

Pancreatic enzyme replacement therapy for pancreatic exocrine insufficiency: When is it indicated, what is the goal and how to do it?

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ABSTRACT

Pancreatic exocrine insufficiency with steatorrhea is a major consequence of pancreatic diseases (e.g. chronic pancreatitis, cystic fibrosis, severe acute necrotizing pancreatitis, pancreatic cancer), extrapancreatic diseases like celiac disease and Crohn's disease, and gastrointestinal and pancreatic surgical resections. Recognition of this entity is highly relevant to avoid malnutrition-related morbidity and mortality. Therapy of pancreatic exocrine insufficiency is based on the oral administration of pancreatic enzymes aiming at providing the duodenal lumen with sufficient amount of active lipase at the time of gastric emptying of nutrients. Administration of enzymes in form of enteric-coated minimicrospheres avoids acid-mediated lipase inactivation and ensures gastric emptying of enzymes in parallel with nutrients. Despite that, factors like an acidic intestinal pH and bacterial overgrowth may prevent normalization of fat digestion even in compliant patients. The present article critically reviews current therapeutic approaches to pancreatic exocrine insufficiency.

Key words: pancreatic exocrine insufficiency, pancreatic enzyme substitution therapy, maldigestion, nutritional status, chronic pancreatitis

INTRODUCTION

Pancreatic exocrine insufficiency is a major consequence of diseases leading to a loss of pancreatic parenchyma (e.g. chronic pancreatitis, cystic fibrosis), obstruction of the main pancreatic duct (e.g. pancreatic and ampullary tumors), decreased pancreatic stimulation (e.g. celiac disease), or acid-mediated inactivation of pancreatic enzymes (e.g. Zollinger-Ellison syndrome). In addition, gastrointestinal and pancreatic surgical resections (e.g. gastrectomy or duodenopancreatectomy) are frequent causes of pancreatic exocrine insufficiency due to post-cibal asynchrony, decreased pancreatic stimulation and loss of pancreatic parenchyma. The majority of patients with chronic pancreatitis will develop pancreatic exocrine insufficiency sooner or later depending on the etiology of the disease. In patients with chronic alcoholic pancreatitis half of the patients will suffer from pancreatic exocrine insufficiency after twelve years from the onset of the disease [1].

Together with abdominal cramps and the typical characteristics of fatty stools associated with steatorrhea (loose, greasy, foul-smelling voluminous stools that are difficult to flush), which are not always evident because patients tend to limit fat ingestion, the main clinical consequence of pancreatic exocrine insufficiency is malnutrition. Actually, maldigestion is the main cause of weight loss in patients with pancreatic exocrine insufficiency. These patients present with low circulating levels of micronutrients, fat soluble vitamins and lipoproteins, which have been related to a high morbidity and mortality secondary to an increased risk of malnutrition-related complications and cardiovascular events [2]. In fact, chronic pancreatitis is associated to a 4 to 5-fold increased risk of death compared to the general population matched by age and gender [3,4].

Quantification of the coefficient of fat absorption (CFA) after fecal fat quantification by the classical Van de Kamer test is the gold standard for the diagnosis of pancreatic exocrine insufficiency [5]. Despite that, this test has several

and important disadvantages limiting its clinical applicability. Patients must keep on a standard diet containing around 100 g of fat daily during 5 consecutive days and collect the whole amount of feces produced over the last 3 days of diet. This is not easy to comply for many patients. A three-day collection is needed to reduce errors and variability that may occur if a shorter collection period is used. A mixed ¹³C-triglyceride (¹³C-MTG) breath test has been developed and optimized as an alternative to CFA for the diagnosis of pancreatic exocrine insufficiency in clinical routine [6]. The sensitivity of the breath test for the diagnosis of fat maldigestion is higher than 90% [6]. This test is easily applicable to the clinical routine and can be repeated as frequent as needed. In this way, utility of the test is not only limited to the diagnosis of pancreatic exocrine insufficiency but can also be extended to the control of the efficacy of oral enzyme substitution therapy in these patients [6].

Despite CFA and ¹³C-MTG breath test are the methods of choice for the diagnosis of pancreatic exocrine insufficiency, none of these tests are widely available in clinical practice. Some practical aspects may be provided to manage these patients properly. First, the probability of pancreatic exocrine insufficiency after severe necrotizing pancreatitis, gastrointestinal and pancreatic surgery, as well as in patients with cancer of the head of the pancreas tends to be higher than 80%. Therefore, in these cases no diagnostic test is required before pancreatic enzyme replacement therapy is started. Secondly, it is well known the close correlation between function and morphology in patients with advanced chronic pancreatitis. In fact, the vast majority of chronic pancreatitis patients with pancreatic calcifications and main duct dilation suffer from pancreatic exocrine insufficiency requiring pancreatic enzyme substitution therapy (unpublished personal data). These morphological findings can be thus used as an indirect way to diagnose pancreatic exocrine insufficiency.

REVIEW

The aim of pancreatic enzyme substitution therapy is not only to avoid maldigestion-related symptoms, but mainly to ensure a normal nutritional status. Therapy of pancreatic exocrine insufficiency is based on the oral administration of exogenous pancreatic enzymes. Together with that, dietary modifications have classically played an important role that nowadays should probably be reconsidered.

1. When is pancreatic enzyme replacement therapy indicated?

Pancreatic exocrine insufficient patients who lose weight, those with daily fecal fat excretion of more than 15g under a diet containing 100g fat daily, and those with relevant steatorrhea-related symptoms are classically and generally considered as requiring enzyme substitution therapy [7]. Indication

for treatment in patients with asymptomatic steatorrhea of less than 15g/d is under debate. A recent study has however demonstrated that patients with asymptomatic steatorrhea of less than 15g/d present consistently low circulating levels of nutritional parameters like liposoluble vitamins, prealbumin and ferritin, which normalize under enzyme substitution therapy [8]. Although the relevance of this subclinical malnutrition status remains unclear, this study supports the prescription of enzyme substitution therapy in every patient with pancreatic exocrine insufficiency and fat maldigestion, independently of the degree of steatorrhea and the presence or absence of associated symptoms, in order to prevent potentially relevant nutritional deficits.

2. Which dietary modifications may be recommended?

Classically, the initial approach to patients with pancreatic exocrine insufficiency is to restrict fat intake in an attempt of reducing steatorrhea. A diet containing less than 20g fat daily is thus generally recommended in this context. Nevertheless, restriction of fat intake is linked to insufficient intake of fat-soluble vitamins, which are in addition malabsorbed in patients with pancreatic exocrine insufficiency [6]. In addition, studies on the fate of both endogenous and exogenous enzymes during small intestinal transit show that survival of enzyme activity is enhanced by the presence of their respective substrates [9]. That means that survival of lipase activity during intestinal transit requires the presence of dietary triglycerides. Actually, it was demonstrated in an experimental model of pancreatic exocrine insufficiency in dogs that fat digestion and absorption is higher when enzyme supplements are taken together with a high-fat diet compared to a low-fat diet [10]. As a consequence, fat restriction should not be longer considered as a rule in the management of patients with pancreatic exocrine insufficiency.

Frequent meals of low volume and avoidance of food difficult to digest (i.e. legumes) are generally recommended. A fibre-rich diet seems to increase pancreatic lipase secretion, but also inhibits pancreatic lipase activity by more than 50% [11], so its use is under discussion and cannot be considered as adequate. Medium-chain triglycerides, which are directly absorbed by the intestinal mucosa, may be useful for providing extra calories in patients with weight loss, and for reducing steatorrhea in patients with a poor response to oral pancreatic enzymes. Finally, patients with pancreatic exocrine insufficiency may require supplements of fat-soluble vitamins.

3. Keys for an adequate pancreatic enzyme replacement therapy

Pancreatic enzyme secretion increases rapidly in response to a meal up to six fold above interdigestive levels and reaches maximal values within 20 to 60 minutes postprandially [12]. Enzyme output decreases thereafter to a three to fourfold sustained increase, which is maintained for three to four hours

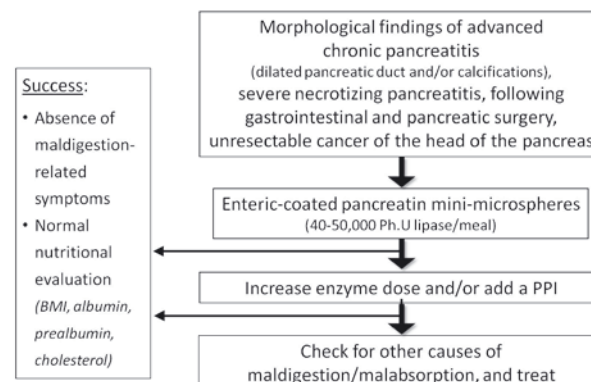
before returning to interdigestive levels. This postprandial pattern means that a maximal output of 3000-6000 IU/min lipase and a mean output of 2000-4000 IU/min lipase occurs after ingestion of a normal mixed meal in healthy subjects [12]. Enzyme substitution therapy should be able to mimic this pattern in situations of pancreatic exocrine insufficiency.

None of the commercially available enzyme preparations is able to deliver the more than 360 000 IU of active lipase into the duodenal lumen that are secreted by the pancreas under physiological conditions. Nevertheless, due to the effect of gastric lipase and to the residual pancreatic exocrine secretion, fat digestion and absorption improves significantly, and may even normalize, in most patients with pancreatic exocrine insufficiency under the available therapies. To prevent steatorrhea in these patients, enzyme preparations should be able to deliver at least 30,000 IU of active lipase into the duodenum together with meals [13,14]. This goal can be only achieved by the administration of the modern enteric-coated preparations in form of mini-microspheres due to factors like gastric acid secretion, nonparallel gastric emptying of nutrients and enzyme preparations, and proteolytic inactivation of released lipase.

Since exogenous enzymes should exert their action on the ingested meal, and since gastric emptying of the enzymes should occur in parallel with nutrients to optimize digestion and absorption, it has been generally accepted that pancreatic enzyme preparations should be administered together with meals and snacks. The effect of the administration schedule on the efficacy of oral pancreatic enzymes for the treatment of pancreatic exocrine insufficiency was evaluated in a prospective, randomized, open, comparative, three-way, crossover study including twenty-four consecutive chronic pancreatitis patients with fat maldigestion secondary to pancreatic exocrine insufficiency [15]. The efficacy of the enzyme substitution therapy appears to be higher when enzymes are administered either portioned along meals or just after meals compared to the intake just before meals [15].

A recently published randomized, double-blind, placebo-controlled trial in chronic pancreatitis patients has shown the significant therapeutic efficacy of pancreatic enzyme preparations in form of enteric-coated minimicrospheres in reducing fat excretion, decreasing stool frequency and improving stool consistency [16]. These results have been confirmed by means of the ¹³C-mixed triglyceride breath test, analysis of coefficient of fat absorption and nutritional status in a recent prospective study including forty-nine patients with fat maldigestion secondary to chronic pancreatitis [6]. Similar efficacy was shown in a placebo-controlled trial in patients suffering from cystic fibrosis with pancreatic exocrine insufficiency and steatorrhea [17].

Figure 1. Current recommendations for pancreatic enzyme substitution therapy in patients with pancreatic exocrine insufficiency. BMI, body mass index; PPI, proton pump inhibitor.



4. How to improve the efficacy of the enzyme therapy?

Despite the use of modern enteric-coated enzyme preparations in minimicrospheres, fat digestion cannot become normal in almost half of the patients with pancreatic exocrine insufficiency [18]. Inadequate patient compliance, low dose of enzymes, acidic intestinal pH and intestinal bacterial overgrowth are among the factors preventing total elimination of steatorrhea in this clinical setting [19].

The abnormally low pancreatic secretion of bicarbonate in patients with pancreatic exocrine insufficiency is associated to a limited buffer effect in the proximal intestine. A pH below 4 is associated to an irreversible inactivation of endogenous and uncoated exogenous pancreatic lipase, as well as to precipitation of bile salts, contributing to fat maldigestion [20]. In addition, enteric-coated pancreatic enzymes require a pH>5 to be released, which may first occur in distal segments of the small intestine, thus reducing the efficacy of the therapy [21].

Up to 40% of patients with pancreatic exocrine insufficiency secondary to chronic pancreatitis have concomitant intestinal bacterial overgrowth [22]. This is probably due to a deficient effectiveness of the interdigestive “house keeper” function of gastrointestinal motility and biliopancreatic secretion. In fact, patients with chronic pancreatitis have been shown to lose the physiological synchrony between the interdigestive gastrointestinal motility and pancreatic secretion, which together with a markedly low pancreatic secretion of enzymes may favour the development of bacterial overgrowth [23].

The first step to guarantee an optimal efficacy of oral pancreatic enzymes in the management of pancreatic exocrine insufficiency is to confirm that patients take enzymes properly. Secondly, the dose of enzymes should be high enough, and a minimum dose of 40-50,000 Ph.U. of lipase per meal and 20-25,000 Ph.U. of lipase together with snacks should be given. In cases of insufficient response, inhibition of gastric acid secretion should be attempted. Finally, bacterial overgrowth should be detected and treated in nonresponders (Fig. 1).

As mentioned above, a low intraduodenal pH may inactivate endogenous and uncoated exogenous lipase, may prevent the release of active lipase from enteric-coated granules within the proximal intestine, and may lead to bile salt precipitation. Inhibition of gastric acid secretion, by increasing the intragastric pH and thus decreasing the duodenal acid load, should improve the efficacy of the enzyme substitution therapy. Combining enteric-coated pancreatin microspheres with either a H₂-receptor antagonist or a proton pump inhibitor was reported to be beneficial in patients with cystic fibrosis [24,25]. More recently, addition of a proton pump inhibitor has been shown to significantly improve and even normalize fat digestion in patients with pancreatic exocrine insufficiency and incomplete response to the enzyme substitution therapy in form of enteric-coated minimicrospheres [18]. This combined therapy should not be used in patients with an adequate response to the enzyme substitution monotherapy [18].

Independently of the therapy prescribed, evaluation of the therapeutic efficacy of pancreatic enzymes is generally based on clinical parameters like weight gain or absence of weight loss, and improvement of steatorrhea-related symptoms. This clinical evaluation has been recently shown to be inappropriate and only demonstration of normalization of fat digestion by means of objective methods like normalization of CFA, 13C-MTG breath test, or specific nutritional parameters ensures a normal nutritional status in patients with pancreatic exocrine insufficiency [6,8].

CONCLUSIONS

- Pancreatic exocrine insufficiency is a frequent and life-threatening condition associated to different pancreatic and extrapancreatic diseases (acute pancreatitis, chronic pancreatitis, cystic fibrosis, pancreatic cancer, GI and pancreatic surgery).
- Therapy of pancreatic exocrine insufficiency should avoid symptoms and ensure a normal nutritional status.
- Oral pancreatic enzymes in form of enteric-coated minimicrospheres are the therapy of choice. A minimum dose of 40-50,000 Ph.U/lipase is usually required for main meals and 25,000 Ph.U for snacks.
- Inhibition of gastric acid secretion by administration of proton pump inhibitors is of help in patients with insufficient response to enzyme monotherapy.
- Therapy should be individualized based on objective evaluation of nutritional status.

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