DOI: 10.1002/ncp.11129

INVITED REVIEW

Fat malabsorption in pancreatic cancer: Pathophysiology and management

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Funding information
The production of this publication was financially supported in part by a grant from Alcresta Therapeutics, Inc., which had no involvement in the editorial decisions, content, or writing of this supplement.

Abstract

Exocrine pancreatic insufficiency (EPI) is common in pancreatic ductal adenocarcinoma (PDAC) and may lead to significant nutrition compromise. In the setting of cancer cachexia and gastrointestinal toxicities of cancer treatments, untreated (or undertreated) EPI exacerbates weight loss, sarcopenia, micronutrient deficiencies, and malnutrition. Together, these complications contribute to poor tolerance of oncologic therapies and negatively impact survival. Treatment of EPI in PDAC involves the addition of pancreatic enzyme replacement therapy, with titration to improve gastrointestinal symptoms. Medical nutrition therapies may also be applicable and may include fat-soluble vitamin replacement, medium-chain triglycerides, and, in some cases, enteral nutrition. Optimizing nutrition status is an important adjunct treatment approach to improve quality of life and may also improve overall survival.

KEYWORDS
digestion, exocrine pancreatic insufficiency, malabsorption, malnutrition, nutrition support, pancreatic cancer, pancreatic enzymes

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is a malignancy arising from the exocrine pancreas that may result in impaired exocrine pancreatic function. Depending on the tumor size and location, exocrine pancreatic insufficiency (EPI) may occur, which has a negative impact on nutrition status and overall patient survival. Treatment of EPI among individuals with PDAC includes administration of exogenous pancreatic enzyme replacement therapy (PERT) as well as dietary strategies and nutrition interventions, including nutrition supplements. In this review, we will discuss pancreatic anatomy and physiology as it relates to EPI in PDAC, and we will review treatment approaches to maintain nutrition status during the course of PDAC treatment.

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FAT ABSORPTION AND MALABSORPTION

Overview of pancreatic anatomy and physiology

Anatomically, the pancreas is located transversely in the upper abdomen and measures approximately 15 cm from head to tail (Figure 1). The head is nested within the C-loop of the duodenum, the body is positioned behind the stomach, and the tail extends toward the hilum of the spleen. The common bile duct courses through the head of the pancreas for approximately 3 cm, running parallel to the main pancreatic duct until these ducts fuse to form a common channel at the ampulla.

The pancreas is often divided into two conceptual compartments based on endocrine and exocrine functions. The islets of Langerhans are responsible for endocrine functions by producing hormones such as insulin, glucagon, and somatostatin. The exocrine component accounts for most of the pancreas mass and includes acinar and ductal cells. Acinar cells have a highly developed rough endoplasmic reticulum and Golgi apparatus, which produce vast quantities of proenzymes, including trypsinogen and pro-lipases. In the fasting state, proenzymes are located at the periphery of the acini within zymogen granules. With stimulation, there is a surge of zymogen granules that release proenzymes into the pancreatic duct. This occurs during the cephalic and gastric phases of digestion but is most strongly stimulated during the intestinal phase.[1] Once secreted into the lumen of the pancreatic duct, proenzymes are carried by bicarbonate- and chloride-rich fluid into the duodenum lumen, where they can be activated by enterokinase on the luminal membrane of enterocytes. The pancreatic fluid is produced by pancreatic ductal cells, and the bicarbonate further serves to buffer the acidic chyme in the duodenum and maintains a consistent viscosity to facilitate rapid transport of proenzymes into the duodenum.

Fat digestion and absorption

When food enters the oral cavity, mastication and lingual amylase start the digestive process. As the food bolus arrives in the acidic environment of the stomach, protein begins to denature, carbohydrate digestion is halted, and triglycerides are cleaved into monoacylglycerides and diacylglycerides. As chyme enters the duodenum, I-cells located in the duodenal mucosa release cholecystokinin (CCK), which stimulates the acinar cells of the pancreas to secrete pancreatic proenzymes and stimulates the ductal cells to release bicarbonate.[1] Pancreatic proenzymes are converted to active enzymes by enterokinase, located on the brush border of the intestinal villi, and begin the process of cleaving carbohydrate to monosaccharides and disaccharides, protein to amino acids, and fat to monoglycerides and diglycerides to facilitate absorption by enterocytes. Unlike carbohydrate and protein, which can be digested by salivary amylase and gastric pepsin,

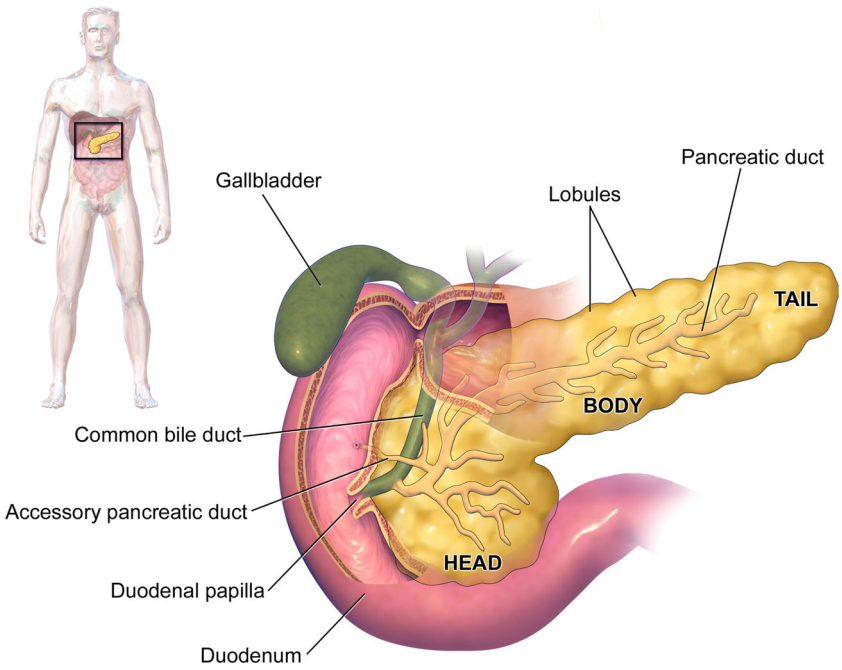


FIGURE 1 Anatomy of the pancreas. Reprinted with permission Blausen.com staff. Medical gallery of Blausen Medical 2014. *WikiJournal of Medicine*. 2014;1(2). doi:10.15347/wjm/2014.010; https://commons.wikimedia.org/w/index.php?curid=28909219. Accessed January 10, 2024.

respectively, the digestion of fat relies almost exclusively on pancreatic enzyme production.

Digestion of fat relies on several processes occurring in tandem at the proximal intestine. Dietary fat is first emulsified through the action of bile salts, which leads to increased surface area for the action of pancreatic lipases to hydrolyze the triglyceride into free fatty acids and monoglycerides. These fatty acids and monoglycerides arranged in micelles are absorbed by the enterocyte. Within the enterocyte, resynthesis of triglycerides occurs as chylomicrons are formed and released into lymphatic circulation. Medium-chain triglycerides escape this process and are free to enter directly into portal circulation. In summary, the combination of complex processes for digestion and absorption with a lack of salvage pathways makes patients with diseases of the exocrine pancreas, including PDAC, more prone to developing signs and symptoms of fat malabsorption than other macronutrients.

Exocrine pancreatic insufficiency

Fat malabsorption exists on a spectrum and can therefore result in a variety of clinical manifestations.[2] When >90% of exocrine function is lost, fat malabsorption can cause steatorrhea.[3] Milder cases of fat malabsorption may cause foul-smelling stool, abnormal stool frequency, flatulence or bloating, and potentially fat-soluble vitamin deficiencies. As EPI progresses, the injured pancreatic cells cannot produce enough sodium bicarbonate to neutralize the gastric chyme, leading to a low pH in the intestines, which further degrades available pancreatic enzymes.[4] Further physiological changes occur as postprandial enzyme secretion decreases, causing the maximum site of nutrient absorption to shift from the proximal to distal small intestine.[5] Additionally, both gastroduodenal and small intestine transit are accelerated, compounding the effects on fat absorption from less contact with the intestinal mucosa. The clinical symptoms of EPI can be nonspecific, which has led to the development of a variety of diagnostic tests to identify and quantify EPI.[6,7]

The test used most often for the diagnosis is fecal elastase (FE-1), followed by fat quantification and coefficient of fat absorption (CFA) (Table 1).[6,11] FE-1 provides an indirect assessment of pancreas enzyme production but is not able to assess for the presence or severity of fat malabsorption. Conversely, measurement of fecal fat percentage assesses the severity of fat malabsorption but can be elevated in pancreatic or nonpancreatic disease states.[12] The CFA compares the amount of fat excreted in stool with the amount of orally ingested fat. However, this test is difficult because a patient must follow a strict high-fat diet for 5–7 days, which may result in increased gastrointestinal symptoms, in addition to a 72-h stool collection. Stool fat content >7 g per day corresponds with a CFA of <93% and is considered diagnostic of EPI in patients with pancreatic disease. Notably, fat measurement tests are not pancreas-specific and therefore cannot distinguish between primary EPI and secondary EPI.[13,14] There are several other tests available, such as direct sampling of pancreatic secretions in the intestine, secretin-CCK stimulation test, and breath tests.[11] However, each test has limitations, and there is no current consensus on a preferred test for EPI diagnosis.[15] Nevertheless, at diagnosis, around 50% of patients may have laboratory indications of EPI without experiencing any symptoms.[15] Therefore, objective testing is recommended for individuals at high risk of EPI in order to identify this condition and commence treatment.

CLINICAL FEATURES OF PDAC

EPI can occur in the setting of various pancreatic disorders that cause a loss of pancreatic acinar cells or dysfunction of ductal cells. It is increasingly recognized that PDAC can cause EPI, which has negative impacts on nutrition status and overall prognosis.

Based on global estimates, PDAC is the 12th most common malignancy but the seventh leading cause of cancer mortality.[16] Furthermore, the incidence is rising in many countries.[17] Improvements in clinical outcomes have lagged behind other cancer types, and survival remains poor because of several challenges. First, because of its nonspecific symptoms and lack of an effective screening strategy, PDAC is detected at a late stage in most patients. Second, PDAC is less responsive to many cancer treatments, including multidrug chemotherapy regimens, which are often poorly tolerated in this patient population.[18] Third, PDAC often leads to interruptions in the normal functions of the pancreas, which has detrimental effects on health. For example, diabetes mellitus commonly develops as a para-neoplastic phenomenon before PDAC diagnosis.[15] Additionally, PDAC commonly leads to reduced exocrine pancreatic function and may impair absorption of nutrients. Finally, PDAC causes a severe cancer cachexia phenotype, which leads to rapid loss of skeletal muscle and body fat, impairing an individual's ability to withstand the side effects of treatment.[19] The cachexia process involves increased systemic inflammation and increased energy expenditures, which is further compounded by limitations on caloric intake and absorption due to treatment side effects and fat malabsorption.[20,21] In light of these challenges, clinicians should take advantage of any treatment benefits that improve the quality of life or prolong survival for individuals with PDAC.

TABLE 1 Available assessments to diagnose EPI, including the rationale and limitations for use.[8–10]

Assessment	Description/rationale	Limitations
Clinical signs and symptoms		
Symptoms	• Abdominal pain • Abdominal bloating • Diarrhea • Excessive flatulence • Weight loss	Clinical features are common, including in this patient population, and are nonspecific for EPI
Stool characteristics	Evaluation of presence of steatorrhea: yellow/orange colored stools, greasy and floating stools, foul-smelling stools	• Stool characteristics can present with other malabsorptive etiologies and are not specific to EPI • Steatorrhea is only present in severe EPI and may be masked by self-restricted dietary fat intake
Fat-soluble vitamins	To assess for fat-soluble vitamin deficiencies, the following are suggested assays. A measurement of C-reactive protein level will assist assessment during inflammation: • Vitamin A: retinol, serum or plasma • Vitamin D: 25-OH, vitamin D • Vitamin E: alpha-tocopherol • Vitamin K: PT/INR	• Limited interpretation during an inflammatory state • Nonspecific for fat maldigestion and malabsorption • Poor predictive evidence for EPI
Indirect pancreas function tests		
Fecal elastase-1	Measures elastase enzyme levels in a random stool sample	• False positives are common in nonformed stool specimens • Does not indicate fat maldigestion and malabsorption
Coefficient of fat absorption	• Current gold standard for fat malabsorption • A high-fat diet (100 g/d) is consumed for up to 7 days before fecal collection. Stool is collected during the terminal 3 days of the diet	• Indirect measure of lipolysis • Cumbersome to patients
^{13}C mixed triglyceride breath test	Measures exhaled carbon dioxide after a standardized test meal as an indirect measurement of lipolysis	• 89% sensitivity with 81% specificity • Not widely available
Malabsorption blood test	Utilizes pentadecanoic fatty acid and triheptadecanoic acid to determine the degree of pancreatic associated fat malabsorption	Tested in healthy controls and in individuals with cystic fibrosis
Direct pancreas function tests		
Endoscopic pancreas function test	Endoscopic measurement of pancreatic secretions of bicarbonate and lipase following intravenous administration of secretin and cholecystokinin into the duodenum	• Not FDA-approved for analysis of duodenal aspirate • Invasive • Not widely available

Abbreviations: EPI, exocrine pancreatic insufficiency; FDA, Food and Drug Administration; INR, international normalized ratio; PT, prothrombin time.

Cancer staging and treatments

Among individuals with PDAC, the longest overall survival is seen when PDAC is identified at an operable stage, which is based on anatomic considerations and the absence of identifiable metastases on imaging or laparoscopy.[22] Because of advances in chemotherapy response rates, patients with borderline resectable (and often anatomically resectable) tumors are most commonly offered initial treatment with systemic chemotherapy to improve the chances of surgical resection with microscopically negative margins. These therapies involve combination chemotherapy regimens such as fluorouracil, irinotecan, oxaliplatin, and leucovorin (FOLFIRINOX) or gemcitabine with nab-paclitaxel; treatment may also include external beam radiation therapy targeting the primary tumor. These regimens have high risks of gastrointestinal toxicities, including nausea, vomiting, and diarrhea, which often

result in impaired oral intake in the absence of aggressive symptom control and targeted nutrition therapies.[23] It is critical to maintain nutrition intake during neoadjuvant therapy because the ultimate goal is to successfully undergo surgical resection, and malnutrition may present a barrier to surgery. Unfortunately, up to 40% of individuals who present with borderline resectable PDAC are not ultimately candidates for resection.[24] Therefore, early identification of PDAC and early nutrition interventions may improve rates of resection and therefore overall survival among individuals with this deadly disease.

Exocrine pancreatic insufficiency

An additional opportunity to improve survival may include optimized treatments for EPI among individuals with PDAC.[25] EPI is a contributing factor to malnutrition in both resectable and nonresectable PDAC owing to increased fecal fat and energy loss.[25–28] A small study assessed whether steatorrhea in PDAC could be related to enterocyte function rather than malabsorption using the citrulline generation test and ultimately concluded that EPI was responsible for fat malabsorption in this population.[26] Therefore, the mechanism of EPI in PDAC appears to be due to the tumor replacing functional acinar cells and/or obstructing the pancreatic duct, resulting in a deficiency of pancreatic enzymes at the duodenum. Tumor histology, tumor location, and treatment modalities for PDAC impact prevalence rates.[28,29] For example, a meta-analysis by Iglesia et al identified a higher prevalence of EPI in tumors of the head than tumors of the tail of the pancreas (56% vs 32%, respectively).[25] Notably, among individuals who undergo pancreatic resection involving the pancreatic head, the risk of EPI is particularly increased because of the combination of altered gastrointestinal anatomy resulting in postcibal asynchrony, reduced enzyme stimulation due to neurohormonal changes, and/or reduction in functional pancreas volume.[5,30] The reported incidence of EPI varies following pancreaticoduodenectomy vs distal pancreatectomy, although inconsistent diagnosis of EPI complicates the understanding of prevalence rates. Tseng et al reports a pooled prevalence ($N = 9$ studies) after pancreatoduodenectomy of 74% and up to 80% after a distal pancreatectomy (36%–100% vs 67%–80%, respectively).[30] Overall, prevalence of EPI in all PDAC cases is 72%; however, again the lack of a readily available gold-standard diagnostic test may result in underdiagnosis.[25]

Systematic reviews and meta-analyses evaluating the impact of EPI treatment with PERT have associated improved survival, quality of life, nutrition status, body composition, tolerance to treatment including chemotherapy, and gastrointestinal symptoms in PDAC with PERT being optimized, whereas untreated EPI has been associated with high mortality specifically after pancreatic surgery.[25,31–33] Despite these reports, several randomized controlled trials fail to support these findings.[34] Indeed, a recent survey of surgical oncologists suggests that most prescribe PERT as part of multimodality treatment of PDAC, although <20% believe this has an effect on overall survival.[35] Until additional studies are available, PERT should be used to improve nutrition status for individuals with PDAC and EPI, but it is not indicated for a direct survival benefit for all individuals with PDAC. This topic is covered in greater detail in a separate article within this issue.[36] The incidence of EPI among individuals with PDAC is high, and clinicians should have a high suspicion for this important complication. Among asymptomatic individuals with good nutrition status, obtaining objective testing for EPI is reasonable before empirically commencing treatment. Alternatively, among individuals with worsening nutrition status or with clinical signs consistent with fat malabsorption, diagnostic testing may not be necessary, and treatment should be initiated because of the potential survival benefits. The treatment of EPI involves an individualized approach, including administration of PERT and dietary modifications.

EPI AND NUTRITION

Medical nutrition therapy for fat malabsorption

Among individuals with PDAC, cachexia and malnutrition are highly prevalent.[15,37] Thus, early and appropriate initiation of medical nutrition therapy is important. Medical nutrition therapy in PDAC is focused on identifying, treating, and preventing malnutrition. It is clear that poor nutrition status leads to decreased muscle mass, immunologic compromise, and loss of organ function, including pancreatic function.[38] Additionally, changes in gastrointestinal motility that occur during periods of malnutrition may pose challenges to optimize mixing of pancreatic enzymes and luminal nutrients, further exacerbating fat malabsorption. Therefore, concomitant treatment of fat malabsorption and malnutrition is an integral component of overall management in PDAC.[39] Medical nutrition therapy options to target fat malabsorption and malnutrition include oral diet manipulation, with or without specific supplements; enteral nutrition (EN); and rarely, parenteral nutrition (PN) (Table 2).

TABLE 2 Treatment options and rationale for improving fat maldigestion and malabsorption.[40]

Treatment	Properties	Rationale
Oral diet		
Small, frequent meals	Divide dietary fat requirements into six or more small meals or snacks while meeting kilocalorie requirements	• Small meals will improve contact with digestive enzymes further enhancing incorporation of dietary fat into the micelle • Superior to fat restriction, which can exacerbate weight loss and malnutrition
Water-miscible fat-soluble vitamins (A, D, E, K)	High-dose fat-soluble vitamin supplements in water-soluble form	• Delivery is in water-soluble micelles • Do not require bile or pancreatic enzymes for absorption • Absorbed into portal circulation
Pharmacotherapy		
PERT dosing	• Dosing strategies based on total body weight or grams of fat consumed in each meal and snack • Dosing guidelines vary and include recommendations for lipase units per kg of body weight, per g of dietary fat, and per meal	• Consumption of PERT with meals and snacks improves fat digestion and increases the amount of fat entering the enterocyte • Proton pump inhibitors may be useful to enhance the effectiveness of PERT if not responding to standard dosing • Consumption at the beginning of the meal improves effectiveness
MCTs	• Concentrated source of MCTs; dose is typically 15–30 ml • Instructions for use: ◦ Do not exceed 7 tablespoons (approximately 100 ml) per day, as this can lead to increased gastrointestinal intolerance ◦ Divide the dose among each meal and snack per day ◦ If administered via a feeding tube, be sure to flush well before and after administration (30–60 ml) ◦ Do not consume this product as a sole source of fat, as EFAD risk increases	• Water-soluble • Does not require bile or pancreatic enzymes for digestion • Absorption into portal circulation • Carnitine is not necessary for entry into the mitochondriaNote that essential fatty acids are all LCTs. Therefore, this product cannot prevent EFAD
Antidiarrheal medications	• Loperamide • Diphenoxylate/atropine • Codeine • Opium tincture	• Slow transit through the digestive tract in an effort to increase the exposure time to digestive enzymes
Nutrition support		
EN	Consider formulas with a greater proportion of MCT to LCT	• Greater delivery of MCT may improve fat absorption and decrease steatorrhea • Grams of MCT in products varies based on formula preparation • Some formulas with increased MCT amounts may still have too many LCTs for tolerance
Parenteral nutrition		• Rarely utilized for EPI in PDAC • May be considered after a multidisciplinary discussion involving the nutrition team and oncology team in situations in which EN is contraindicated (ie, bowel obstruction) such as for resectable primary tumors with severe malnutrition at the time of diagnosis

Abbreviations: EFAD, essential fatty acid deficiency; EN, enteral nutrition; EPI, exocrine pancreatic insufficiency; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; PDAC, pancreatic ductal adenocarcinoma; PERT, pancreatic enzyme replacement therapy.

Oral diet

First-line medical nutrition therapy includes early nutrition screening and dietary counseling to meet calorie and protein needs via an oral diet. If patients are unable to achieve their nutrient needs on their own, referral to a registered dietitian can assist them in consumption of small, frequent meals[20,41]; use of oral nutrition supplements; and micronutrient supplementation when indicated. Intake of small meals five or six times per day has shown increased caloric intake and may be beneficial in the prevention and treatment of malnutrition with early satiety and anorexia. This practice may also improve fat digestion and absorption by minimizing the requirement of pancreatic enzymes for optimal dietary fat digestion. It is crucial that patients do not avoid dietary fat or follow a low-fat diet for prevention of the nutrition sequelae seen in EPI and PDAC, as these recommendations can exacerbate weight loss and worsen malnutrition. Alternatively, appropriate PERT dosing is superior to reducing the nutrient-rich dietary fat sources.[42]

When selecting oral nutrition supplements in the presence of EPI and fat malabsorption, the fat blends, osmolarity, and fiber content drive selection. Partially hydrolyzed oral nutrition supplements deliver protein as dipeptides and tripeptides and more commonly include medium-chain triglycerides (MCTs) as a component of the fat blend to promote nutrient absorption. However, as protein is hydrolyzed, the osmolarity of the formula increases which poses a challenge to the absorptive process. Because hyperosmolar oral nutrition supplements (>285 mOsm/L) contribute to diarrhea and delayed gastric emptying in some, careful selection and monitoring of enteral tolerance are critical. Dietary fiber has been implicated as a possible contributor to a reduction in pancreatic enzyme activity when fiber intake is >25 g per day; however, the impact of fiber content in oral nutrition supplements on EPI is unknown.[43] The fiber characteristics (ie, solubility, fermentability, and viscosity) likely impact intolerance, with fermentable fibers or poorly soluble fibers posing the greatest challenges to enteral tolerance in EPI. When selecting an oral nutrition supplement for individuals with PDAC and EPI, the clinician should carefully review food and symptom records to drive decisions. For example, if consumption of highly fermentable fiber is consistently associated with abdominal pain, bloating, or diarrhea, the clinician should replace the fiber-containing oral nutrition supplement with a supplement that contains no or less fiber. Continued food and symptom records can confirm improved tolerance.

Optimizing the dietary pattern for improvements in fat digestion is essential to prevent micronutrient deficiencies. Clinicians should observe for signs and symptoms of deficiencies that are common in those with fat malabsorption and identified in PDAC (eg, fat-soluble vitamins, zinc, vitamin B_{12}).[44] Given the inflammatory nature of PDAC, assessment might be compromised as many micronutrients are impacted by the inflammatory response, resulting in an overdiagnosis and treatment of micronutrient deficiency. For example, serum or plasma retinol concentrations should be measured to assess vitamin A status and correlated with clinical findings (ie, poor dietary intake, night blindness, Bitot spots, xerophthalmia).[45] Because the release of retinol binding protein is reduced in the setting of inflammation, concomitant assessment of C-reactive protein can assist in determining vitamin A status and the need for repletion. Similarly, vitamin D status is also impacted by inflammation, and nearly all levels become suboptimal once the C-reactive protein level exceeds 40 mg/L.[46] In those with fat malabsorption, use of water-miscible formulations is warranted to improve the bioavailability of the supplements.[47] The use of these supplements specifically in PDAC is unknown; however, these are readily studied in other pancreatic diseases. A full review of micronutrient assessment and interpretation is reported elsewhere.[46]

Pharmacological management: PERT, MCTs, and antidiarrheal medications

Pancreas enzyme replacement therapy

The National Institute for Health and Care Excellence (NICE) in the United Kingdom recommends that all patients diagnosed with unresectable PDAC be offered enteric-coated PERT.[11,48] However, despite the importance of this approach, there is limited evidence to guide individual management decisions. Evidence supports that PERT can improve fat absorption, decrease maldigestion and associated symptoms, increase survival, and improve quality of life in patients with EPI[25,32,49,50]; however, the impact on nutrition outcomes is inconsistent. In 2017, Saito et al conducted a retrospective analysis of PERT use in a cohort of those with unresectable PDAC and found a higher body mass index was associated with PERT use ($P < 0.001$), but when they performed a prospective randomized controlled trial a year later, the authors found no differences in body weight[51] ($P = 0.780$) and even some weight loss reported with PERT use.[49] Additional randomized controlled trials with longer end points to determine the impact of PERT on body weight parameters are needed. Overall, heterogeneous study designs limit conclusions of the overall impact of PERT on various outcomes in PDAC. More

robust randomized controlled trials are necessary to address these significant limitations.

Prescription PERT formulations include enteric-coated capsules, non–enteric-coated tablets, and a lipase cartridge used exclusively for EN. All enzymes approved by the Food and Drug Administration (FDA) contain various doses of porcine-derived enzymes, including proteases, amylases, and lipases.[13] Non–FDA-approved agents that are available over the counter may have fluctuating quantities of varying types of enzymes (eg, some are lipase only) and are generally not recommended for the management of EPI. The only FDA-approved oral PERT to be delivered through a gastric tube is Pertzye (Digestive Care, Inc). PERT given orally should be taken immediately before and/or during meals. Most guidelines advise starting PERT at a dose of at least 50,000 units of lipase (UL) per meal and 25,000 UL with snacks, which may be further adjusted based on symptoms, laboratory parameters, and anthropometric measures.[20,52,53] Alternatively, PERT may be dosed according to g of dietary fat intake (500–4000 UL per gram of dietary fat) or body weight (500–2500 UL per kilogram of body weight per meal).[8,54] However, it should be noted that these adjusted dosing strategies have primarily been studied and employed in children with cystic fibrosis. Nevertheless, the concept of using an individualized approach is reasonable because dietary patterns vary widely between individuals and may change over time (eg, during chemotherapy treatments).

Despite the potential benefit of PERT for patients with PDAC, PERT is infrequently used in this patient population. In one nationwide study, less than half of patients with unresectable PDAC were prescribed PERT.[55] In a subgroup analysis from this study, dietitian referral was associated with PERT prescription, indicating the value of multidisciplinary management. Furthermore, independent of the indication, PERT is often underdosed for treating EPI.[25,30–32,52] It is important for clinicians to not only start at a proper dose but also titrate the dose to resolution of symptoms (particularly for those with steatorrhea). Consideration of other dietary interventions in addition to PERT may improve the overall nutrition status and fat malabsorption in this population.

Medium-chain triglycerides

MCTs are triglycerides composed of a glycerol backbone with three fatty acids ranging between 6 and 12 carbons in length. MCTs require neither bile nor pancreatic enzymes for emulsification in the gastrointestinal tract to be absorbed into the enterocyte and enter portal circulation, unlike long-chain triglycerides. Because of this physiological property, MCT oil offers benefits to those with fat malabsorption and can serve as a significant calorie source to promote weight gain. When MCT is delivered as a supplemental oil and delivered in low doses (1–2 tablespoons or 14–28 g of fat per meal), tolerance is improved compared with higher doses that have been shown to exacerbate gastrointestinal distress and increase cramping, flatulence, bloating, and diarrhea.[56,57] Despite the physiological benefits of MCT oil, their expense and poor palatability impact acceptability, making implementation and adherence challenging.

Antidiarrheal medications

Rapid intestinal transit results in poor mixing of meals with pancreatic enzymes. Because of this, antidiarrheal medications can be used to slow intestinal transit and increase the contact time between dietary nutrients and the luminal wall. These medications are used frequently in other malabsorptive conditions and have shown improvements in decreasing fecal output and improving stool consistency.[58] As with PERT, the timing of these medications is critical to optimize absorption. Antidiarrheal medications should be taken 30–60 min before meals to allow medication absorption and a subsequent increase in intestinal transit time before the food bolus entering the gastrointestinal tract. There is a lack of consensus on dosing strategies; however, initiation of loperamide 2–4 mg before meals and at bedtime, before advancing to diphenoxylate/atropine, codeine, and tincture of opium, is a common approach in other malabsorptive conditions.[58]

Nutrition support

Enteral nutrition

Intolerance to an oral diet or an inability to meet nutrition needs through oral intake indicates a need for EN.[39] Although standard polymeric formulas can be used in EPI, peptide- and MCT-based formulas (similarly to the recommendations for oral nutrition supplements) should be considered in EPI, especially when tolerance of a standard polymeric formula is poor.[20,59] Gastric and postpyloric enteral feeding tubes can be utilized in PDAC. Unless contraindicated, gastric feeding should be initiated first and assessed for tolerance before progressing to postpyloric feeding because of the practical advantages of placing and maintaining tube placement in the stomach. There are currently no standardized recommendations regarding the use of PERT with EN, but the introduction of in-line lipase cartridges on the enteral tubing has provided an alternative route for

PERT delivery without exacerbating the risk of tube clogging.[27] Rather than requiring weight or grams of fat for dosing, one lipase cartridge is needed for every 500 ml of enteral formula. Fat hydrolysis occurs within the cartridge, with lipids being broken down into free fatty acids or monoglycerides before reaching the patient.[27] In the absence of lipase cartridges, recommendations vary on the administration of PERT in feeding tubes, and currently, only one available PERT product has an FDA indication for EN. Some suggest PERT should not be crushed and/or administered through the feeding tube,[4] whereas others suggest flushing enzymes through the feeding tube every 2 h or by adding the enzymes to the EN product before administration.[20] Most recently, Klang reported that uncoated pancreatic enzyme formulations are the only suitable pancrelipase appropriate for tube feeding administration and that this should only be considered for gastric feedings; however, these are not FDA-approved for this indication.[60]

Parenteral nutrition

PN should be used (in contrast to EN) when the gastrointestinal tract is nonfunctional or when EN is not tolerated. PN is rarely used for patients with PDAC in clinical practice (aside from in the perioperative setting).[39,52,61] In the hospitalized patient, supplemental PN should be considered when the patient is unable to meet >50% of nutrition needs through EN or during prehabilitation for those planning to undergo a surgical intervention for cancer treatment.[62]

CONCLUSION

Among individuals with PDAC, EPI is common and adversely affects nutrition and clinical outcomes, including survival. The high prevalence rates of EPI in PDAC should lead clinicians to regularly assess for signs and symptoms of fat malabsorption when treating patients with PDAC, and clinicians should have a low threshold for initiating treatment. The mainstay of treatment involves initiation of PERT, although involvement of a medical nutrition team can assist with appropriate selection of supplements and/or nutrition support. Ultimately, by improving the overall nutrition of patients with PDAC, clinicians may positively affect the patients' ability to tolerate therapies and thereby prolong survival.

AUTHOR CONTRIBUTIONS

All authors equally contributed to the conception and design of the manuscript. Gretchen Murray and Mitchell L. Ramsey equally drafted the article as co-primary authors. All authors critically revised the article and agree to be fully accountable for ensuring the integrity and accuracy of the work and for reading and approving the final article.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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How to cite this article: Murray G, Ramsey ML, Hart PA, Roberts KM. Fat malabsorption in pancreatic cancer: pathophysiology and management. *Nutr Clin Pract*. 2024;39:S46-S56. doi:10.1002/ncp.11129