductal obstruction, preventing pancreatic outflow and leading to autodigestion and destruction of pancreatic tissue. Depending on the underlying cause as well as the severity of the CP, relief of the obstruction, either by endoscopic stenting or surgical intervention, may improve and possibly restore normal physiologic pancreatic activity.

**AUTOIMMUNE PANCREATITIS**

Autoimmune pancreatitis (AIP), a rare disorder of unknown etiology, can lead to chronic pancreatic obstruction. The presentation of AIP can range from a focal pancreatic mass to recurrent episodes of acute pancreatitis, leading to pancreatic duct strictures. Over time, PEI can develop as a result of fibrosis and lymphocytic infiltration of the pancreatic parenchyma and chronic ductal obstruction. The diagnosis is supported by elevated serum IgG4 levels, pancreatic histology, and characteristic radiographic findings. Treatment with glucocorticoids can reverse the
inflammation and potentially relieve PEI symptoms.

**Tropical Pancreatitis**

A common cause of CP in southern Asia is tropical pancreatitis. Although the disease has no known etiology, genetic defects in the chymotrypsinogen gene have recently been implicated in the disease.32

**Small Bowel Mucosal Disease**

Disorders affecting the intestinal mucosa, such as celiac disease and Crohn’s disease, have been implicated as causes of PEI. Patients with celiac disease who have persistent symptoms despite adherence to a gluten-free diet have been shown to have low levels of fecal elastase, consistent with PEI.33 Pancreatic autoantibody formation in patients with Crohn’s disease suggests an autoimmune component and is associated with a higher rate of PEI.34,35 Although it may be difficult to determine if diarrhea is due to uncontrolled mucosal disease or PEI, physicians should consider enzyme supplementation in patients whose underlying disease is being treated appropriately but who continue to have persistent steatorrhea.

**Pancreatic Cancer**

The majority of pancreatic cancers—more than 95%—are derived from the exocrine ductal and acinar cells. The most common type is ductal adenocarcinoma, which accounts for up to 85% of all malignant pancreatic cancers and is universally fatal unless found very early in the disease process.36 Cystic pancreatic neoplasms, which include intraductal papillary mucinous neoplasms, serous cystadenomas, and mucinous cystadenomas, are increasingly identified with the widespread use of radiographic imaging and account for slightly more than 1% of pancreatic neoplasms.37 These lesions have varying degrees of malignant potential but their prognosis is generally better than that of ductal adenocarcinomas.

Neuroendocrine tumors of the pancreas, such as gastrinomas, insulinomas, glucagonomas, VIPomas, and somatostatinomas, account for less than 5% of all pancreatic cancers and are associated with more favorable survival than exocrine malignancies.38 Virtually any type of pancreatic neoplasm, either benign or malignant, can lead to PEI owing to destruction of glandular tissue or obstruction of pancreatic outflow.

**Postsurgical Disorders**

PEI is a common disorder after gastric and pancreatic surgeries. Clinically significant PEI has been found in up to 62% of postsurgical patients, although a significant proportion of these patients may have had preexisting obstructive pancreatitis and PEI was likely not a consequence of the procedure. The type of procedure (pancreatogastrostomy vs pancreaticojunostomy) does not appear to affect the rate of postoperative PEI, but anastomotic stricturing, especially of the pancreatogastrostomy, is a factor in the development of postoperative PEI.39,40

**Diagnosis of PEI**

Clinical manifestations of severe PEI include steatorrhea, weight loss, and fat-soluble vitamin deficiencies, which occur when more than 90% of the glandular tissue has been destroyed.1 Patients with mild disease may have subclinical manifestations and normal bowel movements. Testing for PEI can be cumbersome and difficult with respect to patient compliance, and an empiric trial of PERT is an alternative diagnostic option in lieu of specific laboratory testing. Numerous tests of pancreatic function have been developed that use both direct hormonal pancreatic stimulation as well as indirect markers of malabsorption.

**Direct Tests of Pancreatic Function**

Direct tests of pancreatic function employ methods to directly stimulate pancreatic secretion. The Lundh test involves administration of a test meal composed of protein, fat, and carbohydrate. Duodenal fluid is collected 2 hours after the test meal to analyze pancreatic secretion.41 However, this test is cumbersome and less sensitive than those that employ hormonal stimulation because surgical anatomy and intestinal mucosal disease can affect the results of the tests.42 Cholecystokinin (CCK) and secretin are 2 hormones that are used to stimulate pancreatic secretion in order to test for pancreatic insufficiency. CCK leads to acinar secretion of digestive enzymes, whereas secretin causes ductal production of bicarbonate. A cutoff lipase concentration of 780,000 IU/L can differentiate patients with normal pancreatic function from those with CP after CCK infusion.43 and a bicarbonate peak concentration of 90 mEq/L or less corresponds to pancreatic insufficiency after secretin stimulation.44,45 The combined CCK–secretin stimulation test is now more widely used as a direct test of pancreatic secretion because it provides information about ductal and acinar function simultaneously.46 Although these tests are sensitive markers of early PEI, they usually are available only at select research centers, are moderately invasive, and require continuous monitoring during the procedure. Additionally, it can be challenging to convince patients, especially those who only have mild to moderate symptoms, to undergo these tests.

**Indirect Tests of Pancreatic Function**

The most commonly used tests for PEI are indirect tests of pancreatic function that measure malabsorption. These tests are widely available, less invasive, and more useful in daily clinical practice with the tradeoff that they are useful only in patients with advanced disease and may not identify patients who have less
The accuracy of the fecal elastase test is reduced in severe PEI. Indirect tests that have been used include serum trypsinogen, fecal fat, fecal chymotrypsinogen, fecal elastase, breath $^{13}$C levels, and secretin-enhanced magnetic resonance pancreaticocholangiography. All of these have good diagnostic accuracy for severe PEI but may not be useful early in the course of disease. The indirect test that has shown to be the most sensitive and reliable is measurement of fecal elastase-1, which has a sensitivity of 100% and a specificity of 93% for the detection of severe PEI. The accuracy of the fecal elastase test is reduced in patients with intestinal mucosal disease and type 1 diabetes, so other laboratory tests or an empiric trial of enzyme supplementation should be considered in these patients.

**Management of PEI**

The goals of PEI management are to improve absorption of fat, prevent symptoms of steatorrhea, and improve nutritional status. Dietary modification should be addressed, especially in patients with no or only mild symptoms. Indications for PERT include weight loss, daily fecal fat excretion of more than 15 g while consuming a diet of 100 g of fat per day, and clinical evidence of steatorrhea. Because fat malabsorption does not occur until 90% of pancreatic function is lost, the goal of supplementation is to provide enough enzymatic activity to restore 5% to 10% of pancreatic enzyme activity. The majority of patients have some degree of residual pancreas function (except in cases of total pancreatectomy), and gastric lipase excretion is increased up to 4 times in patients with PEI, making complete enzyme replacement unnecessary in most cases. It is important to consider that any level of steatorrhea can lead to nutritional deficiencies, and PERT also should be considered in asymptomatic patients who exhibit less than 15 g of fecal fat excretion per day.

**Nutritional Considerations**

Dietary modification may relieve symptoms of steatorrhea, especially in cases of mild disease where residual pancreas function may allow for adequate absorption of dietary fat. Frequent, small-volume meals that are easily digested are recommended in these cases. For patients with persistent steatorrhea, vitamin supplementation (A, D, E, K, and B₁₂) may be required to reverse or prevent fat-soluble vitamin deficiencies until enzyme supplementation takes effect. Although a reduction to 20 g or less of dietary fat per day has been recommended historically for patients who have mild symptoms, fat is a necessary substrate for lipase activity; therefore, fat restriction may actually decrease the efficacy of enzyme supplementation and should not be recommended in patients taking PERT. Fat restriction also is associated with insufficient uptake of fat-soluble vitamins, thus potentiating nutritional deficiencies in patients with PEI. If dietary modification is ineffective in controlling symptoms, PERT is indicated to increase absorption of fat and fat-soluble vitamins and to prevent further nutritional compromise.

**Enzyme Preparations**

PERT should be started at a low dose and titrated upward based on clinical response. All currently available pancreas enzyme supplements contain combinations of lipase, amylase, and protease (Table). Because lipase is the most sensitive enzyme to proteolytic degradation in an acidic environment, fat malabsorption occurs faster than protein deficiency and is usually the more clinically relevant nutritional concern. For this reason, PERT is based on the amount of exogenous lipase per dose and titration involves increasing the amount of enzyme needed to meet clinical goals.

Permanent inactivation of pancreatic enzymes, whether they be derived from residual pancreatic function or orally administered uncoated enzyme supplements, occurs at a pH less than 4.0. Protection from proteolytic degradation and gastric acid inactivation have led to the development of enteric-coated formulations that have been shown to increase fat absorption compared with uncoated preparations. Current formulations consist of enteric-coated, mini-microspheres that resist degradation and are activated at a pH greater than 5.0, thus releasing their components after passage through the duodenum in patients who have normal gastric acid secretion. A change in FDA regulations in 2004 required greater standardization of pancreatic enzyme formulations. The Table lists the 3 preparations that are currently approved by the FDA for prescription use.

An understanding of the labeling of the enzyme preparations is important in order to administer appropriate dosages. Preparations in the United States are demarcated by the amount of lipase contained in 1 pill and are dosed in United States Pharmacopeia (USP) units. The USP unit for lipase administration is roughly 3 times the value of international units (IU), which is used commonly in many academic publications. It is crucial to understand this difference and to know which unit is considered when prescribing the medication.

During a meal, normal pancreatic secretion delivers more than 360,000 IU (>1 million USP units) of active lipase into the duodenum in healthy adults, of which only 10% is needed to prevent steatorrhea and fat malabsorption. This observation, in addition to enzyme secretion from residual pancreatic tissue and extrapancreatic sources (eg, gastric mucosa), explains why supplementation with only 30,000 IU (90,000 USP units) is usually effective to prevent steatorrhea in most cases of symptomatic PEI. Current recommendations suggest starting with a low dosage of lipase per meal, with a 50% reduction for...
<table>
<thead>
<tr>
<th>Product</th>
<th>Indications</th>
<th>Dosage and Administration</th>
<th>Dosage Forms and Strength&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>Creon (Abbott</td>
<td>Combination of porcine-derived lipases, proteases, and amylases indicated</td>
<td>Dosage is based on clinical symptoms, the degree of steatorrhea, and fat content of the</td>
<td>Delayed-Release Capsules: 3,000 USP units of lipase; 9,500 USP units of protease; 15,000 USP</td>
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<td>Laboratories)</td>
<td>for the treatment of PEI due to CF, chronic pancreatitis, pancreatectomy,</td>
<td>diet. Capsules should not be crushed or chewed. For infants or patients unable to swallow</td>
<td>units of amylase</td>
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<td></td>
<td>or other conditions</td>
<td>intact capsules, the contents may be sprinkled on soft acidic food (eg, applesauce).</td>
<td>Delayed-Release Capsules: 6,000 USP units of lipase; 19,000 USP units of protease; 30,000 USP</td>
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<td>units of amylase</td>
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<td>Delayed-Release Capsules: 12,000 USP units of lipase; 38,000 USP units of protease; 60,000 USP</td>
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<td>units of amylase</td>
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<td></td>
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<td></td>
<td>Delayed-Release Capsules: 24,000 USP units of lipase; 76,000 USP units of protease; 120,000 USP</td>
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<td>Pancreaze (Ortho-McNeil-Janssen Pharmaceuticals, Inc.)</td>
<td>Combination of porcine-derived lipases, proteases, and amylases indicated for the treatment of PEI due to CF, or other conditions</td>
<td>Therapy should be initiated at the lowest recommended dose and gradually increased. Dosage should be individualized based on clinical symptoms, the degree of steatorrhea, and the fat content of the diet. Capsules should be swallowed whole. For infants or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food with a pH of 4.5 or less (eg, applesauce).</td>
<td>Capsules: 4,200 USP units of lipase; 10,000 USP units of protease; 17,500 USP units of amylase</td>
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<td>Capsules: 10,500 USP units of lipase; 25,000 USP units of protease; 43,750 USP units of amylase</td>
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<td>Capsules: 16,800 USP units of lipase; 40,000 USP units of protease; 70,000 USP units of amylase</td>
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<td>Capsules: 21,000 USP units of lipase; 37,000 USP units of protease; 61,000 USP units of amylase</td>
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<td>Zenpep (Aptalis)</td>
<td>Combination of porcine-derived lipases, proteases, and amylases indicated</td>
<td>If symptoms and signs of steatorrhea persist, the dosage may be increased by a health care professional. There is great interindividual variation in response to enzymes; thus, a range of doses is recommended. Changes in dosage may require an adjustment period of several days. Capsules should be swallowed whole. For infants or patients unable to swallow intact capsules, the contents may be sprinkled on soft acidic food (eg, applesauce).</td>
<td>Capsules: 3,000 USP units of lipase; 10,000 USP units of protease; 16,000 USP units of amylase</td>
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<td>for the treatment of PEI due to CF, or other conditions</td>
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<td>Capsules: 5,000 USP units of lipase; 17,000 USP units of protease; 27,000 USP units of amylase</td>
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<td>Capsules: 10,000 USP units of lipase; 34,000 USP units of protease; 55,000 USP units of amylase</td>
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<td>Capsules: 15,000 USP units of lipase; 51,000 USP units of protease; 82,000 USP units of amylase</td>
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<td>Capsules: 20,000 USP units of lipase; 68,000 USP units of protease; 109,000 USP units of amylase</td>
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<td>Capsules: 25,000 USP units of lipase; 85,000 USP units of protease; 136,000 USP units of amylase</td>
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</table>

**CF,** cystic fibrosis; **PEI,** pancreatic exocrine insufficiency; **USP,** United States Pharmacopeia

<sup>a</sup> The information outlined in this Table is based on the Prescribing Information for the drugs listed.

<sup>b</sup> Dosages of pancreatic enzyme replacement therapy products in the United States are demarcated by the amount of lipase contained in 1 pill and are dosed in USP units. The USP unit for lipase administration is roughly 3 times the value of international units, which is used commonly in many academic publications. It is crucial to understand this difference and to know which unit is considered when prescribing the medication.
snacks), and increasing supplementation as needed depending on the patient's response. Patients should be counseled regarding compliance with therapy and appropriate timing of therapy. PERT is optimized when supplements are taken during or just after meals instead of before meals.

**Monitoring Therapy**

Once therapy is initiated, patients should have frequent office visits in the first few months to discuss compliance issues, determine the effect of therapy, and decide if an alteration in treatment is indicated. Weight should be closely monitored, as well as signs of ongoing nutritional deficiencies. If symptoms of steatorrhea persist after a trial of PERT, patient compliance with therapy should be confirmed. Fecal chymotrypsin has been evaluated as a marker of compliance, although this test is not available in the United States. If compliance with PERT is verified, dosage should be gradually increased. Dosages up to 80,000 USP units per meal may be required to normalize bowel movements. However, higher dosages have been associated with fibrosing colonopathy in young patients with CF and caution is warranted in this population. If symptoms continue, despite an increase in dosage, patients should be placed on acid suppression therapy with a proton pump inhibitor in order to prevent enzyme deactivation, which can help normalize fat malabsorption in patients who have an incomplete response to therapy. For patients who derive no benefit from acid suppression, alternate diagnoses should be considered. Up to 40% of patients with PEI have small bowel bacterial overgrowth, which may account for a significant number of cases of refractory diarrhea. Persistent gastrointestinal diarrheal illnesses, such as amebiasis and giardiasis, also should be excluded. Medium chain triglycerides, which are directly absorbed by the intestinal mucosa, may be initiated to increase caloric intake and help prevent steatorrhea if other etiologies of insufficient response to therapy have been excluded.

**Summary**

Many clinical situations may result in PEI, which is associated with morbidity and mortality, and can severely compromise QoL. Weight loss and steatorrhea are the predominant features of PEI and are indications for the implementation of PERT. Several tests have been developed to diagnose PEI, the most convenient of which is the fecal elastase test in the context of an appropriate clinical evaluation. Nutritional deficiencies are common consequences of fat maldigestion, even in patients with minimal or no symptoms of steatorrhea, and vitamin supplementation may be a necessary component of therapy for PEI. Once PERT is initiated, close follow-up should be emphasized in the early phase of treatment in order to address compliance issues and to exclude other possible causes of incomplete response. Current preparations are dosed according to lipase content and should be started at a low dose and titrated upward based on clinical response. When administered appropriately, PERT can reverse the ill effects of malnutrition from persistent steatorrhea and dramatically improve QoL.

**References**


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