Chronic pancreatitis and persistent steatorrhea: what is the correct dose of enzymes?

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Clinical Scenario

A 55-year-old man is referred by the general practitioner to your office because of a history of chronic diarrhea lasting for more than one year. He had no relevant previous medical history, no allergy, and no previous surgical intervention. He referred a daily alcohol intake of about 80 g for more than 30 years, and is smoker of about 20 cigarettes a day. Diarrhea improved initially by modification of dietary habits (reduction of dietary fiber and fat intake), recommendation of alcohol abstinence and on-demand antidiarrheal therapy.

At the time he presented to your office he had stopped any medication. He had 4-5 bowel movements per day, consisting of nonformed, sometimes liquid, foamy, usually light brown in color, foul-smelling stools. He had occasional nocturnal bowel movement. Other symptoms as urgency and cramps, as well as bloody stools, were not present. The patient also referred relapsing abdominal epigastric pain and discomfort for years, nonrelated to the ingestion of meals, occasionally irradiated to the back, at a mean frequency of 1 to 2 episodes per month, with long asymptomatic periods. Pain relieved by the on-demand intake of nonopioid analgesics, and it was not as relevant as for seeking medical assistance. Together with that, he had noticed a loss of 4 kg body weight despite maintaining a normal food intake. He still drank 20-

30 g ethanol per day and maintained the previous smoking habit. His family history was negative for any relevant digestive and malignant disease.

His physical examination is significant only for mild to moderate pain in epigastrium to deep palpation. He is thin, with a body mass index (BMI; calculated as weight in kg divided by the square of height in m) of 18.9. An abdominal ultrasound reveals a hepatic hemangioma of 18 X 14 mm, as well as a heterogeneous pancreas with parenchymatous microcalcifications and an irregularly dilated main pancreatic duct. Blood cell count, serum electrolytes, glucose, liver biochemistry, blood urea nitrogen, creatinine, and triglycerides are within normal ranges. He has a serum amylase activity of 121 U/L (upper normal limit of 110 U/L), lipase of 120 U/L (upper normal limit of 57 U/L), and albumin of 3.3 g/dL (normal >3.5 g/dL). Serum cholesterol is in the lower limit of normal.

You recommend a fecal elastase-1, which is of 32 μg (lower normal limit of 200 μg), and an endoscopic ultrasound (EUS), which is conclusive for chronic pancreatitis with 3 major criteria and 6 minor criteria of the disease according to the Rosemont classification. You make the diagnosis of chronic pancreatitis and suspected exocrine pancreatic insufficiency.

Is it necessary to confirm by other tests the diagnosis of exocrine pancreatic insufficiency? If yes, what test should be used? How to treat this patient? What is the aim of therapy? What is the correct dose of oral pancreatic enzymes and based on what endpoint?

Management Strategies

Therapy of exocrine pancreatic 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. The goal of the enzyme therapy is to deliver a sufficient amount of active lipase at the right place, ie, duodenum and proximal jejunum, and at the right time, ie, in parallel with gastric emptying of nutrients.

Classically, the initial approach to patients with exocrine pancreatic insufficiency is to restrict fat intake to reduce steatorrhea. A diet containing less than

20 g 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 exocrine pancreatic insufficiency. Moreover, 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, thus survival of lipase activity during intestinal transit requires the presence of dietary triglycerides. Actually, it was demonstrated in an experimental model of exocrine pancreatic insufficiency in dogs that fat digestion and absorption is higher when enzyme supplements are taken together with a high fat diet compared with a low fat diet (coefficient of fat absorption [CFA] of 4% to 20% higher with a high fat diet versus a low fat diet by giving the same amount of oral pancreatic enzymes). As a consequence, fat restriction should not be considered as a rule in the management of patients with exocrine pancreatic insufficiency.

Treatment of exocrine pancreatic insufficiency is clearly indicated in patients with symptomatic steatorrhea (diarrhea and/or weight loss) or steatorrhea of more than 15 g/day, whereas the need to treat asymptomatic patients with less severe steatorrhea (from 7.5 to 15 g/day) is under debate.

Enzyme substitution therapy should mimic as much as possible the postprandial physiological secretion of pancreatic enzymes in terms of secretion pattern and amount. 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 postprandially by the pancreas under physiological conditions. Nevertheless, due probably to the effect of gastric lipase and to the residual exocrine pancreatic secretion, fat digestion and absorption improves significantly, and may even normalize, in most patients with exocrine pancreatic insufficiency by 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. This goal may be difficult to achieve due to factors like gastric acid secretion, nonparallel gastric emptying of nutrients and enzyme preparations, and proteolytic inactivation of released lipase. All these problems are at best avoided by the use of

enteric-coated preparations of enzymes in form of minimicrospheres. Contrary to uncoated enzyme preparations, the efficacy of enteric-coated enzymes in minimicrospheres for the treatment of exocrine pancreatic insufficiency has been proven in well designed randomized double-blind placebo-controlled trials including a proper number of chronic pancreatitis patients. In these studies, CFA improved by 32-37% in patients receiving enzyme therapy compared with 8-12% in those receiving placebo, and the difference was consistently significant. Similar results have been reported in patients with exocrine pancreatic insufficiency secondary to clinical conditions other than chronic pancreatitis, mainly cystic fibrosis and after gastrointestinal or pancreatic surgery. Early pancreatic enzyme preparations consisting of tablets or encapsulated powder were not protected against acid-mediated lipase inactivation in the stomach, and only as little as 8% of ingested lipase was bioavailable in the small intestine. Therefore, it was necessary to administer orally up to 5 to 10 times as much lipase as was required for intraluminal digestion.

The therapeutic use of such different enzyme preparations was possible because pancreatic enzymes available before the passage of the 1938 Federal Food, Drug and Cosmetic Act were marketed in the USA without any requirements for safety and efficacy testing. Citing concerns about the significant differences in bioavailability among pancreatic enzyme replacement therapy products and consequent instances of serious under- and overdosing, the Food and Drug Administration (FDA) formally announced in 2004 the New Drug Application requirement for exocrine pancreatic insufficiency drug products. Several pancreatic enzyme preparations are already on the market in the USA after receiving FDA approval. These products represent the first enteric-coated pancrelipase preparations approved in the USA, and all are of porcine origin. As new dosage forms are approved, some manufacturers have taken the opportunity to modify their formulations with regards to excipients, improved packaging, and stability to allow for a more consistent delivery of pancreatic enzymes.

How Should Enzymes Be Administered?

Because exogenous enzymes should exert their action on the ingested meal, and because 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 exocrine pancreatic insufficiency was evaluated in a prospective, randomized, open, comparative, 3-way, crossover study. This study confirmed that the efficacy of the enzyme substitution therapy is higher when the same enzyme dose is administered portioned along meals compared with the intake just after meals or just before meals. The proportion of patients who normalized fat digestion in this study was 63%, 54%, and 50% with these 3 different schedules, respectively.

What Is the Aim of Therapy?

In addition to symptoms, the major consequence of maldigestion secondary to exocrine pancreatic insufficiency is malnutrition. As mentioned above, low circulating levels of micronutrients, fat-soluble vitamins, and lipoproteins in these patients have been related to a high morbidity secondary to an increased risk of malnutrition-related complications and cardiovascular events. Based on that, the aim of enzyme substitution therapy should be not only to avoid diarrhea and weight loss, as classically considered, but also to ensure a normal nutritional status.

What Is the Correct Dose of Oral Pancreatic Enzymes?

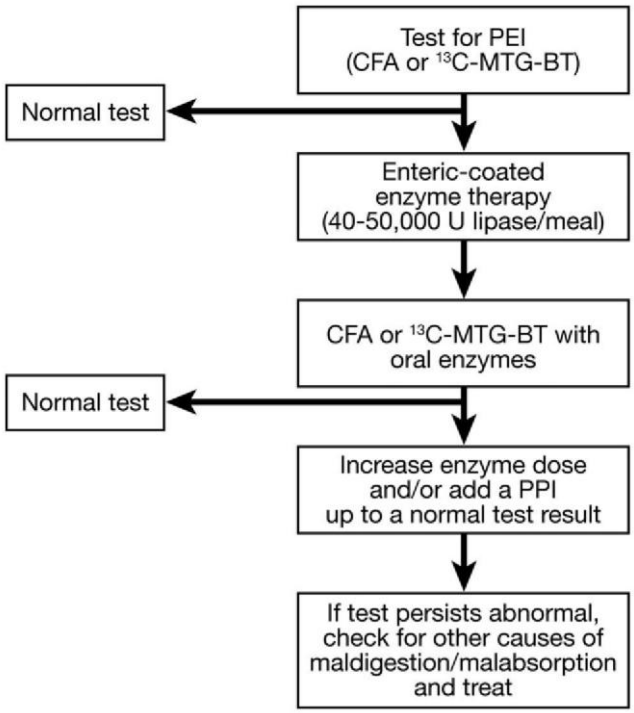
Oral pancreatic enzymes should be given at a dose able to improve digestion as much as possible. From a theoretical point of view, the dose selection could be based on: (1) symptomatic response (avoidance of diarrhea and weight loss); (2) size or ideal size of the patient; (3) size of the meal; (4) fat content of the stool; or (5) nutritional status of the patient. Unfortunately there is no scientific evidence to answer this question, although some reported studies may help us to make a decision in clinical practice.

We have recently demonstrated in a prospective study that an adequate symptomatic response to oral enzyme substitution therapy in patients with exocrine pancreatic insufficiency is not associated with a normal nutritional status in up to

67% of patients. Therefore, oral pancreatic enzyme supplementation in these patients cannot be correctly optimized based on the clinical evaluation of maldigestion-related symptoms. This is important since a recent US study has shown that pancreatic enzyme replacement therapy is used in 70% of patients with chronic pancreatitis, but mainly in symptomatic patients (pain and/or exocrine insufficiency).

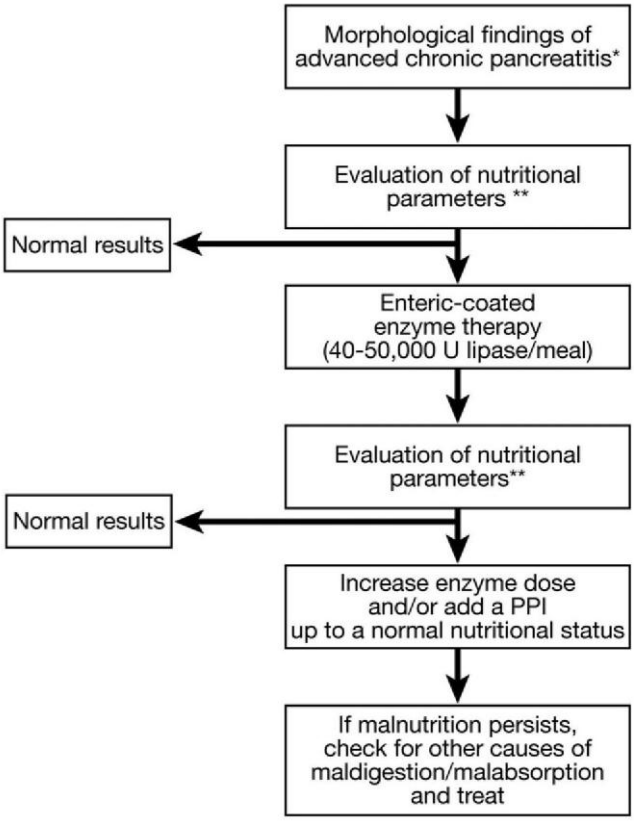
Based on the concept that enzyme therapy should normalize digestion, normalization of the CFA should be used as an objective endpoint. With this aim, the ^{13}C-mixed triglyceride (MTG) breath test could be used as an alternative to CFA in countries where the test is available. According to this approach, the optimal enzyme dose in each individual patient is that able to normalize the CFA or the breath test result (Figure 1). Starting at a dose of 40,000-50,000 United States Pharmacopeia (USP) units of lipase per meal, the CFA quantification or the breath test are repeated with increasing enzyme doses to reach a normal result. This approach has been shown to be associated with a normalization of the body mass index and the nutritional status of patients with chronic pancreatitis and exocrine pancreatic insufficiency.

Fig. 1. Pancreatic enzyme substitution therapy in patients with exocrine pancreatic insufficiency secondary to chronic pancreatitis using normalization of fat digestion as an end point. Patients with symptomatic steatorrhea or those with advanced morphological changes of chronic pancreatitis (calcifications, dilated main duct) on imaging techniques are mainly those to be tested for pancreatic exocrine insufficiency (PEI). PPI, proton pump inhibitor.



However, ^{13}C-MTG breath test is still not available in the US for clinical use and CFA quantification, which is the only test accepted by the FDA for steatorrhea evaluation, is too cumbersome for dosing enzyme therapy. Taking into account that the aim of pancreatic enzyme replacement therapy is to normalize the nutritional status of patients, indication for therapy and enzyme dosing can be done based on nutritional evaluation as an alternative to function tests (Figure 2). In this approach, however, it should be taken into account that a malnutrition status can be secondary not only to exocrine pancreatic insufficiency and insufficient response to enzyme substitution therapy, but also to inadequate patient compliance or inadequate nutrient intake.

Fig. 2. Pancreatic enzyme substitution therapy in patients with exocrine pancreatic insufficiency secondary to chronic pancreatitis using normalization of nutritional parameters as an end point. PEI, pancreatic exocrine insufficiency; PPI, proton pump inhibitor. *Pancreatic calcifications and dilated main pancreatic duct. **BMI, lymphocyte count, serum cholesterol, albumin, prealbumin, and liposoluble vitamins (see Table 1).



As in any other disease condition leading to malnutrition, clinical assessment of nutritional status in patients with chronic pancreatitis and exocrine pancreatic insufficiency involves a focused history and physical examination together with selected laboratory tests aimed at identifying specific nutrient deficiencies. Table 1 shows a proposal of parameters to be evaluated in patients with exocrine pancreatic insufficiency in clinical practice. How often these parameters should be checked should be individualized depending on parameters like individual history and clinical course of the disease; age; associated symptoms (eg, pain); limiting food intake; alcohol intake and smoking; initial nutritional status; and response to therapy, among others.

Enzyme therapy should however be flexible. Taking the enzyme dose able to normalize digestion as the minimum dose ensuring a normal nutrition, higher enzyme doses may be occasionally needed to avoid maldigestion-related symptoms (mainly diarrhea) in case of ingestion of highly caloric meals with a high fat content.

Table 1

Proposed Parameters for the Clinical Assessment of Nutritional Status in Patients With Exocrine Pancreatic Insufficiency

1. History
a. Body weight and weight loss (1 and 6 previous months)
b. Alcohol abuse, drugs
c. Previous GI/pancreatic surgery
d. Nutrient intolerance
e. Dietary intake and restrictions (fat? diabetes mellitus?)
f. Symptoms of specific nutrient deficiencies (hair loss, glossitis, dermatitis, paresthesias)
2. Anthropometry
a. Current body weight
b. Body mass index
c. Muscular arm circumference
3. Biochemical tests
a. Plasma proteins (albumin, prealbumin, transferrin, RBP)
b. Liposoluble vitamins
c. Cholesterol
4. Immune competence
a. Lymphocyte count
5. Muscle function
a. Hand grip
6. Nutritional indexes
a. Nutritional risk index
b. Subjective global assessment

GI, gastrointestinal.

Is It Possible to Normalize Digestion?

Studies in this field, by using different enzyme preparations at different doses, have consistently shown that steatorrhea improves significantly, but that CFA rarely normalizes in patients with exocrine pancreatic insufficiency secondary to chronic pancreatitis or cystic fibrosis. In our experience by using the optimal enzyme preparation at the optimal individual dose, digestion normalizes in about 60% of the patients. In compliant patients, the major factor avoiding normalization of digestion in this setting is the acidic duodenal pH secondary to a low pancreatic bicarbonate secretion. Actually, several clinical trials have shown an improvement of fat digestion by inhibiting gastric acid secretion in patients given enzyme substitution therapy. In a previous study reported by our group, fat digestion normalizes in 67% of patients with persistent maldigestion despite optimal enzyme substitution therapy by adding a proton pump inhibitor twice a day.

Is Management of Exocrine Pancreatic Insufficiency Independent of Etiology?

Therapy of exocrine pancreatic insufficiency secondary to conditions leading to a primarily reduced pancreatic secretion (eg, cystic fibrosis, postnecrotizing pancreatitis, pancreatic cancer) should be most probably similar to that exposed above. Clinical trials on cystic fibrosis support this concept. Due to anatomical gastrointestinal changes leading to alteration of the digestive physiology (eg, reduced postprandial cholecystokinin [CCK] release, asynchrony between gastric emptying of nutrients, and biliopancreatic secretion), therapy of exocrine pancreatic insufficiency secondary to gastrointestinal and pancreatic surgery could be to some extent different. Studies evaluating the efficacy of pancreatic enzyme substitution therapy in this setting are scarce. Enteric-coated enzyme microspheres have been shown to be associated with a significantly higher body weight gain compared with uncoated preparations in patients after duodenopancreatectomy. In our experience with patients with pancreatic exocrine insufficiency after duodenopancreatectomy, treatment with oral pancreatic enzymes in the form of enteric-coated minimicrospheres is as effective as in chronic pancreatitis patients. In addition, as in chronic pancreatitis, inhibition of gastric acid secretion by combined therapy with a proton pump inhibitor

may be also helpful in some postsurgery patients with insufficient response to the enzyme therapy. Based on these limited data, and as a general rule, pancreatic exocrine insufficiency in patients after surgery may be managed similarly to patients with chronic pancreatitis.

Areas of Uncertainty

The study of the impact of malnutrition on the prognosis of chronic pancreatitis is a difficult task, and clinical consequences of maldigestion in this setting have been poorly investigated. However, because malnutrition of any etiology is associated with a series of well known severe complications leading to a high risk of death, it is generally accepted that this complication plays an important prognostic role in chronic pancreatitis patients too. In the same way, the clinical impact of normalizing nutrition by an adequate enzyme substitution therapy on the prognosis of the disease is unknown. This is true not only for chronic pancreatitis, but also for other pancreatic diseases associated with exocrine pancreatic insufficiency (cystic fibrosis, pancreatic cancer, and after severe necrotizing pancreatitis).

In the same sense, enzyme therapy at a dose aiming at avoiding symptoms is frequently associated with a subclinical malnutrition of unknown impact. Because of that, what should be the aim of enzyme substitution therapy is uncertain.

Treatment of exocrine pancreatic insufficiency is clearly indicated in patients with symptomatic steatorrhea, or severe steatorrhea of more than 15 g/day. The need to treat patients with less severe asymptomatic steatorrhea (from 7.5 to 15 g/day) is under debate. From a clinical point of view, the absence of symptoms may make enzyme therapy unnecessary. This is especially true in patients with a normal nutritional status. However, we have recently shown that patients with long-standing asymptomatic steatorrhea of less than 15 g/day have abnormally low circulating levels of fat-soluble vitamins and micronutrients. This suggests the need to treat patients with mild-to-moderate steatorrhea, even those who are asymptomatic, to ensure an adequate nutritional status, but further studies including larger series of patients are needed to confirm these results.

Evidence indicating the optimal endpoint for selecting the optimal enzyme dose is lacking. A dose able to normalize digestion seems to be necessary, but the role of severity of maldigestion, maldigestion-related symptoms and malnutrition, size of meals, and ideal size of patients is unknown and deserves further investigation. Because oral enzymes are not absorbed and exert their action on the ingested meal, it is logical to think that size of the meal, and not size of the patient, should be relevant for selecting the enzyme dose. Although no scientific evidence supports this hypothesis, it seems also logical that the more severe the maldigestion, the higher the enzyme dose required. Nevertheless, this may be not as simple, as factors other than exocrine pancreatic insufficiency, like duodenal pH or bacterial overgrowth, may be also involved in chronic pancreatitis-related maldigestion. Finally, the nutritional status of the patient is a consequence of the severity of maldigestion, but also of dietary habits and evolution time of the disease. Therefore, enzyme dose is probably not influenced by nutrition.

Published Guidelines

Unfortunately there are no published guidelines on how to treat exocrine pancreatic insufficiency related to chronic pancreatitis or any other pancreatic disease (pancreatic cancer, after severe necrotizing pancreatitis or after pancreatic surgery) in the adult. Even cystic fibrosis guidelines are mainly focused on pulmonary complications of the disease. Members of the Australian Pediatric Gastroenterological Society published in 1999 the only guidelines on pancreatic enzyme replacement therapy in cystic fibrosis. They support the recommendation of an enzyme dose based on a standard ratio of lipase units per gram of dietary fat consumed for individual patients, which is appropriate for cystic fibrosis children but may not be the optimal approach for chronic pancreatitis adults.

The Italian Association for the Study of the Pancreas has recently published the Italian consensus guidelines for chronic pancreatitis. This consensus includes some questions on nutritional therapy, indications of pancreatic enzyme substitution therapy, and how to deal with this therapy. In summary, they reported as statements that a reduction in dietary fat is recommended if steatorrhea is severe and not

responding to medical treatment, whereas medium-chain triglycerides are not indicated in these patients; quantitative measurement of fecal fat is not mandatory for prescribing pancreatic enzymes; pancreatic enzyme formulations with enteric-coated pH-sensitive minimicrospheres and high lipase content should be used; proton pump inhibitors should be added if steatorrhea is not controlled by pancreatic enzyme supplementation alone; and finally, the clinical improvement of the nutritional parameters and the normalization of gastrointestinal symptoms are sufficient criteria to evaluate the efficacy of pancreatic enzymes.

Despite the absence of specific guidelines on exocrine pancreatic insufficiency, there are some thorough reviews of the topic published by different experts.

Recommendations for This Patient

In our institution exocrine pancreatic insufficiency in this patient was confirmed by a CFA of 79.8% (normal >92.5%). ^{13}C-MTG breath test result was also abnormal. A nutritional evaluation revealed a body weight of 60 kg, BMI 18.9, lymphocyte count of 800/mm^3 (normal higher than 1000/mm^3), serum prealbumin of 17 mg/dL (lower limit of normality 21 mg/dL), retinol binding protein (RBP) of 2.1 mg/dL (lower limit of normality 3.0 mg/dL), vitamin A of 21 μg/dL (normal >30 μg/dL), and vitamin B_{12} of 160 pg/mL (normal >200 pg/mL). Enzyme substitution therapy with enteric-coated minimicrospheres was prescribed at a dose of 40,000 USP of lipase per meal and 20,000 USP of lipase per snack. No dietary restrictions were recommended. He was instructed to avoid any alcohol and smoking. Three months later the patient was symptom-free; he had 1 single bowel movement per day, consisting usually of formed stools. Nutritional evaluation at that time, although slightly improved, was still clearly abnormal. CFA at that time after oral enzyme substitution therapy was 86%, still below the lower limit of normal. Esomeprazole at a dose of 40 mg before breakfast and dinner was added to the enzyme therapy. One year later the patient remained asymptomatic. A nutritional study performed at that time showed a normal status. BMI had increased up to 21.4, serum albumin was 3.8 mg/dL, prealbumin 27 mg/dL, RBP 4.4 mg/dL, vitamin A 42 μg/dL, and vitamin B_{12} 380 pg/mL.

A simpler alternative to treat this patient could be to assume the presence of exocrine pancreatic insufficiency based on symptoms (chronic diarrhea), morphological diagnosis of severe chronic pancreatitis, a fecal elastase concentration below 50 U/g, and an abnormal nutritional status. Enzyme substitution therapy could then be prescribed at the standard dose of 40,000-50,000 USP of lipase per meal (20,000-25,000 USP of lipase per snack) and the symptomatic response and nutritional parameters evaluated during follow-up. Whether this simpler approach is as appropriate as that based on repeated CFA measurement in terms of therapeutic efficacy is unknown.

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Exocrine pancreatic insufficiency with steatorrhea is a major consequence of chronic pancreatitis. Recognition of this entity is highly relevant to avoid malnutrition-related morbidity and mortality. Nutritional counseling and oral pancreatic enzyme replacement are the basis for the therapy for exocrine pancreatic insufficiency. Aim of enzyme therapy is not only to avoid symptoms but also to normalize digestion. With this aim, oral administration of pancreatic enzymes in the form of enteric-coated minimicrospheres is the therapy of choice. This enzyme preparation 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 reviews the current evidence on therapy of exocrine pancreatic insufficiency in chronic pancreatitis patients, with special attention to different potential endpoints to select the optimal enzyme dose for individual patients.