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EDITORIAL

Medical Therapy of Malabsorption in Patients with Head Pancreatic Resection

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Introduction

Exocrine pancreatic insufficiency caused by pancreatic resection results from various factors which regulate digestion and absorption of nutrients. Pancreatic function has been extensively studied in the last 40 years even if some aspects of secretion and gastrointestinal adaptation after pancreatic resection are not completely understood. The pancreatic gland normally secretes more than 2 liters of juice per day which is constituted of water, bicarbonates and enzymes [1]; protein secretion per gram of pancreatic tissue is more elevated than that of any other organ [2] and more than 85% of the protein content is constituted 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, French authors [5] have demonstrated that gastric lipase can compensate pancreatic lipase even if it is not capable of complete lipolytic activity. Enzyme degradation in the intestinal lumen is the main factor for 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 % are present in the ileum; on the other hand, amylases and lipases are more stable [6, 7, 8].

There are various explanations for the loss of enzymatic action of the enzymatic activity during progression in the intestinal lumen: 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 pancreatic juice and optimal intestinal motility.

In pathologic 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 time of transit [12, 13].

Pancreatic Function after Pancreatic Resection Due to Neoplasia

Gastrectomy and pancreatectomy carried out for neoplastic diseases can determine

pancreatic insufficiency and steatorrhea. The majority of patients with pancreatic neoplasia undergo the Whipple technique. Factors responsible for exocrine pancreatic insufficiency are the extension of the pancreatic resection and a pancreatic duct occlusion which determines fibrosis and atrophy of the remaining gland.
The extension of the resection is important for gland insufficiency; we know that patients who undergo radical pancreatectomy have a more severe exocrine pancreatic insufficiency than patients who undergo standard pancreatic resection [14].

Pancreatic Function after Pancreatic Resection for Chronic Pancreatitis

The majority of patients with chronic pancreatitis have an exocrine pancreatic insufficiency before the operation. The type of operation in that group of patients depends on the type of pancreatic lesion and on the expertise of the surgeon. The Whipple technique is generally preferred for lesions situated in the head of the pancreas and approximately 50% of these patients develop severe pancreatic insufficiency [15, 16]. The Whipple technique requires a complete reconstruction of the digestive tract through the creation of a pancreaticojejunostomy, a hepatico Roux-en-Y jejunostomy and a gastroenterostomy. In this way physiologic gastric emptying and the mixing of food, enzymes and biliary acids are altered due to the pyloric and duodenal resection. A pylorus-preserving pancreatectomy such as the Berger technique which saves the stomach and the duodenum and has a more physiologic gastric emptying is an operation capable of maintaining the intestinal anatomy and physiology [17]; this is confirmed by various studies which demonstrate a minimum pancreatic insufficiency caused by this type of operation [18].
However, if the pancreatic disease is diffuse, a total or subtotal pancreatectomy may be necessary with consequent obvious exocrine and endocrine insufficiency [19].

Clinical Manifestations and Diagnosis of Exocrine Pancreatic Insufficiency

The main clinical manifestations of exocrine pancreatic insufficiency are fat malabsorption, called steatorrhea, which consists of fecal excretion of more than 6 g per day of fat, weight loss, abdominal pain and abdominal swelling sensation. Fat malabsorption also determines a deficit of fat-soluble vitamins (A, D, E, K) with the 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 (classified as mild, moderate and severe). The most sensitive test is the secretin-CCK or secretin-cerulein test; it 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 cerulean which can stimulate enzymatic secretion. This test is highly sensitive and specific [20] but it is invasive, lengthy and expensive; moreover, it is possible only 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 [21]. In particular, elastase 1 determination is more sensitive and specific than chymotrypsin. The advantage of these tests is that they can be used in patients who have undergone surgery involving the gastro-intestinal tract, but they cannot reveal a mild degree of exocrine pancreatic insufficiency [21]. A cholesteryl-octanoate breath test is rarely used because of its high cost and possible interference with metabolic and pulmonary diseases [22]. 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 [23].

Exocrine Pancreatic Insufficiency Therapy after Pancreatectomy

The medical therapy target is to correct fat, protein and carbohydrate malabsorption with pancreatic extracts, and secondary diabetes mellitus with insulin. Limitation of fat ingestion is not necessary in most cases. Pancreatic enzyme preparations should have an adequate concentration of lipases, amylases and proteases. The release of 20,000-30,000 U of lipases in the duodenum seems to be an optimal dosage for correcting steatorrhea, even if it is necessary to double the dosage to optimize digestion and fat absorption. It is possible that the steatorrhea does not respond to increased extract doses and that symptoms do not improve [24]. Gastric acidity seems to be very important in steatorrhea maintenance; in fact, some patients with chronic pancreatitis have gastric acid hypersecretion and, in many patients with chronic pancreatitis, the gastric acid is not buffered because of the reduction of bicarbonates in the pancreatic juice. In this case, the lipase is rapidly destroyed in the stomach and duodenum because of its inactivation at a low pH. For this reason, there are now acid resistant preparations which can release the enzymes only when the luminal pH is more than 6. Moreover, it is possible to increase luminal pH with H_2 antagonists or proton pump inhibitors to better protect the lipase from the gastric acid [25]. Another therapeutic problem is the enzyme-food mixing and its correct and synchronous passage into the duodenum. Under normal conditions, food passes into the duodenum as particles having a diameter of 2 mm [26]. For this reason, pancreatic extracts are constituted of 1-1.5 mm gastroprotected microspheres; recent studies demonstrate that these formulations can pass into the duodenum together with food, even if microspheres sometime pass into the duodenum before solid food [27] since gastric emptying is very variable in any subject and this can decrease the efficacy of their action. Microsphere preparations have demonstrated a superior efficacy as compared to other preparations, and they facilitate fat digestion [28, 29]. Pancreatic extracts constituted of fungal or bacterial lipases resistant to acid are now being developed; these preparations have already been tried successfully in steatorrhea therapy and they represent the future of substitutive therapy [30].

There are now many studies of exocrine pancreatic insufficiency secondary to pancreatic resection. The efficacy of commercial pancreatic extract preparations depends on the type of resection. In a non-randomized study carried out [31] on patients with pylorus-preserving pancreaticoduodenectomy for pancreatic neoplasia, gastro-protected microspheres were less effective than those in patients who had undergone a classic Whipple technique. This is possible because microspheres are retained in the stomach and, in this subgroup of patients, it would be better to use powdered enzymatic preparations to optimize their efficacy. One of the few randomized studies explaining the efficacy of pancreatic extracts for the control of malabsorption was carried out in a small group of patients with chronic pancreatitis who had undergone pancreaticojejunostomy [32]. All the patients studied had an exocrine pancreatic insufficiency evaluated using fecal fat determination and the degree of fat malabsorption; in these patients, treatment with pancreatic extracts ameliorated not only nitrogen balance but also fat and protein absorption. Another randomized controlled double-blinded crossover study, explored the comparative efficacy of two pancreatin preparations of gastroprotected microspheres with different doses (Creon® 25.000 and Creon® 8.000) in pancreatectomized patients with chronic pancreatitis [33]. All patients were stabilized before enrolment in the study with a standard dose of pancreatic extracts. After this stabilization period, 56% of the patients still had a fecal fat excretion greater than 7 g/day, and 38% greater than 15 g/day. The results demonstrate that there is a significant relationship between fecal fat excretion, fecal volume and evacuation frequency but there is not a relationship between fecal fat excretion and abdominal

pain or malabsorption symptoms. The majority of patients with steatorrhea were also being treated with antiacids, and some patients took more than 50 capsules of pancreatic extracts per day. Both the pancreatin standard dose and the elevated dose demonstrated equal efficacy; in pancreatectomized patients, high dose pancreatic extracts significantly reduced the number of capsules needed per day with a better compliance to substitutive therapy.

Conclusions

Pancreatic insufficiency therapy in patients with pancreatectomy is the same as that for patients with exocrine pancreatic insufficiency who did not undergo surgery. In these patients, therapy effectiveness depends not only on fecal fat excretion but also on the type of operation. In these patients, it would be useful to administer high dose preparations for improving the compliance. Moreover, it is necessary to undertake further studies to evaluate the presence of bacterial contamination in pancreatectomized patients who are non-responders to enzymatic therapy. Bacterial contamination is poorly evaluated in these patients and more attention should be paid to it [34, 35].

Keywords Exocrine Pancreatic Insufficiency; Pancreatectomy; Pancreatic Extracts; Pancreatic Neoplasms; Pancreatitis, Chronic

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