Review Article

Exocrine pancreatic insufficiency, a literature review

Abstract

Exocrine pancreatic insufficiency (EPI) is a clinical entity that manifests as a mal absorption syndrome. Its relationship with multiple worldwide-highly prevalent pancreatic and extra pancreatic affections constitutes a major health problem due to high morbidity and mortality rates. The underlying disease requires an exhaustive assessment to identify possible nutritional deficiencies so as to prevent future complications. An impaired hydro electrolytic balance and low levels of serum nutritional markers indicate or predict EPI in high risk subjects. Unfortunately, pancreatic exocrine function test available so far do not diagnose early stages of the disease but they are quite effective in advanced EPI. Imaging studies are essential in the overall management of EPI as they may provide information regarding the etiology and structural pancreatic modifications. ERCP, despite post-procedure complications, is considered the gold standard due to its diagnostic and therapeutic properties. Treatment is based on pancreatic enzyme replacement therapy (PERT) along with nutritional supplements intake and good control of the underlying disease.

Keywords: exocrine insufficiency, pancreatic function test, enzyme replacement

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Abbreviations: EPI, exocrine pancreatic insufficiency; CCK, cholecystokinin; HIV, human immunodeficiency virus; FE-1, Fecal Elastase-1; PERT, pancreatic enzyme replacement Therapy; PPI, protompump inhibitors; CF, cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; IBD, inflammatory bowel disease; CD, chron's disease; UC; ulcerative colitis; AIDS, acquired immunodeficiency syndrome; CT, computed tomography; MRCP, magnetic resonance cholangiopancreatography; S-MRCP, secretin-enhanced magnetic resonance Cholangiopancreatography; EUS, endoscopic ultrasound; FNA, fine needle aspiration; ERCP, endoscopic retrograde cholangiopancreatography; Fcht, fecal chymotrypsin; PLT, pancreolauryl test

Introduction

Exocrine pancreatic insufficiency (EPI) is an entity that results from the progressive loss of pancreatic parenchyma and therefore loss of acinar cells that leads to a decreased functionality regarding the production and release of pancreatic enzymes. These hypo functionality provokes mal absorption and mal digestion of fat and proteins making patients experience significant weight loss and malnutrition. EPI symptoms are not visible in the majority patients until the parenchyma loss causes over 90% of pancreatic function loss.[1] The pancreas provides both exocrine and endocrine features. Its endocrine function will not be discussed in this paper. The exocrine function purpose is to help in the digestion and further breakdown of carbohydrates, proteins and fat ingested. The pancreas daily secretes approximately 1,5 liters of pancreatic juice composed by 97% of water and electrolytes with abundant enzymes, mainly proteases, amylase, lipase and nuclease that later on is drained into the duodenum in order to neutralize acid gastric secretions to fulfill digestion. This function is regulated by a negative feedback involving two primary hormones, secretin and Cholecystokinin (CCK).

Secretin release is made throughout the duodenal mucosa in presence of acid and it activates the secretion of water and bicarbonate through interlobular ducts which continuously keep increasing bicarbonate concentration up to 120m Eq/L reducing acid levels in the duodenum. CCK is released through endocrine cells under the presence of fat and a protein in the small bowel. CCK is also a neurotransmitter because it is released by peripheral nerves in the intestine.[2] Even though CCK stimulates the secretion of pancreatic juice, its receptor in the pancreas has much more affinity to gastric, predisposing CCK to be ineffective if administered as a pancreatic secretagogue. CCK receptors located in the pneumo gastric nerve control the effects of CCK on pancreatic juice causing local acetylcholine release in the pancreas.

EPI is highly prevalent in extra pancreatic diseases such as cystic fibrosis, celiac disease, inflammatory bowel disease[4] and HIV infection. Most of the time is under diagnosed. Endocrine entities such as type I and type II diabetes are strongly related to EPI. A multicenter study screening fecal elastase-1 (FE-1) concentrations in diabetic patients confirmed that both types of diabetes develop pathological exocrine function in high prevalence.[4]

Malnutrition is the main consequence of EPI. A study revealed an association between low levels of hemoglobin, albumin, pre albumin, magnesium and HbA1C above upper limit with the onset of EPI, suggesting that serum nutritional markers can diagnose or predict EPI.[.]

Dietary support is also part of the treatment of EPI. The ingestion of decreased quantities of fat, no restriction, is recommended by the Australasian Pancreatic Club along with pancreatic enzyme therapy replacement (PERT) and a proton pump inhibitor (PPI).[6] Pezzilli[7] recommends in patients with history of chronic pancreatitis the use of supplements of bile acids, decontamination of intestinal lumen and administration of probiotics.[7] Lifestyle changes, along with an adequate control of the underlying disease ensure a good control of the disease.

Epidemiology and etiology

Diabetes

Type I and type II diabetes are highly associated with EPI. Both endocrine and exocrine pancreatic cells share the same embryologic origin and have strong structural and functional interrelations.

Therefore, diseases affecting either function could lead to one another. Several prevalence studies and relation of EPI in both types of diabetes show a wide range, being higher in type I diabetes with a prevalence of 25–74% versus a 28–54% in type II diabetics.[8] Associated risk factors for the development of EPI in diabetics include mishandling glycemic control, high demands of insulin, age at onset of diabetes, long duration disease and body mass index. Type I diabetics suffer histological and morphological pancreatic changes such as atrophy and fibrosis. These modifications are probably due to the lack of insulin and its trophic effect on acinar pancreatic tissue, Langer hans islet cells destruction and diabetic micro angiopathy and neuropathy. EPI development in type II diabetes has relatively the same mechanism as type I diabetes but it relies mostly on the severity of micro vascular and neurological damage presented as well as the duration of diabetes and high levels of fibrosis.[4,8,9]

Cystic fibrosis

Cystic fibrosis (CF) corresponds to the extra pancreatic disease mostly associated with EPI. According to the World Health Organization (WHO), in the United States the incidence of CF was reported 1/3500 births and approximately 85% of patients diagnosed with CF have EPI. Age is considered to be an important risk factor for the severity of EPI as it tends to worsen over time. Pancreatic disease in CF results from the mutation of the cystic Trans membrane conductance regulator (CFTR) in proximal and intra lobular ducts. In absence or abnormalities of CFTR, alkaline fluid secretion stops and the intra luminal pH drops difficulty protein solubility.[10] As a result, high levels of insoluble proteins in pancreatic fluid lead to the formation of thick mucus throughout pancreatic ducts. During the course of the disease, the pancreas undergoes four mayor anatomical changes, acinar cells replacement with fatty tissue, fibrosis, atrophy and complete obstruction of ducts.[11] Subsequently, CF patients experience severe mal absorption and malnutrition due to the incapacity of the pancreatic duct to excrete pancreatic enzymes as well as low concentrations of bicarbonate causing an incomplete and unprofitable food breakdown process.

Gastrointestinal and accessory organs surgeries

Optimal digestion and absorption requires full structural and functional integrity from all structures involved in the process. It is very common for patients that underwent gastrointestinal surgeries to experience mal absorption syndrome. Surgical interventions force the gastrointestinal tract to follow different pathways to fulfill food digestion but it usually ends up with severe mal nutrition if not treated. Gastrointestinal resection reduces absorptive surface, chyme transit time and mechanical and hormonal stimuli for pancreatic enzyme secretion. Pancreatic and bowel surgeries, including any kind and extent of resection (classic Whipple operation, duodenum-preserving pancreatic head resections, left pancreatic resections and resections for benign tumors), also leads to EPI due to the modification or gross loss of parenchyma.[12,13]

Pancreatitis

Any situation leading to pancreatitis can produce EPI. Chronic inflammation of the pancreas causes progressive and irreversible loss the exocrine pancreatic function. This is due to the fibrotic destruction, duct obstruction and deformation that damages both exocrine and endocrine functions. Risk factors and etiologies for chronic pancreatitis have been well described in the literature. Patients with history of alcohol and tobacco abuse, familial pancreatitis, biliary

ducts abnormalities, immunological and nutritional risk factors must be evaluated periodically to avoid future development of EPI.[14] EPI is also attributed to pancreatic masses due to the possible structural damage of acinar cells and obstruction of bile. According to the National Cancer Institute, pancreatic cancer is relatively rare representing the 12th most common cancer in the United States, however it is the 4th leading cause of death. Patients that undergo partial or total pancreatic resections are incapable to fulfill endocrine and exocrine functions and continue experiencing pancreatic insufficiency.

Celiac disease

The integrity of the small intestine mucosa is also necessary for proper digestion. It has been reported that approximately 20% of patients with celiac disease develop EPI[15] due to intestinal endocrine cells aberration and lack of secretin cells resulting in an altered synthesis and/or release of CCK and pancreozymin. Amino acid deficiencies and protein malnutrition lead to a decreased pancreatic enzyme production and architectural variations such as pancreatic fibrosis and acinar cells atrophy.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) involves Crohn's disease (CD) and ulcerative colitis (UC). According to the Chron's and Colitis Foundation of America, approximately 1,4 million Americans suffer from IBD, affecting men and women equally. The prevalence of pancreatic insufficiency was reported in a cross sectional study with 200 IBD patients. EPI was found in 22% of UC and 14% in CD patients. Others findings in this study supported prior literature reviews including as risk factors for EPI previous gastrointestinal surgery, duration of the disease and large number of bowel movements.[16] Thromboembolic events are very frequent in autoimmune diseases. These events can occur in pancreatic vessels that can lead to moderate parenchyma ischemia and therefore pancreatic function loss and duct dysfunction. An immune response guided by cytokines and auto antibodies against pancreatic antigens was proved by the presence auto antibodies in 40% of patients with CD and 4% in UC.[17] In a study concerning Hepatopancreatobiliary complications in IBD, histologic pancreatitis was reported on 38%-53% of patients with CD and UC showing a higher risk of pancreatic injury in CD than UC.[18]

HIV infection

Around 40-80% of HIV positive patients experience gastrointestinal diseases.[19]. Some factors involved in pancreatic injury in HIV positive patients are related to infections. Acute pancreatitis has been reported in hospitalized patients. Either opportunistic or disseminated infections can affect the pancreas as well as infiltrative disease such as Kaposi's sarcoma or lymphoma. Kaposi's sarcoma located in or near the pancreas generates a mass effect and a consequent exocrine pancreatic insufficiency due to duct obstruction. Drug-induced pancreatic injuries have been reported in almost half patients with AIDS. Highly active antiretroviral therapy has been associated with pancreatitis due to induction of hyper triglyceridemia. Other medications showing high risk for pancreatic injury are stavudine, didanosine, pentamidine and ritonavir.[20]

Clinical features

EPI manifests as a mal absorption syndrome. The clinical features vary depending on the underlying disease and multiple factors concerning the patient and the disease course. Chronic diarrhea and excessive weight loss are the most common mal absorption symptoms, however these are not specific for EPI. Abdominal pain and bloating

usually are persistent symptoms varying from constant discomfort to severe and incapacitating abdominal pain. Steatorrhea is the best indicator for fat mal absorption even though it does not appear until more than 90% of pancreatic function is gone. Therefore, patients with mal absorption who have not have bouts of Steatorrhea should be considered for a possible EPI diagnosis. Other clinical manifestations are directly related to mal absorbed nutrients. Due to the lack of fat assimilation, patients cannot benefit from fat-soluble vitamins intake and suffer marked hypo vitamin sis.[3] Vitamin A deficiency provokes visual disturbances such as an overall decreased vision and immune activity and hypersensitivity of skin and mucous membranes. Lack of vitamin D leads to a diminished intestinal absorption of calcium and phosphate leading to bones weakening, hyperparathyroidism, osteopenia and osteoporosis. Vitamin D deficiency is one of the most severe pediatrics complications posing as rickets. Low levels of Vitamin E reflect as a higher risk of atherosclerosis, severe fatigue and decreased muscle tone. Vitamin K deficiency is linked to severe bleedings.[21]

Diagnosis

Laboratory studies

A complete laboratory evaluation is essential in the overall approach of EPI. Laboratory studies not only can diagnose EPI, they also provide information regarding the etiology and the severity of the disease. Once the etiology is suspected or known, laboratory studies should be guided to the underlying disease general workup. Patients must undergo complete examination for glycemia and insulin along with a complete hydro electrolytic analysis as well. Hypokalemia, hypocalcemia, hypo magnesemia and metabolic acidosis are frequent in mal absorption diseases and due to protein mal absorption patients may have low levels of serum proteins.[5] Results on a complete blood count may reveal anemia associated with iron, vitamin or folate deficiencies. Prolonged prothrombin times have also been associated with EPI due to vitamin K mal absorption. Pancreatic enzymes behave differently according to the EPI etiology. Fat mal digestion is accounted to lipase deficiency below 10% of normal range debuting with steatorrhea and preceding other macro and micronutrients mal absorption.

Imaging studies

Imaging studies are useful and supportive tools in the diagnosis of pancreatic insufficiency as they may determine possible causes and the extent of pancreatic involvement. Computed tomography (CT) is the overall first-line imaging study for pancreatic parenchyma disease. CT is a highly reliable study with 74% and 85% of sensitivity and specificity respectively as shown in several studies.[22] Common findings in CT include calcifications, cysts, deformation/obstruction of bile ducts, pancreatic/peripancreatic tumors, fibrosis and parenchyma loss. Magnetic resonance cholangiopancreatography (MRCP) stands next to CT as it identifies the same abnormalities. However, as MRCP is an invasive imaging test, it provides better differentiation of biliary and pancreatic strictures compared to CT or other non-invasive techniques. Secretin-enhanced magnetic resonance cholangiopancreatography (S-MRCP) consists on the secretin stimulation to increase the volume of pancreatic juice. This test promised to diagnose early stages of EPI, however there is no reliable data regarding the specificity for this technique as it only quantifies volume and not bicarbonate concentrations. In addition, results can be influenced by other conditions as obstructive lesions or Oddi's sphincter spams.[2]

Endoscopic ultrasound (EUS) has gained more popularity over the past few years. Its low adverse events rates even with fine needle aspiration (FNA) performed has positioned itself as one of the first options for pancreatic disease diagnosis. EUS-FNA is as effective as endoscopic retrograde cholangiopancreatography (ERCP) in chronic pancreatitis with 97% sensitivity and 60% specificity compared to ERCP as shown by Hallerbach et al.[23] ERCP constitutes the gold standard for pancreatic duct diseases. It carries out a sensitivity of 66% and 93% specificity for chronic pancreatitis.[24] Major ERCP disadvantage is the risk of post-ERCP acute pancreatitis. Literature reveals a 20% risk of acute pancreatitis after procedure that can lead to chronic pancreatitis or worsen symptoms.[25] ERCP, as well as EUS are both operator-depending demanding many endoscopic skills. Also, both procedures require sedation and depending on the patient's comorbidities, other specialties evaluation and in some cases assisted ventilation.

Pancreatic function test

Pancreatic function can be evaluated by direct or indirect tests. Direct test involves the recollection of pancreatic juice after the intake of food or administration of hormones to further evaluation and quantification of exocrine secretory function. A double lumen tube for gastric antrum and duodenum along with pyloric and duodenal occlusion balloons are placed under fluoroscopic guidance for collection of pancreatic juice and to prevent gastric fluid to enter the duodenum. Secretin and CCK are used to investigate pancreatic function. Secretin-related test measures the capacity of bicarbonate production by ductal cells. In the other hand, CCK-related tests reveals the ability of pancreatic enzymes' secretion by acinar cells. The use of both secretin and CCK test constitute the best method to evaluate exocrine pancreatic function.

Direct test

Secretin test

The purpose of this test is to measure the volume, concentration and total release of bicarbonate. First, a small 0.2 mcg dose of secretin is administered and then a complete dose of 0.2 mcg/kg is administered throughout an IV bolus. Pancreatic fluid is collected every 15 minutes for one or two hours. Results stating a bicarbonate concentration inferior than 80m Eq/L for every 15-minute collection reveals exocrine insufficiency and concentrations below 50m Eq/L represent severe exocrine insufficiency. Volume and total output is not completely reliable due to the incapacity of full collection of fluid. The use of endoscopic pancreas function tests has provided an alternative 30 and 45 minute fluid collection after the administration of secretin.[26]

CCK test

This test demands a double and single lumen gastric tube for the same reasons stated before but one tube releases a mannitol saline solution with polyethylene glycol. The analysis of pancreatic fluid volume and enzyme output and concentration are based on the quantification of the non-absorbable marker. Lipase can also be measured in a 2 hour fluid collection; a concentration of 780 IU/L was determined to be a limit between patients with chronic pancreatitis and healthy individuals.[27]

Secretin-CCK test

This test allows ductal and acinar pancreatic functions evaluation while both hormones are administered simultaneously by bolus or infusion. Several studies have been conducted to determine whether

the reduction of fluid collection time, cessation of non-absorbable markers use and the measurement of a single enzyme somehow influence the final results of the pancreatic exocrine function determination. Reduced time of fluid collection is not recommended because it is impossible to recover a proper volume of fluid to achieve an accurate exocrine function. Likewise, the use of non-absorbable markers is essential for the proper measurement of volume as the tube fails to recover all fluid from the duodenum lumen.[28] Also, the measurement of more than one pancreatic enzyme makes the test more sensitive because some patients may develop an isolated parameter deficiency so a broader assessment involving more pancreatic markers is recommended.

Lundh test

This test requires a 2 hour-pancreatic fluid collection after the administration of 300 cc of a liquid meal containing 5% of protein, 6% of fat and 15% of carbohydrates. This test demands secretin and CCK secretion to be fulfill so it is not completely accurate in patients with mucosal or anatomical abnormalities. Even though this is an inexpensive and quite accessible test, it has been left behind due to greater effectiveness of other tests.

Indirect tests

Indirect test are for advanced EPI diagnosis due to their lack of sensitivity in early stages.

Fecal fat

The presence of fat in stools does not only indicate pancreatic insufficiency. As steatorrhea may be a result from other mal absorption syndromes, the fecal fat test is not specific for EPI and it is not useful in early stages of the disease. However, it is the most accurate indirect test for fat malabsorption. A 72-hour stool is collected prior the ingestion of 100g/day of fat during 5 days. Fat quantification greater than 7g/day indicates fat malabsorption. Disadvantages for this test include marked malabsorption symptoms due to the high intake of fat, especially in chronic pancreatitis and that the collection of feces during three days is quite unpleasant for the patient and for the healthcare worker.

Fecal elastase-1 and fecal chymotrypsin

Fecal elastase-1 (FE1) has the highest sensitivity for severe EPI diagnosis. It does not experience variations throughout intestinal transit and does not have other enzymes interference. It is test of choice in pediatrics due to its lack of invasive tools. This same reason makes it appealing for adult's assessments. Disadvantages include false positives due to intestinal dilution in other cause of diarrhea and poor sensitivity for early stages of EPI. Unlike FE-1, fecal chymotrypsin (FChT) suffers variations during its intestinal transportation. False positives may also appear. Fecal chymotrypsin is highly sensitive for advanced EPI (85%) but its sensitivity for early stages is even lower than FE-1.FE-1 and FChT sensitivity was compared in CF pediatric patients. FE-1 was shown to be superior to fecal ChT in the evaluation of CF pancreatic involvement in patients with steatorrhea and in patients with preserved pancreatic function.[29]

Breath test

The breath test is unremarkably accurate diagnosing fat mal absorption. It requires the ingestion of 13C triglycerides-marked substrates with any meal. These substrates pass through a hydrolyzation process in relation to lipase activity. Hydrolyzed products are later metabolized and release through the lungs as 13C02

and then analyzed by mass spectrometry or infrared. The test has proven to be effective monitoring fat digestion in patients with PERT. This provides an alternative follow-up method leaving behind other test such as fecal fat quantification.[30,31]

Pancreolauryl test

The Pancreolauryl test (PLT) is sensitive for mild and severe EPI with sensitivity rates varying from 50-85% respectively. The tests consist on the ingestion of fluoresce in dilaurate (a cholesterol esterase substrate) with the first meal. Fluorescein is absorbed from the intestine and later on excreted by urine. Either serum fluorescein measurement or a 24 hour urine collection reveals the integrity of exocrine pancreatic function. PLT is not sensitive for extra pancreatic diseases causing fat mal absorption. Dominguez-Muñoz and Mal fertheiner conducted a study using an optimized PLT test to analyze possible sensitivity and specificity rates increase. The optimization consisted basically the intravenous administration of secretin before the test. Sensitivity and specificity increased to 95% and 81% respectively in patients with chronic pancreatitis. The use of the optimized PLT test can increase sensitivity for EPI in mild and moderate chronic pancreatitis by 30%.[32]

Serum trypsinogen

Serum trypsinogen levels less 20ng/mL are specific and sensitive for chronic pancreatitis and advanced EPI. Low levels of serum trypsinogen were found in 69.2% of patients with chronic EPI, 100% post-pancreatectomy patients and 14% of patients with pancreatic neoplasm.[33] However, normal levels of trypsinogen in patients with mal digestion symptoms do not rule out EPI and further examination and measurement of trypsinogen are required as this test is not positive in earlier stages of the disease.

Treatment

For a successful treatment, several factors should be taken into consideration. The underlying disease must be properly identified and managed followed by an exhaustive evaluation for possible complications related to malnutrition. The intake of pancreatic enzymes is the main target for clinical improvement. Pancreatic enzyme dosage must be individualized for each patient depending on the degree of mal absorption and its etiology. Initial dosage of pancreatic lipase should be quantified according to the individual's weight, but in several cases patients have been under dosed. Intake between 500-2,500 units of lipase per kilogram is recommended, but as a general rule an intake must be between 30.000 to 50.000 IU per meal and half a dose per snack.[3] Enzyme intake abuse > 10.000 IU has been associated with fibrosing colonopathy.[34] Patients also benefit from proton pump inhibitors or H2 antagonist therapy since it reduces persistent symptoms. Vetch et cols concluded that during PPI or H2 antagonist therapy, pancreatic enzymes doses lower than usual are as effective as recommended standards[35]

Diarrhea is one of the most discomforting symptoms significantly diminishing the quality of life. Patients with EPI suffer from chronic diarrhea and therefore tend to have significant dehydration and electrolyte disturbances. For diarrhea management, loperamide or diphenoxylate with atropine are recommended as first drugs. Loperamide is a very effective and inexpensive ant diarrheal, which is rapidly metabolized in the liver and has very low risk of central nervous system adverse effects. Tincture of opium has shown to be highly effective but its use should be limited to severe cases of diarrhea due to possible drug-dependency.

Another EPI treatment goal is to identify nutritional deficiencies and to correct them properly. Patients with severe weight loss (weight loss > 10% of usual body weight) require aggressive nutritional treatment due to their higher morbidity and mortality risk. Almost all concomitant diseases are related to micronutrient deficiencies, therefore vitamin and mineral supplements intake is essential in EPI management. Due to fat mal absorption, vitamins should be given in a more polar form. Patients with microcytic anemia should take iron and folate supplements; individuals who underwent intestinal resections benefit from taking magnesium and calcium supplements.

Even though patients have favorable responses to PERT and nutritional supplements intake, treatment success demands much more than medicine intake requiring lifestyle modifications. Patients should avoid caffeine and sugar-free drinks or meals because they may induce diarrhea;[36] Smoking and alcohol must be avoided.[1,3,37] Patients who suffer from celiac disease, and lactose or fructose intolerance should continue their gluten, lactose and fructose-free diets. Normal fat diet is recommended due to marked fat deficiency and any reduction on the intake may worsen symptoms.[3,6]

Conclusion

EPI is the consequence of multiple pancreatic or extra pancreatic conditions affecting the normal digestion process interfering in the intestinal absorption of essential nutrients. Under diagnose and misdiagnose of EPI leads to severe nutritional deficiencies producing generalized malnutrition, excessive weight loss, worsening of underlying disease and diminished quality of life. Direct, indirect, genetic or acquired structural changes affecting one or more organs involved in digestion produces mal absorption. As a result, the risk of complications increases as well as the rate of morbidity and mortality rates due to malnutrition.

Steatorrhea is the best indicator for fat mal absorption. Unintentional weight loss, chronic diarrhea and bloating are the most common symptoms referred in present illness. Hydro electrolytic disorders and fat mal absorption-induced hypovitaminosis are common in EPI. Lipase quantification is the most specific blood test for EPI diagnosis.

CT and MRCP can identify possible causes of EPI and provide a complete pancreatic morphological evaluation. S-MRCP has not proven its utility in EPI assessment. ERCP provides a diagnostic and therapeutic option. Its high sensitivity and specificity makes it the gold standard for pancreatic duct diseases. Major disadvantage for ERCP is the risk for post-ERCP. EUS and EUS-FNA have also proven to be useful in pancreatic disorders and its low risk of adverse events post procedure makes it even more appealing for gastroenterologist. Both ERCP and EUS demand high endoscopic skills.

Diagnosis based on pancreatic function tests continues to be a challenge due to false negatives in early stages. Secretin-CCK is the best direct test. It evaluates both acinar and ductal cells function by measuring bicarbonate and enzyme concentrations and total pancreatic juice volume. Indirect test fecal E-1 has the highest sensitivity and specificity for advanced EPI. It is the gold standard test for EPI in pediatrics but it can be false positive in other causes of diarrhea. The breath test is more useful monitoring PERT efficacy than diagnosing EPI.

Treatment main goals include identification of underlying disease and proper treatment, coverage of nutritional deficits with supplements, reduction of fat diet ingestion, antidiarrheals and PERT between 30.000 – 50.000 IU per meal and half the dose per snacks with PPI or H2 antagonist.

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