CLINICAL UPDATE

Advances in the Treatment of Pancreatic Insufficiency

Pancreatic Enzyme Therapy for Pancreatic Exocrine Insufficiency

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G&H What are the most common causes of pancreatic exocrine insufficiency?

JED-M Pancreatic exocrine insufficiency is a major consequence of diseases that lead to loss of pancreatic parenchyma (eg, chronic pancreatitis or cystic fibrosis), obstruction of the main pancreatic duct (eg, pancreatic and ampullary tumors), decreased pancreatic stimulation (eg, celiac disease), or acid-mediated inactivation of pancreatic enzymes (eg, Zollinger-Ellison syndrome). In addition, gastrointestinal and pancreatic surgical resections (eg, gastrectomy or duodenopancreatectomy) are frequent causes of pancreatic exocrine insufficiency due to postcibal asynchrony, decreased pancreatic stimulation, and loss of pancreatic parenchyma. All these patient populations are at high risk for pancreatic exocrine insufficiency.

G&H What are typical symptoms of pancreatic exocrine insufficiency?

JED-M Apart from abdominal cramps and steatorrhea (loose, greasy, foul-smelling, voluminous stools that are difficult to flush), the main clinical manifestation of pancreatic exocrine insufficiency is malnutrition. However, steatorrhea is not always evident because patients tend to limit fat ingestion. In addition, malnutrition tends to be subclinical, except for the presence of low body weight, low body mass index, and an increased risk of low-trauma fractures. Because of these limitations, diagnosis of pancreatic exocrine insufficiency cannot rely on symptoms alone.

G&H How should clinicians diagnose pancreatic exocrine insufficiency?

JED-M The gold standard for the diagnosis of fat maldigestion is quantification of the coefficient of fat absorption (CFA) after fecal fat determination using the classical Van de Kamer test. Unfortunately, this test has several important disadvantages that limit its clinical applicability. Specifically, patients must maintain a strict diet, usually containing 100 g of fat daily over 5 consecutive days; they must collect the whole amount of feces excreted over the last 3 days of the diet; and the whole amount of feces must be manually processed in the laboratory, which is very unpleasant and cumbersome. A mixed ^{13}C-triglyceride breath test has therefore been developed and optimized as an alternative to CFA testing for the diagnosis of pancreatic exocrine insufficiency. However, neither of these tests is widely available in clinical practice.

Some practical tips may be of help in diagnosing pancreatic exocrine insufficiency in clinical practice: First, the probability of pancreatic exocrine insufficiency is very high after severe necrotizing pancreatitis, gastrointestinal surgery, or pancreatic surgery, as well as in patients with cancer of the head of the pancreas; therefore, the use of diagnostic testing in these cases may be unnecessary. Second, the vast majority of chronic pancreatitis patients with pancreatic calcifications and main duct dilation suffer from pancreatic exocrine insufficiency and therefore require pancreatic enzyme therapy. These morphologic findings can thus be used as an indirect way to diagnose pancreatic exocrine insufficiency.

G&H What are the possible consequences of misdiagnosis or delayed diagnosis?

JED-M Misdiagnosis or delayed diagnosis of pancreatic exocrine insufficiency is associated with malnutrition and thus increases the risk of developing malnutrition-related complications.

G&H When is treatment indicated for patients with pancreatic exocrine insufficiency?

JED-M Patients with pancreatic exocrine insufficiency who experience weight loss and those with relevant steatorrhea and steatorrhea-related symptoms are classically considered to be suitable candidates for enzyme substitution therapy. Whether treatment is indicated in patients with asymptomatic steatorrhea is debatable, but a recent study demonstrated that these patients consistently suffer from malnutrition. Although the relevance of this malnutrition remains unclear—as it is often subclinical—the frequent occurrence of malnutrition supports the prescription of enzyme substitution therapy in every patient with pancreatic exocrine insufficiency, independent of the degree of steatorrhea and/or the presence of associated symptoms, in order to prevent potentially relevant nutritional deficits.

G&H What are the available treatment options for pancreatic exocrine insufficiency? Are these treatments usually effective?

JED-M Therapy for pancreatic exocrine insufficiency involves administration of oral pancreatic enzymes. At the appropriate enzyme dose, this therapy is highly effective, and digestion improves and even normalizes in the majority of patients. In addition to pancreatic enzyme replacement therapy, patients should be advised to eat as normal a diet as possible in order to avoid malnutrition. Nutritional supplements are usually not required.

G&H Which pancreatic enzyme formulations are most effective for treatment of pancreatic exocrine insufficiency? What are the specific benefits of these formulations?

JED-M Pancreatic enzymes in the form of enteric-coated minimicrospheres are considered to be the most elaborate commercially available enzyme preparation. These preparations contain a high lipase activity (U/mg) and were designed both to avoid acid-mediated inactivation of lipase and to ensure gastric emptying of microspheres in parallel with nutrients, thus optimizing the efficacy of the enzyme substitution therapy. Clinical trials have shown the significant therapeutic efficacy of these enzyme preparations for reducing fat excretion, decreasing stool frequency, improving stool consistency, and normalizing the nutritional status of patients with pancreatic exocrine insufficiency secondary to chronic pancreatitis, cystic fibrosis, and other clinical conditions.

G&H What are the risks of pancreatic enzyme therapy?

JED-M Oral pancreatic enzymes are very well tolerated, so adverse events are not expected. In my personal experience treating hundreds of patients, none have had to stop pancreatic enzyme replacement therapy due to adverse events. Years ago, isolated cases of fibrosing colopathy were described in children with cystic fibrosis who were undergoing enzyme replacement therapy; these side effects were related to the enteric coating. This problem has never been described in adults and also was never again reported in children, even among those receiving a high enzyme dose.

G&H What patient factors can influence the effectiveness of these enzymes?

JED-M The main patient factor affecting the efficacy of this therapy is compliance. Patients need to understand the importance of pancreatic enzyme insufficiency and its therapy, as well as the relevance of an appropriate enzyme dose and optimal administration schedule. Aside from noncompliance, a low intestinal pH secondary to gastric acid secretion and low pancreatic bicarbonate secretion may limit the efficacy of enzyme therapy. Finally, other causes of maldigestion that can be associated with pancreatic exocrine insufficiency (eg, bacterial overgrowth) should be considered in patients who do not respond adequately to enzyme therapy.

G&H What are current recommendations regarding the dosage and timing of pancreatic enzyme replacement therapy?

JED-M Dosage is a key factor for achieving success with pancreatic enzyme substitution therapy. Although the enzyme dose should be individualized for each patient, a minimum dose of 40,000–50,000 USP units of lipase per meal and 20,000–25,000 USP units per snack should be generally prescribed. Regarding timing of therapy, studies have demonstrated that the efficacy of the enzyme substitution therapy is higher when enzymes are administered with meals rather than just before meals.

G&H Do patients with pancreatic exocrine insufficiency need to restrict their fat intake?

JED-M Classically, patients with pancreatic exocrine insufficiency were instructed to restrict fat intake in an attempt to reduce steatorrhea. A diet containing less than 20 g of fat daily was generally recommended. However, restriction of fat intake is linked to insufficient intake of fat-soluble vitamins (which are already malabsorbed in patients with pancreatic exocrine insufficiency) and malnutrition. As a consequence, fat restriction is no longer considered necessary in the management of patients with pancreatic exocrine insufficiency. In addition, efficacy of enzyme substitution therapy has been shown to be superior when enzymes are administered together with a high-fat diet compared to a low-fat diet.

G&H Overall, what can clinicians do to optimize the efficacy of pancreatic enzyme therapy in patients with pancreatic exocrine insufficiency?

JED-M Prescribing the appropriate dose of enzymes and ensuring patient compliance are the 2 key factors for optimizing enzyme therapy. This therapy should also be individualized, with the aim of normalizing digestion and patients' nutritional status. In patients who show an insufficient response to enzyme substitution therapy, addition of a proton pump inhibitor may improve the efficacy of this therapy, by increasing gastric pH and thus decreasing the intestinal acid load.

Suggested Reading

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