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Pancreatic Exocrine Insufficiency Following Pancreatic Resection

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The problem of the exocrine pancreatic insufficiency in patients having a pancreatic resection

Exocrine pancreatic insufficiency caused by pancreatic resection results from various factors which regulate digestion and absorption of nutrients. However, many aspects of secretion and gastrointestinal adaptation after pancreatic resection are not completely understood. In this paper we will review the current knowledge on these pancreatic pathophysiology aspects and we will also revise the current modalities of treatment regarding pancreatic exocrine insufficiency following pancreatic resection.

Physiology of the exocrine pancreatic secretion

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 fats, proteins and glucides [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]. It has been also 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 for controlling nutrient absorption. The activity of pancreatic enzymes progressively decreases during their progression in the intestinal lumen: sixty percent of active trypsin and chymotrypsin are present in the jejunum whereas only 20 % are present in the ileum; amylases and lipases are more stable during their passage in the intestinal tract [6-8.].

There are various explanations for the loss of enzymatic action of the enzymatic activity during progression in the intestinal lumen: proteolytic degradation by chymotrypsin [9], lipase 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.

Pathophysiology of exocrine pancreatic secretion

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].

In patients with pancreatic resection and gastrointestinal reconstruction the anatomical changes due to both gastrointestinal and pancreatic surgery lead to alterations that may cause maldigestion. In fact, total or partial resections of the stomach, with or without duodenal resection, as well as partial pancreatic resection, are associated with disturbance of fundus relaxation caused by the disappearance of antro-fundic and duodeno-fundic reflexes, absence of neurally stimulated pancreatic secretion caused by the lack of fundus relaxation; reduction in CCK-mediated stimulation of pancreatic secretion secondary to duodenal resection; large and hard-to-digest nutrient particles reaching the jejunal lumen because of resection of the distal stomach; and, finally, asynchrony between the gastric emptying of nutrients and bilio-pancreatic secretion as a result of anatomical reconstruction [14]. Thus, maldigestion may be observed in up to 80% of patients who have been operated upon for gastric or pancreatic diseases [15-17].

Clinical manifestations and assessment of exocrine pancreatic insufficiency

The main clinical manifestations of exocrine pancreatic insufficiency are fat malabsorption that resulted in 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 such as night blindness, poor quality skin and hair due to vitamin A deficiency, spontaneous fractures due to vitamin D deficiency, reproductive failure, brown bowel syndrome due to vitamin E deficiency and increased clotting time and hemorrhage due to vitamin K deficiency.

The diagnosis of exocrine pancreatic insufficiency is based on these clinical symptoms and the laboratory confirmation by means of direct and indirect exocrine pancreatic function tests. Some of these tests can be used to determine the degree of insufficiency. 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 cerulein which can stimulate enzymatic secretion. This test is highly sensitive and specific [18] 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 as in pancreatic head resected patients. Fecal chymotrypsin and elastase 1 are more frequently used [19]. 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

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insufficiency [19]. A cholesteryl-octanoate breath test is rarely used because of its high cost and possible interference with metabolic and pulmonary diseases [20]. 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 [21,22]. Fecal fat determination can be utilized at initial evaluation and in monitoring lipid malabsorption therapy [23].

Pancreatic function after pancreatic resection for chronic pancreatitis

The majority of patients with chronic pancreatitis have an exocrine pancreatic insufficiency before the operation and the surgical procedures may worsen the exocrine pancreatic function. Furthermore, in resective procedures there is also a deficiency of pancreatic polypeptide, an intestinal hormone mainly produced by the pancreatic gland and able to regulate the pancreatic endocrine and exocrine secretion activities and this further impairs the exocrine pancreatic function in patients with chronic pancreatitis [24].

The Whipple technique is generally preferred for masses situated in the head of the pancreas and approximately 50% of these patients develop severe exocrine pancreatic insufficiency [25, 26]. This surgical procedure 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, saves the stomach and the duodenum and it has a more physiologic gastric emptying and it is capable of maintaining the intestinal anatomy and physiology [27]; this is confirmed by various studies which demonstrate a minimum pancreatic insufficiency caused by this type of operation [28]. In order to preserve the residual exocrine pancreatic function the Frey procedure or the Peustow's operation can be carried out; in these operations the pancreatic juice is therefore drained directly into the small intestine [29]. However, if the pancreatic disease is diffuse, a total or subtotal pancreatectomy may be necessary with consequent obvious exocrine and endocrine insufficiency [30].

Pancreatic function after pancreatic resection due to neoplasms

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 [31]. In patients operated of pancreatic head resection, it has been also demonstrated that deficiency of gastrointestinal hormones may worsen the exocrine pancreatic insufficiency. In fact, in a randomized prospective study performed in patients who underwent pylorus-preserving pancreatoduodenectomy for periampullary neoplasms, patients were allocated to either a lansoprazole group or a control group [32]. The lansoprazole members were given oral lansoprazole (30 mg/d) over 12 weeks postoperatively to induce hypergastrinemia and in the control group no proton pomp inhibitors were given. The volume of the distal pancreas was determined using thin-sectioned spiral CT data, nutritional status, and endocrine (insulin level, glucose tolerance test) and exocrine function (stool elastase) of the pancreas and serum gastrin levels were measured before surgery and 3 months after surgery. In the lansoprazole group the mean volume of the distal pancreas was reduced by 10% after pylorus-preserving pancreatoduodenectomy, whereas severe pancreatic atrophy occurred in the control group. Postoperative insulin and stool elastase levels were higher in the lansoprazole group than in the control group.

In the study of Falconi et al. [33], the authors explored the incidence of pancreatic insufficiency after different resections for benign pancreatic tumors and they found that the probability of developing exocrine insufficiency was higher for pancreatoduodenectomy and left pancreatectomy than for atypical resection. On the other hand, the exocrine pancreatic function Speicher and Traverso reported that pancreatic function is preserved after distal pancreatectomy [34]. Probably a different selection of patients may explain these differences.

Finally, it has been recently reported that reduced postoperative pancreatic parenchymal thickness is a reliable indicator of exocrine pancreatic insufficiency after pylorus-preserving pancreatoduodenectomy (PPPD) with pancreaticogastrostomy [35]. These authors, performed (13)C-labeled mixed triglyceride breath test was in 52 patients after PPPD and they found that 65.4% patients had exocrine pancreatic insufficiency. With ROC analysis for identification of exocrine pancreatic insufficiency, the areas under the ROC curve for the postoperative pancreatic parenchymal thickness were higher than those for the preoperative pancreatic parenchymal thickness. When the cut-off value of the postoperative pancreatic parenchymal thickness was set at 13.0 mm, the sensitivity and specificity for identifying exocrine pancreatic insufficiency were 88.2% and 88.9%, respectively.

Cachexia after resection for pancreatic ductal adenocarcinoma

In patients operated for pancreatic ductal adenocarcinoma, the causes of weight loss include also tumor progression in addition to exocrine pancreatic insufficiency. Nutritional care in these patients presents numerous challenges because they suffer from many gastrointestinal symptoms also due to chemotherapy-induced side effects [36]. However, we should take in mind that weight loss in patients with unresectable cancer of the pancreatic head region and occlusion of the pancreatic duct can be prevented, at least for the period immediately after insertion of a biliary endoprosthesis, by high dose enteric coated pancreatin enzyme supplementation in combination with dietary counseling. [37].

Treatment of exocrine pancreatic insufficiency after pancreatectomy

The medical therapy target is to correct fat, protein and carbohydrate malabsorption with pancreatic extracts. Limitation of fat ingestion is not necessary in most cases [29]. Pancreatic enzyme preparations should have an adequate concentration of lipases, amylases and proteases. The release of 20,000-30,000 U of lipases 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 [38]. 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 [29]. Moreover, it is possible to increase luminal pH with H2 antagonists or proton pump inhibitors to better protect the lipase from the gastric acid [39]. 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 [40]. 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 [41] 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 [42,43]. 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 [44].

At present, there are 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 [45] 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 [46]. 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 gastro-protected microspheres with different doses in pancreatectomized patients with chronic pancreatitis [47]. 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 antacids, 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. From the clinical point of view, pancreatic enzyme replacement therapy needs to be routinely considered and based on pragmatic clinical evaluation of the patient [48,49]. 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 [50].

Conclusion

Pancreatectomy carried out for benign and malignant diseases can determine pancreatic insufficiency and steatorrhea. 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. 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 and it would be useful to administer high dose preparations for improving the efficacy of the drug.

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