ORIGINAL ARTICLE

Oral Pancreatic Enzyme Substitution Therapy in Chronic Pancreatitis: Is Clinical Response an Appropriate Marker for Evaluation of Therapeutic Efficacy?

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ABSTRACT

Context Malnutrition secondary to pancreatic exocrine insufficiency plays a prognostic role in chronic pancreatitis. Enzyme substitution therapy is generally prescribed to avoid diarrhea and weight loss, although it is unknown whether this is associated with normal absorption of nutrients and a normal nutritional status. **Objective** We aimed to evaluate whether an adequate clinical response to enzyme therapy can be used to predict a normal nutritional status in patients with chronic pancreatitis. **Patients** Thirty-one consecutive patients (25 males, 6 females; mean age 52 years,) with severe chronic pancreatitis and steatorrhea were enrolled in the study. **Intervention** Enzyme substitution therapy was indicated in cases with severe steatorrhea (more than 15 g/day), diarrhea and/or weight loss. Therapy was optimized in individual patients to obtain complete symptom relief. **Main outcome measure** A nutritional evaluation including body mass index and serum levels of retinol-binding protein, prealbumin and transferrin was carried out. **Results** Ten out of ten patients with asymptomatic steatorrhea, who did not fulfill the criteria for enzyme substitution therapy, and 11 out of 21 patients (52.4%) with symptomatic or more severe steatorrhea, who were under enzyme substitution therapy, showed a deficient nutritional status. **Conclusions** An appropriate clinical response to enzyme substitution therapy does not allow the prediction of a normal nutritional status in patients with chronic pancreatitis.

INTRODUCTION

Pancreatic exocrine insufficiency with maldigestion is a major consequence of chronic pancreatitis. About 50% of patients with chronic pancreatitis develop maldigestion at a median time of 10 to 12 years from the onset of the disease, and only rarely cases does clinically relevant exocrine insufficiency not develop at later stages [1].

Although the clinical consequences of maldigestion secondary to chronic pancreatitis have been poorly studied, it is generally accepted that this complication plays an important prognostic role. In fact, maldigestion is associated with life-threatening complications, such as cardiovascular events, which have been related to abnormally low plasma levels of high-density lipoprotein C, apolipoprotein A-I and lipoprotein A [2]. An appropriate maldigestion therapy is therefore crucial for reducing morbidity and mortality associated with chronic pancreatitis.

Treatment of pancreatic exocrine insufficiency is clearly indicated in patients with symptomatic steatorrhea, or steatorrhea of more than 15 g/day, whereas the need to treat patients with less severe asymptomatic steatorrhea (from 7.5 to 15 g/day) is under debate. Oral administration of pancreatic enzyme supplements is the therapy of choice for maldigestion secondary to pancreatic exocrine insufficiency [3]. Because of problems related to acid-mediated inactivation of lipase and the need for an adequate gastric mixture and emptying of enzymes with the nutrients, enteric-coated mini-microspheres are generally the preferred pharmacological formulation of pancreatic enzymes [4, 5, 6, 7, 8, 9, 10].

Due to the unavailability of objective and easily applicable methods for establishing the optimal oral dose of pancreatic enzymes for each individual patient, this dose is usually calculated with the aim of avoiding diarrhea and weight loss. It is however unknown whether this clinical evaluation can be used to predict the adequate absorption of nutrients and a normal nutritional status of the patients.

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Key words Body Mass Index; Enzyme Replacement Therapy; Nutritional Status; Pancreatitis, Chronic; Prealbumin; Retinol-Binding Proteins; Transferrin

Abbreviations BMI: body mass index; CI: confidence interval; RBP: retinol-binding protein

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We carried out the present study with the following aims: a) to evaluate the nutritional status of patients with advanced chronic pancreatitis and steatorrhea undergoing enzyme substitution therapy; b) to evaluate whether a good symptomatic response to oral enzyme therapy in these patients is associated with a normal nutritional status and c) to analyze the nutritional status of chronic pancreatitis patients with asymptomatic steatorrhea of less than 15g/day.

MATERIAL AND METHODS

Patients with chronic pancreatitis, who were followed-up in the Pancreas Unit of the University Hospital of Santiago de Compostela, Spain, were considered for this prospective study. From this patient population, those patients fulfilling the following criteria were enrolled in the study:

a) the presence of severe chronic pancreatitis based on MRCP (Cambridge criteria) [11] and EUS (8 or more criteria of chronic pancreatitis) [12]; b) the presence of steatorrhea defined as a daily fecal excretion of more than 7.5 g of fat based on near-infrared analysis of stool samples collected over the last 72 hours of a 5-day period of a standardized diet containing 100 g of fat per day and c) the absence of steatorrhea-related diarrhea and weight loss over a period of at least 12 months prior to study entry.

Based on generally accepted indications, enzyme substitution therapy had been prescribed to patients who developed either severe steatorrhea (daily excretion of more than 15 g fat) or steatorrhea-related diarrhea and/or weight loss during the evolution of chronic pancreatitis. On the contrary, patients with steatorrhea of less than 15 g/day and the absence of diarrhea and weight loss did not receive any enzyme therapy. Enzyme substitution therapy consisted of the oral administration of pancreatic enzymes in the form of enteric-coated mini-microspheres (Kreon®, Solvay-Pharma, Hannover, Germany) at a dose capable of preventing diarrhea and weight loss. Enzyme therapy was started by giving 20,000 Eur.Ph.U lipase/meal (10,000 Eur.Ph.U lipase/snack). This dose was increased in intervals of 20,000 U lipase/meal if necessary to avoid diarrhea and weight loss. Patients who did not require enzyme therapy were seen at 6-month intervals for clinical follow-ups. In cases in which enzymes were prescribed, visits were made at 3-month intervals until relief of symptoms (diarrhea and weight loss), and at 6-month intervals thereafter. All patients, with and without enzyme substitution therapy, were actively instructed to maintain a normal balanced homemade diet, with no dietary restriction other than alcohol abstinence. Dietary supplements were not prescribed.

A nutritional evaluation consisting of the quantification of serum levels of retinol-binding protein as a marker of liposoluble vitamins, prealbumin and transferrin, as well as quantification of the body mass index (BMI), was carried out in all patients at study entry.

STATISTICS

Quantitative data are shown as mean and standard deviations (SD) and are compared by the analysis of variance (ANOVA) after confirming normal distribution by the Kolmogorov-Smirnov test. Post-hoc analysis was performed by the Games-Howell test in order to evaluate pairwise differences between groups. Qualitative results are shown as relative frequencies (percentages). Categorical variables were compared by the Fisher's exact and the linear-by-linear chi-square tests, as appropriate. Absolute frequencies and age range were also reported. Analyses were performed by using the SPSS 16.0 statistical package for Windows. Two-tailed P values less than 0.05 were considered statistically significant.

ETHICS

The study was conducted in accordance with the current guidelines of good clinical practice. Patients participated voluntarily in the study after it had been explained properly by the investigator. A written, dated and signed informed consent was obtained from all subjects before entry into the study.

Table 1. Clinical features of patients according to nutritional status at study entry. Deficient nutritional status is defined by abnormally low serum levels of retinol-binding protein. Continuous data are shown as mean±SD.

	Patients with deficient nutritional status (Groups A+C; No. 21)	Normally nourished patients (Group B; No. 10)	P value
Age (years)	53.6±11.2	50.1±4.7	0.356 [a]
Gender			0.358 [b]
- Males	18 (85.7%)	7 (70.0%)	
- Females	3 (14.3%)	3 (30.0%)	
Years of disease	12.5±5.3	11.0±5.0	0.468 [a]
Number of EUS criteria:			0.011 [c]
- 8 criteria	14 (66.7%)	2 (20.0%)	
- 9 criteria	5 (23.8%)	4 (40.0%)	
- 10 criteria	2 (9.5%)	4 (40.0%)	
Fecal fat excretion (g/day)	17.7±10.0	23.5±5.7	0.124 [a]
Patients with diabetes mellitus	3 (14.3%)	4 (40.0%)	0.172 [b]
Patients with calcifications	5 (23.8%)	4 (40.0%)	0.417 [b]

[a] ANOVA
[b] Fisher's exact test
[b] Linear-by-linear chi-square

RESULTS

Thirty one consecutive patients (25 males, 6 females; mean age 52 years, range 24 to 83 years) with alcohol-related chronic pancreatitis were included. All patients were smokers of 10 to 30 cigarettes per day. Every patient was able to stop alcohol intake and was abstinent at study entry. No patient was able to stop smoking. Seven patients required insulin therapy because of endocrine pancreatic insufficiency and nine had pancreatic calcifications as shown by endoscopic ultrasound. Severe liver and biliary diseases explaining fat maldigestion were excluded in all cases by standard blood biochemistry and abdominal ultrasound. Baseline characteristics of patients are shown in Table 1.

The mean daily fecal fat excretion at entry was 19.6±9.7 g. Ten patients had asymptomatic steatorrhea of less than 15 g/day and thus did not receive enzyme substitution therapy. The remaining 21 patients required a median dose of oral pancreatic enzymes of 20,000 Eur.Ph.U lipase/meal (range 20,000 to 60,000 Eur.Ph.U lipase/meal) to avoid diarrhea and weight loss. All 31 patients were in a good clinical state, with stable body weight and absence of diarrhea over a range of 12 to 26 months before entry into the study.

Serum levels of retinol-binding protein, pre-albumin and transferrin in these patients at study entry, as well as the BMI, are shown in Figure 1. All 10 patients (100%) with asymptomatic steatorrhea who were not under enzyme substitution therapy (Group C) and 11 out of 21 patients (52.4%) with symptomatic or more severe steatorrhea showed a deficient nutritional status

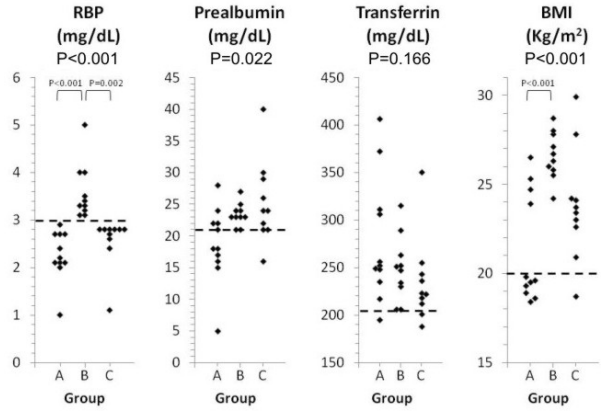

Figure 1. Nutritional parameters in individual patients with severe chronic pancreatitis, steatorrhea (as demonstrated by near-infrared analysis of stool samples collected over the last 72 hours of a 5-day period of a standardized diet containing 100 g of fat per day) and a good clinical status defined by the absence of steatorrhea-related diarrhea and weight loss. Patients are divided into three groups: Patients with severe steatorrhea (more than 15 g/day) and nutritional deficiencies on enzyme supplementation (Group A; No. 11); patients with severe steatorrhea (more than 15 g/day) and no nutritional deficiency on enzyme supplementation (Group B; No. 10); and patients with mild-moderate steatorrhea (less than 15 g/day) not on enzyme supplementation (Group C; No. 10).
The lower limit of reference for each individual parameter is shown as a dashed line. P values are computed by ANOVA with post-hoc analysis by the Games-Howell test.
BMI: body mass index; RBP: retinol binding protein.

(as defined by abnormally low serum retinol-binding protein levels (Group A) despite a good symptomatic response to oral enzyme substitution therapy. The remaining 10 patients with severe steatorrhea (47.6%) had no nutritional deficiency on enzyme supplementation (Group B).

Seven patients (22.6%) had abnormally low values of serum pre-albumin, three (9.7%) had decreased serum levels of transferrin and eight (25.8%) had a low BMI. All nutritional parameters were within normal range in patients with normal serum retinol-binding protein levels. Serum retinol binding protein (P<0.001), prealbumin (P=0.022), and BMI (P<0.001), but not transferrin (P=0.166), were significantly different among the groups (Figure 1). The post-hoc analysis showed that retinol-binding protein was significantly higher in patients with no nutritional deficiency on enzyme supplementation (Group B) than in the other two groups (P<0.001in Group A and P=0.002 in Group C). The BMI was significantly lower in Group A (severe steatorrhea and nutritional deficiencies on enzyme supplementation) when compared with Group B (P<0.001) but not with Group C (patients with mild-moderate steatorrhea not on enzyme supplementation; P=0.171). Finally, serum prealbumin levels tended to be lower in Group A than in the other two groups (P=0.069 in Group B and P=0.068 in Group C) (Figure 1).

A deficient nutritional status, as defined by abnormally low serum retinol-binding protein levels, was not dependent on age, gender, years of disease and the presence of diabetes mellitus or pancreatic calcifications. Patients with a normal nutritional status under enzyme substitution therapy had a significantly (P=0.011) higher number of EUS criteria and tended to have a higher basal fecal fat excretion than patients with a deficient nutritional status (Table 1).

DISCUSSION

The present study shows that an adequate symptomatic response to oral enzyme substitution therapy in patients with pancreatic exocrine insufficiency is not associated with a normal nutritional status in a relevant proportion of patients. In addition, patients with asymptomatic steatorrhea of less than 15 g/day consistently showed a deficient nutritional status if not treated.

Pancreatic exocrine insufficiency with maldigestion develops in most patients with chronic pancreatitis over time, leading to a situation of malnutrition which may have an important prognostic impact [1, 2]. 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, since malnutrition of any etiology is associated with a series of severe well-known complications leading to a high risk of death [13], it is generally accepted that this complication plays an important prognostic role in chronic pancreatitis patients. In fact, maldigestion has been shown to be associated with a high risk of life-

threatening cardiovascular events in patients with chronic pancreatitis, which seems to be related to abnormally low plasma levels of high-density lipoprotein C, apolipoprotein A-I, and lipoprotein A [2]. Therefore, appropriate maldigestion therapy should be defined by its ability to normalize digestion and absorption of nutrients and to assure a normal nutritional status, and not only the prevention of diarrhea and weight loss.

The efficacy of oral pancreatic enzymes is usually tested in individual patients by the simple clinical evaluation of body weight and, mainly, the presence of diarrhea. In the present study, about two-thirds of the patients with maldigestion secondary to chronic pancreatitis had a deficient nutritional status despite their adequate clinical response to oral pancreatic enzyme supplements. Therefore, oral pancreatic enzyme substitution therapy cannot be correctly optimized based on the clinical response to therapy (absence of weight loss and diarrhea). Actually, serum levels of fat soluble vitamins frequently remain abnormally low despite the theoretically adequate oral substitution of pancreatic enzymes. An objective demonstration of the normalization of fat digestion during therapy can be best obtained either by quantification of the coefficient of fat absorption or the optimized ^{13}C-mixed triglycerides breath test as previously described [14]. Normalization of digestion and absorption of nutrients by adequate enzyme substitution therapy is associated with a normalization of the nutritional status in most of the patients [14].

The need to treat patients with asymptomatic steatorrhea of less than 15 g/day (fecal fat excretion of 7.5 to 15 g/day) is under debate. The present study shows that asymptomatic patients with steatorrhea of less than 15 g/day consistently have a nutritional deficit based on the nutritional parameters evaluated (mainly retinol-binding protein as a marker of fat-soluble vitamins) if not treated. Almost half of the patients with severe steatorrhea had a normal nutritional status with enzyme substitution therapy at a dose capable of preventing symptoms. In the remaining symptomatic cases, therapy was able to avoid diarrhea and weight loss, but it was not sufficiently adequate to normalize nutrition. Therefore, symptom response to enzyme substitution therapy does not assure normal nutrition, which should be the aim of the therapy. This explains why patients with asymptomatic fat maldigestion have a deficient nutritional status and suggests that these patients may benefit from enzyme substitution therapy designed to normalize digestion. This finding is in agreement with previous studies from our group [9, 10, 14]. It must be taken into account that, since pancreatic exocrine insufficiency develops slowly over years in patients with chronic pancreatitis, they tend to adapt their diet progressively, so that diarrhea is frequently absent despite the presence of clinically relevant maldigestion.

Since a deficient nutritional status is present in a high proportion of patients with severe and/or symptomatic steatorrhea under enzyme therapy as well as in patients with asymptomatic mild-moderate steatorrhea, malnutrition could be related to factors other than fat maldigestion (e.g. deficient dietary intake, extra-pancreatic diseases affecting absorption of nutrients). There is no doubt that a balanced diet is needed as the basis of the therapy for every patient with chronic pancreatitis. A previous randomized controlled trial showed that dietary counseling for a balanced diet is as good as commercial food supplements in improving malnutrition in patients with chronic pancreatitis under enzyme substitution therapy [15]. In the present study, patients were actively instructed to maintain a normal balanced homemade diet, with no dietary restriction other than alcohol abstinence. Together with diet, oral enzyme substitution becomes the key therapy for improving nutrition in patients with pancreatic exocrine insufficiency. This is supported by a previous study in which most patients with malnutrition related to pancreatic exocrine insufficiency were able to normalize their nutritional status by normalizing digestion with an adequate enzyme substitution therapy [14].

In conclusion, the present study demonstrates that oral pancreatic enzyme supplementation in patients with pancreatic exocrine insufficiency resulting from chronic pancreatitis cannot be correctly optimized based on the clinical evaluation of maldigestion-related symptoms and signs (diarrhea and weight loss). Serum levels of fat soluble vitamins frequently remain abnormally low despite a theoretically adequate oral enzyme substitution therapy. Thus there is a clear need for using objective methods evaluating digestion and absorption of nutrients in order to optimize oral pancreatic enzyme substitution therapy in patients with pancreatic exocrine insufficiency. Finally, this study suggests the need to treat patients with steatorrhea, even asymptomatic patients in order to assure an adequate nutritional status. Further studies including larger series of patients are needed to confirm these results.

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Conflict of interest The authors have no potential conflicts of interest

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