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A Primer on Exocrine Pancreatic Insufficiency, Fat Malabsorption, and Fatty Acid Abnormalities

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Normal Pancreatic Physiology

Positioned next to the duodenum and behind the stomach, the pancreas is an essential part of the gastrointestinal system.[1] The location of the pancreas and its unique cellular organization facilitate its physiological role in the digestion and absorption of nutrients. The pancreas is composed of exocrine and endocrine glands; the exocrine portion accounts for roughly 85% of the total volume of the pancreas, whereas the endocrine pancreas represents less than 2%. The remaining pancreatic mass is accounted for by extracellular matrix (10%) and ductal cells and blood vessels (4%).[2] The exocrine pancreas is composed of acinar cell clusters and epithelial cells which line pancreatic ducts (ductal cells). The pancreatic acini produce and secrete digestive enzymes which are delivered to the duodenum and along with bile salts are responsible for the majority of the digestive process within the small intestine. Ductal cells produce large quantities of an alkaline mixture of water and bicarbonate, which guides enzyme transport through the pancreatic ducts for delivery to the duodenum, as well as providing the optimum pH for enzyme activity. Clusters of endocrine cells, or pancreatic islets, make up the endocrine portion of the pancreas.[1] The endocrine pancreas is involved in the production of several hormones (ie, insulin, glucagon, somatostatin) that are secreted directly into circulation via the dense network of capillaries associated with pancreatic islets.[1] There is no separation of exocrine and endocrine pancreatic components; pancreatic islets are scattered among the pancreatic acini and acinar cells are vascularized through the islet capillaries.[1] Thus, disease states which cause malfunction or damage in one of the components of the pancreas may lead to functional defects in the other component.[3]

Under normal physiological conditions (Figure 1[1,4,5]), the exocrine pancreas post-prandially produces approximately 1.5 L of an aqueous digestive solution that contains 3 main types of enzymes: amylase, protease, and lipase, which aid in digestion of carbohydrates, proteins, and fats, respectively.[1,6,7] The relative quantity of these enzymes varies based on multiple factors including diet, age, and gender.[6] Pancreatic enzyme synthesis begins during the cephalic phase of digestion, before food reaches the stomach. However, pancreatic enzymes are not secreted until the initiation of the intestinal phase—after food has been converted to chyme and passed into the duodenum. The intestinal phase controls the rate of gastric emptying to ensure that digestive and absorptive processes are appropriately carried out in the small intestine.[1]

When chyme reaches the duodenum, pancreatic secretions are triggered exby 2 duodenal hormones: secretin and cholecystokinin (CCK).[1] Entry of acidic chyme stimulates the release of secretin into the bloodstream, which in turn stimulates pancreatic production of an aqueous buffer solution (pH 7.5 to 8.8) containing bicarbonate and

phosphate ions, from pancreatic ductal cells. The secretion of this pancreatic fluid enables the activity of pH-sensitive pancreatic digestive enzymes by neutralizing acidic chyme. CCK stimulates the production and secretion of pancreatic enzymes from acini, and movement of bile from the gallbladder.[1,6] Pancreatic enzymes are delivered to the duodenum through the pancreatic duct via pancreatic fluid, which merges with incoming bile from the liver and gallbladder to initiate intestinal digestion.[1]

Post-prandial secretions of salivary amylase in the mouth aid in the first steps of carbohydrate digestion; pancreatic amylase and enzymatic activity from the intestinal brush border continue to break down carbohydrates, and the digested products are absorbed in the duodenum. Proteins are hydrolyzed in the stomach by gastric acid and pepsin, and protein digestion continues in the duodenum via pancreatic proteases and proteolytic activity in the small intestine brush border.[6,8] Lingual and gastric lipases are responsible for fat digestion in the stomach and hydrolysis continues in the duodenum through the action of pancreatic and gastric lipases. Fat molecules are emulsified by bile salts into micelles and absorbed in the jejunum.[8]

Postprandial fat digestion relies on three critical events facilitated by the pancreas; disruption in these processes may lead to clinical manifestations of maldigestion and malabsorption of fat (steatorrhea). Clinical symptoms of steatorrhea are prevented when pancreatic lipase output remains greater than 10% of normal physiological output.[3,9] Postprandial synchrony—the appropriate timing and delivery of gastric contents into the duodenum and discharge of pancreatic and biliary secretions for digestive action following nutrient intake—is an essential process in fat digestion and absorption.[3] Additionally, the acidic contents of the stomach must be neutralized to prevent degradation and allow normal function of pancreatic enzymes.[3]

Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency (EPI) is a condition characterized by deficiency of exocrine pancreatic enzymes, resulting in the inability to properly digest fats, carbohydrates, and proteins.[10,11] The most common cause of EPI is chronic pancreatitis (CP), followed by cystic fibrosis (CF), which is the most common cause of EPI in children.[6] EPI is also associated with a variety of conditions, including pancreatic cancer, pancreatic and gastric surgery, diabetes mellitus, Crohn's disease, Zollinger-Ellison syndrome, and Celiac sprue.[6,9]

EPI commonly leads to fat malabsorption and can manifest as a wide spectrum of symptoms, including steatorrhea (fatty, frothy, loose, greasy, foul-smelling stools), weight loss, abdominal discomfort, and abdominal bloating.[6,12] The enzymatic digestion of carbohydrates and proteins may also be affected by EPI. Deficiency of amylase and protease in EPI is typically masked by the multiple other sources of these enzymes (salivary, gastric, and small intestine).[10,12] Therefore, adequate digestion of proteins and carbohydrates is usually maintained, even with complete loss of pancreatic function. As a result, these insufficiencies are generally not clinically significant in EPI.[10,13] Conversely, extrapancreatic sources for fat digestion by gastric lipase and lingual lipase are unable to compensate for pancreatic lipase deficiency in EPI.[6,8,12] The clinical manifestations

of fat malabsorption with EPI are, therefore, generally noted earlier than clinical manifestations due to deficiencies of other pancreatic enzymes.[10] The management of EPI includes dietary and lifestyle modifications (eg, smoking cessation, limiting or avoiding alcoholic drinks, and limiting dietary fat intake), as well as pancreatic enzyme replacement therapy (PERT); vitamin supplementation may also be necessary.[9]

EPI is often under-diagnosed because of its wide spectrum of symptoms. The exact incidence and prevalence of EPI is difficult to determine, due to its multiple causes, and because it is not typically recorded as a medical statistic. The prevalence of CP, the leading cause of EPI, is higher in men than women and is estimated to be approximately 50 per 100,000 persons.[14,15] EPI is estimated to occur in 30% to 40% of individuals with CP.[6] The age- and sex-adjusted prevalence of CP as measured by a study of the population of 100,000 inhabitants in Olmsted County, Minnesota was 41.76 (95% CI, 30.21-53.32) per 100,000 person-years in 2006, with an age-adjusted prevalence in women of 33.88 per 100,000 person-years (95% CI, 19.65-48.10) compared with 51.45 per 100,000 person-years for men (95% CI, 32.37-70.55).[14] The incidence of EPI, as measured in this study (1977-2006), was observed to be 4.05 per 100,000 person-years (95% CI, 3.27-4.83), and was also higher in men than women (5.21 vs 3.11 per 100,000 person-years).[14]

Excess alcohol consumption is a common cause of CP, as alcohol is toxic to the pancreatic acinar cells.[6] In a well-designed multicenter study conducted in the United States (North American Pancreatic Study 2 [NAPS2]), very heavy alcohol consumption, defined as consuming 5 or more drinks per day, was associated with a more than 3-fold increase in the risk of developing chronic pancreatitis (OR, 3.10; 95% CI, 1.87-5.14; P <.001). Notably, among heavy drinkers who were also heavy smokers, defined by a greater than 35 pack-year history of smoking, the risk of developing CP was further elevated 13-fold compared with heavy drinkers who were nonsmokers (OR, 13.41; 95% CI, 5.23-34.4; P <.001).[16] Alcohol intake was thought to be the causative factor in CP among 44.5% of patients, with other factors including genetics, autoimmune conditions, and other causes accounting for the remaining cases.[17] These results were replicated in another multicenter Italian study that identified alcohol as a causative factor in 34% of CP cases, with multiple other causes accounting for the remaining 66% of cases.[18]

There is an age-dependent negative linear correlation between patient age at symptomatic disease onset of CP and time to development of EPI; there is a shorter time to development of EPI in late-onset CP or alcohol-induced pancreatitis compared with patients with early-onset CP. Approximately 20% of patients with CP develop EPI over time, as this disease is characterized by the progressive loss of acinar cell function.[19] As expected, the prevalence of EPI increases with disease duration—between 5 and 10 years after diagnosis of CP, more than half of patients will develop EPI.[9,20]

Approximately 90% of patients with CF have EPI.[21] Estimates of prevalence for CF vary greatly, with estimates of less than 40 per 100,000 persons, and some studies reporting a much lower prevalence.[22] In patients with insulin-dependent diabetes mellitus, EPI may occur in up to 43% of patients; severity is mild to moderate, with

1% requiring therapy.[6]

Etiology

EPI has numerous etiologies, which are typically classified into one of two categories: pancreatic and non-pancreatic. Pancreatic causes include CP, CF, pancreatic duct obstruction, pancreatic surgery, and the rare Shwachman-Diamond syndrome.[6,9,10,13] Conditions leading to EPI are shown in Table 1[6,10,12,13]. Nonpancreatic conditions associated with EPI include celiac disease, Crohn's disease, Zollinger-Ellison syndrome, and gastrointestinal surgery.[6,9]

The most common cause of EPI is CP, which is characterized by an initial pancreatic insult leading to progressive tissue damage and pancreatic fibrosis.[6,7] The destruction of pancreatic tissue in CP affects both exocrine and endocrine functions; CP leads to EPI and also loss of endocrine pancreatic function in later stages of disease.[8,10] Other than alcohol use (described previously), common factors associated with CP include smoking, genetic predisposition, severe necrotizing pancreatitis, autoimmune pancreatitis, obstruction of the pancreatic duct, and idiopathic causes.[23,24]

CF is another potential cause of EPI.[19] CF is an autosomal recessive disease caused by mutations in the gene that encodes the CF transmembrane conductance regulator (CFTR) protein. CFTR protein dysfunction results in reduced chloride and bicarbonate transport and malfunction/deregulation of other transporters across epithelial cells.[13] The most common sites of disease manifestation include epithelial secretory tissues (respiratory tract and pancreatic duct epithelium), where CFTR protein dysfunction results in pulmonary and pancreatic dysfunction. With regard to EPI, reduced chloride/bicarbonate transport in the pancreas leads to reduced water content of secretions entering the ductal lumen, and highly concentrated secretions obstruct the pancreatic ducts and acini, preventing pancreatic enzymes from being secreted and emptied into the small intestine.[13] Sustained obstruction can lead to pancreatic tissue destruction, or autodigestion, due to retained proteolytic enzymes.[6]

Tumors that obstruct the main pancreatic duct (ie, periampullary tumors, pancreatic head cancer, or benign tumors) can also lead to EPI.[6] Pathophysiology in this case include replacement of pancreatic tissue by tumor cells in the head of the pancreas, and as tumors grow, normal pancreatic tissue is lost in the head of the pancreas. In addition, chronic obstructive pancreatopathy develops in the remaining part of the pancreas, which manifests as pancreatic duct dilation and pancreatic atrophy, leading to the development of EPI.[25] Following surgical resection of pancreatic tumors, patients may continue to experience clinical symptoms of EPI due to exocrine dysfunction of the residual part of the pancreas.[3]

Unlike EPI in patients with CP and CF, decreased stimulation and production of endogenous pancreatic lipase as seen in celiac disease, Crohn's disease, or Shwachman-Diamond syndrome occurs without glandular destruction.[6] Zollinger-Ellison syndrome involves a non-pancreatic etiology of EPI characterized by acid-

mediated inactivation of pH-sensitive pancreatic enzymes in acidic duodenal environments despite normal pancreatic secretions.[3,12] Patients with diabetes mellitus may develop EPI in part as a result of disturbances in acinar-islet interactions. Although these patients may also experience EPI-related clinical symptoms, cases of EPI in this population are generally mild to moderate.[3,6]

Surgery, such as gastrectomy, gastric bypass, extensive small bowel surgery, and other gastrointestinal surgeries can affect the postprandial synchrony between the delivery of gastric contents to the duodenum and the discharge of pancreatic and biliary secretions. Additionally, gastrointestinal surgeries can cause motility disorders, which decrease "contact time" of food within the gastrointestinal tract, and result in decreased stimulation and secretion of pancreatic enzymes.[6] Motility disorders related to EPI can be self-exacerbating, and if left untreated, patients with EPI may develop rapid gastric emptying with faster small intestinal transit. These changes hamper digestion and absorption and reduce pancreatic enzyme activity.[6]

Pathophysiology

Exocrine pancreatic function plays a vital role in the digestion of all macronutrients, but is most important in the digestion of lipids.[8] The pancreas secretes 3 main types of enzymes: lipase, amylase, and protease pro-enzymes (which are converted to the active form in the duodenum).[6] As described above, pancreatic enzyme release is initiated in the cephalic phase of digestion, before food enters the stomach.[1,6] This process is mediated by orosensory perception of food and continues during ingestion of the meal.[6] Digestion of fats begins in the mouth with lingual lipase and continues in the stomach where gastric lipase further breaks down undigested triglycerides into monoglycerides and fatty acids.[6,8] However, the majority of fat digestion occurs in the small intestine and is facilitated by pancreatic lipase. Gastric lipase, which remains active in the acidic environment of the stomach, is responsible for approximately 10% of total lipid digestion under normal physiological conditions; however, in patients with EPI, gastric lipase may account for up to 90% of all lipase activity.[8]

The monoglycerides and fatty acids produced in gastric digestion are gradually transferred to the duodenum and stimulate duodenal endocrine cells to produce CCK. This duodenal hormone stimulates pancreatic enzyme secretion and mediates the rate of gastric emptying.[6] It is important to note that after gastrointestinal surgery, this process can become disrupted, which can alter the highly coordinated processes of digestion, gastric emptying, and pancreatic enzyme release.[6]

Under normal physiological conditions, the acidic pH of chyme entering the duodenum triggers release of secretin, which stimulates the release of bicarbonate ions and water from the pancreas.[6] This aqueous pancreatic secretion combines with bile to neutralize chyme acidity.[8] This neutralization of acidity is an essential process in the digestion of lipids as pancreatic lipases are inactivated in acidic environments (typically below a pH of 3 to 5).[6,26] This is important primarily because the pH of chyme entering the duodenum is typically as low as 1 or 2, and as it travels the length of the duodenum, it is neutralized to a pH of 7 or 8.[1] Specifically, pancreatic lipase,

which is responsible for hydrolysis of 40% to 70% of triglycerides, operates optimally at a pH 8 to 9 *in vitro*, but bile salts *in vivo* allow it to function at a pH as low as 6 or 6.5.[6] Bile salts facilitate hydrolysis of undigested triglycerides into fatty acids and monoglycerides by pancreatic lipase, and solubilize these breakdown products to form micelles, which are then absorbed across the intestinal membrane by enterocytes in the proximal two-thirds of the jejunum.[6,8]

Patients with CF or CP experience irreversible enzyme deficiencies, including lipase deficiency, due to tissue damage or destruction within the pancreas.[6] Generally, fat malabsorption precedes that of other nutrients; however, any undigested macronutrients in the intestines can exacerbate dysmotility by altering neurohormonal regulation of the production of CCK and pancreatic enzymes, potentially leading to rapid gastric emptying.[6,27] This loss of postprandial synchrony, as in patients with previous gastrointestinal surgery or other alteration to the anatomy of the gastrointestinal tract, can lead to a state of maldigestion due to a mismatch between gastric emptying and the release of pancreatic and biliary secretions.[6,11,28]

The physical and biochemical causes of EPI include[6]:

- Decrease in production and secretion of lipase
- Increased lipase destruction (with acidic pH in CP, CF)
- Pancreatic duct obstruction (leading to fibrosis and tissue destruction)
- Decreased lipase stimulation and production (as seen in celiac disease, Crohn's disease, and more rarely, Shwachman-Diamond syndrome)
- Motility disorders (eg, gastric emptying, rapid small bowel transit leading to decreased hormonal response and stimulation of pancreatic enzymes, and gastrointestinal surgery)

Presentation of EPI

Fat malabsorption is characteristic of EPI and is associated with symptoms including steatorrhea, weight loss, abdominal discomfort, and abdominal bloating.[6] EPI is associated with malabsorption of fat-soluble vitamins A, D, E, and K and reduced levels of circulating lipoproteins resulting from insufficient lipid digestion.[6]
EPI can often go unrecognized, as the signs and symptoms are similar to those of other more common gastrointestinal disorders. This can be further confounded, especially in cases where patients may reduce dietary fat intake to minimize unpleasant symptoms.[6,29] Other common symptoms include weight loss, abdominal pain, abdominal bloating/distention, fatigue, and diarrhea.[11,13,29] Notably, in some cases, use of opioids for pain in patients with CP may mask signs of diarrhea.[30] Objective signs of EPI include edema (as a result of protein malnutrition and hypoalbuminemia), anemia, coagulopathy (due to vitamin K deficiency), metabolic bone disease, and neurologic manifestations.[11,29,31]

Diagnosis of EPI

Laboratory evaluation and imaging

A complete laboratory evaluation is helpful in determining the extent of malabsorption, and ruling out other disease processes.[29] Abdominal imaging may help in identifying features consistent with CP and evaluating for masses, lesions, and pancreatic abnormalities.[9,29]

Fat malabsorption

The most common clinical manifestation of EPI is steatorrhea, which is defined as greater than 7 grams of fecal fat daily while consuming a diet of 100 grams of fat per day.[6,12,27] Steatorrhea does not usually develop until pancreatic lipase output is at or below 10% of normal, indicating a large reserve capacity for enzyme secretion within the exocrine pancreas.[3] This may also account for the late development of symptoms in EPI, and indicates that steatorrhea typically does not occur until 90% of the pancreas has been functionally destroyed or obstructed.[32]

Fat maldigestion is the principal cause of weight loss in EPI. Patients with fat maldigestion generally present with low circulating levels of micronutrients, lipoproteins, and fat-soluble vitamins.[12] Abdominal pain, flatulence, and diarrhea are common symptoms of fat malabsorption, and are often used as clinical indicators of EPI.[13] Some patients with EPI experience chronic debilitating abdominal pain most likely due to the underlying cause of EPI (eg, chronic pancreatitis).[15,33]

Quantitative fecal fat collection and qualitative fecal fat assessment

The gold standard for diagnosis of fat maldigestion is quantification of the coefficient of fat absorption (CFA) after 72-hour fecal fat determination using the van de Kamer test.[34] However, this test has several disadvantages: it can be burdensome to perform, and it requires a strict diet of 100 g fat daily for 5 days with stool collected over the last 3 days to be manually processed in a laboratory.[34] As a result, the CFA is not commonly used in clinical practice. As quantification of fecal fat can be difficult and cumbersome, a positive qualitative stool test with reasonable clinical suspicion of disease may be sufficient to aid in diagnosis, however, a negative result on a qualitative test does not rule out fat malabsorption.[6,7]

Fecal elastase

Quantification of fecal elastase-1 (FE-1) is a diagnostic tool which measures the pancreatic enzyme, elastase-1, which serves as a marker for exocrine pancreatic secretion.[19] Unlike the 72 hour fecal fat test, this test does not require timed stool collection, a special diet, or discontinuation of PERT. This test measures the concentration of the enzyme in stool, and in fully formed stools, it can screen for moderate to severe EPI with high sensitivity. Testing for fecal elastase in those with watery stool is less reliable as levels of FE-1 are diluted, which may result in a false-positive result.[19]

Both of these tests are indirect measures of pancreatic function, whereas direct functional measurement may involve secretin-cerulein or secretin-pancreozymin tests.[6] In patients with suspected early pancreatic disease, these more direct tests are recommended as they have improved sensitivity for identification of mild EPI compared with other tests.[29] Although they provide an accurate assessment of pancreatic exocrine function, they

are only performed in specialized centers because they are time-consuming and expensive.[6] Other helpful tests include evaluation of serum nutritional markers (eg, fat-soluble vitamins, and magnesium). Abdominal imaging may be helpful in identifying features of CP, pancreatic cancer, or pancreatic duct obstruction.[9] Despite the many available tests, diagnosis of EPI is largely clinical, and the etiology can be relevant to the clinical presentation and symptoms.[6]

Distinguishing Between EPI and Other Causes of Malabsorption

The human gastrointestinal tract, specifically the small intestine, is the site of nutrient absorption. Digestion and absorption depend on several factors including mechanical mixing, mucosal function, blood supply, intestinal motility, microbial environment, and enzyme production/activity.[11] A malfunction in one or more of these constituents can result in malabsorption and other gastrointestinal signs and symptoms similar to those seen in EPI (ie, steatorrhea, diarrhea, malnutrition, weight loss).[11,13]

Overall, malabsorption syndromes can be grouped into four broad categories: maldigestion (inability to digest food properly), mucosal/mural pathology, bile salt/enzyme deficiency beyond EPI, and causes related to imbalance of the intestinal microbiome.[11] Malabsorption stemming from maldigestion, as previously discussed, may be due to the functional or structural loss of the gastric reservoir following surgery, resulting in inadequate mixing of macronutrients with bile salts and pancreatic enzymes.[11] This can result in lower levels of pancreatic enzyme release, as poor digestion and rapid transit reduce the nutrient contact time in small intestines, affecting the stimulation of pancreatic function.[6]

Likewise, instances of enzyme or bile salt deficiencies beyond those seen in EPI can occur as a result of abnormal liver function. Normally, fats are emulsified by bile salts from the liver prior to hydrolysis by enzymes.[11] Abnormal liver function may result in a decrease in bile salt production causing symptoms of malabsorption.[11] For example, cholestasis can often result in steatorrhea unrelated to EPI.[35] Another potential important cause of malabsorption independent of EPI is mucosal/mural pathology, which includes numerous diseases, which include decreased amount of mucosal absorptive surface area due to surgery, gluten sensitivity, and inflammatory bowel disease. Immunodeficiency and AIDS, and Whipple's disease can also contribute to malabsorption.[11] Similarly, mucosal fatty acid uptake is altered in bacterial overgrowth, Crohn's disease, and short bowel syndrome, all of which may also result in malabsorption.[11,19]

EPI and Fatty Acid Deficiencies

Patients with EPI often experience fatty acid deficiencies. Essential fatty acids cannot be synthesized, and must be obtained from the diet.[36] The intake and proportion of the two families of long-chain polyunsaturated fatty acids, omega-3 and omega-6, impact disease states and overall health outcomes. Diets rich in omega-6 fatty acids promote pathogenesis of several diseases (eg, cardiovascular, inflammatory, and autoimmune diseases), whereas elevated omega-3 fatty acids relative to omega-6 can have suppressive effects on these same

conditions.[36] CF is associated with several fatty acid abnormalities.[36] For example, decreased levels of linoleic acid and docosahexaenoic acid have been observed in CF, and it is possible that they play a central role in both severity of symptoms and progression of the disease.[36]

EPI Treatment

Patients with EPI may be treated with PERT to aid in the digestion and absorption of fats; PERT is recommended for patients with EPI to address weight loss, malnutrition, and steatorrhea. [6,12,19,29] Briefly, treatment is primarily based on oral PERT regimens with the goal of correcting malnutrition and improving symptoms.[8,12] Underlying diseases leading to EPI should be treated, and lifestyle modifications should also be undertaken, including alcohol abstinence (to reduce pain and increase gastric lipase secretion) and supplementation of fat-soluble vitamins as needed.[12] Dietary fat restriction is not necessary, especially for patients on enzyme supplementation.[12] Frequent, low-volume meals are recommended, and difficult-to-digest foods such as legumes should be avoided.[12]

Approximately 44% of patients with CF require oral supplemental nutrition, and 11% require enteral tube feeding.[37,38] Nutrient utilization may be improved using semielemental or elemental enteral products or dosing PERT with enteral feedings.[39] Additionally, a recently approved in-line medical device with immobilized lipase (RELiZORB) has been developed to hydrolyze fats in enteral formula.[40] Treatment options for patients with EPI will be discussed in further detail in other articles in this supplement.

Conclusion

EPI, a relatively uncommon but severe condition, is associated with a variety of disorders, including CP, CF, pancreatic cancer, pancreatic and gastric surgery, and diabetes mellitus. EPI commonly causes malabsorption with typical symptoms of steatorrhea, weight loss, abdominal discomfort, and abdominal bloating. EPI affects the activity of all pancreatic enzymes involved in digestion of fats, proteins, and starches. The most important clinical consequence of EPI is fat maldigestion with subsequent malabsorption and related symptoms.

The diagnosis of EPI is largely clinical, and can be difficult because patients often present with nonspecific symptoms that are similar to those of other gastrointestinal diseases, and the tendency for patients to reduce fat intake in order to minimize discomfort and other unpleasant symptoms. The gold standard for diagnosis of fat maldigestion is quantification of the CFA after a 72-hour fecal fat determination using the van de Kamer test. However, this test is cumbersome and has several disadvantages. A complete laboratory evaluation is also required to determine the extent of malabsorption and to evaluate for other diseases that may be the underlying etiology for EPI. Management of EPI is primarily based on PERT, but lifestyle modifications are also recommended. Though dietary fat restriction was previously recommended, this is rarely necessary, especially for patients on appropriate enzyme supplementation.

After proper evaluation and monitoring, EPI can be successfully managed, with the goal of restoring normal

digestion and absorption of dietary nutrients and improving overall quality of life.