COMMENTARY

Children with Exocrine Pancreatic Insufficiency: Nutrition Evaluation and Management

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DESCRIPTION

The pancreas has two functions: Exocrine and endocrine. The exocrine function involves the secretion of digestive enzymes. The endocrine function includes secreting insulin, glucagon, etc., which help regulate blood glucose. Exocrine Pancreatic Insufficiency (EPI) refers to impaired production of digestive enzymes and bicarbonate, which can cause maldigestion and malabsorption. Cystic fibrosis, chronic pancreatitis, Schwachman-Diamond syndrome, Pearson syndrome, and Johanson-Blizzard syndrome are more common causes of EPI in the pediatric population. Pancreatic aplasia or hypoplasia, Jeune syndrome, pancreatectomy, and isolated pancreatic enzyme deficiencies are less common etiologies [1-3]. Moreover, EPI may occur in inflammatory bowel disease, celiac disease, diabetes, and Sjogren's syndrome.

It is estimated that the pancreas secretes around two and a half liters of fluid in adults every day. In children, the volume and rate of secretion are closely correlated with their Body Surface Area (BSA) [4,5]. The secretion of the pancreas reacts to nutrient intake. Pancreatic fluid is isotonic, with a pH slightly over 8. The secretion contains bicarbonate, proteins, electrolytes, and water. Acinar cells are responsible for producing, storing and releasing zymogens (inactive digestive enzymes), which possess proteolytic, amylolytic, or lipolytic properties. The release of zymogens into the pancreatic ducts is regulated by receptors and is calcium dependent. These proenzymes are activated in the intestine by trypsin, which is first activated through enterokinase located on the brush border of the mucosa of the proximal small intestine. Ductal cells secrete one to two liters of neutral pH fluid, mainly including water and bicarbonate. Ductal secretion is regulated by various channels in the membrane, for example, Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), intracellular carbonic anhydrase, etc. Pancreatic fluid secretion is controlled by various hormones and neural mediators, including secretin, Cholecystokinin (CCK), Acetylcholine (ACh), Peptide YY (PYY), Vasoactive Intestinal Polypeptide (VIP), substance P, and Gastrin-Releasing Peptide (GRP) [5-7].

Malabsorption, in general, doesn't occur until pancreatic exocrine function is reduced by 90% or more [8,9]. EPI can result in impaired digestion of food if left untreated. Patients may present bloating, steatorrhea, compromised weight gain and fat-soluble vitamin or essential fatty acid deficiency. Deficiencies in water-soluble vitamins like vitamin B12 and folic acid, as well as electrolytes such as calcium, zinc and magnesium, may also be observed [10]. Additionally, undernutrition can cause alterations in the composition of muscle and fat tissue, potentially interrupting mineral density and bone mass homeostasis [11].

Early detection of EPI in children is challenging. Two types of modalities are used to assess pancreatic exocrine function: Either direct or indirect Pancreatic Function Tests (PFTs). 72-hour fecal fat test, the 13C-labeled triglyceride breath test, and Fecal Elastase-1 (FE-1) are indirect tests [1,3,12]. FE-1 is the most commonly utilized method for EPI screening, typically identifying severe cases and potentially missing mild to moderate ones [1]. FE-1 levels may also be influenced if measured during episodes of non-steatorrheic diarrhea due to dilutional effects or during acute pancreatitis when fewer digestive enzymes

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are produced or secreted. For direct PFTs. The Dreiling tube test, which is cumbersome and uncomfortable, is seldom performed in the pediatric population. Endoscopic Pancreatic Function Tests (ePFTs) are considered a most accurate diagnostic method for EPI. However, protocols tend to vary among centers. Secretin-Enhanced Magnetic Resonance Cholangiopancreatography (sMRCP) is a non-invasive modality to evaluate pancreatic exocrine function by assessing pancreatic fluid secretion. However, it has not been validated in pediatrics.

Pancreatic Enzyme Replacement Therapy (PERT) is major for managing patients with EPI. Typically derived from porcine pancreas, pancreatic enzymes exhibit high activity across all three classes: Amylases, lipases and proteases. Lipase is the primary supplemental pancreatic enzyme in PERT. It is also the least stable, particularly susceptible to acid environments and proteolysis [13]. Except for VIOKACE, all FDA-approved brands in the USA are available in delayed-release preparations, which incorporate enteric-coated microspheres, beads, or microtablets. Enteric-coated enzymes protect lipase from gastric acid denaturation, making delayed-release (enteric-coated) capsules the preferred option for pediatric patients. RELiZORB is designed as a digestive enzyme cartridge that can be connected directly to feeding tubes, serving tube-fed patients. However, it exclusively contains lipase [14].

Once in the duodenum, enteric coating disintegrates at a higher pH, enabling enzyme release for digestion. PERT is recommended to be taken with food [2,15]. The supplementation goal is focused on improving nutrition and relieving symptoms. Dose adjustment is based on body weight, severity of symptoms, and dietary fat intake. In pediatrics, PERT dosing for EPI is age and weight-dependent. Delayed-release formulations can be opened, and enteric-coated microspheres can be sprinkled onto low-pH foods (e.g., applesauce) for those who have difficulty swallowing capsules.

PERT products typically exhibit good tolerance, with a consistently observed acceptable safety and tolerability profile over time. Commonly reported adverse effects include dizziness, headache, gas, abdominal pain and diarrhea [16]. High doses (>10,000 lipase U/kg/day) have been reported to develop fibrosing colonopathy in children with cystic fibrosis [17].

In instances where there is a suboptimal response to standard PERT dosage, clinicians should initially assess therapy adherence. If adherence is deemed satisfactory, PERT dosage adjustments are advised, typically in small increments. Additionally, the initiation of acid-suppressive therapy, such as Proton Pump Inhibitors (PPIs), may be considered to mitigate acid denaturation of enzymes [18,19].

Children with EPI are vulnerable to fat-soluble vitamin deficiencies. Supplementation should be administered if fat-soluble vitamin deficiencies are present. In children with EPI, understanding of water-soluble vitamin deficiencies is limited. Insufficiency of vitamin C and vitamin B12 has been reported in adults with chronic pancreatitis [20-22]. Essential Fatty Acid Deficiency (EFAD) has been noted in patients with CF [23]. Although some studies have shown the benefits of supplementation with antioxidants or Docosahexaenoic Acid (DHA), the evidence is not consistent enough to recommend routine supplementation at this time [23,24].

A balanced diet containing protein, fats, carbohydrates, fruits, and vegetables should be encouraged. Children with chronic conditions, such as cystic fibrosis, tend to present a hypermetabolic state due to chronic inflammation. The energy expenditure and energy requirement can increase up to 110%-200% of the Estimated Average Requirement (EAR) [25]. Adequate hydration and staying away from alcohol or tobacco are encouraged [26].

The etiology of malnutrition can be complicated in patients with EPI. Energy losses, increased energy requirements, reduced nutrient intake and declining lung function, as perceived in patients with cystic fibrosis, could all contribute to poor nutritional status and should be addressed carefully. Individuals with steatorrhea, who may limit fat intake due to diarrhea, require adjustments in PERT dosage and advocacy for a balanced diet. Additionally, optimizing pain management for patients with persistent pain due to chronic pancreatitis is critical. For the best patient care, a multidisciplinary team consisting of nurses, dietitians, social workers, pharmacists and clinicians can offer effective management of individual nutritional and caloric requirements.

EPI is common among patients with various pancreatic diseases. It leads to maldigestion and malabsorption if left untreated. Early diagnosis of EPI is critical to initiating nutritional support and PERT supplementation. It is important perform a thorough nutritional assessment in patients with EPI. The PERT treatment goal is focused on improving nutritional status and relieving symptoms. Fat-soluble vitamins should be supplemented in patients with deficiencies. A multidisciplinary team may be beneficial in optimizing patient outcomes [27].

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest..

AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the work, drafted, or revised the manuscript and gave final approval of the version to be published. All authors agreed to be accountable for all aspects of the work. Yuhua Zheng prepared initial manuscript, Shikib Mostamand contributed to the sections of the manuscript. Both reviewed, edited and extended the draft.

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