JGH Journal of Gastroenterology and Hepatology

JGHF

doi:10.1111/j.1440-1746.2010.06600.x

Pancreatic exocrine insufficiency: Diagnosis and treatment

J Enrique Domínguez-Muñoz

Department of Gastroenterology and Hepatology, University Hospital of Santiago de Compostela, Spain

Key words
lipase, pancreatic exocrine insufficiency, pancreatitis.

Correspondence
Professor J Enrique Domínguez-Muñoz, Department of Gastroenterology and Hepatology, University Hospital of Santiago de Compostela C/ Choupana, s/n 15706-Santiago de Compostela, Spain. Email: enriquedominguezmunoz@hotmail.com

Conflicts of interest
Dr Dominguez-Muñoz is a consultant and speaker for Abbott Pharmaceuticals and Axcan Pharma Inc.

Abstract

Pancreatic insufficiency is a major consequence of pancreatic diseases leading to a loss of pancreatic parenchyma, obstruction of the main pancreatic duct, decreased pancreatic stimulation, or acid-mediated inactivation of pancreatic enzymes. In addition, gastrointestinal and pancreatic surgical resections are frequent causes. Clinical manifestations include abdominal cramps, steatorrhea and malnutrition. Malnutrition, the main contributing factor of weight loss, has been related to a high morbidity and mortality secondary to an increased risk of malnutrition-related complications and cardiovascular events.

Assessments of exocrine pancreatic function, such as fecal fat quantification and ^{13}C-triglyceride breath test, are the method of choice for diagnosis. In clinical practice, high-risk patient populations include those with severe necrotizing pancreatitis, gastrointestinal and pancreatic surgery, cancer of pancreas head, and those with pancreatic calcifications.

Apart from relief of maldigestion-related symptoms, the main goal of pancreatic enzyme substitution therapy is to ensure a normal nutritional status. Therapy of pancreatic insufficiency is based on the oral administration of exogenous pancreatic enzymes. Restriction of fat intake, though traditionally important in conventional treatment, should be reconsidered.

Enzyme substitution therapy should ideally mimic the physiological pattern of pancreatic exocrine secretion, and pancreatic enzymes in the form of enteric-coated minimicrospheres are considered as the most elaborated commercially available enzyme preparations. In general, pancreatic exocrine insufficiency in patients after surgery may be managed similarly to patients with chronic pancreatitis. This review focuses on current perspectives in diagnosis and treatment of pancreatic exocrine insufficiency and practical suggestions on its clinical management.

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 eventually develop pancreatic exocrine insufficiency depending on the etiology of the disease. Half of the patients with chronic alcoholic pancreatitis will suffer from pancreatic exocrine insufficiency after 12 years from the onset of the disease.[1]

Apart from 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 manifestation of pancreatic exocrine insufficiency is malnutrition. In fact, 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 with a 4- to 5-fold increased risk of death compared to the general population matched by age and gender.[3,4]

How to diagnose pancreatic exocrine insufficiency?

Functional evaluation of the exocrine pancreas may be important to support the diagnosis of chronic pancreatitis in cases of inconclusive morphological findings on imaging methods. However, the most relevant role of the functional evaluation of the pancreas is the detection of primary or secondary pancreatic insufficiency in patients with known pancreatic disease or after gastrointestinal surgery, to aid in the indication of enzyme substitution therapy and to monitor the efficacy of this therapy.

Quantification of the coefficient of fat absorption (CFA) after fecal fat determination by the classical Van de Kamer test is the gold standard for the diagnosis of fat maldigestion. Despite that, this test has several important disadvantages limiting its clinical applicability. Patients must keep on a standard diet containing around 100 g of fat daily for 5 consecutive days and collect the whole amount of feces produced over the last 3 days. This is not easy to comply for many patients. A three-day collection is needed to allow a sufficiently long period to reduce errors and variability. Not only patient compliance is a limitation for the fecal fat quantification but mainly difficulty in handling of stool samples in the lab. Stool samples collected over 3 days must be first homogenized and then processed according to a manual method that renders this test unpleasant and cumbersome. A methodology based on near infrared reflectance analysis (NIRA) has greatly simplified the quantification of fat in stool and thus helps enable the wide application of this test in clinical routine.[5] Nevertheless, difficulties associated with patient compliance remain to be addressed.

A mixed ^{13}C-triglyceride (^{13}C-MTG) breath test has been developed and optimized as an alternative to CFA for the diagnosis of pancreatic exocrine insufficiency in clinical routine.[6] In this test, the labeled substrate is given orally together with a test meal. After intraduodenal hydrolysis of the substrate by specific pancreatic enzymes, ^{13}C-marked metabolites are released, absorbed from the gut and metabolized within the liver. As a consequence of the hepatic metabolism, $^{13}CO_2$ is released and thereafter eliminated with the expired air (Fig. 1). The amount of $^{13}CO_2$ expired, which indirectly reflects the exocrine pancreatic function, can be measured by means of mass spectrometry or infrared analysis. According to the protocol developed by our group, a total of 250 mg of ^{13}C-MTG is mixed in a solid test meal containing 16 g of fat.[6] Breath samples are collected in 10 mL tubes before (basal sample) and in 30-min intervals for 6 h after the ingestion of the meal. A single dose of a prokineticum (i.e. metoclopramide) is orally given 20–30 min before the meal in order to avoid potential problems related to gastric emptying. The amount of $^{13}CO_2$ in breath samples is measured by mass spectrometry. The result of the test is expressed as the total amount of recovered $^{13}CO_2$ over the 6 h. The sensitivity of the ^{13}C-MTG breath test for the diagnosis of fat maldigestion is higher than 90%.[6] The test is also highly accurate for the diagnosis of maldigestion in clinical situations of secondary exocrine pancreatic insufficiency, such as partial or total gastrectomy or duodenectomy (unpublished personal data). This test is easily applicable to the clinical routine and is highly robust and reproducible. In this way, utility of the test is not only limited to the diagnosis of exocrine pancreatic insufficiency but can also be extended to monitor the efficacy of oral enzyme substitution therapy in these patients.[6]

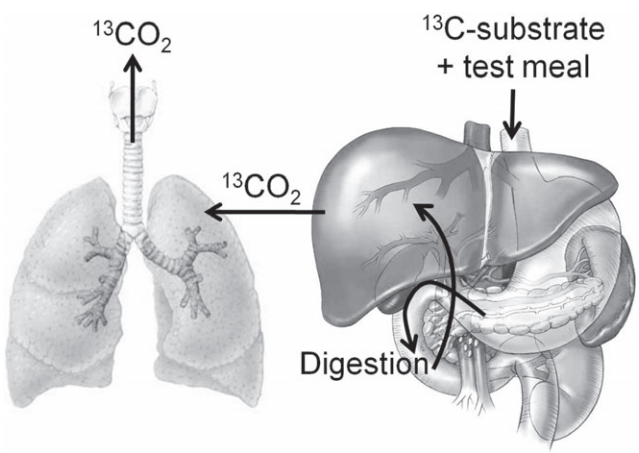

Figure 1 Basis of the ^{13}C-labelled breath test.

Despite that CFA and ^{13}C-MTG breath test are the methods of choice for the diagnosis of pancreatic exocrine insufficiency, neither of these tests are widely available in clinical practice. Some practical aspects may aid in proper management of these patients. 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 that a close correlation between pancreatic function and morphology exists 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 thus be used as an indirect way to diagnose pancreatic exocrine insufficiency.

Therapy of pancreatic exocrine insufficiency

The aim of pancreatic enzyme substitution therapy is not only to relieve maldigestion-related symptoms, but mainly to achieve a normal nutritional status. Therapy of pancreatic exocrine insufficiency is based on the oral administration of exogenous pancreatic enzymes. The role of complementary dietary modifications, though important in conventional therapy, should probably be reconsidered.

When is pancreatic enzyme replacement therapy indicated?

Pancreatic exocrine insufficient patients who experience weight loss, those with daily fecal fat excretion of more than 15 g under a diet containing 100 g fat daily, and those with relevant steatorrhea-related symptoms are classically and generally considered as suitable candidates for enzyme substitution therapy.[7] Indication for treatment in patients with asymptomatic steatorrhea of less than 15 g/d is debatable. A recent study has, however, demonstrated that patients with asymptomatic steatorrhea of less than 15 g/d and consistently low circulating levels of nutritional parameters like liposoluble vitamins, prealbumin and ferritin, can revert to normal status 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.

Which dietary modifications should be recommended for patients with pancreatic exocrine insufficiency?

Classically, the initial approach to patients with pancreatic exocrine insufficiency is to restrict fat intake in an attempt 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 already malabsorbed in patients with pancreatic exocrine insufficiency.[6] In addition, studies on the metabolism of both endogenous and exogenous enzymes during small intestinal transit show that the half-life of enzyme activity is enhanced by the presence of their respective substrates.[9] That means that maintenance 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 was higher when enzyme supplements were taken together with a high-fat diet compared with a low-fat diet.[10] As a consequence, fat restriction should no longer be 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 appears to increase pancreatic lipase secretion, but also inhibit 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.

What should be known for an adequate enzyme substitution therapy?

Pancreatic enzyme secretion increases rapidly in response to a meal up to 6-fold above interdigestive levels and reaches maximal values within 20–60 min postprandially.[12] Enzyme output decreases thereafter to a 3- to 4-fold sustained increase, which is maintained for 3–4 h 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 occur 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 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 administration of the modern enteric-coated preparations in form of minimicrospheres, due to factors like gastric acid secretion, nonparallel gastric emptying of nutrients and enzyme preparations, and proteolytic inactivation of released lipase.

Based on the conceptions that exogenous enzymes should exert their action on the ingested meal, and 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, three-way, crossover study including 24 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 with the intake just before meals.[15]

How effective is enzyme substitution therapy for pancreatic exocrine insufficiency?

Pancreatic enzymes in form of enteric-coated minimicrospheres are considered as the most elaborated commercially available enzyme preparations. These preparations were developed to contain a high lipase activity (U/mg), to avoid acid-mediated inactivation of lipase, and to ensure a gastric emptying of spheres in parallel to nutrients, thus optimizing the efficacy of the enzyme substitution therapy in patients with pancreatic exocrine insufficiency. A recently published randomized, double-blind, placebo-controlled trial in chronic pancreatitis patients has shown the significant therapeutic efficacy of these modern enzyme preparations in reducing fat excretion, decreasing stool frequency and improving stool consistency.[16] These results have been confirmed by means of the ^{13}C-MTG breath test, analysis of coefficient of fat absorption and nutritional status in a recent prospective study including 49 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]

Which factors do hinder normalization of fat digestion despite an adequate enzyme substitution therapy?

Despite the use of modern enteric-coated enzyme preparations in minimicrospheres, fat digestion cannot revert to 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 hampering total elimination of steatorrhea in this clinical setting.[19] Patient compliance is a key factor in the management of pancreatic exocrine insufficiency with oral pancreatic enzymes. Patients should understand the importance of the therapy and the correct administration schedule.[15] In addition, the prescribed dose of enzymes should be high enough, and a minimum dose of 40 000–50 000 Eur. Ph. U of lipase per meal is required.[7,8]

The abnormally low pancreatic secretion of bicarbonate in patients with pancreatic exocrine insufficiency is associated with a limited buffering effect in the proximal intestine. A pH below 4 is

associated with an irreversible inactivation of endogenous and uncoated exogenous pancreatic lipase, as well as with 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 defect in 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. These, together with a markedly low pancreatic secretion of enzymes, may favor the development of bacterial overgrowth.[23]

How to improve the efficacy of the enzyme therapy?

The first step to guarantee an optimal efficacy of oral pancreatic enzymes in the management of pancreatic exocrine insufficiency is to confirm the proper use of enzymes by patients. Secondly, the dose of enzymes should be sufficiently high, and a minimum dose of 40 000–50 000 Eur. Ph. U of lipase per meal and 20 000–25 000 Eur. 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 non-responders (Fig. 2).

As mentioned above, a low intraduodenal pH may inactivate endogenous and uncoated exogenous lipase, prevent the release of active lipase from enteric-coated granules within the proximal intestine, and 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, however, should not be used in patients with an adequate response to the enzyme substitution monotherapy.[18]

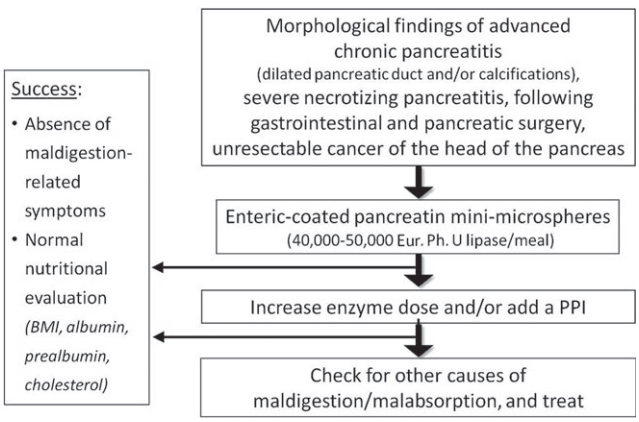

Figure 2 Current recommendations for pancreatic enzyme substitution therapy in patients with pancreatic exocrine insufficiency. BMI, body mass index; PPI, proton pump inhibitor.

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 normalization of fat digestion, demonstrated by means of objective methods like normalization of CFA, ^{13}C-MTG breath test, or specific nutritional parameters, ensures a normal nutritional status in patients with pancreatic exocrine insufficiency.[6,8]

How to treat pancreatic exocrine insufficiency in operated patients?

Pancreatic exocrine insufficiency develops in most patients after partial or total gastrectomy and duodenopancreatectomy.[26,27] Multiple factors have been implicated, including decreased postprandial stimulation of pancreatic secretion secondary to the disruption of neural reflexes and reduced cholecystokinin (CCK) release, primarily decreased pancreatic secretion, arrival of big, hard-to-digest nutrient particles to the jejunal lumen due to pylorus resection, and postprandial asynchrony between gastric emptying of nutrients and biliopancreatic secretion.[26–28] Despite the relevance of pancreatic exocrine insufficiency in the nutritional status of operated patients, the number of studies evaluating the usefulness of pancreatic enzyme substitution therapy in this setting is limited, and data regarding the best preparation to be used are scarce.[28] Enteric-coated enzyme microspheres have been shown to be associated with a higher body weight gain compared with uncoated preparations in patients after duodenopancreatectomy.[29] In addition, a recent study in patients with pancreatic exocrine insufficiency after duodenopancreatectomy demonstrated that treatment with oral pancreatic enzymes in form of enteric-coated minimicrospheres is highly effective in this setting (personal unpublished data). In addition, inhibition of gastric acid secretion by combined therapy with a proton pump inhibitor may be also of help in those operated patients with insufficient response to the enzyme monotherapy. Based on these data and as a general rule, pancreatic exocrine insufficiency in patients after surgery may be managed similarly to patients with chronic pancreatitis.

References

1 Layer P, Yamamoto H, Kalthoff L, Clain JE, Bakken LJ, DiMagno EP. The different courses of early- and late-onset idiopathic and alcoholic chronic pancreatitis. *Gastroenterology* 1994; **107**: 1481–7.
2 Montalto G, zorreéis M, Carroccio A *et al*. Lipoproteins and chronic pancreatitis. *Pancreas* 1994; **9**: 137–8.
3 Lankisch PG. Natural course of chronic pancreatitis. *Pancreatology* 2001; **1**: 3–14.
4 Norjgaard C, Bendtsen F, Becker U, Andersen JR, Holst C, Matzen P. Danish patients with chronic pancreatitis have a 4-fold higher mortality rate than the Danish population. *Gastroenterology* 2010; **138** (Suppl. 1): S393.
5 Stein J, Purschian B, Bieniek U, Caspary WF, Lemcke B. Near-infrared reflectance analysis (NIRA): a new dimension in the

investigation of malabsorption syndromes. *Eur. J. Gastroenterol. Hepatol.* 1994; **6**: 889–94.
6 Domínguez-Muñoz JE, Iglesias-García J, Vilariño-Insua M, Iglesias-Rey M. ^{13}C-mixed triglyceride breath test to assess oral enzyme substitution therapy in patients with chronic pancreatitis. *Clin. Gastroenterol. Hepatol.* 2007; **5**: 484–8.
7 Domínguez-Muñoz JE. Pancreatic enzyme therapy for pancreatic exocrine insufficiency. *Curr. Gastroenterol. Rep.* 2007; **9**: 116–22.
8 Domínguez-Muñoz JE, Iglesias-García J. Oral pancreatic enzyme substitution therapy in chronic pancreatitis: is clinical response an appropriate marker for evaluation of therapeutic efficacy? *JOP* 2010; **11**: 158–62.
9 Holtmann G, Nelly DG, Sternby B, DiMagno EP. Survival of human pancreatic enzymes during small bowel transit: effects of nutrients, bile acids and enzymes. *Am. J. Physiol.* 1997; **273**: G553–8.
10 Suzuki A, Mizumoto A, Rerknimitr R *et al*. Effect of bacterial or porcine lipase with low- or high-fat diets on nutrient absorption in pancreatic insufficient dogs. *Gastroenterology* 1999; **116**: 431–7.
11 Isaksson G, Lundquist I, Ihse I. Effect of dietary fiber on pancreatic enzyme activity in vitro. *Gastroenterology* 1982; **82**: 918–24.
12 Keller J, Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005; **54** (Suppl. 6): 1–28.
13 DiMagno EP, Go VLW, Summerskill WHJ. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N. Engl. J. Med.* 1973; **288**: 813–15.
14 Lankisch PG, Lembcke B, Wemken G, Creutzfeldt W. Functional reserve capacity of the exocrine pancreas. *Digestion* 1986; **35**: 175–81.
15 Dominguez-Munoz JE, Iglesias-Garcia J, Iglesias-Rey M, Figueiras A, Vilarino-Insua M. Effect of the administration schedule on the therapeutic efficacy of oral pancreatic enzyme supplements in patients with exocrine pancreatic insufficiency: a randomized, three-way crossover study. *Aliment. Pharmacol. Ther.* 2005; **21**: 993–1000.
16 Safdi M, Bekal PK, Martin S, Saeed ZA, Burton F, Toskes PP. The effects of oral pancreatic enzymes (Creon 10 capsule) on steatorrhea: a multicenter, placebo-controlled, parallel group trial in subjects with chronic pancreatitis. *Pancreas* 2006; **33**: 156–62.
17 Stern RC, Eisenberg JD, Wagener JS *et al*. A comparison of the efficacy and tolerance of pancrelipase and placebo in the treatment of steatorrhea in cystic fibrosis patients with clinical exocrine pancreatic insufficiency. *Am. J. Gastroenterol.* 2000; **95**: 1932–8.
18 Domínguez-Muñoz JE, Iglesias-García J, Iglesias-Rey M, Vilariño-Insua M. Optimizing the therapy of exocrine pancreatic insufficiency by the association of a proton pump inhibitor to enteric-coated pancreatic extracts. *Gut* 2006; **55**: 1056–7.
19 Domínguez-Muñoz JE. Management of maldigestion in chronic pancreatitis: a practical protocol. In: Domínguez-Muñoz JE, ed. *Clinical Pancreatology for Practising Gastroenterologists and Surgeons*. Oxford: Blackwell Publishing, 2005; 288–93.
20 DiMagno EP, Malagelada JR, Go VLW, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency: comparison of two dosage schedules. *N. Engl. J. Med.* 1977; **296**: 1318–22.
21 Guarner L, Rodriguez R, Guarner F, Malagelada JR. Fate of oral enzymes in pancreatic insufficiency. *Gut* 1993; **34**: 708–12.
22 Casellas F, Guarner L, Vaquero E, Antolin M, de Gracia X, Malagelada JR. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. *Pancreas* 1998; **16**: 481–6.
23 Pieramico O, Dominguez-Munoz JE, Nelson DK, Bock W, Buchler M, Malfertheiner P. Interdigestive cycling in chronic pancreatitis: altered coordination among pancreatic secretion, motility, and hormones. *Gastroenterology* 1995; **109**: 224–30.
24 Carroccio A, Pardo F, Montalto G *et al*. Use of famotidine in severe exocrine pancreatic insufficiency with persistent maldigestion on enzymatic replacement therapy: a long-term study in cystic fibrosis. *Dig. Dis. Sci.* 1992; **37**: 1441–6.
25 Proesmans M, DeBoeck K. Omeprazole, a proton pump inhibitor, improves residual steatorrhea in cystic fibrosis patients treated with high dose pancreatic enzymes. *Eur. J. Pediatr.* 2003; **162**: 760–3.
26 Friess H, Bohm J, Muller MW *et al*. Maldigestion after total gastrectomy is associated with pancreatic insufficiency. *Am. J. Gastroenterol.* 1996; **91**: 341–7.
27 Yamaguchi K, Yokohata K, Nakano K *et al*. Which is a less invasive pancreatic head resection: PD, PPPD, or DPPHR? *Dig. Dis. Sci.* 2001; **46**: 282–8.
28 Lankisch PG. Appropriate pancreatic function tests and indication for pancreatic enzyme therapy following surgical procedures on the pancreas. *Pancreatology* 2001; **1** (Suppl. 1): 14–26.
29 Braga M, Cristallo M, De Franchis R *et al*. Pancreatic enzyme replacement therapy in post-pancreatectomy patients. *Int. J. Pancreatol.* 1989; **5** (Suppl.): 37–44.