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REVIEW

Exocrine pancreatic insufficiency: prevalence, diagnosis, and management

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Abstract: Exocrine pancreatic insufficiency (EPI) is a condition caused by reduced or inappropriate secretion or activity of pancreatic juice and its digestive enzymes, pancreatic lipase in particular. EPI can result in clinical manifestation and biochemical alterations causing reduced quality of life and life-threating complications. EPI is common in pancreatic disorders, where it should be suspected and actively investigated, and in many extrapancreatic conditions. There are various tests available to diagnose EPI, with indirect, noninvasive ones, such as concentration of fecal elastase being more commonly employed. Administration of pancreatic enzymes replacement therapy remains the mainstay of EPI treatment. The present review article will discuss current evidence regarding the prevalence of EPI, the available tests to diagnose it and its treatment.

Keywords: exocrine pancreatic insufficiency, chronic pancreatitis, pancreatic cancer, elastase, malnutrition, diagnosis, therapy

Introduction

Exocrine pancreatic insufficiency (EPI) is a condition caused by reduced or inappropriate secretion or activity of pancreatic juice and its digestive enzymes, pancreatic lipase in particular. EPI can result in clinical manifestation such as steatorrhea, weight loss, and biochemical alterations related to lipids and liposoluble micronutrients malabsorption and maldigestion.[1,2] While overt maldigestion is associated with easily detectable symptoms, impairment of quality of life[3] and risk of significant complications due to malnutrition such as changes in bone density,[4] EPI is also associated with an increased risk of mortality in patients with chronic pancreatitis (CP) due to cancer, infections, and cardiovascular events.[5] Less-severe degrees of EPI cause subclinical consequences that might also result important for the nutritional status of patients.[6] Therefore, EPI should be suspected, diagnosed, and treated early in subjects with conditions associated with its presence and symptoms such as bloating, abdominal discomfort, and otherwise unexplained nutritional deficiencies.[7] The present review article will discuss current evidence regarding the prevalence of EPI, the available tests to diagnose it, and its treatment in adults patients.

Prevalence of EPI

The prevalence of EPI in the general population is unknown. It is most commonly associated with diseases of the exocrine pancreas, being a common late-stage manifestation of CP. However, as pancreatic function and pancreatic secretion are not synonymous,

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EPI can be due to extrapancreatic diseases (Table 1) affecting regulatory signals and/or altering the complex lipase–food–duodenal juice mix-up and interaction.[2]

EPI caused by pancreatic disorders

CP is the most common pancreatic disease associated with EPI.[1] In CP, progressive loss of acinar cells and fibrosis reduce lipase secretion. Clinically significant EPI in CP requires a reduction of almost 90% of pancreatic enzymes and is reported in 60%–90% of CP patients within 10–12 years from diagnosis.[8] Alcoholic and hereditary CP and smoking are associated with an increased risk of EPI.[2] While patients with advanced CP are usually followed in tertiary centers, the rate of EPI in those with early or idiopathic CP who are most commonly evaluated at a primary care level has been reported to be of only 18.7%.[9]

EPI can also be the consequence of a previous AP episode with significant loss of parenchyma. The rate of EPI after AP has been reported to be 20% in a recent meta-analysis,[10] being 30% after severe AP. Recurrence of AP, the extent of

Table 1 Prevalence of EPI in different clinical conditions

EPI caused by pancreatic disorders		
Disease	EPI prevalence	Factors associated with EPI occurrence
Chronic pancreatitis	30%–90%	• Long disease duration • Alcoholic etiology • Extensive calcifications • Ductal obstruction
Acute pancreatitis	Mild pancreatitis: 15%–20% Severe pancreatitis: 30%–40%	• Necrosis extent (>30%) • Alcoholic etiology
Autoimmune pancreatitis	30%–60%	Extensive mass/calcification
Unresectable pancreatic cancer	20%–60%	• Head localization • Large size • Ductal obstruction • Coexistent chronic pancreatitis
Pancreatic neoplasms after surgery	Pancreaticoduodenectomy: 80%–90% Distal pancreatectomy: 20%–50%	• Whipple intervention* • Gastropancreatic anastomosis*
Benign pancreatic tumor (before surgery)	30%–60%	• Head localization • Large size • Ductal obstruction • Coexistent chronic pancreatitis
Cystic fibrosis	80%–90%	Classes I, II, III, VI CFTR mutations
Shwachman–Diamond syndrome	80%–90%	–
EPI caused by extrapancreatic disorders		
Type I diabetes	30%–50%	• High insulin requirement • Poor glycemic control • Early diabetes onset
Type II diabetes	20%–30%	• Insulin requirement • Poor glycemic control • Long diabetes duration
Inflammatory bowel disease	Ulcerative colitis: 10% Crohn's disease: 4%	• Disease reactivation (only for temporary EPI) • Long disease duration • Surgical patients
Celiac disease	5%–80%	Untreated disease (no gluten-free diet)
Pediatric intestinal transplantation	10%	
HIV syndrome	10%–50%	Retroviral therapy
Gastrointestinal surgery	Total/subtotal gastrectomy: 40%–80% Esophagectomy: 16%	• Extensive intestinal resection • Vagal denervation
Sjogren's syndrome	10%–30%	
Aging	15%–30%	Age >80 years
Tobacco usage	10%–20%	Alcohol usage
Somatostatin analogs therapy	20%	

Note: *Only for head tumor.

Abbreviation: EPI, exocrine pancreatic insufficiency; CFTR, cystic fibrosis transmembrane conductance regulator; AP, acute pancreatitis; AIP, autoimmune pancreatitis; CT, computed tomography; USP, United States Pharmacopeia; EUS, endoscopic ultrasonography.

pancreatic necrosis, and an alcoholic etiology are factors associated with EPI. In this view, guidelines suggest to monitor the exocrine pancreatic function after a severe AP episode.[11] Mass-forming type I autoimmune pancreatitis is also often associated with EPI. In a recent retrospective study, the rate of EPI, as evaluated by fecal elastase dosage, in AIP was 47%, being as high as 76% in the severe forms.[12]

Pancreatic malignancies can also cause EPI. Unresectable tumors of the pancreatic head, most commonly pancreatic ductal adenocarcinoma (PDAC), determine ductal obstruction and functional tissue substitution causing EPI in 60%–90%, while this rate is lower, being 30%–50% in tumors of the pancreatic body.[13] Notably, exocrine pancreatic function also has a prognostic significance, as reduced fecal elastase is associated with reduced survival in patients with advanced PDAC.[14]

Intuitively, resective pancreatic surgery causes EPI. Pancreatic surgery alters digestive anatomy, the correct mixing of food, bile, and pancreatic enzymes and reduces the pancreatic volume. Different procedures are associated with different degrees of EPI: Whipple procedure (pancreatic duodenectomy) determines the highest rate of EPI (85%–95%), which is slightly lower for pylorus-preserving intervention (80%–90%).[15] Similarly, pancreaticojejunum anastomosis is associated with lower rates of EPI compared to gastropancreatic one.[16] Distal pancreatectomy is associated with a much lower rate of EPI (20%–50%).[17]

Neuroendocrine and benign serous or mucinous pancreatic tumors variously impair exocrine function similar to PC according to size, localization, ductal involvement, and surgical intervention.[18] In advanced well-differentiated pancreatic or extrapancreatic neuroendocrine tumors, moderate EPI may be also observed in 20% of subjects treated with somatostatin analogs therapy due to pancreatic secretion inhibition.[19]

Cystic fibrosis (CF) is always associated with some degree of pancreatic damage. Approximately 75% of infants with new diagnosis of CF have EPI.[20] The type of CFTR mutation determines the risk of pancreatitis and of EPI in CF patients.[21] Some 85% of infants with biallelic severe (classes I, II, III, VI) CFTR mutations have moderate PEI within 3–4 months of age, whereas heterozygote severe or homozygote mild mutation may develop PEI during life course.[22]

Schwachman–Diamond syndrome is the second most common inherited cause of EPI.[23] The disease is characterized by extensive fatty replacement of the acinar cells leading to EPI in 80% of cases with severe reduction of fecal elastase levels.[24]

EPI caused by extrapancreatic disorders

The exocrine pancreatic secretion is tightly regulated by a number of factors, such as vagal stimulation, neural pathways activated by gastric distension, and secretin release upon acidic content in the duodenum. The optimal pH for the activity of pancreatic enzymes in the duodenum is between 7 and 8. Other factors have a trophic effect on the pancreatic exocrine parenchyma. The endocrine part of the pancreas represented by islet tissue is in close anatomical and physiological contact with the exocrine cells, and insulin produced by beta cells has a trophic effect on acini. Also, in diabetics, microvascular damage may induce pancreatic fibrosis,[25] and the pancreatic volume is reduced.[26] Therefore, not surprisingly, EPI is not uncommon both in type I and type II diabetes.[27] Insulin requirement, poor glycemic control, and long disease duration have been associated with exocrine impairment with a rate of 30%–50% moderate and 5%–30% severe EPI in type I and 15%–35% moderate and 5%–15% severe EPI in type II diabetes.[27] An important limitation of studies on this topic is that the presence of underlying pancreatic pathology in diabetics was usually not excluded, thus at least in a quote of patients with supposed type II diabetes, a nondiagnosed type IIIc diabetes with CP might have been present.

Pancreatic involvement during the course of inflammatory bowel disease (IBD) has been reported.[28] Apart from AIP (usually type II), transient EPI is not unusual during IBD reactivation while persistent fecal elastase reduction has been retrospectively reported in 4% of Crohn's disease and 10% of ulcerative colitis patients, with an increased risk for long disease duration and surgical patients.[29] As patients with IBD often have diarrhea, which is unrelated with EPI, and this can cause false-positive results at fecal elastase measure, with reduced values due to dilution, it is important not to measure elastase levels in liquid stools.

Transitory fecal elastase decrease has also been reported in patients with untreated celiac disease, with extremely heterogeneous rates (5%–80%).[30,31] While this might also be due to a dilution effect, intestinal inflammation and atrophy seem to impair pancreatic signaling.[29] As far as intestinal damage is concerned, a temporary reduction of fecal elastase levels has also been observed in 70% of infants within 3 months from intestinal transplantation.[32]

As the activity of pancreatic enzymes depends from a delicate synchrony with gastric emptying and biliary secretion, gastrointestinal surgery that impairs gastric relaxation and hormonal signaling can negatively affect exocrine function.

EPI occurs in 40%–80% of gastric total/subtotal resection both for gastric tumors and peptic ulcer.[33,34] Esophagectomy has also been associated with a rate of EPI of 16%.[35]

Aging also involves the pancreas determining hypoperfusion, fibrosis, and atrophy, which in turn results in moderate EPI in 10% and severe EPI in 5% of subjects aged >70 years evaluated by fecal elastase levels.[36] In another study investigating the pancreatic function by means of secretin-stimulated magnetic resonance, EPI was diagnosed in 30% of individuals aged >80 years.[37]

Moderate (20%–30%) to severe EPI (3%–40%) has also been reported in chronic patients with heart failure or critically ill ones,[38] possible due to vascular or drug-related injuries or impaired signaling,[39] and, although this is not very common, EPI has been associated with Sjogren's syndrome.[40] Among infective disorders, EPI is common in HIV-positive patients, as recently confirmed in a prospective study detecting 32% of moderate and 20% of severe fecal elastase reduction in 100 patients treated with antiretroviral therapy.[41]

Finally, a recent cross-sectional study associated EPI with tobacco exposure in subjects without pancreatic disease, reporting a higher rate of moderate (18%) and severe (10%) fecal elastase reduction in smokers as compared to controls.[42]

Diagnosis of EPI

The diagnostic approach to EPI can be addressed to evaluate the maldigestion of nutrients or to specifically quantify the exocrine pancreatic secretion. Two categories of tests can be distinguished: direct and indirect.

Indirect tests assess the consequence of exocrine insufficiency, evaluating quantitative changes of pancreatic secretion. These tests have the characteristic to be less expensive and easier to be performed as compared with direct pancreatic functional tests.

Direct tests, on the contrary, evaluate directly the secretive production, and, despite their good sensitivity, are invasive, time-consuming, expensive, and not useful in monitoring the response to pancreatic enzyme replacement therapy (PERT). Moreover, they are not standardized because of lack of consensus about protocol, and present extensive variation in results, and are not widely available.[43,44]

Fecal elastase-1 test (FE-1)

The determination of FE-1 levels is the most commonly employed indirect test for exocrine pancreatic function. The available commercial assay is an ELISA quantifying CELA2 and/or CELA3 isoforms of the human "chymotrypsin-like elastase".[45]

There are five isoforms (CELA1, CELA2A, CELA2B, CELA3A, and CELA3B) of these proteins, the biological specificity of which is largely unknown. Elastase 1 is a proteolytic enzyme produced by pancreatic acinar cells, which binds to bile salts and passes through the gut with slight degradation, therefore being dosable in fecal samples.

The concentration of this enzyme in the feces is five times higher than that in the pancreatic juice. It reflects the level of pancreatic output and correlates also with the output of other pancreatic enzymes such as lipase, amylase, and trypsin.[47,48]

Elastase-1 is highly stable in feces for up to 1 week at room temperature, and for 1 month when stored at 4°C, thus making conservation simpler.[49] The only caution is that the measurement must be performed on solid stools; liquid stool indeed can be associated with false-positive result.[46,47]

A concentration <200 μg/g in the feces is considered abnormal. The sensitivity of FE-1 for mild, moderate, and severe EPI in patients with CP is 63%, 100%, and 100%, respectively. Fecal elastase has a specificity of 93% in patients with EPI.[50,52]

Two commercially ELISAs are available for the measurement of FE-1 respectively using a monoclonal and polyclonal antibody.

The monoclonal FE-1 assay (mAB's) (ScheBo Biotech AG, Giessen, Germany) has good sensitivity and specificity for moderate and severe EPI in comparison with cholangiopancreatography (MRCP) combined with diffusion-weighted MRI and endoscopic retrograde cholangiopancreatography (ERCP) that have been considered for a long time the gold standard of pancreatic imaging for CP.[49–53] The sensitivity remains instead poor in mild CP.

This test uses two monoclonal antibodies that recognize different epitopes of human pancreatic elastase-1 capable of measuring elastase-1 in feces and duodenal fluids.[54]

The measurement of FE-1 concentrations is highly specific for human elastase-1, and it has become an accepted indirect test of exocrine pancreatic function.

This assay has demonstrated to be a useful screening tool for exocrine dysfunction also in patients with CF, diabetes mellitus, and gallstones.[55–57]

A polyclonal FE-1 assay (pAB's) (BioServ Diagnostics, Rostock, Germany) is also available employing two different polyclonal antisera to human pancreatic elastase recognizing different antigenic epitopes.[58] The elastase polyclonal assay has been demonstrated to be less specific for elastase 1 and

to overestimate the overall concentration of elastase.[59,60] The monoclonal test seems to be more accurate in the evaluation of pancreatic elastase secretion.[58,60,61] Furthermore, the monoclonal assay is not affected by PERT, while the polyclonal one is.[58]

Serum trypsinogen

Serum trypsinogen levels are associated with pancreatic acinar cell mass.[62,63] Serum trypsinogen, however, is not specific for EPI and while its sensitivity is high for advanced EPI (trypsinogen levels <20 ng/mL), it has low sensitivity in case of mild insufficiency (trypsinogen levels between 20 and 29 ng/mL). This test is not commonly employed in clinical practice.

Fecal chymotrypsin

Chymotrypsin is another enzymatic product of pancreatic secretion, which can be dosed in fecal samples and is used in the diagnostic approach to EPI. The specificity of fecal chymotrypsin for EPI is lower as compared with FE-1 (49% and 85%, respectively, for mild to moderate and advanced pancreatic insufficiency).[64,65] Furthermore, it is variably degraded during transit in the intestinal lumen and its dosage requires an interruption of 2 days of PERT.

Breath tests

Breath tests for the evaluation of EPI consist of oral administration of a ^{13}C-marked test meal.[66,67] The substrates are hydrolyzed in proportion to the amount of pancreatic lipase activity. Breath samples reflect absorption and metabolization of products. They are collected by blowing into collection tubes, and $^{13}CO_2$ exhaled is quantified.

The ^{13}C-mixed triglyceride breath test monitors the digestion of an isotope-labeled fat meal, thus quantifying fat malabsorption.

The main limitation of the test is that it is nonspecific and has a low sensitivity for the diagnosis of mild EPI. Furthermore, the test is relatively time-consuming, requires specific instrument and reagents, is only available in few referral centers, and is not approved in the United States. On the other hand, the test has the advantage to be modified by PERT, thus permitting to monitor response to treatment.

Coefficient of fat absorption (CFA)

This test consists of 72-hour fecal fat collection. The result is expressed as CFA (ie, the percentage of fat in the diet that is absorbed, given a known fat content in the diet).

Normal CFA is ~93% of fat content. Steatorrhea is classically defined by the presence of at least 7 g of fecal fat over 24 hours, in the context of a 72-hour stool test, when diet includes 100 g of fat daily. It represents the gold standard for the evaluation of steatorrhea and at present is the only test accepted by the American Food and Drug Administration (FDA) and the European Medicines Agency for the indication and monitoring of PERT in clinical trials. This test has several limitations in clinical practice because of limited patients' compliance and too much time required to obtain the stool sample. The test is nowadays uncommonly used in clinical practice.

Direct pancreatic function tests

Direct pancreatic function tests are the most sensitive diagnostic tests for the diagnosis of EPI.

They are based on stimulating the pancreas with hormonal secretagogues and then collect duodenal fluid to measure directly its secretory content (enzymes and bicarbonate). Cholecystokinin (CCK) and secretin have both been used to stimulate pancreatic secretion.[68] However, it is unclear which is the secretagogue providing the superior sensitivity for mild pancreatic insufficiency. Studies assessing the performance of direct pancreas function tests in patients with proved CP on imaging have demonstrated a sensitivity of 72%–94%.[69]

The traditional direct pancreas function test consists of fluoroscopic placement of a double-lumen gastroduodenal (Dreiling) collection tube. The proximal lumen is situated in the gastric antrum to collect and remove gastric secretion. The distal lumen is deep within the duodenum with the tip of the tube at the ligament of Treitz for continuous collection of duodenal fluid. After a test dose (0.2 mcg) of synthetic secretin, a full dose (0.2 µg/kg) is injected as an intravenous bolus. Duodenal aspirates are obtained 0, 15, 30, 45, and 60 minutes after administration of secretin. Fluid is examined for volume, concentration, and bicarbonate output. A bicarbonate concentration <80 mEq/L in all of the four samples is diagnostic for EPI.[70] Severe EPI is characterized by a peak bicarbonate concentration <50 mEq/L. However, bicarbonate output and fluid volume are known to be imprecise measures because of the incomplete collection of duodenal fluid.

Endoscopic pancreatic function tests are carried out under sedation and are better tolerated as compared with tradition direct pancreas function test.[71] Duodenal fluid is collected through the endoscope into a specimen trap.

The protocol for the secretin endoscopic pancreatic function test is analogous to the traditional secretin test protocol. Duodenal aspirates are obtained in 15-minute aliquots for

1 hour (0, 15, 30, 45, and 60 minutes after administration of secretin). A peak bicarbonate concentration <80 mEq/L is considered abnormal. The accuracy of secretin endoscopic pancreatic function test is equal to the traditional secretin test.[72] In one retrospective study that included 25 patients with CP, endoscopic secretin pancreas function test showed a sensitivity and a specificity, respectively, of 86% and 67% for the diagnosis of CP.[73] Intraductal collection of secretin-stimulated pure pancreatic juice at the time of ERCP has also been investigated as an alternative to standard secretin testing because it consents concurrent evaluation of pancreatic morphology and function. However, studies of intraductal secretin tests have provided mixed results, and the procedure carries the risk of acute pancreatitis.[74–77]

The use of CCK receptor agonists gives information on the enzyme secretory capacity of the pancreas. However, a minimum value of lipase concentrations has not been well defined, and results from studies have been conflicting.[74,78] Traditionally, this test requires the placement of two tubes: a duodenal and a gastric tube.[79] The gastric tube collects and discards gastric fluid to prevent acidification of the duodenum. The duodenal tube, which is double lumen, continuously collects duodenal drainage fluid and, at the same time, perfuses a mannitol–saline solution with a nonabsorbable marker (polyethylene glycol [PEG]). An accurate determination is made of fluid volume, enzyme concentration, and enzyme output based upon collection of the PEG marker. CCK pancreas function test has also been conducted endoscopically.[78]

The use of the secretin–CCK test is limited to pancreatic research centers in Japan and Europe. The secretin–CCK test offers concurrent evaluation of ductal and acinar secretory activity. Several dosing regimens have been assessed for the secretin–CCK test. Whether the use of combined stimulants can improve the sensitivity for mild EPI or mild CP remains controversial.[80] Furthermore, a number of factors causing poor accuracy and increasing variability have been reported, such as shortening of the time of collection, failure to correct for intestinal losses, and to aspirate gastric content[81] and somehow limit the reliability of endoscopic pancreatic function tests.

Secretin-enhanced magnetic resonance cholangiopancreatography (MRCP)

In patients with CP, MRCP is often performed as second-level imaging technique to investigate the pancreatic ductal system.[82] MRCP not only is superior to CT scan to diagnose subtle ductal changes but also allows a semiquantitative assessment of pancreatic exocrine function when coupled with secreting injection (S-MRCP). Indeed, a specific classification based on the degree of duodenal filling has been developed and validated.[83]

Management of EPI

The real function of pancreatic juice was completely comprehended only in 1,856 when Claud Bernard in his "*Mémoires sur le pancreas*" demonstrated that pancreatic juice had the ability to emulsify fats and to break them down. Later, in 1859, Bernard was also able to isolate a substance from pancreatic juice that was called *pancreatin*, which showed experimentally all its natural effects when dissolved in water.[84] Afterwards, the term "enzyme" was coined by Kuhne who referred to chemical ferments and named "trypsin" the pancreatic enzyme with proteolytic activity.

The first successful attempt to convert pancreatin into a gastric acid-resistant preparation was made when a new product called "*pankreon*" was developed by bounded pancreatin with 10% tannin. Porcine pancreas is nowadays the most common source of pancreatic enzymes (with the highest enzyme activity of all three classes), and all available products contain a mixture of porcine-derived amylases, lipases, and proteases. Lipase is the main pancreatic enzyme whose function is barely compensated by extrapancreatic mechanisms; however, because of its high sensitivity to acid and proteolysis it is the least stable.[85] Modern preparations are administered as pH-sensitive enteric-coated minimicrospheres (>2 mm) to protect lipase from denaturation by gastric acid. Since 2010 FDA approved different pancreatic enzyme replacement products for the treatment of EPI all consisting of extracts from porcine pancreas (pancrelipase).[86] All but one of those preparations have a delayed release (Creon, Pancreaze, Zenpep, Pertzie) due to enteric-coated beads that protect lipase from denaturation from gastric acid. Only Viokace has an immediate release because of uncoated enzyme preparation so that it should be used in combination with a proton pump inhibitor (PPI) to maximize its activity in the duodenum.[87]

The majority of the particles in PERT products have a size of 1–1.5 mm, able to guarantee uninhibited pylorus passage with the nutrients.[88] Micro- or mini-tablets of 2.2–2.5 mm in size appear to be comparable to mini-microspheres in the setting of EPI associated with CF, but less scientific evidence is available for other conditions.[89] Once in the duodenum, the high pH permits the release of the enzymes and their activation in the correct site for digestion, after dissolving the

acid-resistant enteric coating. For this reason, enzymes should be taken alongside meals and snacks to mimic postprandial enzyme output in healthy subjects.[90]

Although the optimal pH for enzyme activation in the duodenum is >6, it has been showed that in patients with CF, it is often lower.[91] It has been hypothesized that adding PPI in CF patients not responding to PERT (eg, refractory steatorrhea) might improve treatment efficacy. However, in a retrospective study, there was no improvement of the CFA in a large cohort of pediatric patients with CF treated with PERT together with PPIs.[90]

There are several available guidelines[91–97] with different recommendation regarding PERT dosages. The aim of the therapy is to normalize the nutritional status and relief the symptoms; consequently the correct dosage is the one able to reach this goal. It is recommended to start treatment with 25,000–50,000 lipase units per main meal in adults and 20,000 per snack. Such dosages have been able to increase fat absorption in patients with benign disease (eg, CP) without alteration of the gastric transit.[96] Since the optimal PERT therapy is based on its clinical efficacy, the initial dose might be doubled or tripled based on the clinical need and results. PERT, indeed, has shown over time an acceptable safety and tolerability with abdominal pain, abdominal distension, and diarrhea being the reported side effects (7.8%–13%).[98] At the doses of 72,000 USP, lipase/meal hypersensitivity reactions/allergy have also been rarely reported (mainly skin rash). In CF patients, fibrosing colonopathy was also described.[99]

In malignant condition (unresectable pancreatic cancer) and in patients who underwent duodenopancreatectomy or gastrointestinal surgery, standard PERT dosages might be insufficient to improve the impaired nutritional status. The adequate dosage for these conditions is still not well established, and there is need of further investigation. In a randomized controlled trial,[100] patients who had pancreatic surgery were treated with PERT with a dose of 75,000 units per meal vs placebo. The study showed a good efficacy of PERT in fat and protein digestion although after therapy, the CFA was still below the normal range (78.4%±20.7%), suggesting that higher doses might be necessary.

Whichever is the initial cause of the EPI, in the case of no response to a standard PERT dosage, the first step is to check the compliance to the therapy. If compliance is adequate, an increase of PERT dosage by small increments is recommended. A dose of 80,000 units with meals can be reached and in the case of insufficient response (steatorrhea, continued weight loss, or poor weight gain) adding an acid suppressing medication to reduce acid inactivation of lipase can be considered.[101] Alternative causes of maldigestion should be checked in cases of poor response to treatment, such as infection with *Giardia lamblia*, celiac serology, liver disease, and small intestinal bacterial overgrowth (SIBO) tests. Recently, a systematic review and meta-analysis were published with the aim to evaluate the prevalence of SIBO in CP[102] showing that almost one-third of CP patients are affected by SIBO. SIBO might cause symptoms and nutritional deficits that are similar to those of EPI and should therefore be excluded before increasing PERT dosage.

The future of EPI treatment will focus on identifying recombinant microbial lipases, as already reported in the literature[103] in pig models that might be good candidates to overcome difficulties in the production of porcine pancreatin and possible side effects (allergic reactions, potential risk of virus transmission to humans).

Conclusion

EPI is an important and often undiagnosed clinical condition with potential deleterious effects on the nutritional status of patients with pancreatic and extrapancreatic disorders (Table 1). Although knowledge on EPI in pancreatic disorders is more diffuse compared to that on extrapancreatic ones, many aspects need to be better investigated. CP is probably the pancreatic pathology in which EPI is more frequently diagnosed in clinical practice. In this view, the shift toward diagnosis of CP at earlier stages might be an opportunity to diagnose EPI and start PERT before significant complications have occurred.[4–6]

In patients with high prevalence of EPI such as these with CP, changes of a panel of nutritional parameters, including prealbumin, retinol-binding protein, transferrin, magnesium, ferritin, and hemoglobin, might be used as surrogate to diagnose EPI with good accuracy.[104] An empirical treatment in the absence of a defined diagnosis of EPI might be considered in the presence of symptoms and nutritional deficiencies in patients with a diagnosed pancreatic disease. The importance to diagnose EPI and treat it after pancreatic surgery has been recently underlined by a panel of experts who provided evidence-based guidelines on this topic.[105] The guidelines suggest not to rely on symptoms to diagnose EPI and to start PERT with enzyme doses of at least 72,000–75,000 at main meals. Notably, this treatment is often prescribed at lower doses. The importance to monitor exocrine pancreatic function and treat its deficiency in patients with pancreatic cancer, independently from surgery, relies on the impact of the nutritional status on patients' prognosis. In a recent

study, it has been reported that most patients with pancreatic cancer do not receive PERT and that survival is 262% longer in patients receiving this treatment independently from stage of other received treatments.[106]

The actual incidence and relevance of EPI in extrapancreatic disorders is instead an area in which high-quality evidence is needed, as controversies on the methods to diagnose EPI limit current knowledge on this topic especially, and overall, the cost-effectiveness of diagnostic tests for EPI remains debated.[107]

The clinical relevance of EPI in very common conditions such as diabetes, smoking, and aging is still largely an unexplored issue. Another interesting and poorly investigated area for research regards the association between pancreatic insufficiency and fatty infiltration of the pancreas. It is well described that in patients with specific syndromes such as CF, fatty infiltration of the pancreas is common and its degree as measured through MRI is associated with EPI.[108] In another recent study, however, fatty pancreas as measured with a ratio between pancreatic and splenic parenchyma at CT scan was associated with pancreatic endocrine impairment but not with EPI.[109] As quantitative analyses of texture and tissue strains have become routine part of radiological evaluations, it will be interesting to further analyze this aspect in future studies conducted with either MRI or CT scan or EUS.

Disclosure

The authors report no conflicts of interest in this work.

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