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EDITORIAL

Undiagnosed Exocrine Pancreatic Insufficiency in Diarrhea-Predominant Irritable Bowel Syndrome

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The exocrine function of the pancreas is essential for normal digestion and nutrient absorption. Exocrine pancreatic insufficiency (EPI) occurs when obstructed or mistimed duodenal delivery or insufficient secretion of pancreatic enzymes and/or sodium bicarbonate impairs digestion with resultant malabsorption. Symptoms of EPI depend on severity and can include abdominal discomfort, cramping, bloating, flatulence, malodorous steatorrhea, weight loss, fat-soluble vitamin deficiency, and metabolic bone disease [1]. Pancreatogenic diabetes can also occur, particularly in patients with severe disease. Though the condition is most commonly associated with primary pancreatic diseases such as chronic pancreatitis, cystic fibrosis, severe acute pancreatitis, pancreatic cancer, or surgical pancreatic resection, there is increasing evidence and interest in EPI associated with non-pancreatic diseases such as foregut surgery. Furthermore, irritable bowel syndrome, inflammatory bowel disease, and celiac disease have all been implicated as non-pancreatic diseases associated with EPI [2, 3].

The contribution of undiagnosed EPI to non-pancreatic causes of diarrhea is a difficult question to pursue, in large part due to difficulties in diagnosing EPI, particularly in patients with diarrhea. The accepted gold standard for the diagnosis of EPI is the secretin-cholecystokinin test, in which duodenal fluid is collected by invasive means and assayed for enzymes and bicarbonate after intravenous injection of pancreatic prosecretory hormones [4]. The fecal elastase test, which measures the concentration of pancreatic elastase that is secreted into the duodenum, is the most commonly used and studied indirect test used for the diagnosis of exocrine pancreatic function due to its ease of collection and wide availability [5]. It is further superior to the fecal chymotrypsin test due to the greater stability of elastase and non-interference by pancreatic enzyme replacement therapy (PERT) [6]. Even so, fecal elastase can be confounded by watery stool samples where dilution can create false positive results, though this can be overcome by methods to remove excess water [7]. The question of the prevalence of EPI in diarrhea-predominant irritable bowel syndrome (IBS-D) can be difficult to study due to the low prevalence of EPI in IBS, as well as the low sensitivity of the fecal elastase test for mild disease [8].

In this issue of *Digestive Diseases and Sciences*, Olmos and colleagues describe the prevalence and characteristics of undiagnosed EPI in a cohort of patients with diarrhea-predominant IBS [9]. This prospective, cross-sectional study assessed fecal elastase levels in 140 patients with diarrhea-predominant IBS, as defined by the Rome IV criteria. Participants were not excluded based on stool consistency. Although all participants had diarrhea, with most scoring 6–7 on the Bristol stool scale, only 7 (5%) had fecal elastase < 100 µg/g, suggestive of EPI. These 7 patients also had significantly lower serum levels of fat-soluble vitamins A and E compared with the rest of the cohort ($p = 0.04$), further validating their diagnosis of EPI. The presumed EPI group was then started on PERT, and reassessment of symptoms after 12 weeks demonstrated significant improvement in the Bristol stool scale, frequency of bowel movements, distension score, pain score, and IBS severity. Therefore, despite the aforementioned limitations of fecal elastase interpretation in loose stool samples, the concurrent low levels of fat-soluble vitamins and significant response to PERT found in the EPI group together provide reasonable confidence in the specificity of the authors' concluded prevalence of EPI in their IBS-D cohort.

Endoscopic ultrasound (EUS), considered the optimal imaging modality for assessment of pancreatic pathology,

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found five of the seven EPI subjects with pancreatic steatosis, 1 with chronic pancreatitis, and 1 with a normal pancreas. The finding of pancreatic steatosis in 71.4% of the patients is interesting in that there is growing but incomplete knowledge of the clinical significance of this entity. Although it has been suggested that nonalcoholic fatty pancreas disease could lead to pancreatic insufficiency through an increase in oxidative stress leading to acinar cell apoptosis, clinical studies of this association have been limited [10].

This study adds to the literature that suggests the prevalence of EPI in IBS is likely around 4–6% [3, 11]. It is a reminder of the challenge that lies in lacking an ideal diagnostic test for EPI in patients with diarrhea. In the case of this study, the group of patients deemed to have pancreatic insufficiency likely had moderate-severe EPI, characterized by lower levels of fat-soluble vitamins and response to pancreatic enzyme supplementation [5]. Since patients with mild EPI typically have normal vitamin A and E levels and do not require PERT, this nuanced diagnosis may have been missed in this study, consistent with data that suggest fecal elastase has poor characteristics for diagnosing and excluding mild EPI [8]. Since PERT has few adverse effects, treatment of patients even with suspected mild disease is one approach that should be considered, given the potentially significant positive impact on quality of life [1].

Further studies on reliable, non-invasive methods to diagnose pancreatic insufficiency, particularly of mild-moderate severity in the setting of diarrhea, are warranted. The authors did find a significant and independent association between dyspepsia and the EPI group compared with the remaining IBS-D group ($p = 0.0007$), which may be an interesting area for further research. Finally, the study findings also encourage further investigation of the association between pancreatic steatosis and EPI. Many of the EPI patients in this cohort had concurrent pancreatic steatosis as diagnosed by EUS, but it is unclear whether this finding represents a causal relationship or two downstream consequences of a common pathologic process. There remains much to be elucidated on the clinical consequences of pancreatic steatosis and its temporal relationship with EPI.

Key Points

- Exocrine pancreatic insufficiency (EPI) may present a diagnostic challenge, particularly in the setting of mild disease and watery stools.
- Diagnosis of EPI by fecal elastase can be supported by findings of fat-soluble vitamin deficiencies and response to pancreatic enzyme replacement therapy (PERT).
- Several studies including this current analysis by Olmos et al. have determined an approximate 5% prevalence of EPI in diarrhea-predominant irritable bowel syndrome. These patients appear to experience significant symptom improvement with PERT. An additional high prevalence of pancreatic steatosis was found in EPI patients.
- Further studies on reliable and non-invasive methods to diagnose EPI in the setting of diarrhea are warranted.
- There also remains much to be explored in the relationship between EPI and pancreatic steatosis.

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