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Chronic Pancreatitis and Nutrition Therapy

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Abstract

Chronic pancreatitis is a complex and irreversible disease of the pancreas and is associated with significant morbidity and mortality. Nutrition deficiencies in chronic pancreatitis are common and can be atypical in nature. As such, the management of these deficiencies can be individualized for patients. The aim of this review is to discuss the components of nutrition deficiencies in chronic pancreatitis, their management, and the current areas of research that are being explored. The clinical guidelines of major national and international societies were analyzed for recommendations on the nutrition management of chronic pancreatitis. The etiology of nutrition deficiencies in chronic pancreatitis is multifactorial and includes aspects of exocrine and/or endocrine dysfunction, significant abdominal pain, often persistent alcohol consumption, and increased metabolic activity. A large number of patients with nutrition deficiencies are underrecognized and undertreated. Although the majority of these patients can be managed by oral and pancreatic enzyme supplementation, some patients may require enteral tube feeding and, in rare cases, parenteral feeding. Current areas of research include the accurate identification of patients at risk for nutrition deficiencies, optimization of feeding regimens, and research into islet cell autotransplantation. (*Nutr Clin Pract.* 2019;34(suppl 1):S13–S26)

Keywords

chronic pancreatitis; diabetes mellitus; endocrine dysfunction; enteral nutrition; exocrine dysfunction; exocrine pancreatic insufficiency; malnutrition; nutrition deficiencies; nutrition support; sarcopenia

Introduction

Chronic pancreatitis is characterized by a chronic and progressive inflammation of the pancreas leading to irreversible pancreatic damage, which results in both exocrine and endocrine dysfunction. It has a multifactorial etiology, including environmental, genetic, and epigenetic risk factors,[1,2] and advances in the understanding of the pathophysiology have improved understanding of the disease (Table 1). In Western countries, alcohol is a common cause of chronic pancreatitis.[3] Recurrent episodes of severe acute pancreatitis are another well-defined cause of chronic pancreatitis. Oftentimes, multiple causes for chronic pancreatitis are present in an individual patient.[4] In contrast, alcohol, gall stones, and an idiopathic etiology are the common causes of acute pancreatitis. Recent consensus guidelines indicate that the correct categorization of patients based on etiology is important, as the incidence of pancreatic cancer varies between different etiologies.[5] Data on the incidence and prevalence of chronic pancreatitis are hampered by diagnostic difficulties, but current estimates suggest that a yearly incidence of 10 cases per 100,000 population, with the age-adjusted and sex-adjusted prevalence in the United States of 42 cases per 100,000 population.[6,7]

Chronic pancreatitis poses a major public health concern from the perspective of patient quality of life and represents a significant multidisciplinary challenge for healthcare professionals. Over 90% of patients are hospitalized at least once for pain associated with their disease.[8] There are numerous causes of malnutrition in chronic pancreatitis, which often coexist. There is a significant cost associated with treating the endocrine and exocrine dysfunction in chronic pancreatitis, occurring as both medical and surgical intervention.[9] Pancreatic exocrine insufficiency is often underrecognized and undertreated, with up to 70% of

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Table 1. Etiology of Chronic Pancreatitis by TIGAR-O Classification.

Class	Examples
Toxin-metabolic	Alcohol
	Tobacco smoking
	Hypercalcemia
	Hyperlipidemia
	Chronic renal failure
	Medications
	Toxins
Idiopathic	Early onset (slower development of calcification and exocrine and endocrine insufficiency)
	Late onset (faster development of calcification and exocrine and endocrine insufficiency)
	Tropical calcific pancreatitis
Anatomical obstruction	Pancreatic divisum
	Post irradiation
Autoimmune	Autoimmune pancreatitis
Recurrent and severe acute pancreatitis	Recurrent acute pancreatitis
Genetic pancreatitis	PRSS1 mutation
	PRSS2 mutation
	CFTR mutation
	SPINK1 mutation
	CTRC mutation
	Cationic trypsinogen mutation
	α-1 antitrypsin deficiency

CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; PRSS1, serine protease 1; PRSS2, serine protease 2; SPINK1, serine peptidase inhibitor, Kazal type 1; TIGAR-O, Toxic-metabolic, idiopathic, genetic, autoimmune, recurrent, obstructive.

patients reporting symptoms of steattorhea.[10] Up to 35% of patients with diabetes mellitus can have concomitant pancreatic exocrine insufficiency.[11,12] Management of the malnutrition in chronic pancreatitis is more challenging than in other chronic illnesses, as the pathology is within the very structure involved in nutrient digestion, absorption, and assimilation. Anatomically, the pancreas is located in the retroperitoneum, with the exception of the pancreatic tail, which can make accessing the pancreas challenging. Functional pancreatic acinar cells are required for enzyme secretion, in addition to a functional and patent pancreatic ductal system for the delivery of pancreatic secretions to the duodenum. Pancreatic endocrine function is essential for cellular and systemic metabolism. In chronic pancreatitis, either or both of these functions can be partially or completely impaired.

The aim of this review is to describe components of malnutrition associated with chronic pancreatitis, including endocrine and exocrine insufficiency and some of the other major contributors to malnutrition. A description of the spectrum of micronutrient and mineral deficiency and the effect of malnutrition on patient outcomes is discussed. The modalities for nutrition therapy that are available to healthcare professionals are reviewed. It will also describe some of the current avenues of innovation that are being explored to address current shortcomings in these regards.

Malnutrition Associated With Chronic Pancreatitis

Malnutrition is an acute, subacute, or chronic state of nutrition in which combinations of varying degrees of overnutrition or undernutrition, with or without inflammatory activity, lead to changes in body composition and diminished physical function.[13-15] The cause of malnutrition associated with chronic pancreatitis is multifactorial and can result from an aggregation of exocrine insufficiency, endocrine insufficiency, chronic abdominal pain, alcohol use, delayed gastric emptying, and increased metabolic activity.[16,17]

No studies have specifically addressed the relative importance of the different causes of malnutrition in patients with chronic pancreatitis. Pancreatic enzyme insufficiency, leading to steatorrhea and malabsorption, is one of the most important causes of malnutrition in chronic pancreatitis and should always be considered when malnutrition is suspected in these patients.[18]

Exocrine Insufficiency

Pancreatic exocrine insufficiency can arise from insufficient production of pancreatic enzymes, blockage of enzyme from being excreted via the pancreatic duct, reduced

Table 2. Tests Used to Evaluate Pancreatic Exocrine Insufficiency.

Test	Details	Advantages	Limitations
Fecal fat quantitation	Collection of all stool samples in a 3-day period to quantitate fecal fat, and the coefficient of fat absorption	Accurate quantitation of fat absorption	3-day test Requires patient adherence to strict diet Handling of large volumes of feces by laboratory personnel
Fecal elastase 1	Quantitative measurement of elastase-1 in single stool sample	Noninvasive Single stool sample required	Inaccurate with large-volume diarrhea Inaccurate in mild to moderate exocrine insufficiency
^{13}C-mixed triglycerides breath test	Measurement of $^{13}CO_2/^{12}CO_2$ in serial exhaled breath samples following ingestion of ^{13}C-mixed triglycerides in a standardized meal ^{13}C-mixed triglycerides are degraded to fatty acids and metabolized. Exhaled $^{13}CO_2$ can be measured in exhaled breath samples	Measurement of fat absorption and metabolism	Variation in protocols between institutions Long test (6 hours)
Secretin-cholecystokinin stimulation test	Gastroduodenal tube is inserted. Gastric limb collects gastric secretions. Basal pancreatic secretions are collected in the duodenal tube Intravenous secretin is administered over 2 hours, and cholecystokinin is administered over the second hour. Pancreatic secretions are collected from the duodenal limb every 15 minutes Quantitation of the fluid volume, bicarbonate, and pancreatic enzymes is performed	Direct measurement of pancreatic secretions Allows measurement of pancreatic ductal and acinar cells	Poorly tolerated by patients Relatively long test Invasive Requires specialized endoscopy and fluoroscopy services

bicarbonate, and/or asynchrony in getting the enzymes to meet food in the intestine.[5] The identification of patients with pancreatic exocrine insufficiency in chronic pancreatitis is on the basis of clinical suspicion, diagnostic tests, and imaging.[19] Clinical symptoms and signs of exocrine insufficiency include diarrhea, bloating, and cramping with meals; abdominal pain; foul-smelling and greasy-appearing stools; and weight loss. Optimal testing to diagnose pancreatic exocrine insufficiency consists of a test that can detect poor digestion of fats with high sensitivity and specificity (Table 2).[19]

Historically, the coefficient of fat absorption was the standard for the diagnosis of severe pancreatic exocrine insufficiency. It is the only test currently acceptable to the US Food and Drug Administration (FDA) and the European Medicines Agency for the indication and monitoring of pancreatic enzyme replacement therapy in clinical trials.[5] This test requires patients to adhere to a strict diet containing 100 g of fat per day for 5 days, with the collection of all patient feces for the final 3 days of this 5-day period. A coefficient of fat absorption of <93% is considered pathological for severe pancreatic enzyme insufficiency.[20] There is significant variability and error with this test, and it has largely been replaced. The secretin-cholecystokinin (CCK) stimulation test is a direct measure of pancreatic function and is the current gold standard for diagnosis.[21] The secretin-CCK test is a combination of 2 tests—the secretin test, which measures pancreatic ductal cell bicarbonate and fluid secretion, and the CCK test, which measures pancreatic acinar cell enzyme secretion. The combined test involves the direct collection of pancreatic secretions through placement of a gastroduodenal tube to collect duodenal juice. A gastric tube is used to remove acidic gastric secretions for the duration of the test. After collecting basal secretions, intravenous secretin is administered over a 2-hour period, a CCK analogue (cerulean) is administered in the second hour, and serial samples of pancreatic juice are collected over a 2-hour period.[22,23]

However, the use of secretin-CCK stimulation is diminishing, as it is invasive, poorly tolerated by patients, and time-consuming, and it has been essentially replaced by fecal elastase 1 (FE-1) in most centers. FE-1 is a pancreatic enzyme that is stable as it passes through the gastrointestinal tract. This allows it to be a simple and noninvasive test to evaluate pancreatic secretion.[22,24,25] This test is widely

Table 3. Rosemont Classification of Chronic Pancreatitis on Endoscopic Ultrasound and Association With Pancreatic Exocrine Insufficiency.

	Feature Observed on Endoscopic Ultrasound	Histological Correlation	Association With Pancreatic Exocrine Insufficiency[31]
Parenchymal features			
Major criteria	Hyperechoic foci with shadowing	Parenchymal calcifications	X
	Parenchymal lobularity with honeycombing	Unknown	
Minor criteria	Parenchymal lobularity with honeycombing	Unknown	
	Hyperechoic foci without shadowing	Unknown	
	Parenchymal cysts	Pseudocyst	
	Stranding	Unknown	
Ductal features			
Major criteria	MPD calculi	Stones	X
Minor criteria	Irregular MPD contour	Unknown	
	Dilated side branch	Side-branch ectasia	
	MPD dilation	MPD dilation	X
	Hyperechoic MPD margin	Ductal fibrosis	

MPD, main pancreatic duct.

available, only requires a small stool sample for analysis, and has been shown to have a role in the diagnosis of pancreatic exocrine insufficiency.[26] Lower stool concentrations of FE-1 are correlated with the increased probability of pancreatic exocrine insufficiency, but it is accepted that FE-1 is not suitable for excluding mild to moderate pancreatic enzyme insufficiency.[27] In these cases, tests such as the secretin-CCK stimulation test are more reliable in detecting mild to moderate exocrine insufficiency. Additionally, as FE-1 measurement is a quantitative test per gram of feces, the test can be inaccurate with excessive dilution, as in the case of patients with large-volume diarrhea.[28]

In addition to these diagnostic tests, anatomical imaging has a significant role in assessing exocrine insufficiency, as structural causes can contribute to impaired pancreatic enzyme secretion into the duodenum. These tests include endoscopic retrograde cholangio-pancreatography (ERCP), computed tomography (CT), endoscopic ultrasound (EUS), or magnetic resonance imaging (MRI) to identify a structural irregularity with the pancreatic ductal system.[29,30] However, CT, ERCP, and MRI have poor sensitivity for the identification of mild to moderate chronic pancreatitis.[31] The risk of pancreatic enzyme insufficiency can be estimated using the Rosemont classification system, which was originally created for EUS-based criteria for a diagnosis of chronic pancreatitis.[31] These features consist of ductal and parenchymal changes (Table 3). A recent study of 128 patients with chronic pancreatitis demonstrated that the presence of intraductal calcifications, hyperechoic foci with shadowing, and main pancreatic duct dilation were significant risk factors for pancreatic exocrine insufficiency, for which the probability is 82.8% with the presence of main pancreatic duct calculi and dilation.[29] This is an important aspect in the nutrition care of patients with chronic pancreatitis, as anatomical obstruction is 1 of the core features of exocrine insufficiency.

Endocrine Insufficiency

Endocrine dysfunction in chronic pancreatitis is complex and can be as a result of reduced insulin production, increased insulin resistance, or a combination of both.[32,33] Pancreatogenic diabetes (type 3c diabetes mellitus) differs from other types of diabetes mellitus, as it arises from diseases of the exocrine pancreas.[34] In a large study that reclassified patients on the basis of guidelines from the American Diabetes Association, 8% of patients were classified as having type 3c diabetes mellitus, the majority of whom were patients with chronic pancreatitis.[35] Although diagnostic criteria have been reported, it is generally an underappreciated subtype of the disease and can be challenging to manage.[36] There are major criteria that must be present for diagnosis: pancreatic exocrine insufficiency, absence of antibodies associated with type 1 diabetes mellitus, and pathological pancreatic imaging. Minor criteria include absent pancreatic polypeptide secretion, impaired incretin secretion, no excessive insulin resistance, impaired β cell function, and low serum levels of fat-soluble vitamins.[36] Patients with type 3c diabetes mellitus can have reduced glucagon secretion and decreased pancreatic polypeptide, which is a distinguishing factor from type 1 diabetes mellitus.[37] With a combination of nutrient malabsorption, a poor oral diet, chronic pain, smoking, and potentially alcohol use, these patients are at high risk of large swings in blood glucose and poor nutrition.[38] This can be a significant challenge for patients requiring oral supplementation or

enteral tube feeds with the timing and quantity of insulin administration.

Abdominal Pain

There is considerable pain associated with chronic pancreatitis, with rates of 77% reported in a prospective multi-institutional cohort study of 540 patients.[8] This is a central factor for patients with chronic pancreatitis, as it has a multifaceted effect on nutrition. As patients can experience increased pain with eating, food intake can be substantially reduced, resulting in weight loss. This often necessitates patients to require opioids as part of an analgesia regimen, which are also associated with poor nutrition intake.[39] As sufficient pain control is difficult to achieve, this can often be a major obstacle for effective nutrition intervention.

Delayed Gastric Emptying

Delayed gastric emptying is a common feature in patients with chronic pancreatitis, but it can be challenging to distinguish pancreatitis from delayed gastric emptying clinically, as they share similar symptoms.[40] Although the exact etiology of this is unclear, gastric dysmotility is also a common feature following pancreatic resection, and there are a number of hypothesized mechanisms. These include intraoperative vagus nerve injury and duodenal resection, which affects hormone levels and normal gastric motility.[41] Some studies have shown a reduction in delayed gastric emptying with modifications of the classical pancreaticoduodenal resection.[42] As previously mentioned, opioid use is common in patients with chronic pancreatitis, which also likely contributes to delayed gastric emptying.

Alcohol Use

Alcohol use is typically the most common cause of chronic pancreatitis globally.[43] However, patients often continue to consume alcohol following diagnosis, which has multiple effects on nutrition. Alcohol use is significantly associated with abdominal pain in chronic pancreatitis, and as such, this adds a challenging element to the nutrition management of patients.[8] This can further precipitate micronutrient deficiencies and increase the difficulty in managing diabetes mellitus. Oftentimes, alcohol can replace part or the majority of a patient's diet, and effective intervention for alcohol addiction can require extensive multidisciplinary input. Alcohol can also have a direct effect on the gastrointestinal tract to interfere with small-intestinal absorption and with colonic microbial metabolism.[44]

Metabolic Activity

Increased metabolic activity and systemic inflammation are seen in patients with chronic pancreatitis,[45] and this is further compounded by poor nutrition. Chronic pancreatitis has a well-defined association with increased resting energy expenditure.[46] A recent systematic review demonstrated that chronic pancreatitis is associated with differential expression of 41 serum inflammatory mediators (eg, interleukin [IL]-10, IL-6, IL-4, IL-12, IL-8; tumor necrosis factor [TNF]α; transforming growth factor [TGF]-β; interferon [IFN]-γ).[47] Rasch et al hypothesized that there is an integral reciprocal relationship between local pancreatic inflammation and systemic inflammation. TGF-β was found to be increased in patients with chronic pancreatitis compared with controls and is a central regulator of fibrosis. Similarly, macrophage inhibiting cytokine-1 is increased in chronic pancreatitis, is a member of the TGF-β superfamily, and is known to act in the hypothalamus to regulate appetite.[48] There is a reciprocal decrease in IFN-γ in patients with chronic pancreatitis, which has an association with an inhibitory effect on fibrosis.[49] TNF-α is also significantly increased in patients with chronic pancreatitis compared with controls. TNF-α has a well-defined role in muscle catabolism and sarcopenia, mediated in part through the mammalian target of rapamycin signaling cascade.[50] These mediators have been associated with the "inflammageing" phenomenon, which is the term coined for inflammation associated with increased biological ageing.[47,51] However, the role of a number of these mediators in chronic pancreatitis needs further investigation.

Micronutrient and Vitamin Deficiency

A recent review described the spectrum of micronutrient and mineral deficiencies associated with chronic pancreatitis.[16] Micronutrient deficiency can be common in chronic pancreatitis, which can be precipitated because of a number of reasons.[52,53] There is a well-established spectrum of fat-soluble vitamin deficiencies associated with chronic pancreatitis, and patients can be deficient in a number of them simultaneously.[54] Although the loss of fat-soluble vitamins such as vitamins A, D, E, and K can correlate with the severity of steatorrhea, other altered aspects of nutrition, such as poor intake and increased requirement, contribute to the deficiency state. Rates of between 1% and 16% for vitamin A deficiency, 33% and 87% for vitamin D deficiency, 2% and 27% for vitamin E deficiency, and 13% and 63% for vitamin K deficiency have been reported in studies on chronic pancreatitis.[53,55-57] Vitamin supplementation is recommended when clinically indicated on an individualized basis.[58] Oral supplementation with vitamin D (1520 IU/d) was shown to increase vitamin D levels significantly in chronic pancreatitis patients compared with placebo.[59] This is particularly important because of the association of increased osteopenia/osteoporosis in patients with chronic pacreatitis.[60] Intervention studies on other fat-soluble vitamin deficiencies are warranted. Although biochemical deficiency of the fat-soluble vitamins appears to

Table 4. Summary of the Types of Nutrition Supplementation for Patients With Chronic Pancreatitis.

Type of Supplementation	Function	Challenges
Oral supplementation	For patients with caloric deficits despite normal diet	Coordination of oral supplementation with pancreatic enzyme supplementation Delayed gastric emptying Nausea and vomiting Diarrhea Constipation from opioid use
Pancreatic enzyme replacement therapy	Supplements diminishing endogenous pancreatic enzyme	Titration of dose Timing of dose Addition of acid suppression medication
Enteral feeding	For patients unable to meet caloric intake through normal oral intake	Maintenance of enteral feeding tube Feeding-tube intolerance Continuous vs bolus feeds for patients Coordination of pancreatic enzyme delivery Risk for aspiration of contents Cost of feeding-tube home supplies
Parenteral feeding	Complex anatomical disease Malnourished patients with GI dysfunction prior to surgery Failed enteral nutrition	Maintenance of vascular access Adverse effect on liver function No long-term data on safety or efficacy in chronic pancreatitis

GI, gastrointestinal.

be reasonably common, clinical manifestations of deficiency in chronic pancreatitis are rare, take years to develop, and occur when there is an additional comorbidity such as diabetes or celiac disease or after surgery.[61] However, empirical treatment with pancreatic enzyme replacement therapy and vitamin supplementation is successful in treating these deficiencies.

Deficiencies of water-soluble vitamins in chronic pancreatitis are less frequent, but studies are scarce.[62] However, the risk of thiamin deficiency secondary to concomitant alcoholism should be considered. Mineral deficiencies of magnesium, zinc, copper, and selenium have been reported, and although supplementation of these is likely to be of benefit in chronic pancreatitis, intervention studies are warranted.[63-65]

Effect of Malnutrition on Patient Outcomes

Malnutrition can have a major negative impact on patient outcomes. It severely impacts patient quality of life and is a major component of patient disability and loss of work productivity.[66] Chronic pancreatitis patients with constant pain and/or severe pain are more likely to require hospitalizations.[8] The prevalence of chronic pancreatitis patients being underweight is reported to be between 8% and 39%, with higher rates being reported in India.[67-71] However, variations of malnutrition can exist in the absence of these criteria (eg, sarcopenia or specific nutrient deficiencies), and the sole use of weight loss or change in body mass index may not identify all patients.[72] A single study reported 17% of chronic pancreatitis patients to have sarcopenia.[73] As expected from the oncology literature, sarcopenia was a significant risk factor for increased hospitalizations, increased length of stay, and reduced overall survival.[73] However, further studies are required to fully delineate the role of sarcopenia in chronic pancreatitis.

Management of Nutrition

The nutrition management of chronic pancreatitis can be challenging, but there are number of different approaches to facilitate an individualized patient regimen. Because of the potential combination of inadequate caloric intake and maldigestion, patients require detailed nutrition care. In addition to these different modalities, a particular focus should be placed on alcohol and smoking cessation. Smoking can affect the nutrition status of patients through a number of mechanisms. It is independently associated with chronic pancreatitis development and progression and is a significant risk factor for pancreatic cancer.[74] In alcoholic chronic pancreatitis, smoking is associated with earlier age of diagnosis.[75] Additionally, smoking is associated with pancreatic and systemic inflammation[76] and is a risk factor for diabetes mellitus.[77] The majority of patients can be managed with normal food with exogenous pancreatic enzyme supplementation. Typically, 10%–15% of patients will require oral nutrition supplementation (this can be higher in clinical practice), and 5% will require tube feeding.[78,79] Some of the different approaches to nutrition management are described in Table 4. Serial dietary assessment should be

Table 5. Examples of Oral Dietary Supplements.

Type of Supplement	Characteristic and Indications
Standard 1–1.5 kcal/mL polymeric supplement	Standard balanced nutrition supplement Available with various macronutrient contents May contain fiber
Clear supplement	Useful when patients are limited to a clear liquid diet or when patients do not tolerate standard supplements Usually lower in fat than standard supplements but may be higher in carbohydrates
Nutrient-dense supplement	2 kcal/mL Useful when patients need low-volume, high-density supplement
Low-carbohydrate supplement	Available with various kcal and protein contents Reduced carbohydrate content for patients with diabetes mellitus or those who want to restrict carbohydrates
Renal Supplement	Contains reduced potassium, phosphorus, and volume compared with standard formulas Suitable for patients with electrolyte disorders or renal insufficiency or on dialysis
Thickened supplement	Suitable for patients with dysphagia or swallowing disorders requiring texture and/or liquid-consistency modifications Available in low-sugar varieties

an integral part of the management and should include type, amount, and volume of food eaten (fat content); timing of enzymes; and monitoring of weight and muscle mass. Food diaries and smartphone applications have previously been used in patients with diabetes mellitus, which could be translated for recording the diets of patients with chronic pancreatitis.[80]

Oral Diet and Supplements

Nutrition requirements for patients with chronic pancreatitis have been described previously by Duggan et al.[58] A low-fat diet has been advocated by the American Gastroenterology Association and American College of Physicians to aid in managing abdominal pain associated with chronic pancreatitis.[81,82] However, the persistence of this having an effect long term is questionable and may put already-at-risk patients at further risk for malnutrition. Special consideration should be given to carbohydrates in the setting of patients with diabetes mellitus and chronic pancreatitis.[52] A low-fiber diet is also recommended, as dietary fiber can absorb or prevent the mechanism of action of pancreatic enzymes.

In the setting of failing normal oral nutrition intake, oral supplements can be considered as a support (Table 5). There are many oral dietary supplements available on the market, which are selected on the basis of individualized patient needs. The addition of oral elemental supplements in patients with chronic pancreatitis has been suggested. Oral elemental supplements (eg, Vivonex, Nestle HealthCare Nutrition; Bridgewater, NJ) have been associated with a marked reduction in pain scores and an improvement in nutrition indices.[82,83] However, its unpalatable taste significantly affects adherence by patients. Moreover, the use of this diet for long-term nutrition is significantly hampered, as patients can become deficient in other nutrients such as essential fatty acids. Although a liquid diet has previously been advocated in the setting of a flare of acute pancreatitis, a meta-analysis showed no difference in pain score compared with a solid diet, with the negative addition of fewer calories consumed.[84]

Enteral Nutrition

Tube feeding is used in the setting of failed oral nutrition (pain, nausea, vomiting with oral intake), and nasojejunal feeding has previously been shown to be effective for patients with chronic pancreatitis, in terms of weight gain, pain control, and a reduced requirement for opioid analgesia.[85,86] Although whole-protein formulas are typically well tolerated, peptide-based or elemental formulas may be required for tube feeds. There are a large number of different products on the market, which can make the choice of enteral product challenging.[87,88] However, there are a number of patients-specific factors that help to direct care.[87] For patients who are unable to tolerate large fluid volumes or are on bolus feeds, calorie-dense formulas are an appropriate choice. Fiber-supplemented formulas can assist in bulking stool to aid peristalsis, which may not be an optimal choice for patients with chronic pancreatitis, because of the interaction with pancreatic enzymes. In the case of patients with diabetes mellitus, formulas that are

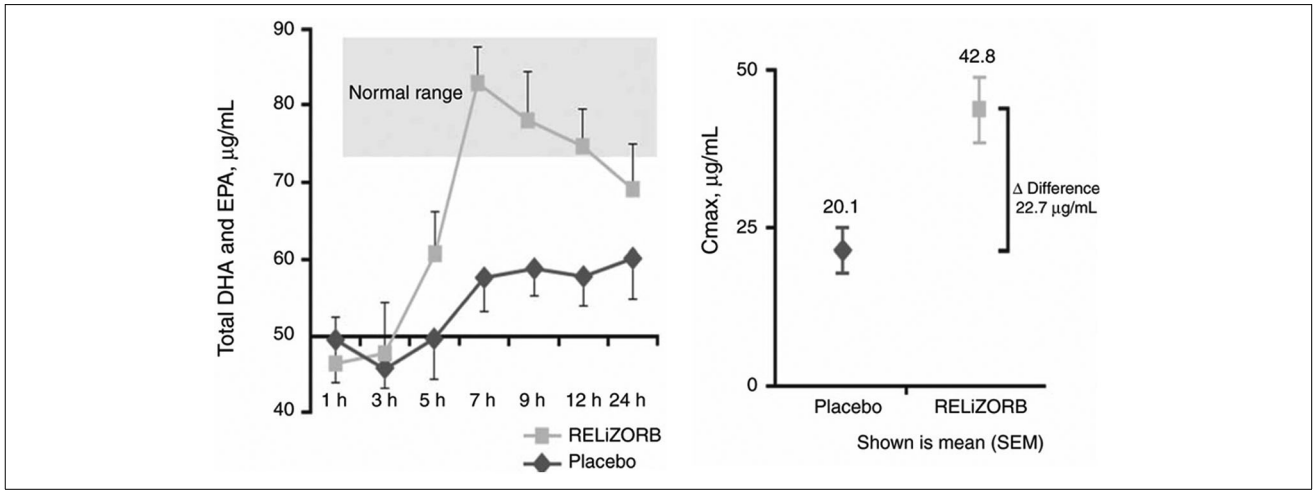

Figure 1. Increased plasma absorption of docosahexaenoic acid (DHA)and eicosapentaenoic acid (EPA) (baseline adjusted) with use of lipase cartridge compared with placebo maximum concentration (C_{max}). Reproduced with permission from Freedman S, Orenstein D, Black P, et al. Increased Fat Absorption From Enteral Formula Through an In-line Digestive Cartridge in Patients With Cystic Fibrosis. *J Pediatr Gastroenterol Nutr.* 2017;65(1):97-101. https://doi.org/10.1097/MPG.0000000000001617.

carbohydrate-restricted with increased fat content are an appropriate option. A number of these elements could be associated with chronic pancreatitis and should be considered in the product choice.

A nasal approach is the least invasive and the cheapest approach, and a trial of naso-jejunal feeding can be considered to assess whether the nutrition status improves and is tolerated.[52] However, if longer-term nutrition support (>4–6 weeks) is being considered, a gastrostomy tube with a jejunal extension or a direct jejunal tube can be placed for convenience (radiological, endoscopic, or surgical approach).[52] The optimal route of the delivery and type of tube is uncertain and is dependent on individual patient factors such as past operations or abnormal gastrointestinal anatomy, such as hepatomegaly.[89]

The effect of continuous or bolus (intermittent) feed regimen on glycemic control is complex, as educated patients can dose insulin for their bolus feed as they would for a regular meal, but there are some challenges with it. This allows patients to have significantly more independence. However, bolus tube feeds should not be advised in patients who are medically unstable, are at risk for aspiration, or have not shown a tolerance to bolus feeds.[89]

The timing for tube feeds is a current area of difficulty for patients. Coordinating sufficient enzymatic supplementation with the delivery of tube feeds is challenging. A recent clinical trial in pediatric patients with cystic fibrosis described the use of a pancreatic lipase cartridge (RELiZORB, Alcresta Therapeutics, Inc.; Newton, MA) inserted into the delivery system of enteral feeding tubes, to help improve fat absorption (Figure 1).[90] It is a single-use cartridge containing lipase-coated beads through which the enteral feed passes. The lipase hydrolyzes >90% of triglycerides to monoglycerides and free fatty acids in most formulas tested, and importantly, the beads do not enter the patient and are not counted against the maximum lipase dose count for a patient (Figure 2).[91]

Parenteral Nutrition

Guidelines from The European Society for Parenteral and Enteral Nutrition (ESPEN) indicate that <1% of chronic pancreatitis patients will require parenteral nutrition.[52,78] This is often reserved for cases of duodenal stenosis, complex fistulization, or malnourished patients with gastrointestinal dysfunction prior to surgery, as enteral nutrition is preferred for the management of chronic pancreatitis.[92] There are currently no trials examining the long-term use of parenteral nutrition in chronic pancreatitis.

Pancreatic Enzyme Replacement Therapy

There are 6 formulations of pancreatic enzyme currently approved by the FDA in the United States (Table 6). Multiple studies have demonstrated the safety and efficacy of oral exogenous pancreatic enzyme preparations, but patient education is key to its function.[93-95] The efficacy of pancreatic enzyme replacement therapy is dependent on a number of factors: (1) efficient mixture with meal, (2) gastric emptying with meal, (3) mixing with duodenal chyme and bile acids, and (4) timely delivery of enzymes into the duodenum.[5] Enzyme dosing is calculated by the size and fat content of a meal. Typical starting recommendations is 500 units of lipase/kg of body weight per meal and half of that for snacks, which are titrated as per individual patient needs. Patient education with the fat content of food is important to aid in this titration. In the setting

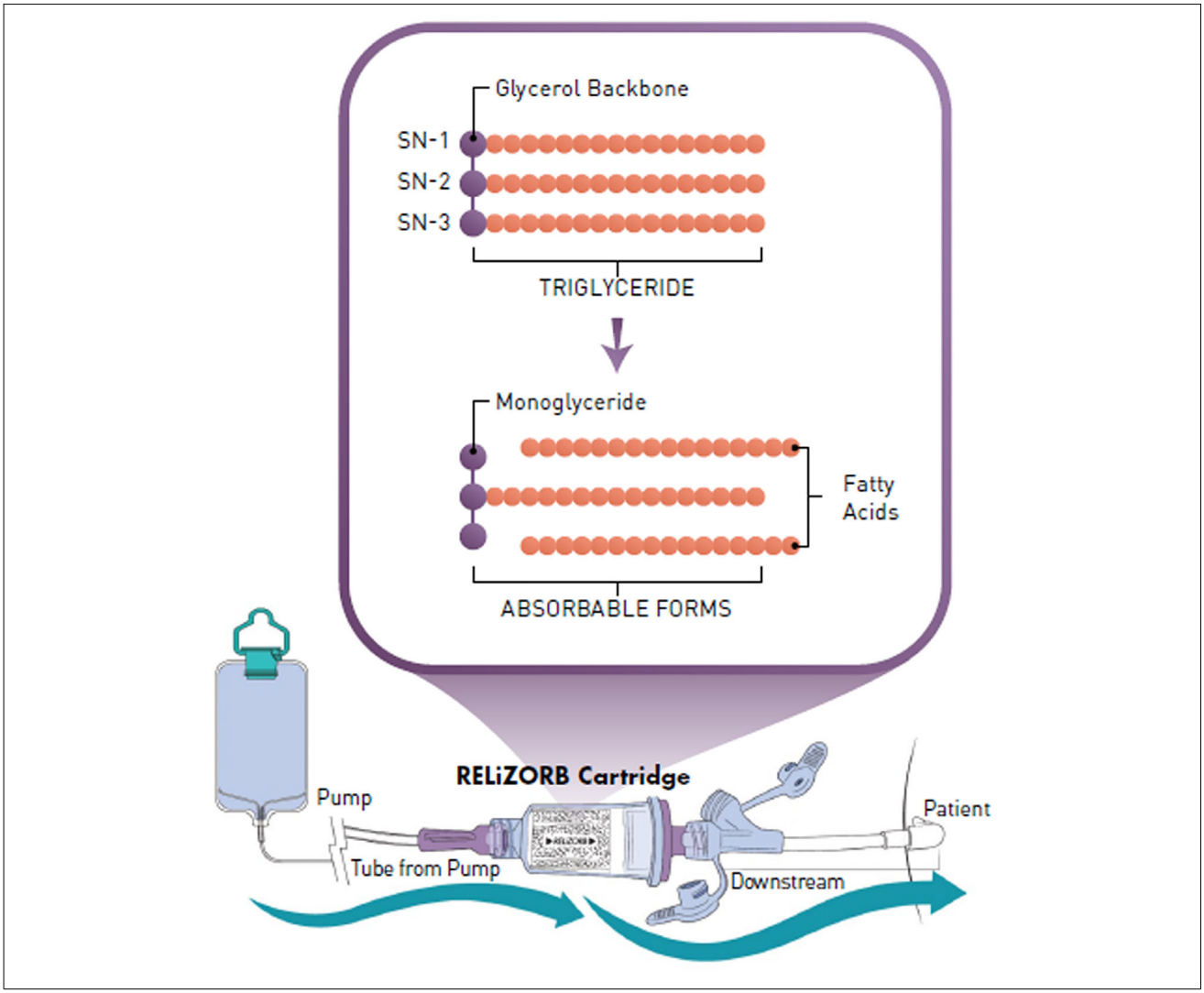

Figure 2. Representation of the lipase cartridge system. The Relizorb cartridge is sited in line between the tube feed bag and the patient in the tube. SN, stereospecific number. Reproduced with permission from Freedman SD. Options for addressing exocrine pancreatic insufficiency in patients receiving enteral nutrition supplementation. *Am J Manag Care*. 2017;23(12 Suppl):S220-S228.

of poor clinical response, the dose with each meal can be increased (doubled or tripled). However, it is important for patients not to exceed the maximum recommended dose of 10,000 units/kg/d or 4000 units/g of fat per day.[96,97] A recent study demonstrated the benefit of combined vitamin supplementation with pancreatic enzyme replacement therapy on the serum vitamin levels.[98] This suggests a role for combined therapy in patients with chronic pancreatitis. Additionally, despite the chemical formulation, exogenous preparations can be degraded by gastric acid. Some studies have demonstrated a clinical benefit to the addition of a proton pump inhibitor or H2 antagonist to prevent enzymatic degradation.[99,100] Others have advocated for spreading out oral pancreatic enzymes throughout a meal.

Pancreatic Surgery and Effect on Nutrition

Procedures for the treatment of chronic pancreatitis vary from minimally invasive to extensive surgical resections, which have major effect on patient nutrition.[101] As previously mentioned, patients require additional nutrition supplementation prior to surgery. Endoscopic sphincterotomy and/or stenting of the pancreas can assist in alleviating anatomical obstruction of the pancreas. There are a number of well-described drainage procedures (eg, Frey procedure, Berger procedure, Berne procedure) that can alleviate anatomical abnormalities not amenable to endoscopic decompresion.[101,102] Pancreatic resection can be an option in cases of a pancreatic mass, common bile duct obstruction, and previously failed drainage.[102]

Table 6. FDA-Approved Oral Pancreatic Enzyme Preparations.

	Pancreatic Enzyme Preparation				
Name	Amylase units	Lipase units	Protease units	Formulation	Manufacturer
Creon	15,000	3000	9500	Oral, delayed-release capsule	AbbVie, Inc
	30,000	6000	19,000		
	60,000	12,000	38,000		
	120,000	24,000	76,000		
	180,000	36,000	114,000		
Zenpep	14,000	3000	10,000	Oral, delayed-release capsule	Allergan, Inc
	24,000	5000	17,000		
	42,000	10,000	32,000		
	63,000	15,000	47,000		
	84,000	20,000	63,000		
	105,000	25,000	79,000		
	168,000	40,000	126,000		
Pancreaze	10,850	2600	6200	Oral, delayed-release capsule	Vivus, Inc
	17,500	4200	10,000		
	43,750	10,500	25,000		
	70,000	16,800	40,000		
	61,000	21,000	37,000		
Ultresa	8000	4000	8000	Oral, delayed-release capsule	Aptalis Pharma, Inc
	27,600	13,800	27,600		
	41,400	20,700	41,400		
	46,000	23,000	46,000		
Viokace	39,150	39,150	39,150	Nonenteric coated, immediate-release tablet	Allergan, Inc
	78,300	78,300	78,300		
Pertyze	15,125	4000	14,375	Oral, delayed-release capsule with bicarbonate-buffered enteric-coated microspheres	Digestive Care, Inc
	30,250	8000	28,750		
	60,500	16,000	57,500		
	90,750	24,000	86,250		

FDA, US Food and Drug Administration.

Importantly, there may be a need for postoperative pancreatic enzyme replacement and there is a risk of diabetes mellitus, depending on the extent of pancreatic resection. In the setting of failure of other treatments to control symptoms, some specialized centers perform a total pancreatectomy for chronic pancreatitis with the potential for islet cell autotransplantation to prevent diabetes mellitus, which has major implications for nutrition care.[103] These centers adopt a multidisciplinary approach, and criteria for assisting in patient selection have been described, as patients with chronic pancreatitis often have a significant β-cell reserve.[104] Patients who already require insulin but who are thought to have some islet function are still considered for transplantation.[103,105] Although these patients will not be insulin-free, the islets may help to prevent large swings in blood glucose. As there is considerable complexity to the management of diabetes mellitus and pancreatic enzyme replacement, patients with active alcoholism, illicit substance abuse, or untreated psychiatric issues are not considered for islet cell autotransplantation. Additionally, specific conditions such as significant liver disease, portal hypertension, known pancreatic cancer, or the presence of high-risk cardiopulmonary disease are contraindications for the procedure.[104]

Future Directions

Current screening methods for the diagnosis of exocrine deficiency in patients with chronic pancreatitis are lacking. As previously mentioned, a significant proportion of patients with chronic pancreatitis reported symptoms of steatorrhea.[10] Serial and affordable testing of pancreatic function and response to current therapies are required for patients with chronic pancreatitis to prevent nutrition deterioration. Rasch et al demonstrated that there are blood-based analytes that are differentially expressed in chronic pancreatitis, but multi-institutional studies are required for biomarker characterization and validation.[47]

A recent study indicated that sarcopenia in chronic pancreatitis was associated with increased hospitalizations and reduced overall survival.[106] The protocol for a clinical trial examining the role of exercise therapy in sarcopenic patients with chronic pancreatitis was recently published, the results of which have not been published, to the best

of our knowledge.[107] However, evidence from the oncology literature would indicate that prehabilitation, including nutrition optimization and exercise therapy, is associated with improved outcomes.[108] This could suggest that exercise therapy will have a major role for chronic pancreatitis patients in the future, but a robust screening tool for sarcopenia is needed, as there is variability in the current screening tools.[109]

Although tube feeding in chronic pancreatitis is only required in a minority of patients, this consists of a major change and challenge to the lives of patients with chronic pancreatitis. Additionally, the tube-feeding sets currently available on the market may be difficult for patients to physically set up. The increased use of community-based registered dietitian clinics or home nursing support could be a solution in a transition period for commencing new regimens.

Advances in molecular and stem cell biology have the potential to help improve postoperative nutrition care in chronic pancreatitis patients requiring pancreatic resection. The yield of islet cells from pancreases for islet cell autotransplantation can vary, and cellular reprogramming technology is being used to reprogram pancreatic ductal cells to insulin-producing cells.[110]

Conclusion

The nutrition management of patients with chronic pancreatitis is complex and requires a multidisciplinary approach. A deepened emphasis needs to be placed on patient education and awareness surrounding the condition. Research needs to be focused in the different areas that contribute to malnutrition to improve the overall patient status. Although there have been advances in the understanding of exocrine and endocrine insufficiencies and in other areas contributing to malnutrition, objective and reproducible biomarkers are needed to allow for earlier referral to nutrition professionals. This may allow the implementation of simpler strategies for nutrition intervention without the presence of challenging complications of chronic pancreatitis. Significant improvements in care have been made over the past number of years, but integrating modern technology and institutional collaboration may help to make further progress in the future.

Statement of Authorship

Both authors were involved in data acquisition, interpretation, drafting of the manuscript, and critical revision of the manuscript. Both authors approved the final draft.

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