Review paper

Exocrine pancreatic insufficiency in systemic diseases: unravelling the complex interplay – a comprehensive review

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Exocrine pancreatic insufficiency (EPI) is characterised by the pancreas's inadequate synthesis or release of digestive enzymes, which impairs digestion and causes nutritional malabsorption. To effectively manage concomitant systemic disorders and provide personalised therapy, early identification is essential. The production of digestive enzymes is a key component in the processes of EPI, which is linked to several conditions such as pancreatic cancer, cystic fibrosis, chronic pancreatitis, and diabetes-related fibrosis. Other causes include aging, smoking, inflammatory bowel disease (IBD), and stomach removal. Exocrine pancreatic insufficiency causes prolonged diarrhoea in celiac disease, perhaps resulting in pancreatitis and autoimmune processes. With mechanisms involving inflammation, bile duct scarring, pancreatic autoantibodies, and extraintestinal manifestations, EPI prevalence in IBD is noteworthy. Both indirect and direct tests are used in the diagnosis of EPI, and secretin-induced magnetic resonance cholangiopancreatography imaging provides a thorough evaluation. Modifications to lifestyle, therapy modalities such as pancreatic enzyme replacement therapy, and innovative therapies for genetic disorders are all part of the management. Pancreatic enzyme replacement treatment is important because micronutrient deficits, including calcium, magnesium, zinc, and vitamins, are present in EPI patients. Innovative treatments investigate machine learning and PARP enzymes for prophylactic and diagnostic purposes, advancing more accurate EPI diagnosis and treatment in systemic disorders.

Key words: exocrine pancreatic insufficiency, systemic diseases, pancreatic dysfunction, digestive enzyme deficiency, gastrointestinal disorders, multiorgan dysfunction.

Introduction

Definition of exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency (EPI) is described by the insufficient production or release of digestive enzymes from the pancreas, leading to impaired digestion and malabsorption of nutrients. Exocrine pancreatic insufficiency is often found in medical conditions like chronic pancreatitis, cystic fibrosis (CF), and pancreatic cancer, where damage to

the pancreatic tissue leads to a decrease in the release of enzymes [1]. Exocrine pancreatic insufficiency can have significant impacts on overall health and nutritional status, leading to symptoms like weight loss, diarrhoea, steatorrhoea, and deficiencies in fat-soluble vitamins [2].

Prevalence and impact of exocrine pancreatic insufficiency in systemic diseases

The prevalence of EPI varies among different systemic diseases, with estimates ranging from 20 to 90% in chronic pancreatitis and 75% in infants with CF [2]. An investigation into EPI occurrence among individuals hospitalised due to acute pancreatitis (AP) revealed its presence in over half (62%) of the cases, with this figure decreasing to 35% during follow-up. The likelihood of developing EPI was notably elevated when alcohol was the underlying cause [3].

In the absence of treatment for exocrine pancreatic insufficiency, individuals face the risk of developing complications stemming from inadequate fat absorption and malnutrition, resulting in a diminished quality of life. It's noteworthy that approximately 65% of individuals with a chronic pancreatitis diagnosis display either osteoporosis or osteopaenia. This leads to a decline in their overall well-being due to ongoing symptoms, impaired work capacity, and subsequent financial strain. Moreover, the failure to implement intervention strategies leads to increased rates of morbidity and mortality, primarily stemming from issues related to malnutrition and cardiovascular problems [4].

Significance of understanding the interplay between exocrine pancreatic insufficiency and systemic diseases

Understanding the interplay between EPI and systemic diseases is crucial for several reasons. Firstly, the presence of EPI in various systemic conditions underscores the importance of early diagnosis and tailored treatment approaches. Accurate diagnosis of EPI and its underlying cause can improve a patient's quality of life and prevent complications related to malnutrition and nutrient deficiencies. However, EPI often goes overlooked in initial diagnoses by many healthcare professionals, resulting in inadequate treatment for affected patients in the United States [2]. Secondly, recognising the connections between EPI and systemic diseases can guide clinicians in managing coexisting conditions more effectively. For example, managing both EPI and CF involves addressing nutritional deficiencies alongside lung function.

Moreover, insights into the relationship between EPI and systemic diseases can inform research efforts and therapeutic interventions. Investigating the mechanisms by which different systemic diseases lead to EPI can shed light on potential targets for treatment or prevention. This holistic approach may also provide insights into shared genetic or biochemical pathways that could be targeted for novel therapies.

Mechanisms of exocrine pancreatic insufficiency

Physiology of pancreatic digestive enzymes

The pancreas's exocrine function revolves around generating alkaline pancreatic juice with an isoosmotic nature, which carries enzymes crucial for the digestive process in the intestines. These enzymes are synthesised within intravesical cells and are subsequently conveyed to the duodenum through the pancreatic ducts. The juice also contains a small amount of mucus secreted by goblet cells in the ducts. The juice comprises enzymes for digesting proteins, fats, carbohydrates, and nucleic acids, along with electrolytes. Proteolytic enzymes like trypsin and chymotrypsin digest proteins, while lipase, phospholipase, and esterase break down fats. Glycolytic enzymes, such as amylase, digest carbohydrates, and nucleolytic enzymes like ribonuclease and deoxyribonuclease break down nucleic acids. Enzyme secretion is regulated by food intake and neurohormonal mechanisms, with daily volume varying (1–4 litres) based on diet [5].

Causes of exocrine pancreatic insufficiency – pancreatic and extra-pancreatic origins

Exocrine pancreatic insufficiency can arise from both pancreatic and extra-pancreatic factors. The leading factor is chronic pancreatitis [6], as it involves a gradual decline in acinar cells and the development of fibrosis, which leads to a decrease in the secretion of lipase. Clinically significant EPI in chronic pancreatitis occurs when nearly 90% of pancreatic enzymes are reduced, influencing 60–90% of patients with chronic pancreatitis in no less than 10 years to 12 years after their diagnosis [7]. The risk of EPI is heightened in cases of alcohol-induced and hereditary chronic pancreatitis, as well as in individuals who smoke [2]. Previous AP episodes with substantial parenchymal loss also led to EPI. A meta-analysis reports EPI after AP at 20%, increasing to 30% for severe AP cases [8]. Recurrent AP, extent of necrosis, and alcohol aetiology are associated with EPI development, prompting guidelines for monitoring after severe AP [9]. Mass-forming type I autoimmune pancreatitis commonly links EPI. In a recent retrospective investigation, EPI prevalence, assessed through faecal elastase measurement, stood at 47% for autoimmune pancreatitis, surging to 76% in severe instances [10]. Pancreatic malignancies, especially unresectable tumours in the head (60–90%)

and body (30–50%), cause EPI due to ductal obstruction and tissue replacement [11]. Cystic fibrosis invariably leads to pancreatic damage. In CF patients, the likelihood of developing both pancreatitis and EPI is contingent on the specific CFTR mutation they carry. Around 85% of infants who possess severe CFTR mutations (belonging to classes I, II, III, and VI) encounter moderate pancreatic enzyme insufficiency within 3–4 months of their birth. On the other hand, individuals with either heterozygous severe mutations or homozygous mild mutations may experience pancreatic enzyme insufficiency at a later stage in life [12]. Furthermore, it is important to note that the second most prevalent genetic cause of EPI is Schwachman-Diamond syndrome [13]. Regarding extra pancreatic causes of EPI, diabetes-related microvascular damage can cause fibrosis [14], reducing pancreatic volume and leading to EPI. In cases of both type I and type II diabetes, a significant proportion of individuals, ranging 30–50% in type I and 15–35% in type II, exhibit moderate EPI, while approximately 5–30% in type I and 5–15% in type II experience severe EPI. The need for insulin, inadequate glycaemic management, and prolonged disease duration correlate with exocrine dysfunction. For individuals with type I diabetes, there is a correlation with moderate EPI rates ranging 30–50% and severe EPI rates ranging 5–30%. Meanwhile, type II diabetes is associated with moderate EPI rates in the range 15–35% and severe EPI rates between 5–15% [15]. Moreover, during inflammatory bowel disease (IBD) reactivation, temporary EPI occurrences are common. Nevertheless, a retrospective analysis has revealed a continual decrease in faecal elastase levels in 4% of patients with Crohn's disease and 10% of patients with ulcerative colitis. Prolonged disease duration and surgical history elevate the risk [16]. Moreover, EPI arises in 40–80% of instances after the complete or partial removal of the stomach due to tumours or ulcers [17]. The aging process impacts the pancreas, resulting in diminished blood flow, fibrosis, and a decrease in size. This leads to moderate EPI rates of 10% and severe EPI rates of 5% in individuals aged over 70 years, as shown by faecal elastase levels [18].

An illustration depicting intra- and extra-pancreatic causes of EPI is shown in Figure I. In another research study using secretin-stimulated magnetic resonance, it was discovered that 30% of individuals aged 80 years and above experienced exocrine pancreatic insufficiency [19]. Furthermore, EPI was associated with tobacco use in individuals who did not have pancreatic disorders. In a cross-sectional study, smokers exhibited a higher incidence of moderate (18%) and severe (10%) reductions in faecal elastase compared to the control group [20].

Pathophysiology of exocrine pancreatic insufficiency development in systemic diseases

The development of EPI within systemic diseases involves intricate mechanisms. In CF, genetic mutations disrupt ion transport, leading to thickened mucus obstructing pancreatic ducts [21]. Chronic pancreatitis causes gradual acinar cell loss and fibrosis, reducing enzyme secretion [6]. In diabetes, microvascular damage and reduced pancreatic volume contribute to EPI [15]. It can occur because of reduced cholecystokinin (CCK) release, which is a consequence of villous atrophy in celiac disease (CD) or milk protein enteropathy [22], while aging causes pancreatic hypoperfusion and atrophy [18].

Exocrine pancreatic insufficiency in diabetes

Association between diabetes and exocrine pancreatic insufficiency

The precise cause of EPI in diabetes remains unclear. Research has predominantly explored pathophysiological aspects in situations involving insulin deficiency, particularly in autoimmune cases. Factors such as reduced insulin growth effects, inflammation, fibrosis, and fat accumulation have been proposed as potential contributors to EPI. Additionally, there is ongoing discussion regarding the impact of diabetic microangiopathy leading to reduced blood flow in the exocrine pancreas and disrupted enteropancreatic reflexes due to autonomic neuropathy in the progression of EPI [23].

Mechanisms linking diabetes to exocrine pancreatic insufficiency development

Beyond mere size alteration, research using various diabetes animal models indicates altered extracellular matrix remodeling. This highlights the accumulation of collagen, especially at the junction between the islets and acini, along with the increased development of blood vessels [24]. Studies have shown that nearly 59.4% of individuals diagnosed with either type 1 or type 2 diabetes display histopathological evidence of fibrosis in the exocrine section of the pancreas [14]. In addition to fibrosis, diabetes is linked to abnormal fat accumulation in the pancreas. The literature remains uncertain whether pancreatic steatosis triggers or results from β-cell dysfunction, elevated glucose levels, and increased fatty acid levels. Its impact on EPI is even more ambiguous [25].

Although the presence of immune cells within the islets in type 1 diabetes is widely known, studies have revealed significant infiltration of CD8+ T-cells in the exocrine pancreas of individuals with this condition. Interestingly, even in type 1 diabetes cases lacking obvious insulitis, significant immune cell infiltration in the exocrine region was observed. In

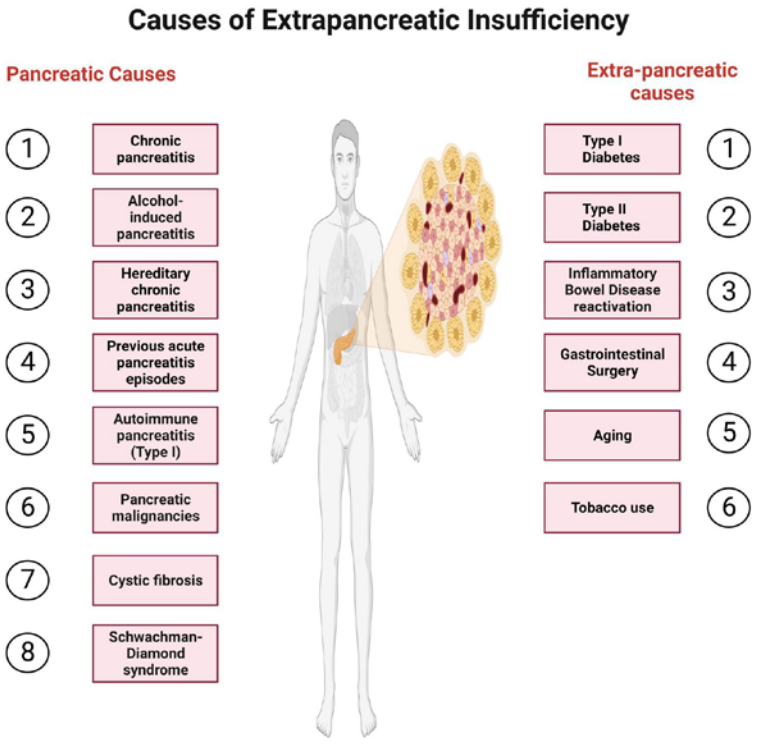

Fig. 1. An illustration of intra- and extra-pancreatic causes of exocrine pancreatic insufficiency

cases of long-standing diabetes, the exocrine pancreas contains not only CD8+ T-cells but also CD4+ T-cells and CD11c+ cells. The precise role of these immune cells in the development of acinar atrophy and fibrosis remains a subject of ongoing research and is not completely comprehended. It is worth noting that type 2 diabetes is similarly linked to an elevated presence of immune cells within the exocrine portion of the pancreas [26].

Impact of exocrine pancreatic insufficiency on diabetes management and glycaemic control

The treatment approach for EPI combines dietary guidance and the use of exogenous pancreatic enzymes. Typically, individuals with symptomatic EPI are advised to avoid fat-restricted and high-fibre diets [27]. Individuals dealing with EPI are advised to tailor their pancreatic enzyme replacement therapy (PERT) dosages. The recommendation is to use at least 40,000 U of lipase for each main meal and 10,000–25,000 U for snacks [28]. Notably, there are no established dietary recommendations specifically for individuals with both diabetes and EPI based on intervention studies. Previous research suggests that enzyme replacement therapy could yield positive outcomes. Some research has suggested that replacement therapy may be associated with improved management of blood sugar or an increase in insulin and incretin response in patients with pancreatic conditions and glucose intolerance [29]. However, the results of a prospective study involving individuals with type 1 diabetes indicated that enzyme replacement did not result in better glycaemic control [30].

Exocrine pancreatic insufficiency in celiac disease

Relationship between celiac disease and exocrine pancreatic insufficiency

Exocrine pancreatic insufficiency is linked to CD and is acknowledged as a contributing factor to chronic diarrhoea. This association was initially documented more than 5 decades ago [31], and its validity has been repeatedly confirmed through various assessments of pancreatic function [32]. Evaluation of celiac patients experiencing persistent diarrhoea while adhering to a gluten-free diet revealed the existence of EPI in approximately 12% (as determined through pancreatic testing or PERT trials to 18%), as assessed using steatorrhoea and PERT trials [33].

Role of autoimmunity in exocrine pancreatic insufficiency pathogenesis

The underlying pathophysiological mechanisms behind EPI in CD are probably multifaceted. A key mechanism might involve an impaired postprandial reaction to luminal contents due to the atrophic mucosa of the upper intestine. This alteration could lead to modifications in the synthesis, storage, and/or secretion of secretin and CCK, potent triggers of pancreatic secretion. Studies have indicated that

untreated CD patients exhibit significantly diminished postprandial plasma CCK levels in comparison to controls. These lower CCK levels were notably associated with faecal elastase levels, providing insight into the relationship between altered hormone secretion and EPI in celiac disease [23].

Moreover, various mechanisms have been proposed to explain the increased susceptibility to pancreatitis in individuals with celiac disease, including malnutrition, papillary stenosis, and immune-related processes. Autoimmune conditions like autoimmune pancreatitis or the presence of islet-specific autoantibodies in celiac disease-associated type 1 diabetes mellitus can play a role in establishing the connection between pancreatitis and celiac disease [34]. Furthermore, a study evaluated EPI in CD patients. Among 83 CD patients, 15.6% exhibited EPI. Genetic analysis of CTLA-4 +49A/G and TNF-α308 polymorphisms did not show a significant difference between groups with and without EPI [35].

Impact of exocrine pancreatic insufficiency on nutritional status and malabsorption in celiac disease

For individuals with low faecal elastase levels on a gluten-free diet, PERT should be administered [36]. While pancreatic enzyme supplementation is sometimes employed as a treatment approach for non-responsive celiac disease, its effectiveness is inconsistent, and the available evidence to substantiate its use is of limited quality. A prospective, cross-over randomised, placebo-controlled study revealed that PERT did not yield symptom improvement among patients with non-responsive CD [37]. Nonetheless, in a previous clinical trial, 19 out of 20 patients were assessed, and their average age was 59.7 years (7 males). The average duration of CD in these patients was 13.2 years. Among the participants, 11 out of 19 were still using enzyme supplementation, averaging 45,000 units of lipase *per* day. Merely 1 out of 11 reported no symptomatic improvement, while 8 out of 19 patients had ceased supplementation due to the amelioration of their diarrhoea. Across the entire group, a notable increase in Fel-1 levels was observed over time [38].

Exocrine pancreatic insufficiency and inflammatory bowel disease

Exocrine pancreatic insufficiency is commonly found in patients with IBD. The prevalence of EPI in IBD is 21% according to para-aminobenzoic acid testing. Based on low faecal elastase levels, EPI is found in 14–30% of patients with Crohn's disease and 22% of patients with ulcerative colitis [33]. Inflammatory bowel disease is linked to a range of pancreatic disorders, including benign asymptomatic elevations in pancreatic enzymes, AP, autoimmune pancreatitis, chronic pancreatitis, and pancreatic insufficiency [39].

The possible mechanism of EPI in IBD is quite unclear. One of the mechanisms is the inflammation and scarring of the bile duct, impeding the flow of digestive enzymes into the gastrointestinal tract, and causing the EPI symptoms. Scarring and inflammation of the intestinal tract reduce intestinal hormonal secretion, a trigger needed to release pancreatic enzymes, thus leading to EPI [33].

Another causative factor for EPI might be the prevalence of pancreatic autoantibodies (PABs) in IBD. 20–30% of patients with CD and 2–9% with UC contain PABs. Pancreatic autoantibodies are IgA and IgG subtypes in nature and mainly target major zymogen glycoprotein 2 causing pancreatic destruction and EPI. Inflammation of the pancreas could also be one of the extraintestinal manifestations of the IBD, which over time damages the pancreas causing EPI [40–42].

Diagnosing EPI can pose difficulties in individuals with IBD. It is difficult to diagnose pancreatic inflammation because blood tests cannot detect it. Other reasons could be the asymptomatic and mild nature of the disease, which over time can cause pancreatic damage and EPI. Even if the symptoms of laboratory findings are present, they might be attributed to the presentation of IBD. It is crucial to investigate an IBD patient of EPI to initially detect or rule out pancreatic involvement [43].

Diagnosis of exocrine pancreatic insufficiency

The diagnostic methods for EPI are used to quantify the pancreatic enzyme secretion or nutritional maldigestion.

Indirect tests

Indirect tests measure changes in pancreatic secretion's quantitative composition to determine the effects of exocrine insufficiency. These tests differ from direct pancreatic functional testing in that they are less expensive and simpler to carry out.

Faecal fat measurement

The most reliable method for diagnosing EPI is 72-hour faecal fat measurement and assessing the fat absorption coefficient. Nevertheless, its application is constrained due to resistance from both patients and laboratories [44]. There are 2 methods to measure fat globules in faeces. The old method's sensitivity and specificity were 76% and 99%, respectively, compared to the quantitative microscopic method's 94% and 95%. A focused strategy for counting and measuring the size of fat globules during faecal fat Sudan microscopy can provide a quantitative outcome that closely matches chemically determined faecal fat output, exhibiting high diagnostic precision [45].

Faecal elastase levels

The most commonly employed indirect test to check EPI is to measure the levels of Elastase-1 in faeces. A concentration of < 200 μg/g is considered abnormal. Elastase 1 is a digestive enzyme produced by pancreatic acinar cells, which forms complexes with bile salts and passes through the stomach with minimal breakdown. It is therefore measured as 5 times higher in faecal samples than the pancreatic juice. The only requirement is that solid stools be used for the measurement; watery stools can lead to false-positive results. This measurement gauges the production of the pancreas and is connected to the quantities of other pancreatic enzymes such as trypsin, lipase, and amylase. The test quantifies CELA 3A and 3B, known as chymotrypsin-like elastases [3]. With a threshold of 200 mcg elastase 1/g stool, the test displayed a sensitivity of 63% for mild cases, 100% for moderate cases, 100% for severe cases, and 93% for all patients with exocrine pancreatic insufficiency. The specificity of the test was 93% [46].

Additionally, in individuals who have had a pancreatic resection, FE-1 levels are not accurate for detecting EPI [3].

Chymotrypsin levels

Exocrine pancreatic insufficiency can be diagnosed using chymotrypsin, another pancreatic enzymatic secretion, which can be quantified in faecal samples. When compared to FE-1, faecal chymotrypsin has a lower specificity for EPI. Additionally, its dosage necessitates a 2-day PERT interval, and it is less readily available in laboratories and variable in how it degrades during intestinal lumen transit [47]. The sensitivity and specificity for chymotrypsin were 64% and 89%, respectively [46].

Trypsinogen levels

For the diagnosis of pancreatic insufficiency, serum pancreatic enzymes are not considered to be an adequate test. However, the only efficient marker assessment for EPI is serum trypsinogen. Pancreatic steatorrhoea, an advanced EPI, was detectable at serum concentrations < 20 ng/ml [48].

Breath test

The breath test evaluates the breakdown of fat by pancreatic lipase. This test depends on calculating the rate at which 13 CO_2 is detected in the breath during 6 hours after the oral intake of 250 mg of triglycerides labelled with 13 C. According to the level of pancreatic lipase activity, the substrates are hydrolysed. Samples of your breath can show how products are absorbed and metabolised. The samples are obtained by blowing into collection tubes, and the amount of 13 CO_2 exhaled is measured. While it can be employed for EPI diagnosis, this method, despite having similar sensitivity to faecal elastase, is not widely accessible and has not received approval in the United States [49]. For diagnosing EPI, the test demonstrates sensitivity, specificity, and an overall accuracy of 92.9%, 91.7%, and 92.3%, respectively [50]. Direct pancreatic function tests are the most precise diagnostic methods for identifying EPI in individuals.

Direct tests

Direct tests assess the secretory output directly and, despite their high sensitivity, are intrusive, time-consuming, expensive, and useless for gauging the effectiveness of PERT. Additionally, they provide significant result diversity, are not generally available, and are not standardised due to a lack of agreement on the technique.

Direct pancreatic function test

To quantify the pancreas' secretory content (enzymes and bicarbonate), they first stimulate it with hormonal secretagogues before collecting duodenal fluid. Secretin and CCK have both been used to increase pancreatic output.

In the typical direct pancreatic function test, a double-lumen gastroduodenal (Dreiling) collection tube is introduced with the aid of fluoroscopy. Synthetic secretin is first given as a test dosage of 0.2 mcg, and then the complete dosage of 0.2 grams *per* kilogram is administered as a rapid intravenous injection. At 0, 15, 30, 45, and 60 minutes following secretin administration, duodenal aspirates are taken. Volume, concentration, and bicarbonate production of the fluid are all analysed. In all 4 samples, a bicarbonate concentration of 80 mEq/l is indicative of EPI. A peak bicarbonate concentration of 50 mEq/l indicates severe EPI. Due to the poor collection of duodenal fluid, bicarbonate output and fluid volume are not considered dependable indicators [51]. Studies evaluating the sensitivity of direct pancreatic function testing in individuals with confirmed cholangiopancreatography (CP) on imaging have shown a range of 72–94% [52].

Endoscopic pancreatic function test

The endoscopic pancreatic function test has replaced the previous secretin-CCK stimulation test. It assesses pancreatic secretion by measuring bicarbonate concentration in duodenal samples obtained through endoscopy 45 to 60 minutes after the administration of intravenous secretin. It is a very sensitive test that can be utilised in circumstances where the diagnosis of EPI is uncertain [53]. Endoscopic secretin pancreas function testing for the diagnosis of CP demonstrated sensitivi-

Table I. Diagnostic tests for exocrine pancreatic insufficiency, their significance, sensitivity, and specificity

Diagnostic test	Description	Sensitivity (%)	Specificity (%)
Indirect tests for EPI			
Faecal fat measurement	Gold standard test for EPI diagnosis; measures faecal fat and fat absorption	76–94	95–99
Faecal elastase levels	Measures elastase-1 in faeces; concentration $< 200\ \mu g/g$ is considered abnormal	63–100	93
Chymotrypsin levels	Measures chymotrypsin in faecal samples; lower specificity compared to elastase	64	89
Trypsinogen levels	Detects serum trypsinogen; detectable at concentrations < 20 ng/ml in advanced EPI	–	–
Breath test	Measures 13 CO_2 recovery rate after oral administration of 13c-marked triglycerides	92.90	91.70
Direct tests for EPI			
Direct pancreatic function test	Stimulates pancreas with secretagogues and collects duodenal fluid; measures bicarbonate production	72–94	–
ePFT	Measures bicarbonate concentration in duodenal samples after secretin injection *via* endoscopy	86	67
MRCP	Examines pancreatic ductal system; enhanced with secretin injection for better exocrine function assessment	69	90

ePFT – endoscopic pancreatic function test, EPI – exocrine pancreatic insufficiency, MRCP – magnetic resonance cholangiopancreatography

ty and specificity of 86% and 67%, respectively, in retrospective research with 25 CP patients [54]. Assessing nutritional deficiencies, which includes testing for magnesium, fat-soluble vitamins (A, E, D, and K), and lipoproteins, can aid in both diagnosing EPI and monitoring treatment progress [55].

A summary of diagnostic tests, their importance, and their sensitivity and specificity for EPI is given in Table I.

Imaging techniques

Magnetic resonance cholangiopancreatography (MRCP) is frequently used as a secondary imaging technique to examine the pancreatic ductal system in CP patients. When combined with a secretin injection (S-MRCP), MRCP not only outperforms CT scans at detecting minute ductal alterations, but it also allows for a partially quantitative assessment of pancreatic exocrine function. The most effective structural examination to assess EPI would be secretin-induced magnetic resonance cholangiopancreatography (S-MRCP). It could potentially serve as an indicator of pancreatic function [56]. S-MRCP has a sensitivity and specificity of 69% and 90%, respectively, for the diagnosis of EPI [57].

Effects and complications of exocrine pancreatic insufficiency

Due to EPI's protracted subclinical course, patients with diseases like Chronic Pancreatitis can go without receiving a diagnosis. Symptoms of EPI, like steatorrhea, diarrhoea, weight loss, signs of vitamin deficiency, abdominal swelling, and gas, can significantly diminish a patient's quality of life and likelihood of survival. Nutritional deficits of fat-soluble vitamins may result in further lifetime issues like osteoporosis, which causes bones to weaken and become less able to support weight, anaemia, and haemorrhagic disorders. Osteopenia or osteopenia are present in over 65% of people with chronic pancreatitis. Poorer quality of life as a result of ongoing symptoms and diminished capacity for employment, with accompanying financial difficulties, and increased morbidity and mortality brought on by cardiovascular issues and malnutrition [58].

Management of exocrine pancreatic insufficiency

Treatment for EPI occurring in systemic conditions such as chronic pancreatitis includes the following steps.

Lifestyle modifications

It is presumed historically that a low-fat diet could be helpful to reduce steatorrhoea. However, due to the presence of fat-soluble vitamin deficiencies, this presumption has been eradicated.

Certain dietary modifications are beneficial in the optimisation of the symptoms of EPI and nutritional deficiencies. Advice for adequate calorie intake

and healthy fat content should be part of a diet consultation. Large, high-calorie meals are typically not as well accepted as smaller, more frequent meals. Patients with EPI frequently have deficiencies in fat-soluble vitamins; hence. vitamin supplementation therapy should be administered as needed. Although there is no obvious nutritional advantage of medium-chain triglycerides over long-chain triglycerides, they can be tried in patients who are unable to gain or maintain a sufficient body weight despite increasing their energy consumption.

All patients with alcohol-related CP should be encouraged to abstain from alcohol. Alcohol withdrawal has been shown to have positive effects on overall health, as well as slowing the further decline of pancreatic exocrine function. Smoking is associated with a higher risk of reduced pancreatic exocrine function in conditions like chronic pancreatitis, AP, and pancreatic cancer, as indicated by the findings of an endoscopic pancreatic function test. In individuals with chronic pancreatitis, persistent smoking has been connected to an accelerated development of calcification. Smoking cessation needs to be promoted for all CP patients, EPI or not [59].

Therapeutic management

For patients with EPI, pancreatic digestive enzymes can be taken orally along with meals to make up for the lack of endogenous enzyme release. Pancreatic lipase, an extract from the swine pancreas, is used in contemporary pancreatic enzyme preparations and is delivered as enteric-coated mini microspheres. Pancreatic enzyme replacement therapy is now more commonly thought of as a means to address maldigestion in CP patients rather than a way to reduce diarrhoea. The Australasian Pancreatic Club's recommendations for PERT suggest that its main objective is to eradicate maldigestion. The goal of PERT is to increase lipolytic activity to match the quantity of fat consumed at each meal.

As a result, larger, higher-fat meals require higher doses, but snacks and leaner meals only need smaller doses. A regular intake of fat-soluble vitamin supplements combined with other antioxidants, like vitamin C and selenium, can assist in curing an inflamed pancreas or one under metabolic stress [60, 61].

Novel treatment modalities

Several *CFTR* gene mutations contribute to the hereditary condition CF, which more frequently affects children and young adults and causes pancreas damage and EPI due to CFTR dysfunction. Epigenetic, genetic, environmental, and socioeconomic factors all have an impact on the prognosis of CF patients. There are 5 categories of CFTR modulators, which include potentiators, correctors, stabilisers, read-through agents, and amplifiers, each functioning based on their unique mechanisms. The usage of ivacaftor, lumacaftor-ivacaftor, tezacaftor-ivacaftor, and elexacaftor-tezacaftor-ivacaftor entails the use of 4 CFTR modulators. To restore CFTR function in the case of the most common CFTR mutation, F508del, a combination of 2 modulator medications – a corrector and a potentiator – is required. In individuals with a specific mutation, such as ivacaftor, a CFTR potentiator, enhances CFTR protein activity on the surface of epithelial cells. This treatment seems to slow down the progression of the disease, and it can potentially enhance and partially restore the function of the exocrine pancreas in certain patients, which may necessitate adjustments in enzyme doses.

Additionally, besides CFTR modulators, emerging therapeutic approaches for CF and EPI include nucleotide and cell-based therapies like mRNA correction or replacement, gene transfer, gene editing, and stem cell replacement [62].

Figure 2 gives an illustrative summary of the symptoms and treatment of EPI.

Exocrine pancreatic insufficiency and micronutrient deficiencies

People with exocrine pancreatic insufficiency, insufficient nutrient consumption, and malnutrition along with malabsorption lead to important micronutrient deficits, specifically calcium, magnesium, zinc, and vitamins A, D, E, and K. Remembering that these individuals often encounter limited absorption of key minerals due to their compromised pancreatic enzymes is crucial. This signifies the importance of pancreatic enzyme replacement in EPI patients [63]. A decline in the secretion and synthesis of lipase, accompanied by an impeding of unobstructed pancreatic duct flow, leads to aberrant gastrointestinal motility [64].

Collaborative care for comprehensive disease management

Recent studies shed light on the use of human pluripotent stem cells to treat exopancreatic insufficiency. Creating pancreatic exocrine cells from human pluripotent stem cells offers the ability to ameliorate the absence of pancreatic enzymes and bicarbonate in PEI patients [65].

Novel therapies for preventing or treating exocrine pancreatic insufficiency in systemic diseases

PARP in exopancreatic insufficiency

Studies have shown that PARP enzymes are related to the development and progression of exopancreatic

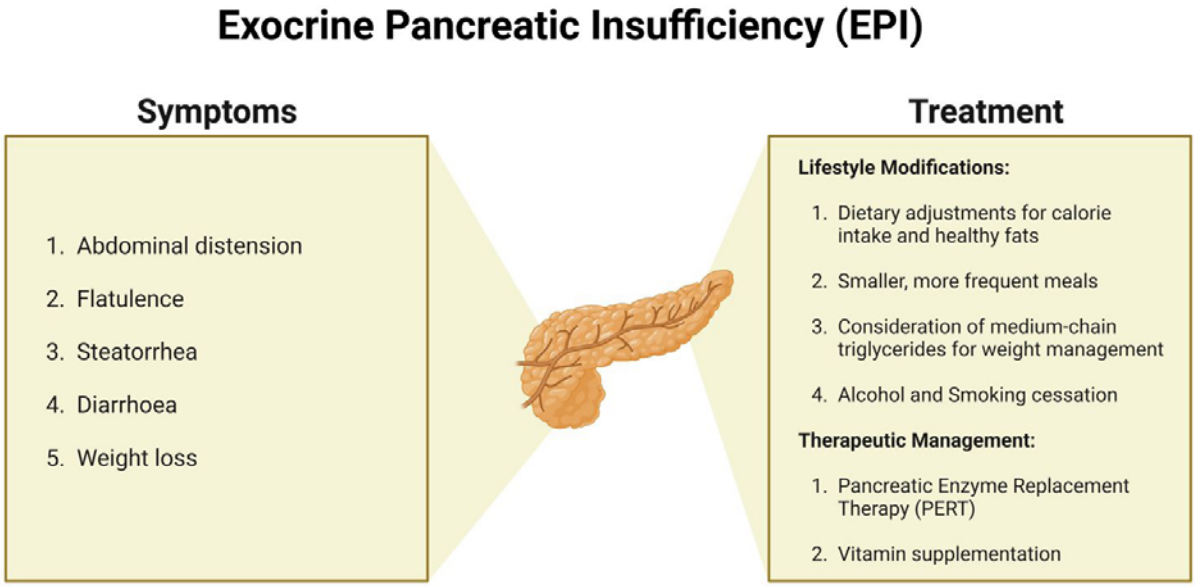

Fig. 2. A summary of symptoms and treatment of exocrine pancreatic insufficiency

insufficiencies such as pancreatic cancer and chronic pancreatitis [66].

Machine learning in diagnosing and evaluating exocrine pancreatic insufficiency

Machine learning can help diagnose individuals with EPI. Researchers can construct a machine learning model to accurately anticipate the probability of patients having EPI based on diverse factors, including the presence or absence of diagnosis codes associated with digestive and pancreatic conditions. This can augment the comprehension of EPI's aetiology and facilitate the identification of patients for potential diagnosis and treatment [67]. The use of machine learning algorithms and the development of models are aided by adjusting to the subject data, which allows for learning and increased predictive accuracy. The adoption of these procedures can produce a meaningful understanding of the patient's medical condition and outcomes.

Future directions for exocrine pancreatic insufficiency research and treatment

Physician and patient education is required to enhance knowledge and comprehension of EPI, as diagnostic testing for EPI is seldom performed and PERT is utilised infrequently and at insufficient doses [2]. More research is needed to enhance access to suitable therapy, and identify barriers to adopting PERT, for example, cost and insurance coverage. More research is needed to assess the accuracy and inaccuracy of diagnostic tests for EPI, including faecal elastase and breath tests, and to enhance diagnostic skills.

Additionally, future research should concentrate on comprehending the intricate interactions between systemic illnesses and the development of EPI. Future studies should focus on determining how micronutrient shortages affect EPI in systemic disorders, and on creating focused therapies to address these deficiencies. Further disease management techniques can benefit from investigating the efficiency of collaborative care models in treating micronutrient deficiencies in systemic disorders and managing EPI.

Figure 3 explores some of the potential future directions in the research and treatment of EPI.

Conclusions

According to this literature review, it can be concluded that there is a complicated connection between systemic diseases and exocrine pancreatic insufficiency, which might emerge from them. Exocrine pancreatic insufficiency can cause fat-soluble micronutrient deficiencies, which can lead to several complications. Collaborative care for complete illness management is one strategy to address these nutritional shortages in EPI patients. To achieve optimal intake of vital micronutrients, specific interventions could include dietary adjustments and supplementation.

Deficiencies can be addressed with the use of routine micronutrient assessment and supplemental adjustment. In extreme situations, intravenous delivery of certain micronutrients may be required. In micronutrient-deficient EPI, patients need personalised treatment, which can be done by collaboration of the healthcare team including a nutritionist and gastroenterologist.

Disclosures

1. Institutional review board statement: Not applicable.

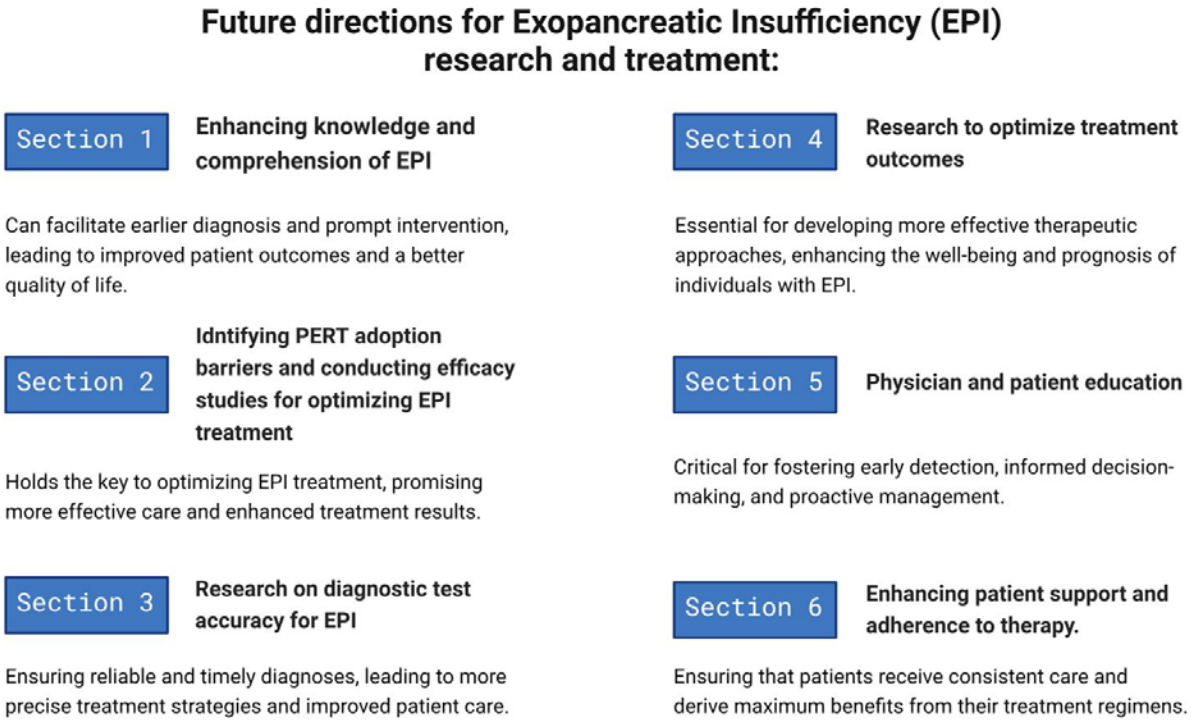

Fig. 3. A summary of potential future directions for exocrine pancreatic insufficiency research and treatment

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