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EDITORIAL

Chronic pancreatitis: Maldigestion, intestinal ecology and intestinal inflammation

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Abstract

Exocrine pancreatic insufficiency caused by chronic pancreatitis results from various factors which regulate digestion and absorption of nutrients. Pancreatic function has been extensively studied over the last 40 years, even if some aspects of secretion and gastrointestinal adaptation are not completely understood. The main clinical manifestations of exocrine pancreatic insufficiency are fat malabsorption, known as steatorrhea, which consists of fecal excretion of more than 6 g of fat per day, weight loss, abdominal discomfort and abdominal swelling sensation. Fat malabsorption also results in a deficit of fat-soluble vitamins (A, D, E and K) with consequent clinical manifestations. The relationships between pancreatic maldigestion, intestinal ecology and intestinal inflammation have not received particular attention, even if in clinical practice these mechanisms may be responsible for the low efficacy of pancreatic extracts in abolishing steatorrhea in some patients. The best treatments for pancreatic maldigestion should be re-evaluated, taking into account not only the correction of pancreatic insufficiency using pancreatic extracts and the best duodenal pH to permit optimal efficacy of these extracts, but we also need to consider other therapeutic approaches including the decontamination of intestinal lumen, supplementation of bile acids and, probably, the use of probiotics which may attenuate intestinal inflammation in chronic pancreatitis patients.

Key words: Chronic pancreatitis; Exocrine pancreatic insufficiency; Leukocyte L1 antigen complex; Pancreatic elastase; Pancreatic extracts

INTRODUCTION

Exocrine pancreatic insufficiency caused by chronic pancreatitis results from various factors which regulate digestion and absorption of nutrients. Pancreatic function has been extensively studied over the last 40 years, even if some aspects of secretion and gastrointestinal adaptation are not completely understood. The pancreatic gland normally secretes more than 2 L of juice per day which is composed of water, bicarbonates and enzymes[1]; protein secretion per gram of pancreatic tissue is elevated more than that of any other organ[2], and more than 85% of the protein content is composed of enzymes which are able to digest lipids, proteins and carbohydrates[3]. The pancreas normally produces more enzymes than are necessary for food digestion[1], and normal digestion is guaranteed up to a loss of 95% of pancreatic secretive capacity[4]. Recently, it has been demonstrated that gastric lipase can compensate pancreatic lipase even if it is not capable of complete lipolytic activity[5]. Enzyme degradation in the intestinal lumen is the main factor controlling nutrient absorption. The activity of pancreatic enzymes progressively decreases during their progression in the intestinal lumen: 60% of active trypsin and chymotrypsin are present in the jejunum, whereas only 20% of these enzymes are present in the ileum; on the other hand, amylases and lipases are more stable[6-8]. There are various explanations for the loss of enzymatic activity during progression in the intestinal lumen, including proteolytic degradation (chymotrypsin is the main lipase degradation factor)[9], lipase acid inactivation (lipase is particularly sensitive to acid inactivation)[10], and the brief half-life of some

enzymes, particularly lipase[11]. This is the reason why, in patients with exocrine pancreatic insufficiency, fat maldigestion is more severe than that of carbohydrates and proteins. In addition to an optimal concentration of biliary acids and colipases in the intestinal lumen, good fat digestion requires an adequate blending of nutrients with the pancreatical juice and optimal intestinal motility. In pathological conditions, such as chronic pancreatitis, there is a deficit in bicarbonate production; a low duodenal pH determines biliary acid precipitation and the remaining lipase activity worsens. Finally, other causes of malabsorption may be an accelerated gastric emptying and a lower intestinal transit time[12,13].

CLINICAL MANIFESTATIONS AND DIAGNOSIS OF EXOCRINE PANCREATIC INSUFFICIENCY

The main clinical manifestations of exocrine pancreatic insufficiency are fat malabsorption, known as steatorrhea, which consists of fecal excretion of more than 6 g of fat per day, weight loss, abdominal discomfort and abdominal swelling sensation. Fat malabsorption also results in a deficit of fat-soluble vitamins (A, D, E and K) with consequent clinical manifestations. The diagnosis of exocrine pancreatic insufficiency is based on these clinical symptoms and signs observed with direct and indirect tests. Some of these tests can be used to determine the degree of insufficiency which is usually classified as mild, moderate or severe. The most sensitive test is the secretin-cholecystokinin (CCK) or secretin-cerulein test; this test has a double-lumen tube capable of separately draining the gastric juice and the pancreatic juice. The test starts with pancreatic stimulation by secretin which produces the hydro-electrolyte pancreatic secretion and CCK or cerulein, which can stimulate enzymatic secretion. This test is highly sensitive and specific[14] but is invasive, lengthy and expensive; moreover, it is only possible in patients with a normal gastrointestinal tract, and it is not useful in patients with an altered digestive anatomy. At present, fecal chymotrypsin and elastase 1 are more frequently used to diagnose exocrine pancreatic insufficiency[15]. In particular, the determination of elastase 1 is more sensitive and specific than chymotrypsin determination. The advantage of these tests is that they can be used in patients who have undergone surgery involving the gastrointestinal tract, but they can not reveal a mild degree of exocrine pancreatic insufficiency[15,16]. A cholesteryl-octanoate breath test is rarely used because of its high cost and possible interference with metabolic and pulmonary diseases[17]. Fecal fat determination is useful in monitoring lipid malabsorption therapy. Pancreatic exocrine evaluation during magnetic resonance cholangiopancreatography with secretin administration is still under study and the results of the published studies seem to be promising[18-20].

MALDIGESTION, INTESTINAL ECOLOGY AND INTESTINAL INFLAMMATION

The relationships between pancreatic maldigestion, intestinal ecology and intestinal inflammation have not received particular attention, even if in clinical practice these mechanisms may be responsible for the low efficacy of pancreatic extracts to abolish steatorrhea in some patients.

One mechanism which has been hypothesized between maldigestion and intestinal alterations relates to bacterial overgrowth in the small intestine; bacterial overgrowth is often seen in experimental models of exocrine pancreatic insufficiency[21]. Furthermore, bacterial overgrowth has been observed in dogs with naturally occurring exocrine pancreatic insufficiency[22]. The presence of bacterial overgrowth in human exocrine pancreatic insufficiency has been studied using non-invasive breath tests based on ^{14}C-cholylglycine[23], ^{14}C-xylose[24], glucose[25,26] or by intubation followed by culture of intestinal aspirates[27]. These studies indicated that bacterial overgrowth complicates 25%-50% of patients with exocrine pancreatic insufficiency, and it was suggested that bacterial overgrowth might either contribute to diarrhea or account for the persistence of diarrhea in patients with exocrine pancreatic insufficiency who receive adequate pancreatic enzyme supplementation. Furthermore, bacterial overgrowth might give rise to bile acid malabsorption and changes in intestinal permeability[28].

However, Madsen *et al*[29] found no bacterial overgrowth in any of their patients with exocrine pancreatic insufficiency, and these findings seem to conflict with previous observations seen in both humans and animals. In fact, in the study based on intestinal culture[27], it was observed that bacterial overgrowth occurred in 50% of patients with severe pancreatic insufficiency who were not receiving enzyme replacement therapy, and studies in dogs indicated that bacterial overgrowth from ligation of the pancreatic duct can be reversed by bovine pancreatic extract replacement therapy; thus these results indicate that pancreatic enzymes might have an important influence on small-intestinal bacterial flora[21]. Since all the patients studied by Madsen had oral enzyme supplementation, it is possible that enzyme substitution treatment normalized the luminal conditions of the small intestine, which otherwise would have facilitated bacterial overgrowth.

In a previous study, a wide range of bile salt malabsorption was observed in patients with exocrine pancreatic insufficiency secondary to alcoholic pancreatitis[30]. Moreover, these data suggested that intraluminal factors, rather than a primary defect in the ileal mucosa, were responsible for bile salt malabsorption. The fecal loss of bile salts in their patients was markedly reduced by oral administration of pancreatic enzymes, indicating an important role for pancreatic enzymes in bile acid absorption. It has been postulated from studies performed *in vitro* that a lack

of pancreatic enzymes causes generalized maldigestion, which in turn may be responsible for persistent bile salt binding to maldigested protein, carbohydrate, or fiber in these patients[31]. It is conceivable, therefore, that in patients with untreated pancreatic insufficiency, an exceeding low concentration of intraluminal pancreatic enzymes during the postprandial period gives rise to persistent binding of bile acids to undigested dietary components, resulting in bile acid malabsorption.

Low intraluminal pH in the upper small intestine might be another important factor in the pathogenesis of fecal loss of bile acids in pancreatic insufficiency. Thus, bile acid malabsorption in patients with chronic pancreatitis and exocrine dysfunction does not occur until bicarbonate output is below a certain level[32], and cimetidine has been shown to reduce pH-induced precipitation of bile acids, thereby improving the micelle concentration of bile salts in the duodenum[33]. Moreover, food residues seem to absorb more bile salts at pH values less than 6.0[34].

The study by Madsen[29] also evaluated intestinal permeability in exocrine pancreatic insufficiency due to chronic pancreatitis in adult patients; these authors found that patients receiving enzyme replacement therapy had reduced urinary excretion of mannitol. The exact character of the underlying epithelial impairment was at that time not obvious, as the pathways for permeation of both smaller molecules such as mannitol and larger molecules are not yet known. It is possible that larger pores located in the crypts of intestinal epithelium permit absorption of larger molecules, while smaller molecules pass through both these pores and smaller pores located in the villi[35,36]. According to this hypothesis, it is suggested that a defect localized in the villi of the intestinal epithelium may exist. It is possible, however, that more pronounced disturbances in intestinal permeability would have been revealed, if urine excretion of the test substances had been properly corrected for variations in the small-intestinal transit rate[37]. Since bacterial overgrowth which often gives rise to defects in intestinal permeability was not found in any of our patients, it is suggested that pancreatic disease *per se* and not enzyme supplementation therapy caused the permeability defect. In a recent study, we evaluated fecal calprotectin in a total of 90 subjects; 22.2% with chronic pancreatitis, 16.7% with pancreatic cancer, 6.7% with chronic non-pathological pancreatic hyperenzymemia, 17.8% with non-pancreatic diseases and 25.6% with no detectable diseases[38]. Calprotectin is a cytoplasmic antimicrobial component prominent in granulocytes, monocytes, and macrophages. It accounts for approximately 60% of the total protein in the cytosol. The release of calprotectin is most likely a consequence of cell disruption and death[39] and is stable in stools for more than 7 d at varying temperatures, as well as being resistant to proteolysis even after transportation and storage[40]. Calprotectin can inhibit bacterial proliferation both as a component of the innate immune response and through its iron-binding capacity[41]. Fecal calprotectin determination has been demonstrated to be useful in diagnosing various inflammatory diseases of the gastrointestinal tract[42-46]. We found that patients with chronic pancreatitis had abnormally high fecal calprotectin concentrations in 55% of cases and most of these patients (40%) had pancreatic insufficiency[38]. It is possible that, in these patients, pancreatic insufficiency may determine an alteration in intestinal ecology, and in intestinal inflammation. In the population studied, multivariate analysis showed that patients with abnormally low fecal elastase had more than a five-fold risk of increased fecal calprotectin suggesting that, in patients with pancreatic disease, the determination of fecal calprotectin may be useful in evaluating the possible presence of intestinal inflammation which may worsen the intestinal absorption of nutrients. Thus, our data further support the hypothesis that pancreatic insufficiency may cause intestinal inflammation probably due to a modification in intestinal ecology.

CONCLUSION

Pancreatic extracts are the basic treatment for pancreatic insufficiency. However, we need to explore the possibility that other drugs used to treat pancreatic insufficiency such as proton pump inhibitors or H2-blockers should be administered to our patients in order to modify the duodenal pH and to permit optimal efficacy of pancreatic extracts. Furthermore, we need to explore the possibility that other therapeutic approaches including the decontamination of intestinal lumen, supplementation of bile acids and the use of probiotics may attenuate intestinal inflammation permitting optimal efficacy of pancreatic extracts as well as the control of clinical signs and symptoms of pancreatic insufficiency.

REFERENCES

1 **Gullo L**, Pezzilli R, Priori P, Baldoni F, Paparo F, Mattioli G. Pure pancreatic juice collection over 24 consecutive hours. *Pancreas* 1987; **2**: 620-623

2 **Rinderknecht H**. Pancreatic secretory enzymes in the exocrine pancreas. In: Go VLW, editor. The Exocrine Pancreas: Biology, Pathobiology and Diseases. New York: Raven Press, 1986: 163-183

3 **Desnuelle P**, Figarella C. Biochemistry. In: Howat HAT, Sarles H, eds. The Exocrine Pancreas. Philadelphia: WB Saunders, 1978: 86-112

4 **DiMagno EP**, Go VL, Summerskill WH. Relations between pancreatic enzyme ouputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 1973; **288**: 813-815

5 **Carrière F**, Grandval P, Renou C, Palomba A, Priéri F, Giallo J, Henniges F, Sander-Struckmeier S, Laugier R. Quantitative study of digestive enzyme secretion and gastrointestinal lipolysis in chronic pancreatitis. *Clin Gastroenterol Hepatol* 2005; **3**: 28-38

6 **Carrière F**, Grandval P, Gregory PC, Renou C, Henniges F, Sander-Struckmeier S, Laugier R. Does the pancreas really produce much more lipase than required for fat digestion? *JOP* 2005; **6**: 206-215

7 **Layer P**, Go VL, DiMagno EP. Fate of pancreatic enzymes during small intestinal aboral transit in humans. *Am J Physiol* 1986; **251**: G475-G480

8 **Layer P**, Jansen JB, Cherian L, Lamers CB, Goebell H. Feedback regulation of human pancreatic secretion. Effects

of protease inhibition on duodenal delivery and small intestinal transit of pancreatic enzymes. *Gastroenterology* 1990; **98**: 1311-1319
9 **Thiruvengadam R**, DiMagno EP. Inactivation of human lipase by proteases. *Am J Physiol* 1988; **255**: G476-G481
10 **Guarner L**, Rodríguez R, Guarner F, Malagelada JR. Fate of oral enzymes in pancreatic insufficiency. *Gut* 1993; **34**: 708-712
11 **DiMagno EP**, Malagelada JR, Go VL, Moertel CG. Fate of orally ingested enzymes in pancreatic insufficiency. Comparison of two dosage schedules. *N Engl J Med* 1977; **296**: 1318-1322
12 **Suzuki A**, Mizumoto A, Sarr MG, Dimagno EP. Does gastric emptying or small intestinal transit of nutrients affect intestinal absorption of nutrients in canine pancreatic exocrine insufficiency? *Gastroenterology* 1997; **112**: A484
13 **Layer P**, von der Ohe MR, Holst JJ, Jansen JB, Grandt D, Holtmann G, Goebell H. Altered postprandial motility in chronic pancreatitis: role of malabsorption. *Gastroenterology* 1997; **112**: 1624-1634
14 **Gullo L**. Direct pancreatic function test (duodenal intubation) in the diagnosis of chronic pancreatitis. *Gastroenterology* 1986; **90**: 799-800
15 **Gullo L**, Ventrucci M, Tomassetti P, Migliori M, Pezzilli R. Fecal elastase 1 determination in chronic pancreatitis. *Dig Dis Sci* 1999; **44**: 210-213
16 **Naruse S**, Ishiguro H, Ko SB, Yoshikawa T, Yamamoto T, Yamamoto A, Futakuchi S, Goto H, Saito Y, Takahashi S. Fecal pancreatic elastase: a reproducible marker for severe exocrine pancreatic insufficiency. *J Gastroenterol* 2006; **41**: 901-908
17 **Ventrucci M**, Cipolla A, Ubalducci GM, Roda A, Roda E. 13C labelled cholesteryl octanoate breath test for assessing pancreatic exocrine insufficiency. *Gut* 1998; **42**: 81-87
18 **Matos C**, Metens T, Devière J, Nicaise N, Braudé P, Van Yperen G, Cremer M, Struyven J. Pancreatic duct: morphologic and functional evaluation with dynamic MR pancreatography after secretin stimulation. *Radiology* 1997; **203**: 435-441
19 **Merkle EM**, Baillie J. Exocrine pancreatic function: evaluation with MR imaging before and after secretin stimulation. *Am J Gastroenterol* 2006; **101**: 137-138
20 **Calculli L**, Pezzilli R, Fiscaletti M, Casadei R, Brindisi C, Gavelli G. Exocrine pancreatic function assessed by secretin cholangio-Wirsung magnetic resonance imaging. *Hepatobiliary Pancreat Dis Int* 2008; **7**: 192-195
21 **Simpson KW**, Batt RM, Jones D, Morton DB. Effects of exocrine pancreatic insufficiency and replacement therapy on the bacterial flora of the duodenum in dogs. *Am J Vet Res* 1990; **51**: 203-206
22 **Westermarck E**, Myllys V, Aho M. Effect of treatment on the jejunal and colonic bacterial flora of dogs with exocrine pancreatic insufficiency. *Pancreas* 1993; **8**: 559-562
23 **Lembcke B**, Kraus B, Lankisch PG. Small intestinal function in chronic relapsing pancreatitis. *Hepatogastroenterology* 1985; **32**: 149-151
24 **Salemans JMJI**, Nagengast FM, Jansen JBMJ. The 14C-xylose breath test in chronic pancreatitis: evidence for small intestinal bacterial overgrowth [abstract]. *Gastroenterology* 1994; **106**: A320
25 **Casellas F**, Guarner L, Vaquero E, Antolín M, de Gracia X, Malagelada JR. Hydrogen breath test with glucose in exocrine pancreatic insufficiency. *Pancreas* 1998; **16**: 481-486
26 **Trespi E**, Ferrieri A. Intestinal bacterial overgrowth during chronic pancreatitis. *Curr Med Res Opin* 1999; **15**: 47-52
27 **Bang Jørgensen B**, Thorsgaard Pedersen N, Worning H. Short report: lipid and vitamin B12 malassimilation in pancreatic insufficiency. *Aliment Pharmacol Ther* 1991; **5**: 207-210
28 **Mathias JR**, Clench MH. Review: pathophysiology of diarrhea caused by bacterial overgrowth of the small intestine. *Am J Med Sci* 1985; **289**: 243-248
29 **Madsen JL**, Graff J, Philipsen EK, Scharff O, Rumessen JJ. Bile acid malabsorption or disturbed intestinal permeability in patients treated with enzyme substitution for exocrine pancreatic insufficiency is not caused by bacterial overgrowth. *Pancreas* 2003; **26**: 130-133
30 **Dutta SK**, Anand K, Gadacz TR. Bile salt malabsorption in pancreatic insufficiency secondary to alcoholic pancreatitis. *Gastroenterology* 1986; **91**: 1243-1249
31 **Birkner HJ**, Kern F Jr. In virto adsorption of bile salts to food residues, salicylazosulfapyridine, and hemicellulose. *Gastroenterology* 1974; **67**: 237-244
32 **Nakamura T**, Kikuchi H, Takebe K, Ishii M, Imamura K, Yamada N, Kudoh K, Terada A. Correlation between bile acid malabsorption and pancreatic exocrine dysfunction in patients with chronic pancreatitis. *Pancreas* 1994; **9**: 580-584
33 **Regan PT**, Malagelada JR, Dimagno EP, Go VL. Reduced intraluminal bile acid concentrations and fat maldigestion in pancreatic insufficiency: correction by treatment. *Gastroenterology* 1979; **77**: 285-289
34 **Romagnuolo J**, Schiller D, Bailey RJ. Using breath tests wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol* 2002; **97**: 1113-1126
35 **Hollander D**. The intestinal permeability barrier. A hypothesis as to its regulation and involvement in Crohn's disease. *Scand J Gastroenterol* 1992; **27**: 721-726
36 **Bijlsma PB**, Peeters RA, Groot JA, Dekker PR, Taminiau JA, Van Der Meer R. Differential in vivo and in vitro intestinal permeability to lactulose and mannitol in animals and humans: a hypothesis. *Gastroenterology* 1995; **108**: 687-696
37 **Madsen JL**, Scharff O, Rabol A, Krogsgaard OW. Relationship between small-intestinal transit rate and intestinal absorption of (14)C-labelled mannitol and (51)Cr-labelled ethylenediaminetetraacetic acid in healthy subjects. *Scand J Gastroenterol* 1996; **31**: 254-259
38 **Pezzilli R**, Barassi A, Morselli-Labate AM, Fantini L, Tomassetti P, Campana D, Casadei R, Finazzi S, d'Eril GM, Corinaldesi R. Fecal calprotectin and elastase 1 determinations in patients with pancreatic diseases: a possible link between pancreatic insufficiency and intestinal inflammation. *J Gastroenterol* 2007; **42**: 754-760
39 **Voganatsi A**, Panyutich A, Miyasaki KT, Murthy RK. Mechanism of extracellular release of human neutrophil calprotectin complex. *J Leukoc Biol* 2001; **70**: 130-134
40 **Røseth AG**, Fagerhol MK, Aadland E, Schjønsby H. Assessment of the neutrophil dominating protein calprotectin in feces. A methodologic study. *Scand J Gastroenterol* 1992; **27**: 793-798
41 **D'Incà R**, Dal Pont E, Di Leo V, Ferronato A, Fries W, Vettorato MG, Martines D, Sturniolo GC. Calprotectin and lactoferrin in the assessment of intestinal inflammation and organic disease. *Int J Colorectal Dis* 2007; **22**: 429-437
42 **Orlando A**, Modesto I, Castiglione F, Scala L, Scimeca D, Rispo A, Teresi S, Mocciaro F, Criscuoli V, Marrone C, Platania P, De Falco T, Maisano S, Nicoli N, Cottone M. The role of calprotectin in predicting endoscopic post-surgical recurrence in asymptomatic Crohn's disease: a comparison with ultrasound. *Eur Rev Med Pharmacol Sci* 2006; **10**: 17-22
43 **Vermeire S**, Van Assche G, Rutgeerts P. Laboratory markers in IBD: useful, magic, or unnecessary toys? *Gut* 2006; **55**: 426-431
44 **Bremner A**, Roked S, Robinson R, Phillips I, Beattie M. Faecal calprotectin in children with chronic gastrointestinal symptoms. *Acta Paediatr* 2005; **94**: 1855-1858
45 **Vieten D**, Cairns P. The role of calprotectin in the diagnosis of neonatal necrotising enterocolitis. *Ir Med J* 2005; **98**: 69
46 **Røseth AG**. Determination of faecal calprotectin, a novel marker of organic gastrointestinal disorders. *Dig Liver Dis* 2003; **35**: 607-609

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