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UPDATED APPROACH TO EXOCRINE PANCREATIC INSUFFICIENCY: 2023 GUIDELINES

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Abstract: Objective: To analyze the signs, diagnoses and treatments for Exocrine Pancreatic Insufficiency (EPI), according to 2023 updates, aiming to improve identification and management. **Methodology**: Bibliographic review structured by the PVO strategy, through the PubMed – MEDLINE database, through the search strategy: (Exocrine Pancreatic Insufficiency) AND (Management) AND ((2023) OR (Updates) OR (Guidelines), with results of 121 articles, from 2023 and 2024, and, after applying the inclusion and exclusion criteria, 16 articles remained. **Review**: It is noted that the symptoms of EPI are steatorrhoea/diarrhea, abdominal pain, bloating, weight loss, hypovitaminosis and, in children, developmental delay. The diagnosis is made in clinical evaluation, essential to avoid underdiagnosis, and after complementary exams: fecal elastase test, respiratory tests and pancreatic enzymes in the blood, endoscopic test, secretin-stimulated test, computed tomography, magnetic resonance imaging, endoscopic ultrasonography and Endoscopic retrograde cholangiopancreatography. Less commonly used tests are fecal fat collection and disaccharidase tests, in addition to genetic tests. Treatment must be early and consists of nutritional assessment and development of a therapeutic plan, with pancreatic enzyme replacement therapy (PERT) and lifestyle changes. PERT must be taken throughout the meal for better absorption. A new product for EPI is Encala (Envara Health), which does not depend on enzymes and offers good results. Restricted fat diets are a concern for compromising the absorption of vitamins and reducing the effectiveness of PERT. **Final considerations**: Exocrine pancreatic insufficiency (EPI) is characterized by poor digestion and absorption of nutrients, with symptoms such as steatorrhea and abdominal pain. Early diagnosis is crucial, especially in patients at high risk due to conditions such

as chronic pancreatitis. Diagnostic methods include laboratory and imaging tests, and treatment focuses on enzyme replacement and lifestyle adjustments. There is a continued need for research to optimize the diagnosis and treatment of EPI.
Keywords: Exocrine Pancreatic Insufficiency; Treatment; Diagnosis; Clinical manifestations.

INTRODUCTION

Exocrine Pancreatic Insufficiency (EPI) results from decreased secretion or function of pancreatic digestive enzymes, which leads to poor digestion and poor absorption of nutrients. This condition is often associated with symptoms such as steatorrhea, weight loss, abdominal pain, and bloating, which are also common to other gastrointestinal conditions, complicating the diagnosis of the syndrome (Arvanitakis, Hadefi, and Viesca, 2023). Traditionally, the diagnosis of EPI is based on decreased pancreatic enzymes, and primary treatment involves Pancreatic Enzyme Replacement Therapy (PERT) (Bush and Singh, 2023; Walker et al., 2024; Zhou et al., 2023). Due to the wide variety and lack of specificity of the signs and symptoms of EPI, the condition lacks a definition and universal diagnostic criteria, which makes its identification and management difficult (Whitcomb et al., 2023). Recent guidelines are limited and often considered weak due to the scarcity of high-quality studies, highlighting the urgent need for research that addresses existing gaps in the treatment and diagnosis of EPI (Bush and Singh, 2023).

EPI is often underdiagnosed, resulting in inadequate treatments that fail to significantly improve patients' quality of life. Uncommon etiologies such as Type I Diabetes Mellitus, celiac disease, and Roux-en-Y gastrectomy, although rare, must be considered during patient evaluation (Arvanitakis, Hadefi, and Viesca, 2023). In diagnosing EPI, it is essential to measure pancreatic function through laboratory tests. However, the available methods are invasive and non-standardized, and the degree of the disease is often assessed subjectively and inaccurately (Whitcomb et al., 2023). Assessment of nutritional status and glycemic control are crucial, considering the high risk of malnutrition in patients with the disease (Whitcomb, Buchner, and Forsmark, 2023).

Non-pharmacological methods are fundamental in the treatment of EPI, including lifestyle changes such as avoiding large meals, increasing protein intake and ceasing alcohol and tobacco consumption. Recent advances indicate that fat restriction is no longer necessary, with only fat-soluble vitamin supplementation being appropriate (De Rijk et al., 2022). Standard treatment with PERT, which includes synthetic enzymes of porcine origin such as lipase, amylase and protease, is administered for life and is most effective when taken with meals, in conjunction with gastric acid-reducing agents (Berry and Bilbo, 2024).

Although PERT improves fat absorption and gastrointestinal symptoms, it does not completely normalize these functions, requiring a combination with holistic nutritional therapies due to the lack of other effective therapeutic methods (Whitcomb et al., 2023; Walker et al., 2024). The purpose of this article is to review the updated diagnostic criteria and treatment recommendations for exocrine pancreatic insufficiency as per the 2023 update, with a view to improving the identification and management of the condition.

METHODOLOGY

Narrative bibliographic review conducted using the PVO strategy, which includes: Population or research problem, Variables of interest and Expected outcome. The guiding question of the research was: "What are the indicative signs and recommended approaches for the diagnosis and treatment of exocrine pancreatic insufficiency, according to the 2023 update?" To perform the literature search, we used the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) database. The search terms were combined with Boolean operators as follows: "(Exocrine Pancreatic Insufficiency) AND (Management) AND ((2023) OR (Updates) OR (Guidelines))". This strategy resulted in the identification of 121 articles. The defined inclusion criteria were: articles written in English, published between 2023 and 2024, that addressed the themes proposed for this research. Article-type studies, narrative reviews, observational, experimental, qualitative and quantitative studies were considered, all made available in full. The exclusion criteria applied were: duplicate articles, available only in summary form, that did not directly address the proposal studied or that did not meet the previously established inclusion criteria. After applying the inclusion and exclusion criteria, 16 relevant articles were selected from the PubMed database to form the basis of this study.

DISCUSSION

Exocrine pancreatic insufficiency (EPI) is manifested primarily by deficiency in the digestion of micro and macronutrients, especially essential fats and fat-soluble vitamins. This condition is characterized by gastrointestinal symptoms due to poor digestion and systemic symptoms resulting from nutrient malabsorption (Whitcomb, Buchner, and Forsmark, 2023; Meijer et al., 2023). The symptoms of EPI are varied and nonspecific, depending on the degree of involvement and etiology.

The most common symptoms include steatorrhea and/or diarrhea, abdominal pain, bloating and weight loss. In children, growth retardation may be indicative of EPI (Nikfarajan, Wilson, and Smith, 2017).

Enzyme deficiency in the gastrointestinal tract prevents the complete degradation and subsequent absorption of nutrients. It is common for patients to present hypovitaminosis, especially of fat-soluble vitamins (A, D, E, K), in addition to deficiencies of B vitamins, calcium, zinc and folic acid. These deficiencies can lead to complications such as sarcopenia due to calorie deficit, development of osteoporosis, and increased risk of bone fractures (Whitcomb, Buchner, and Forsmark, 2023; Zhou et al., 2023).

To confirm the diagnosis of EPI, computed tomography can identify macroscopic structural changes in the pancreas, although nonspecifically. Other modalities such as magnetic resonance imaging, endoscopic ultrasound and endoscopic retrograde cholangiopancreatography can also be used to reinforce the diagnosis. However, it is possible for pancreatic morphology to be normal even in the presence of the disease (Nikfarajan, Wilson, and Smith, 2017; Meijer et al., 2023). Direct and indirect functional tests are also employed. Direct tests, such as secretin tests, cholecystokinin stimulation and endoscopy of pancreatic function, are more specific and sensitive, but due to their cost and invasiveness, they are less used in clinical practice. Indirect tests, such as stool analysis, respiratory and blood tests, are more accessible, but have lower sensitivity and specificity.

The fecal elastase test, with values below 100 µg/g of feces, offers good evidence of EPI. Measuring FE-1 in feces can also be used to assess pancreatic functionality, where

values below 200 μg/g indicate EPI and values below 50 μg/g may suggest severe EPI. Fecal fat testing, although rarely used, may be considered in high-fat diets (Whitcomb, Buchner, and Forsmark, 2023).

According to Whitcomb, Buchner and Forsmark (2023), there are several diagnostic approaches to confirm exocrine pancreatic insufficiency (EPI). Common methods include the Fecal Elastase Test, which is non-invasive and widely used to assess the exocrine function of the pancreas. Other pancreatic function tests, such as the endoscopic test and the secretin-stimulated test, are used for a more detailed analysis of pancreatic function. Disaccharidase Tests are also used to detect digestive enzyme deficiencies, suggesting the presence of EPI. Clinical evaluation, observing symptoms such as steatorrhea, weight loss, abdominal swelling and fat-soluble vitamin deficiencies, is essential for diagnosing the condition.

Underdiagnosis of EPI is a problem that leads to inadequate treatments. It is crucial to raise awareness about the condition to ensure early diagnosis and effective treatments. The availability and accessibility of pancreatic enzyme replacement therapy (PERT) is essential, and efforts must be made to make PERT accessible to all patients with EPI. Developing more accurate diagnostic tests is essential to facilitate early identification of EPI. Populations such as patients with chronic pancreatitis, recurrent acute pancreatitis, cystic fibrosis and a history of pancreatic surgery are at increased risk of EPI and may require specific diagnostic and therapeutic approaches (Stern et al., 2024; Walker et al., 2024).

According to Berry and Bilbo (2024), methods such as quantitative fecal fat collection and fecal elastase testing are useful in detecting EPI. Systematic review and meta-analysis of 13C triglyceride testing is also mentioned as an effective method for assessing pancreatic function. Sankararaman and Schindler (2023) highlight that, in children, the diagnosis of EPI can be confirmed through laboratory and imaging methods, including measurement of pancreatic enzymes in the blood and fecal elastase tests. Imaging tests such as ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) are used to evaluate the structure and function of the pancreas. Genetic testing is recommended in suspected cases of underlying genetic conditions, such as Shwachman-Diamond syndrome. Diagnosis and treatment of EPI in specific populations, especially children with underlying genetic conditions, require a multidisciplinary and individualized approach. Early diagnosis is crucial to initiating appropriate treatments and preventing complications, and access to specialized treatments can be challenging in some populations.

After confirming the diagnosis of exocrine pancreatic insufficiency (EPI), it is crucial to perform a comprehensive assessment of the patient's nutritional status, symptoms, medications, and lifestyle. This assessment is essential for therapeutic planning, which incorporates pancreatic enzyme replacement therapy (PERT) and lifestyle modifications, including nutritional adjustments (Whitcomb et al., 2023; Zhou et al., 2023).

Pancreatic enzyme replacement therapy (PERT), currently recommended as a primary treatment for EPI, aims to improve nutrient absorption and prevent malnutrition. Enzyme preparations, predominantly of porcine origin, are standardized based on lipase content and include amylase and a mixture of proteases. Some products, such as Viokace, are offered in uncoated tablets, requiring co-treatment with acid inhibitors to prevent enzymatic denaturation. Other formulations contain enzyme micropellets encapsulated in pH-sensitive polymers (Whitcomb; Buchner; Forsmark, 2023).

Current guidelines recommend distributing the PERT dose throughout meals, especially those high in fat. Studies such as those by Berry and Bilbo (2024) and Barkin, Harb, Kort, and Barkin (2024) show that this approach is more effective than taking the full dose at the beginning or end of meals. The correct dosage and timing of ingestion are crucial to maximize the effectiveness of the treatment, which is generally well tolerated, with few adverse effects (Arvanitakis; Hadefi; Viesca, 2023).

Along with PERT, it is essential to avoid alcohol and tobacco and incorporate vitamin supplements, consuming small and frequent meals (Whitcomb; Buchner; Forsmark, 2023). Annual monitoring of levels of fat-soluble vitamins and minerals is recommended to assess the need for adjustments in supplementation (Berry and Bilbo, 2024).

Regarding nutritional management, although Whitcomb, Buchner and Forsmark (2023) suggest a low-fat diet, De Rijk et al. (2022), as well as Hasebe, Karasawa and Nozawa (2023) and Whitcomb et al. (2023), argue that severe fat restriction can compromise the absorption of fat-soluble vitamins, leading to malnutrition. Enzyme therapy shows greater effectiveness when accompanied by a high-fat diet. In advanced stages of the disease, it may be advisable to reduce fat content to alleviate gastrointestinal symptoms (Whitcomb et al., 2023). Diets high in fiber are discouraged as they can increase fat excretion (De Rijk et al., 2022; Phillips et al., 2021).

Recently, a new product, Encala (Envara Health), was developed and tested. Based on structured lipid technology with lysophosphatidylcholine and fatty acids, Encala does not require lipase or bile acids for its digestion and absorption. Results include significant weight gains and reduced gastrointestinal symptoms (Whitcomb et al., 2023; Metz, 2024). Long-term monitoring of patients with EPI is imperative, with regular anthropometric, biochemical and clinical measurements to monitor nutritional status and adjust treatment as necessary (Arvanitakis; Hadefi; Viesca, 2023).

FINAL CONSIDERATIONS

We analyzed the signs, diagnostic criteria and treatments for exocrine pancreatic insufficiency (EPI) based on 2023 updates. The main symptoms of EPI include problems in the digestion and absorption of fats and vitamins, manifesting as steatorrhea, abdominal pain, distension, weight loss, and hypovitaminosis. In children, it can cause developmental delays. Early diagnosis is crucial, especially in individuals at high risk due to conditions such as chronic pancreatitis and pancreatic surgery.

Diagnostic methods include laboratory tests, such as fecal elastase testing and respiratory tests, and imaging tests, such as CT and MRI, although EPI may not show significant morphological changes. Treatment involves nutritional assessment and a therapeutic plan that includes pancreatic enzyme replacement therapy (PERT) and lifestyle changes. New supplements like Encala promise better absorption without relying on enzymes. There are disagreements about the ideal diet in terms of fat content, highlighting the need for further studies to optimize the diagnosis and management of EPI.

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