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Review Article

Review Article

Etiologies of exocrine pancreatic insufficiency

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Abstract

Exocrine pancreatic insufficiency (EPI) is a major cause of maldigestion and malnutrition, resulting from primary pancreatic diseases or other conditions. As the prevalence of EPI continues to rise, accurate identification of its etiology has become critical for the diagnosis and treatment of pancreatic secretory insufficiency. EPI can result from both pancreatic and non-pancreatic disorders. Pancreatic disorders include acute and chronic pancreatitis, pancreatic tumors, cystic fibrosis, procedures that involve pancreatic resection, and other rare causes. Non-pancreatic disorders of EPI include diabetes mellitus, celiac disease, inflammatory bowel disease, gastrointestinal and esophagectomy surgery, as well as advanced patient age. This review aims to provide a comprehensive analysis of the literature on EPI etiology, with a thorough overview to support its consideration as a potential diagnosis.

Keywords: exocrine pancreatic insufficiency; etiologies of EPI; causes in pancreatic disorders; causes in non-pancreatic disorders

Introduction

Exocrine pancreatic insufficiency (EPI) is a syndrome in which pancreatic exocrine dysfunction and digestive function are impaired due to various reasons. Malabsorption occurs when pancreatic digestive enzyme levels in the duodenum drop by 5%–10% below the normal enzyme output, resulting in symptoms, such as steatorrhea (fatty stools), weight loss, abdominal pain, and other digestive issues [1–3]. The symptoms of EPI include irritable bowel syndrome [4], celiac disease [5], inflammatory bowel disease (IBD) [6], Zollinger–Ellison syndrome [7], and small intestinal bacterial overgrowth [8, 9]. The persistence of symptoms impairs the quality of life of patients [10–12].

The diagnosis of EPI currently relies on a comprehensive assessment of dyspeptic/malabsorption symptoms, indicators of malnutrition, and the results of non-invasive pancreatic tests. The combination of any two of these criteria allows a definitive diagnosis and the initiation of appropriate treatment [10]. Quantitative methods for assessing pancreatic exocrine secretion can be categorized into direct and indirect approaches. Direct methods are highly sensitive and specific but are invasive, costly, and time-consuming, such as the collection of duodenal fluid following secretin or cholecystokinin stimulation via probes or endoscopy. Indirect methods, while less sensitive, are more cost-effective and easier to implement [11, 13]. The fecal elastase test is the most widely used non-invasive indirect method in routine clinical practice, requiring one collection of fecal samples and allowing the continuation of pancreatic enzyme replacement therapy (PERT). There is no consensus on the cut-off point for EPI diagnosis, but a value of $<200\,\mu g/g$ is commonly considered indicative. Lower concentrations suggest a higher likelihood of EPI, with concentrations of $<15\,\mu g/g$ demonstrating high sensitivity and specificity. Conversely, concentrations of $>500\,\mu g/g$ effectively rule out the diagnosis of EPI [14]. EPI can be caused by both pancreatic and non-pancreatic disorders. Pancreatic disorders include chronic pancreatitis (CP), acute pancreatitis, pancreatic tumors, cystic fibrosis, pancreatectomy, benign main pancreatic duct obstruction, and other less common causes [15–21]. Non-pancreatic disorders include diabetes mellitus, celiac disease, IBD, gastrointestinal surgery, and esophagectomy surgery [13, 20, 22–24].

The course of EPI is often insidious, with early diagnosis frequently overlooked. This review summarizes the etiology of EPI, aiming to assist clinicians in recognizing potential instances of EPI, thereby enabling early diagnosis and timely treatment to ultimately improve patients' quality of life and nutritional status.

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Pancreatic disorders

Acute pancreatitis and EPI

Acute pancreatitis is one of the most common causes of EPI. Acute pancreatitis refers to a condition that is characterized by the abnormal activation of pancreatic enzymes, leading to autodigestion of the pancreas and surrounding organs, primarily manifesting as local inflammatory response of the pancreas, and potentially resulting in organ dysfunction. Acute pancreatitis is typically caused by stones, alcohol consumption, or endoscopic retrograde cholangiopancreatography. This leads to pathological changes in cells and cellular organelles, ultimately triggering local inflammation that results in EPI. The global incidence of acute pancreatitis is ~34 cases per 100,000 people [25]. The prevalence of EPI after acute pancreatitis is 29% [26]. According to a meta-analysis of 32 studies involving 1,495 patients, the overall occurrence rate of EPI was found to be 19% after mild acute pancreatitis [27]. Relevant study indicates that approximately one-third of patients with severe acute pancreatitis develop EPI—a proportion that is significantly higher than that observed in patients with mild acute pancreatitis who develop EPI [28]. Over time, the incidence of EPI decreased, suggesting gradual recoveries of pancreatic exocrine function in patients who underwent surgery for severe acute pancreatitis. It should be noted that the risk of developing EPI is higher in cases of alcoholic pancreatitis or necrotizing pancreatitis than in biliary pancreatitis or other causes of acute pancreatitis [27]. Possible mechanisms behind EPI after acute pancreatitis may involve (i) obstruction of the pancreatic juice outflow tract, (ii) impaired pancreatic enzymes synthesis, and (iii) reduced trypsin production stimulation. EPI could result from severe acute pancreatitis, in which extensive pancreatic necrosis causes loss of pancreatic parenchyma and function, as demonstrated by one study (Figure 1) [29]. Meanwhile, EPI could develop in cases of mild acute pancreatitis due to reduced enzyme secretion from pancreatic cells and obstruction of the pancreatic duct [29]. Regular monitoring of patients is essential, as both exocrine and endocrine pancreatic insufficiency can arise after acute pancreatitis [30]. Endocrine pancreatic insufficiency can also contribute to EPI, which will be discussed in later sections. The co-occurrence of Acute pancreatitis and EPI is often overlooked, with limited research available and significant under-recognition among clinicians. This leads to malnutrition and a significant decline in quality of life post-discharge, severely impacting patients' overall well-being [31]. Therefore, both severe and mild acute pancreatitis require monitoring for EPI and should be treated actively.

CP and EPI

CP is a progressive chronic inflammatory disease of the pancreatic tissue, primarily caused by genetic and environmental factors. The pathological features include atrophy, destruction of pancreatic acinar cells, and interstitial fibrosis [32]. Clinically, it is characterized by both exocrine and endocrine pancreatic insufficiency and recurrent upper abdominal pain, and may be accompanied by pancreatic duct stones, pancreatic parenchymal calcification, ductal stenosis, irregular ductal dilation, and pseudocyst formation. The disease is persistent and refractory, often requiring lifelong treatment, which significantly impairs the quality of life for patients. CP can be classified into several categories based on its etiological factors: chronic calcific pancreatitis, which is caused by alcohol, genetics, hyperlipidemia, hypercalcemia, idiopathic, or drug factors; chronic obstructive pancreatitis, which is caused by duodenal papillary stenosis, pancreas divisum, pancreatic injury, and other factors; chronic inflammatory pancreatitis, which is caused by vascular or diabetic factors; and autoimmune pancreatitis, which is caused by sclerosing cholangitis, primary biliary cirrhosis, or Sjögren's syndrome. Research reports indicate that 42%–99% of patients with CP suffer from EPI [33–37]. Growing research is uncovering the underlying causes of EPI and CP [18, 38, 39]. Chronic episodes of inflammation result in significant tissue fibrosis, causing a decline in pancreatic parenchyma and reduced secretion of enzymes from the pancreas.

Five to 10 years after the development of CP, severe EPI may occur [40]. CP combined with EPI reduces fat absorption, including essential fatty acids, and the absorption of fat-soluble vitamins A, D, E, and K, as well as calcium, magnesium, zinc, thiamine, and folate [41]. Consequently, CP patients may exhibit various nutritional deficiencies and clinical symptoms due to the degree of EPI and dietary factors. Severe EPI symptoms, such as steatorrhea, diarrhea, flatulence, and weight loss, may occur when fecal fat excretion exceeds 7 g/d [42]. Untreated severe EPI and prolonged malnutrition can

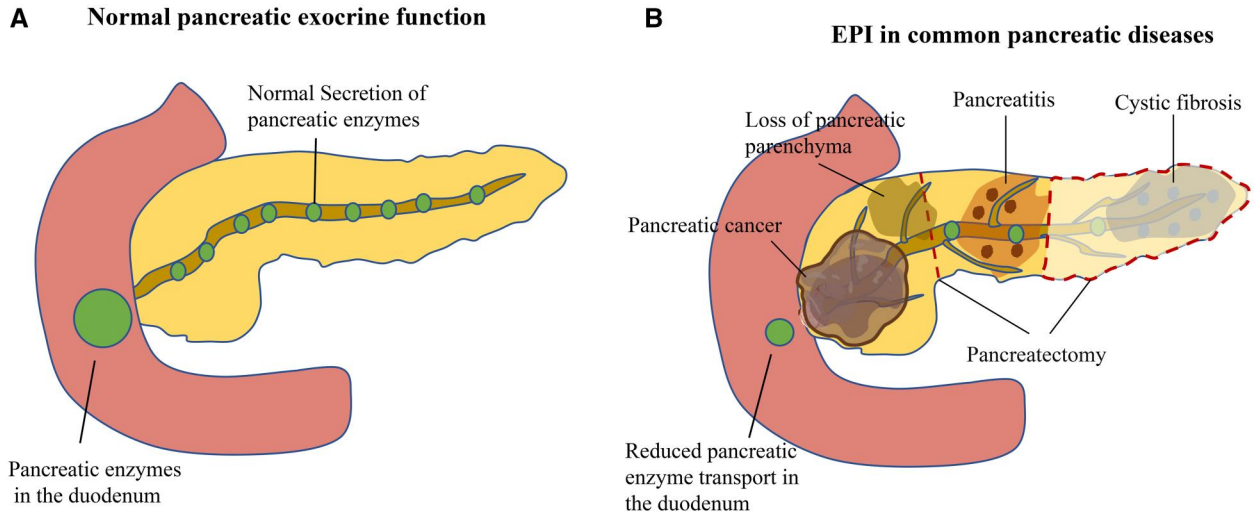

Figure 1. Pathological changes in EPI due to pancreatic diseases. (A) Normal exocrine pancreatic function, illustrating a non-obstructed state. (B) Schematic representation of EPI mechanisms in common pancreatic diseases (including pancreatitis, cystic fibrosis, pancreatic cancer, pancreatic resection, and loss of pancreatic parenchyma).

lead to other health issues [43], increasing the risk of cardiovascular diseases and infections [44, 45].

Tumor-induced EPI

Malnutrition in pancreatic cancer patients is significantly influenced by EPI [46]. Tumor-induced EPI can arise from the primary pancreatic duct obstruction, gland fibrosis, and the depletion of pancreatic exocrine tissue [15]. Tumor-induced EPI leads to reduced pancreatic enzymes production or hindered pancreatic enzymes transportation to the duodenum (Figure 1). The exocrine secretion volume in patients with pancreatic head cancer is significantly lower than that in patients with pancreatic body or tail cancer [47], primarily due to the degree of pancreatic duct obstruction and the amount of pancreatic tissue resected during surgery [48]. The degree of pancreatic blockage increases in direct proportion to the extent of obstructions in the pancreatic duct. Reports indicate that 66%–92% of pancreatic cancer patients experience dyspepsia and inadequate enzyme production [49–51]. Among these patients, ~75% experience fat malabsorption, while protein malabsorption affects 50% of patients [52]. These data confirm that EPI is prevalent in unresectable pancreatic cancer.

Cystic fibrosis of pancreas and EPI

Cystic fibrosis (CF) is a genetic disorder that is caused by mutations in the gene that encodes the chloride ion channel, leading to dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) and affecting multiple body systems [19]. The CFTR protein transports bicarbonate and chloride across the top layer of secretory epithelia, particularly in the sweat gland, airway, gastrointestinal tract, and pancreas. CFTR-mediated chloride and bicarbonate in pancreatic ducts alkalinizes the ductal fluid, neutralizes peptic acid, and optimizes pH for digestive enzyme activity [53]. The CFTR malfunction gene leads to a reduction in the volume of fluid in the cavity and a decrease in the pH value, as well as the formation of protein deposits in the duct cavity and the impairment of normal acinar cell function. Blocked ducts cause a buildup of pancreatic proteins, elevating blood proteins levels such as trypsinogen. Pancreatic destruction is ultimately caused by the persistence of duct obstruction, fibrosis, inflammation, and infiltration of adipose tissue [54]. Waters *et al.* found that 63% of infants with CF had exocrine insufficiency at birth and nearly 20% with pancreatic sufficiency developed insufficiency within the following 36 months [55].

A study was carried out on 1,000 CF patients and compared the results of untreated EPI over a long term. The study found that patients on a high-fat diet and higher doses of external pancreatic enzymes had better outcomes compared with those who were on a low-fat diet with a low pancreatic enzyme regimen [56]. All individuals who are diagnosed with CF, regardless of age, should undergo testing for pancreatic insufficiency as soon as possible [57, 58]. The management of pancreatic insufficiency in CF patients requires lifelong treatment. The cornerstone of therapy involves providing age-appropriate education throughout the lifespan, emphasizing the importance of good nutrition in extending CF survival and the effective use of PERT.

Post-pancreatic surgery and EPI

Figure 1 illustrates that EPI and dyspepsia can arise from alterations in the anatomical composition and physiological conditions subsequently to pancreatic surgery. Pancreatic tissue loss, cholecystokinin production reduction due to duodenectomy, and asynchronous gastric and pancreatic functions are the key factors that contribute to post-operative EPI [59, 60]. In a prospective study of 227 pancreatic surgery patients, 94 who had no preoperative exocrine dysfunction developed EPI after surgery [61]. Based on a study that involved 10 patients with malignant periampullary tumors who underwent Whipple surgery, the assessment of exocrine pancreatic function was conducted ≥6 months post-operatively [62]. The findings showed that all patients had significant EPI, with six having fecal elastase-1 of <15 μg/g. Furthermore, there were also findings of deficiencies in vitamins D, A, E, zinc, selenium, and iron, which are essential fat-soluble vitamins and trace elements. Matsumoto *et al.* analysed data from 138 patients who underwent pancreaticoduodenectomy that was performed by the same surgeon [50]. Of these patients, 94% underwent a pylorus-preserving pancreaticoduodenectomy procedure, with most developing EPI within a 1-year follow-up. A study that involved 133 patients post-pancreatic surgery revealed variations in the incidence of EPI among patients with different disease types and surgical procedures. Specifically, 94% of the patients who underwent surgery for pancreatitis and 89% of those who underwent surgery for malignant pancreatic tumors developed EPI post-operatively. EPI occurred in all patients who underwent total pancreatectomy and in the majority of those who underwent partial pancreatectomy, indicating a significant impact of post-operative pancreatic remnant volume on the development of EPI [63].

The pancreas has strong compensatory mechanisms. Fat leakage occurs exclusively in patients who undergo pancreatic surgery and whose intestinal lipase levels drop to <10% of normal levels. Hence, assessing EPI solely on the presence of steatorrhea is not reliable. EPI can manifest before and after pancreatic surgery, with varying underlying factors. Although there is limited research on EPI in patients who have undergone pancreatic surgery, the connection between EPI and post-operative outcomes in pancreatic surgery patients is undeniable. Large-scale, prospective, multicenter studies are required to collect patients' clinical and laboratory data both before and after surgery. In conclusion, EPI is a frequently overlooked complication of pancreatic surgery that significantly affects both the quality of life and life expectancy of patients.

Other causes in pancreatic disorders and EPI

Other causes of EPI in pancreatic disorders include Shwachman–Diamond syndrome (SDS), Johanson–Blizzard syndrome, and Pearson syndrome. SDS is a rare autosomal recessive genetic disorder and the second-most common genetic factor of EPI [64]. SDS is a disease that affects multiple systems, with patients typically presenting with congenital abnormalities, bone marrow defects, EPI, and short stature. However, the clinical symptoms of SDS can also affect other systems, such as cardiovascular and gastrointestinal systems, among others [65]. In some cases, the disease leads to EPI as acinar cells are replaced by large amounts of fat [66]. Two-thirds of patients exhibit dysplasia and, even with sufficient PERT, the dysplasia generally does not improve. Over time, individuals who are diagnosed with SDS tend to develop myelodysplasia and leukemia. Frequent infections often lead to mortality. Treatment for EPI that is caused by other diseases is not specific. It involves oral administration of exogenous pancreatic enzyme preparations, fat-soluble vitamins (A, D, E, K), and trace elements, as well as the use of low-fat formula milk, to improve digestive function and nutritional status [67]. Nonetheless, there are still few reports on the association between SDS and EPI, and further research is needed to understand its pathogenesis.

Johanson–Blizzard syndrome is caused by UBR1 gene mutations and is an uncommon disorder with autosomal recessive inheritance, which results in the destruction of pancreatic acini

during fetal development. Common clinical symptoms include EPI, multiple birth defects, underactive thyroid, and developmental delays [68]. It is suggested that mutated UBR1 may disrupt the breakdown of proteins and cause the accumulation of unfolded proteins in the endoplasmic reticulum, which in turn causes endoplasmic reticulum stress. In Johanson–Blizzard syndrome patients, the quantitative tests for pancreatic function show a notable decrease in enzyme secretion, while anion outputs are reduced and fluid preservation is observed [69]. Furthermore, the serum trypsinogen concentration is markedly below normal ranges.

Pearson syndrome, which was first reported in 1979 by Pearson, is a rare disorder that is caused by defects in oxidative phosphorylation due to mutations in mitochondrial DNA72. The primary clinical features of Pearson syndrome include EPI, resistant sideroblastic anemia, and the vacuolization of bone marrow precursors. Infants with Pearson syndrome universally exhibit EPI. The pancreas of the patients exhibits histopathological features that include the absence of acinar cells, which are replaced by connective tissue and blood vessels. Nevertheless, assessments of pancreatic function have revealed reduced acinar activity and compromised secretion of fluids and electrolytes [70, 71].

Non-pancreatic disorders

Non-pancreatic conditions that contribute to an increased risk of developing EPI encompass diabetes mellitus, celiac disease, IBD, gastrointestinal surgery, esophagectomy surgery, and advanced age of the patient.

Diabetes and EPI

Diabetes, which is closely related to the pancreatic exocrine and endocrine systems, is a significant risk factor for EPI. Endocrine pathology causes damage to exocrine function and vice versa. When using fecal elastase-1 as the diagnostic criterion, the probability of EPI occurrence is significantly higher in type 1 diabetes patients compared with type 2 diabetes patients. The measurement results from fecal elastase-1 indicate that the prevalence of EPI among patients with type 1 diabetes is an average of 40% whereas, among patients with type 2 diabetes, it is an average of 27% [72]. The presence of exocrine pancreatic dysfunction has been linked to all forms of diabetes [73]. The potential etiologies of EPI in both type 1 and type 2 diabetes are diverse, including (i) autoimmune destruction of pancreatic cells, (ii) absence of the nourishing impact of insulin on acinar cells, (iii) impairment of microvessels in exocrine tissues, and (iv) damage to the enteropancreatic reflex resulting from diabetic neuropathy (Figure 2) [22, 60]. In patients with diabetes, microangiopathy may result in a reduction in blood flow to the pancreas, which can lead to arterial damage and, ultimately, the development of pancreatic fibrosis [74].

Celiac disease and EPI

Celiac disease (CD) is a primary malabsorption syndrome that is characterized by small intestinal mucosal lesions caused by intolerance to gluten (gliadin). Its main symptoms include chronic diarrhea, abdominal pain, anemia, edema, and weight loss. The underlying mechanisms of EPI in CD remain poorly understood and appear to involve multiple factors; the worldwide incidence of CD is 1%–2% [75, 76]. The adverse response of the atrophic intestinal mucosa epithelium to the intestine contents after eating could be a primary mechanism. This response alters the production, retention, and release of gastrin and cholecystokinin, which are powerful triggers for pancreatic secretion. In a study on the structure of the pancreatic parenchyma via magnetic resonance imaging (MRI), no morphological abnormalities were detected in individuals with EPI who had CD, indicating that the cause of EPI is a functional deficiency in the secretion of pancreatic enzymes [77]. Another study that was conducted by Leeds *et al.* at a single center found that low levels of fecal elastase were frequently observed in CD patients with chronic diarrhea, which further supports the presence of EPI [78]. CD is identified by both gastrointestinal and non-gastrointestinal symptoms, including EPI, which is observed in several individuals with CD. Some patients with CD experienced EPI, which was usually temporary and resolved by adopting a gluten-free diet [79, 80]. According to diagnostic tests, it was found that 12% of patients with CD and chronic diarrhea, who were on a gluten-free diet, had EPI [81]. Some studies have shown that the prevalence of EPI in untreated patients with chronic diarrhea ranges from 4% to 15.6%. The significant variation in these figures may be attributed to the small sample sizes [77, 78, 82].

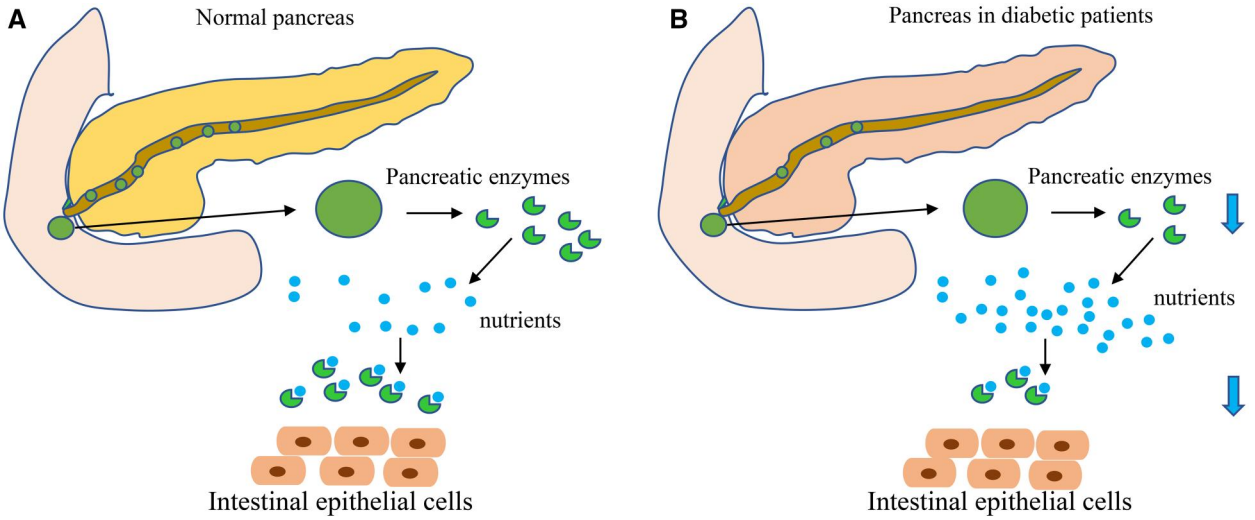

Figure 2. Mechanisms of EPI in diabetic patients. (A) Normal pancreatic tissue and the normal state of exocrine enzymes. (B) Significant reduction in exocrine enzymes in diabetic patients.

IBD and EPI

Crohn's disease and ulcer colitis (UC) are both IBD, which are chronic immune-mediated gastrointestinal conditions that are characterized by recurrent inflammation of the gastrointestinal tract [83]. These conditions arise due to an abnormal immune reaction and an inability to tolerate the normal bacteria in the intestines. According to autopsy studies, pancreatic lesions were present in 38% of patients with Crohn's disease and 53% of patients with UC. However, there was no historical indication of pancreatitis [84]. Research has shown that patients with IBD have a higher risk of developing EPI compared with the general population. Specifically, ~14% of patients with CD and 22% of patients with UC have fecal elastase levels that are ≤200 μg/g, indicating that they may have experienced EPI [85]. Potential causes of EPI in Crohn's disease include increased production of pancreatic autoantibodies, reflux of the duodenum, and decreased secretion of hormones. Around 33% of individuals with Crohn's disease have autoantibodies that target pancreatic elements [86], suggesting that exocrine dysfunction that leads to EPI may be caused by immune-mediated mechanisms. In patients with Crohn's disease and UC, there may be alterations in the pancreatic duct that could impede the flow of enzyme secretion [87]. In conclusion, the secretion of intestinal hormones may be reduced due to scarring or inflammation, resulting in a lack of stimulation for the pancreas [88]. UC and Crohn's disease are important causes of EPI in gastrointestinal diseases.

Gastrointestinal surgery and EPI

Secondary EPI refers to the condition in which EPI occurs following non-pancreatic gastrointestinal surgeries despite the preservation of pancreatic parenchyma. Gastrointestinal surgery can disrupt the complex series of processes that regulate normal digestion and absorption. Approximately 80% of patients experience maldigestion after undergoing surgery on the gastrointestinal tract, with EPI potentially playing a role in the development of this condition [59]. A study revealed that nearly all patients experienced severe EPI following complete gastrectomy [89]. All individuals who had undergone a partial gastrectomy underwent steatorrhea [90]. A study evaluated the efficacy of PERT in 52 hospitalized patients who developed severe steatorrhea following total gastrectomy. The patients underwent a 14-day treatment with either pancreatic enzymes or a placebo. The results indicated that PERT did not produce significant differences between the placebo group and the pancreatic enzyme treatment group in terms of bowel habits, body mass index, or fat malabsorption [91]. Epigastric and modified pancreatic enzymes and levels of gastrointestinal hormones have been observed following complete or partial gastrectomies [92, 93]. After the surgery, patients experienced a decrease in cholecystokinin secretion from the duodenum, leading to reduced pancreatic stimulation and contributing to EPI [59]. Some studies examined the exocrine pancreatic function and digestion process after restrictive and malabsorptive bariatric surgery. The findings showed that bariatric surgery significantly impacts digestion, with approximately one-third of patients developing EPI after the operation [92–94]. Certain mechanisms related to the pancreas also contribute to the development of EPI. In a study, 10 patients (16%) who underwent esophagectomy experienced weight loss and developed symptomatic EPI, including diarrhea and steatorrhea, indicating a connection between esophagectomy and EPI [95]. Under normal physiological conditions, the synthesis and secretion of exocrine pancreatic enzymes (such as lipase, amylase, and trypsin) by acinar cells are regulated by a complex interplay of neural, endocrine, and paracrine mechanisms in response to gastrointestinal distension and food intake. Factors such as reduced gastric capacity, vagal denervation, altered ductal dynamics, and the presence of pyloroplasty may influence the delivery of chyme to the duodenum and potentially play a role in this process. After esophageal resection, the exocrine pancreatic function may decline due to reduced hormonal and neural stimulation [95, 96]. Moreover, the alteration in anatomy after esophagectomy can lead to insufficient blending of chyme and pancreatic enzymes, further impacting exocrine pancreatic function [96, 97].

Other causes in non-pancreatic disorders and EPI

Other causes of EPI in non-pancreatic disorders include age-related exocrine pancreatic dysfunction, drug-induced EPI, as well as uncommon factors, such as diffuse pancreatic serous cystic neoplasm and chronic giardiasis. In a research that involved elderly participants (aged 60 to >79 years) without e diabetes or gastrointestinal disorders, the levels of fecal elastase-1 showed a negative correlation with age. Individuals who were >70 years of age had significantly lower fecal elastase levels than those in the control group who were aged 20–28 years [98].

It is reported that several drugs may have the potential to trigger EPI, especially immunosuppressive drugs. Examples include nivolumab [99], sorafenib [100], and pembrolizumab [101]. The possibility of EPI was taken into account due to the impact of adverse reactions on the functioning of the pancreas caused by immunotherapy medications.

Diffuse pancreatic serous cystic neoplasm has also been reported to cause EPI [21]. The major mechanism of EPI is obstruction of the pancreatic duct. A case report noted that chronic giardiasis is a rarely identified factor for EPI, though its exact mechanism remains unclear [102].

Summary

Many diseases can lead to the development of EPI and affect the recovery of the underlying condition, ultimately reducing the quality of life for patients. In most cases, EPI is associated with the pancreas itself, such as in acute or CP, pancreatic tumors or obstructions, and pancreatic surgery. Additionally, non-pancreatic diseases, including diabetes, IBD, and gastrointestinal surgery, may also trigger EPI. The diagnosis of EPI primarily relies on symptoms and the assessment of pancreatic exocrine function. Various methods are available for evaluating pancreatic exocrine function, with fecal elastase testing being the most commonly used. Due to its often insidious progression, EPI is frequently overlooked. This article has provided guidance for the identification and early diagnosis of EPI, enabling early detection and treatment, and ultimately improving patients' quality of life and nutritional status.

Authors' Contributions

C.T. and J.Z. contributed significantly to analysis and manuscript preparation; Y.S. and S.L. contributed to the conception of the study.

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Conflicts of Interest

The authors have declared that no competing interest exists.

References

1. DiMagno EP, Go VL, Summerskill WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 1973;**288**:813–5.
2. Whitcomb DC, Lehman GA, Vasileva G *et al.* Pancrelipase delayed-release capsules (CREON) for exocrine pancreatic insufficiency due to chronic pancreatitis or pancreatic surgery: a double-blind randomized trial. *Am J Gastroenterol* 2010;**105**:2276–86.
3. Fieker A, Philpott J, Armand M. Enzyme replacement therapy for pancreatic insufficiency: present and future. *Clin Exp Gastroenterol* 2011;**4**:55–73.
4. Ford AC, Lacy BE, Talley NJ. Irritable Bowel Syndrome. *N Engl J Med* 2017;**376**:2566–78.
5. Fasano A, Catassi C. Clinical practice. Celiac disease. *N Engl J Med* 2012;**367**:2419–26.
6. Ghishan FK, Kiela PR. Epithelial transport in inflammatory bowel diseases. *Inflamm Bowel Dis* 2014;**20**:1099–109.
7. Epelboym I, Mazeh H. Zollinger-Ellison syndrome: classical considerations and current controversies. *Oncologist* 2014;**19**:44–50.
8. Krajicek EJ, Hansel SL. Small Intestinal Bacterial Overgrowth: A Primary Care Review. *Mayo Clin Proc* 2016;**91**:1828–33.
9. Mearin F, Lacy BE, Chang L *et al.* Bowel disorders. *Gastroenterology* 2016. doi: 10.1053/j.gastro.2016.02.031.
10. Dominguez-Muñoz JE. Diagnosis and treatment of pancreatic exocrine insufficiency. *Curr Opin Gastroenterol* 2018;**34**:349–54.
11. Ghodeif AO, Azer SA, Pancreatic insufficiency. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing .:January 16, 2023.
12. Nikfarjam M, Wilson JS, Smith RC. Australasian Pancreatic Club Pancreatic Enzyme Replacement Therapy Guidelines Working Group. Diagnosis and management of pancreatic exocrine insufficiency. *Med J Aust* 2017;**207**:161–5.
13. Capurso G, Traini M, Piciucchi M *et al.* Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol* 2019;**12**:129–39.
14. Löhr JM, Dominguez-Munoz E, Rosendahl J *et al.*; HaPanEU/UEG Working Group. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J* 2017;**5**:153–99.
15. Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005;**54** Suppl 6:vi1–28.
16. Perbtani Y, Forsmark CE. Update on the diagnosis and management of exocrine pancreatic insufficiency. *F1000Res* 2019;**8**:8.
17. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol* 2013;**19**:7258–66.
18. Erchinger F, Engjom T, Dimcevski G *et al.*; Scandinavian Baltic Pancreatic Club. Exocrine pancreas insufficiency in chronic pancreatitis—Risk factors and associations with complications. A multicentre study of 1869 patients. *Pancreatology* 2022;**22**:374–80.
19. Elborn JS. Cystic fibrosis. *Lancet* 2016;**388**:2519–31.
20. Thomas AS, Huang Y, Kwon W *et al.* Prevalence and risk factors for pancreatic insufficiency after partial pancreatectomy. *J Gastrointest Surg* 2022;**26**:1425–35.
21. Conti Bellocchi MC, Mottes MC, Crino SF *et al.* Diffuse pancreatic serous cystic neoplasm: a rare cause of pancreatic insufficiency. *Pancreas* 2022;**51**:e83–5.
22. Mohapatra S, Majumder S, Smyrk TC *et al.* Diabetes mellitus is associated with an exocrine pancreatopathy: conclusions from a review of literature. *Pancreas* 2016;**45**:1104–10.
23. Softeland E, Poulsen JL, Starup-Linde J *et al.* Pancreatic exocrine insufficiency in diabetes mellitus—prevalence and characteristics. *Eur J Intern Med* 2019;**68**:18–22.
24. Powell-Brett S, de Liguori Carino N, Roberts K. Understanding pancreatic exocrine insufficiency and replacement therapy in pancreatic cancer. *Eur J Surg Oncol* 2021;**47**:539–44.
25. Petrov MS, Yadav D. Global epidemiology and holistic prevention of pancreatitis. *Nat Rev Gastroenterol Hepatol* 2019;**16**:175–84.
26. Das SL, Kennedy JI, Murphy R *et al.* Relationship between the exocrine and endocrine pancreas after acute pancreatitis. *World J Gastroenterol* 2014;**20**:17196–205.
27. Hollemans RA, Hallensleben NDL, Mager DJ *et al.*; Dutch Pancreatitis Study Group. Pancreatic exocrine insufficiency following acute pancreatitis: systematic review and study level meta-analysis. *Pancreatology* 2018;**18**:253–62.
28. Ru N, Zou WB, Wu H *et al.*; Chronic Pancreatitis Group of Chinese Medical Doctor Association. Chinese guidelines for the diagnosis and treatment of pancreatic exocrine insufficiency (2018 edition). *J Dig Dis* 2019;**20**:567–71.
29. Sand J, Nordback I. Acute pancreatitis: risk of recurrence and late consequences of the disease. *Nat Rev Gastroenterol Hepatol* 2009;**6**:470–7.
30. Vujasinovic M, Tepes B, Makuc J *et al.* Pancreatic exocrine insufficiency, diabetes mellitus and serum nutritional markers after acute pancreatitis. *World J Gastroenterol* 2014;**20**:18432–8.
31. Munigala S, Yadav D. Case-fatality from acute pancreatitis is decreasing but its population mortality shows little change. *Pancreatology* 2016;**16**:542–50.
32. Whitcomb DC, Frulloni L, Garg P *et al.* Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016;**16**:218–24.
33. Layer P, Yamamoto H, Kalthoff L *et al.* The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994;**107**:1481–7.
34. Ammann RW, Akovbiantz A, Largiader F *et al.* Course and outcome of chronic pancreatitis. Longitudinal study of a mixed medical-surgical series of 245 patients. *Gastroenterology* 1984;**86**:820–8.
35. Braganza JM, Hunt LP, Warwick F. Relationship between pancreatic exocrine function and ductal morphology in chronic pancreatitis. *Gastroenterology* 1982;**82**:1341–7.
36. Lankisch MR, Imoto M, Layer P *et al.* The effect of small amounts of alcohol on the clinical course of chronic pancreatitis. *Mayo Clin Proc* 2001;**76**:242–51.
37. Ammann RW, Buehler H, Muench R *et al.* Differences in the natural history of idiopathic (nonalcoholic) and alcoholic chronic pancreatitis. A comparative long-term study of 287 patients. *Pancreas* 1987;**2**:368–77.
38. Kempeneers MA, Ahmed Ali U, Issa Y *et al.*; Dutch Pancreatitis Study Group. Natural course and treatment of pancreatic

exocrine insufficiency in a nationwide cohort of chronic pancreatitis. *Pancreas* 2020;**49**:242–8.
39. de la Iglesia D, Vallejo-Senra N, Lopez-Lopez A *et al.* Pancreatic exocrine insufficiency and cardiovascular risk in patients with chronic pancreatitis: a prospective, longitudinal cohort study. *J Gastroenterol Hepatol* 2019;**34**:277–83.
40. Forsmark CE. Management of chronic pancreatitis. *Gastroenterology* 2013;**144**:1282–91.e3.
41. Duggan SN, Smyth ND, O'Sullivan M *et al.* The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. *Nutr Clin Pract* 2014;**29**:348–54.
42. Pongprasobchai S. Maldigestion from pancreatic exocrine insufficiency. *J Gastroenterol Hepatol* 2013;**28** Suppl 4:99–102.
43. Singh VK, Haupt ME, Geller DE *et al.* Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol* 2017;**23**:7059–76.
44. Yadav D, Timmons L, Benson JT *et al.* Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *Am J Gastroenterol* 2011;**106**:2192–9.
45. Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011;**26** Suppl 2:12–6.
46. Vujasinovic M, Valente R, Del Chiaro M *et al.* Pancreatic Exocrine Insufficiency in Pancreatic Cancer. Nutrients 2017;**9**:183.
47. Sikkens EC, Cahen DL, de Wit J *et al.* Prospective assessment of the influence of pancreatic cancer resection on exocrine pancreatic function. *Br J Surg* 2014;**101**:109–13.
48. Pezzilli R, Andriulli A, Bassi C *et al.*; 28 Exocrine Pancreatic Insufficiency collaborative (EPIc) Group. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. *World J Gastroenterol* 2013;**19**:7930–46.
49. Reber HA, Tweedie JH, Maslin SC *et al.* Pancreatic cancer: diagnostic value of pancreatic function tests. *Cancer Detect Prev* 1981;**4**:443–8.
50. Matsumoto J, Traverso LW. Exocrine function following the whipple operation as assessed by stool elastase. *J Gastrointest Surg* 2006;**10**:1225–9.
51. Sikkens EC, Cahen DL, de Wit J *et al.* A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *J Clin Gastroenterol* 2014;**48**:e43-6–e46.
52. Perez MM, Newcomer AD, Moertel CG *et al.* Assessment of weight loss, food intake, fat metabolism, malabsorption, and treatment of pancreatic insufficiency in pancreatic cancer. *Cancer* 1983;**52**:346–52.
53. Pallagi P, Hegyi P, Rakonczay Z Jr. The physiology and pathophysiology of pancreatic ductal secretion: the background for clinicians. *Pancreas* 2015;**44**:1211–33.
54. Wilschanski M, Novak I. The cystic fibrosis of exocrine pancreas. *Cold Spring Harb Perspect Med* 2013;**3**:a009746.
55. Waters DL, Dorney SF, Gaskin KJ *et al.* Pancreatic function in infants identified as having cystic fibrosis in a neonatal screening program. *N Engl J Med* 1990;**322**:303–8.
56. Corey M, McLaughlin FJ, Williams M *et al.* A comparison of survival, growth, and pulmonary function in patients with cystic fibrosis in Boston and Toronto. *J Clin Epidemiol* 1988;**41**:583–91.
57. Borowitz D, Robinson KA, Rosenfeld M *et al.*; Cystic Fibrosis Foundation. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. *J Pediatr* 2009;**155**:S73–93.
58. Yankaskas JR, Marshall BC, Sufian B *et al.* Cystic fibrosis adult care: consensus conference report. *Chest* 2004;**125**:1s–39s.
59. Dominguez-Munoz JE. Pancreatic enzyme replacement therapy: exocrine pancreatic insufficiency after gastrointestinal surgery. *HPB (Oxford)* 2009;**11** Suppl 3:3–6.
60. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency—Breaking the myths. *BMC Med* 2017;**15**:29.
61. Lim PW, Dinh KH, Sullivan M *et al.* Thirty-day outcomes underestimate endocrine and exocrine insufficiency after pancreatic resection. *HPB (Oxford)* 2016;**18**:360–6.
62. Armstrong T, Walters E, Varshney S *et al.* Deficiencies of micronutrients, altered bowel function, and quality of life during late follow-up after pancreaticoduodenectomy for malignancy. *Pancreatology* 2002;**2**:528–34.
63. Belyaev O, Herzog T, Chromik AM *et al.* Early and late postoperative changes in the quality of life after pancreatic surgery. *Langenbecks Arch Surg* 2013;**398**:547–55.
64. Myers KC, Bolyard AA, Otto B *et al.* Variable clinical presentation of Shwachman-Diamond syndrome: update from the North American Shwachman-Diamond Syndrome Registry. *J Pediatr* 2014;**164**:866–70.
65. Myers KC, Davies SM, Shimamura A. Clinical and molecular pathophysiology of Shwachman-Diamond syndrome: an update. *Hematol Oncol Clin North Am* 2013;**27**:117–28, ix.
66. Bezzerri V, Cipolli M. Shwachman-diamond syndrome: molecular mechanisms and current perspectives. *Mol Diagn Ther* 2019;**23**:281–90.
67. Dror Y, Donadieu J, Koglmeier J *et al.* Draft consensus guidelines for diagnosis and treatment of Shwachman-Diamond syndrome. *Ann N Y Acad Sci* 2011;**1242**:40–55.
68. Atik T, Karakoyun M, Sukalo M *et al.* Two novel UBR1 gene mutations in a patient with Johanson Blizzard Syndrome: A mild phenotype without mental retardation. *Gene* 2015;**570**:153–5.
69. Zenker M, Mayerle J, Lerch MM *et al.* Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). *Nat Genet* 2005;**37**:1345–50.
70. Rotig A, Cormier V, Blanche S *et al.* Pearson's marrow-pancreas syndrome. A multisystem mitochondrial disorder in infancy. *J Clin Invest* 1990;**86**:1601–8.
71. Tumino M, Meli C, Farruggia P *et al.* Clinical manifestations and management of four children with Pearson syndrome. *Am J Med Genet A* 2011;**155A**:3063–6.
72. Zsori G, Illes D, Terzin V *et al.* Exocrine pancreatic insufficiency in type 1 and type 2 diabetes mellitus: do we need to treat it? A systematic review. *Pancreatology* 2018;**18**:559–65.
73. American Diabetes A. (2) Classification and diagnosis of diabetes. *Diabetes Care* 2015;**38** Suppl:S8–S16.
74. Czako L, Hegyi P, Rakonczay Z Jr, *et al.* Interactions between the endocrine and exocrine pancreas and their clinical relevance. *Pancreatology* 2009;**9**:351–9.
75. Fasano A, Berti I, Gerarduzzi T *et al.* Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003;**163**:286–92.
76. Walker MM, Murray JA, Ronkainen J *et al.* Detection of celiac disease and lymphocytic enteropathy by parallel serology and histopathology in a population-based study. *Gastroenterology* 2010;**139**:112–9.
77. Vujasinovic M, Tepes B, Volfand J *et al.* Exocrine pancreatic insufficiency, MRI of the pancreas and serum nutritional markers in patients with coeliac disease. *Postgrad Med J* 2015;**91**:497–500.

78. Leeds JS, Hopper AD, Hurlstone DP *et al.* Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Aliment Pharmacol Ther* 2007;**25**:265–71.
79. Nousia-Arvanitakis S, Karagiozoglou-Lamboudes T, Aggouridaki C *et al.* Influence of jejunal morphology changes on exocrine pancreatic function in celiac disease. *J Pediatr Gastroenterol Nutr* 1999;**29**:81–5.
80. Carroccio A, Iacono G, Montalto G *et al.* Exocrine pancreatic function in children with coeliac disease before and after a gluten free diet. *Gut* 1991;**32**:796–9.
81. Abdulkarim AS, Burgart LJ, See J *et al.* Etiology of nonresponsive celiac disease: results of a systematic approach. *Am J Gastroenterol* 2002;**97**:2016–21.
82. Licul V, Cizmarevic NS, Ristic S *et al.* CTLA-4 +49 and TNF-alpha-308 gene polymorphisms in celiac patients with exocrine pancreatic insufficiency. *Coll Antropol* 2013;**37**:1191–4.
83. Bruner LP, White AM, Proksell S. Inflammatory Bowel Disease. *Prim Care* 2023;**50**:411–27.
84. Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. *J Clin Gastroenterol* 2010;**44**:246–53.
85. Maconi G, Dominici R, Molteni M *et al.* Prevalence of pancreatic insufficiency in inflammatory bowel diseases. Assessment by fecal elastase-1. *Dig Dis Sci* 2008;**53**:262–70.
86. Kovacs M, Lakatos PL, Papp M *et al.* Pancreatic autoantibodies and autoantibodies against goblet cells in pediatric patients with inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2012;**55**:429–35.
87. Montenegro ML, Corral JE, Lukens FJ *et al.* Pancreatic Disorders in Patients with Inflammatory Bowel Disease. *Dig Dis Sci* 2022;**67**:423–36.
88. Antonini F, Pezzilli R, Angelelli L *et al.* Pancreatic disorders in inflammatory bowel disease. *World J Gastrointest Pathophysiol* 2016;**7**:276–82.
89. Friess H, Bohm J, Muller MW *et al.* Maldigestion after total gastrectomy is associated with pancreatic insufficiency. *Am J Gastroenterol* 1996;**91**:341–7.
90. Hillman HS. Postgastrectomy malnutrition. *Gut* 1968;**9**:576–84.
91. Brägelmann R, Armbrecht U, Rosemeyer D *et al.* The effect of pancreatic enzyme supplementation in patients with steatorrhoea after total gastrectomy. *Eur J Gastroenterol Hepatol* 1999;**11**:231–7.
92. Uribarri-Gonzalez L, Nieto-Garcia L, Martis-Sueiro A *et al.* Exocrine pancreatic function and dynamic of digestion after restrictive and malabsorptive bariatric surgery: a prospective, cross-sectional, and comparative study. *Surg Obes Relat Dis* 2021;**17**:1766–72.
93. Borbely Y, Plebani A, Kroll D *et al.* Exocrine Pancreatic Insufficiency after Roux-en-Y gastric bypass. *Surg Obes Relat Dis* 2016;**12**:790–4.
94. Moore HN, Chirco AR, Plescia T *et al.* Exocrine pancreatic insufficiency after bariatric surgery: a bariatric surgery center of excellence experience. *Surg Endosc* 2023;**37**:1466–75.
95. Huddy JR, Macharg FM, Lawn AM *et al.* Exocrine pancreatic insufficiency following esophagectomy. *Dis Esophagus* 2013;**26**:594–7.
96. Heneghan HM, Zaborowski A, Fanning M *et al.* Prospective Study of Malabsorption and Malnutrition After Esophageal and Gastric Cancer Surgery. *Ann Surg* 2015;**262**:803–7. discussion 807–8.
97. Chaudhary A, Dominguez-Munoz JE, Layer P *et al.* Pancreatic exocrine insufficiency as a complication of gastrointestinal surgery and the impact of pancreatic enzyme replacement therapy. *Dig Dis* 2020;**38**:53–68.
98. Herzig KH, Purhonen AK, Rasanen KM *et al.* Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC Geriatr* 2011;**11**:4.
99. Sweep B, Wilgenhof S, Anten S. Nivolumab-Induced Exocrine Pancreatic Insufficiency. *Case Rep Oncol* 2021;**14**:1627–31.
100. Diaz-Gonzalez A, Belmonte E, Sapena V *et al.* Pancreatic insufficiency in patients under sorafenib treatment for hepatocellular carcinoma. *J Clin Gastroenterol* 2021;**55**:263–70.
101. Hong AS, Sarwar N, Goldin RD *et al.* Pembrolizumab-induced pancreatic exocrine insufficiency complicated by severe hepatic steatosis. *Cureus* 2022;**14**:e26596.
102. Pophali P, Veyseh M, Fraij O *et al.* Chronic giardiasis: a rare cause of exocrine pancreatic insufficiency. *BMJ Case Rep* 2021;**14**:e242129.

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