Editorial Commentary

Pancreatic exocrine insufficiency guidelines: more questions than answers!

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Pancreatic exocrine insufficiency (PEI) has classically been described as a maldigestive disorder resulting from decreased secretion or altered function of pancreatic digestive enzymes (1). As a result of this maldigestion and ensuing malabsorption, patients can experience symptoms such as steatorrhea and weight loss as well as complications related to the loss of fat-soluble vitamins and micronutrients. PEI has been most extensively studied in cystic fibrosis, but other causes include acute and chronic pancreatitis (CP), pancreatic adenocarcinoma (PDAC), and rarely, congenital syndromes such as Shwachman-Diamond and Johnson-Blizzard (2).

The recent United Kingdom (UK) practical guidelines for the management of PEI by Phillips *et al.* (3) represent one of the very few guidelines utilizing GRADE methodology to develop management recommendations for clinicians caring for patients with PEI. While most statements in the guideline achieved >90% agreement among a panel of 48 pancreatic specialists, the strength of the recommendations was weak, and the quality of evidence was low to moderate. This is due to the fact that there are a paucity of high quality studies in PEI and the few trials conducted to date have been primarily to evaluate different pancreatic enzyme replacement therapy (PERT) formulations for regulatory approval. As a result, PEI is one of those conditions where more is known about the treatment than the condition itself.

There continues to be no standardized definition for PEI. The UK guidelines define PEI as the loss of functioning pancreatic parenchyma and/or reduced secretion of pancreatic digestive enzymes that overemphasizes the role of pancreatic enzyme production and secretion. The recent American College of Gastroenterology guidelines on CP describes PEI as a syndrome consisting of 4 domains including nutritional need, nutritional intake, decreased pancreatic digestive enzyme output, and intestinal adaptation (3). However, decreased pancreatic enzyme output is typically the only factor that clinicians rely on to diagnose PEI and administer PERT. The incorporation of the other PEI domains into clinical decision making are just as important. For instance, a clinician may decide not to start an asymptomatic obese patient with a low FE-1 but normal fat-soluble vitamin and micronutrient levels on PERT.

FE-1 is the most frequently used laboratory test to diagnose PEI owing to its low cost, convenience, and wide availability. The coefficient of fat absorption (CFA), determined through a 72-h fecal fat collection, is the criterion standard for diagnosing steatorrhea and not PEI despite often being considered as such by clinicians (4). The UK guidelines highlight the importance of adjusting for the water content in a stool specimen when testing for FE-1, as liquid stool can be associated with false positive results. However, not all laboratories adjust the water content of the stool specimen. Therefore, clinicians should ask their patients if the submitted specimens were primarily solid or liquid in consistency before interpreting the results. There are monoclonal and polyclonal ELISA kits that are commercially available for the measurement of FE-1. The monoclonal assay was found to be more sensitive for

evaluating FE-1 levels and was also not affected by the concomitant administration of PERT in comparison to the polyclonal assay (5). Most importantly, the interpretation of any FE-1 result must be clinically contextualized. A low FE-1 in a patient with chronic calcific pancreatitis who experiences weight loss along with evidence of fat-soluble vitamin deficiency is more likely to have PEI than a low FE-1 in a patient with a long history of abdominal pain, diarrhea, and normal abdominal imaging which is statistically far more likely to represent irritable bowel syndrome with diarrhea predominance.

The UK guidelines recommend PERT for all patients with acute necrotizing pancreatitis (ANP) once they resume oral intake. This would result in overtreatment or prolongation of treatment as not all patients with ANP develop PEI and many who develop PEI will recover exocrine function over time, respectively. The risk of PEI after ANP is about 25% over 3 years following discharge from the hospital (6). Huang *et al.* (7). found a cumulative prevalence of 62% of PEI among patients with acute pancreatitis at index presentation; however, this decreased to 33% over long-term follow-up, which is similar to the 27% incidence reported by Hollemans *et al.* (8). Both of these systematic reviews included studies comprised of patients with acute interstitial and necrotizing pancreatitis and utilized variable diagnostic criteria for PEI. The risk of PEI is likely to be much lower in patients with acute interstitial pancreatitis. The decision to treat PEI in acute pancreatitis must be individualized based on the extent of necrosis, disease severity, and assessment of nutritional status. Once treatment is initiated, there needs to be a close follow-up as the recovery of exocrine function in these patients warrants discontinuation of PERT.

Similarly, the UK guidelines recommend initiating PERT in all patients with resectable or unresectable pancreatic adenocarcinoma (PDAC). Patients with a tumor in the head, those with extensive glandular involvement, and post-resection status have been shown to have a higher prevalence of PEI (9). While PERT is often prescribed to PDAC patients, there is no convincing data supporting a positive impact on short- and long-term outcomes in these patients (10). This is likely because most PDAC patients die in the first 6 months after diagnosis which precludes an adequate assessment of the impact of PERT as nutritional parameters change over a longer time period. In addition, nutritional outcomes in PDAC are influenced by many other confounding variables including the quality and quantity of oral intake as well as altered upper gastrointestinal anatomy after pancreatic surgery, use of opioid analgesics for pain and diabetes mellitus all of which can affect appetite and gut motility.

Another controversial aspect of PERT is dosing. The UK guidelines recommend a dose of 50,000 IU of lipase with meals and 25,000 IU with snacks, whereas the ACG guidelines recommend a dose of 40,000 to 50,000 USP of lipase per meal as the initial dosing of PERT which is about two-thirds of the dose recommended by the UK guidelines (1 IU=3 USP). The normal mean postprandial output of lipase is between 480,000–960,000 units per meal and the prevention of steatorrhea requires replacement of 5–10% of pancreatic lipase output, which is about 48,000–96,000 units of lipase per meal (11). Therefore, the recommended starting PERT dose with meals by the UK guidelines exceeds the dose required to prevent steatorrhea and is about three times the starting dose as advocated by the ACG guidelines. While many guidelines also recommend increasing the dose of PERT if the response is inadequate, it should be noted that there is no benefit in dose escalation as response begins to plateau (12). The duration of PERT in patients with PEI is unknown. None of the guidelines to date discuss the situations when PERT can be discontinued as it is assumed that PEI is a permanent condition. However, PEI due to non-pancreatic causes, in particular, can be reversible if treated (e.g., antibiotics for small bowel bacterial overgrowth, gluten free diet for celiac disease, etc.). The UK guidelines also recommend counseling patients with PEI on the timing of PERT which should be administered during the meal, as opposed to before or after, to allow adequate mixing of food and enzymes (13) and to avoid dietary fat restriction as this can compromise an already tenuous nutritional status.

While the UK guidelines support the use of PERT on the premise that it is associated with improvement in survival and QoL among CP patients, there have been no long-term studies that have evaluated nutritional outcomes in patients on PERT. PERT improves, but does not normalize fat absorption, which leads to a resolution of steatorrhea but may not lead to cessation of other PEI symptoms or result in expected weight gain within a particular time frame (14). It is also important to note that PERT is administered to treat pain and PEI with equal frequency across the CP population but its lack of effect on the former may lead many such patients to stop therapy even if they have PEI (15).

The UK guidelines provide a comprehensive and, importantly, practical approach to the diagnosis and management of PEI. It is important to highlight that

PEI is a syndrome where a FE-1 test result needs to be evaluated in relation to the other domains of the syndrome to determine the need for and benefit of PERT in patients with both pancreatic and nonpancreatic causes of PEI. There is a clear need for high-quality longitudinal studies on PEI that help close the gaps in knowledge as they pertain to diagnosis, treatment and outcomes.

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