Postoperative Biological and Physiological Gastrointestinal Changes after Whipple Procedure

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Abstract

In the last years there was an increased interest towards the pancreatic cancer, especially considering its growing incidence (rapidly becoming the fifth cause of death by cancer in the developed countries), lack of any sustainable markers and/or risk factors and the chilling fact that almost 95% of the patients with this disorder are presenting to the hospital in the advanced and unresectable stages. Even more, although known and developed for almost 70 years, the surgical approach for the pancreatic cancer is a subject of debate because its efficacy and postoperative biological changes. It is known that the most common surgery in chronic pancreatitis and pancreatic cancer is represented by the Whipple pancreatico duodenectomy. Still, after an extended resection and reconstruction of the upper gastrointestinal tract, it seems that the digestive physiology can be disrupted. In this way, in the present mini-review we will describe some postoperative gastrointestinal biological and physiological changes after Whipple procedure, by mainly focusing on the gastrointestinal motility, bone demineralization, dumping and re-resection, as well as on the affected pancreatic function, postoperative weight loss and remnant pancreatic fibrosis and how the management of this related pathological aspects can be applied in these cases.

Keywords: Pancreatic cancer; Pancreaticoduodenectomy; Pancreatectomy; Whipple procedure; Gastrointestinal physiology

Background

Lately the oncological research literature depicted an increased interest towards the pancreatic cancer, especially considering its growing incidence (rapidly becoming the fifth cause of death by cancer in the developed countries), lack of any sustainable markers and/or risk factors and the chilling fact that almost 95% of the patients with this disorder are presenting to the hospital in the advanced and unresectable stages [1].

Even more, although known and somehow developed for almost 70 years, the surgical approaches for the pancreatic cancer are only improving the morbidity and hospital postoperative mortality, with very few effects on survival rate. Moreover, there are still a lot of unknowns regarding the efficacy of the surgical approaches in pancreatic tumors and their postoperative biological changes [2].

In this way, it is known that the most common surgical technique in chronic pancreatitis and pancreatic cancer is represented by the Whipple pancreaticoduodenectomy, which represents the classical resection techniques for tumors and basically consists in removing the head of the pancreas, as well as the gallbladder, a part of the duodenum and the pylorus and antrum. Moreover, it is important to mention that in the aforementioned cases, after an extended resection and reconstruction of the upper gastrointestinal tract, the digestive physiology will be disrupted [1,2].

In this way, in the present mini-review we will describe some postoperative gastrointestinal biological and physiological changes after Whipple procedure, by mainly focusing on the gastrointestinal motility, bone demineralization, dumping and re-resection, as well as on the affected pancreatic function, postoperative weight loss and remnant pancreatic fibrosis and how the management of this related pathological aspects can be applied in these cases.

The Gastrointestinal Motility

In this context, we will shortly describe some basal aspects regarding the gastric acid secretion and the gastrointestinal motility. Thus, regarding the gastric acid secretion, the main components of gastric juice are the acid, the pepsin, the gastric lipase and the intrinsic factor. The acid has two major effects: facilitates peptide hydrolysis and reduces the number of bacteria in the stomach and in the proximal small intestine [3]. As a consequence, patients develop a B12 deficiency and require substitution [4]. Moreover, the gastric intrinsic factor is needed to absorb enough vitamin B12 from your normal diet and should therefore be substituted after Billroth I and II resections (e.g. operations in that the greater curvature of the stomach is connected to the first part of the jejunum in end-to-side anastomosis [5] after subtotal or total gastrectomies but not after any type of vagotomy.

With regards to the gastrointestinal motility, we could say that the normal gastric motility makes the stomach function as a reservoir (e.g. evacuating food in the small intestine in a controlled and regularly way). Moreover, the stomach digests and grinds food into smaller particles that are easily accessible to other enzymes in the small intestine, so as to obtain dietary nutrients which will be absorbed [6]. Still, the normal gastric emptying is a complex process. The stomach acts in series with the pylorus, duodenum and proximal jejunum. In this way, the evacuation of food from the stomach is controlled with a balance between propulsive motor activities and non-propulsive in the stomach and the resistance to evacuation of the pylorus and the duodenum [7]. Moreover, some scintigraphy studies on gastric emptying on humans indicated that both liquids and solids are initially stored in the proximal stomach and that the evacuation process only begins when food is propelled towards the gastric antrum where then it passes through the pylorus in the small intestine. Also, the size of the food fragment discharged from the stomach is well regularized [8].

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In this way, very well connected to what we are about to present here, the fragments of food that are passing into the duodenum are distributed by size, nearly all measuring less than 1 mm [9,10]. Thus, vagotomies (both truncal and supraselective) are altering the gastric motility by reducing proximal stomach relaxation and by increasing pressure in the stomach after food ingestion. Moreover, the gastric resections of the stomach alter the shredding process. As the gastric reservoir function is progressively destroyed with the increased resection, gastric emptying processes are profoundly modified. Moreover, after a Billroth I and II resection both gastric emptying of solids and liquids is increased [11,12].

Currently there is not sufficient data to document the differences between the two methods regarding gastric emptying, but existing records suggest that liquids leave the stomach faster than solid components [11]. Also, shredding food seems to be disturbed suggesting that solid fragments larger than 2 mm may leave the stomach [13].

Also, patients with antrectomy discharge solid foods rapidly, approximately 1/3 of the radioactively labelled fragments of the meat leave the stomach being at a size greater than 1 mm. By resecting the distal stomach, the controlled propel of solid food in the duodenum is destroyed. Instead, the discharge of solid foods does not seem to be impaired [8].

Selective vagotomy with pyloroplasty accelerates the gastric emptying of liquids, but does not affect the discharge of solid fragments [11]. Moreover, the grinding process is not affected since the fragments which are leaving the stomach are smaller than 1 mm indicating that the rate of gastric emptying of solids was similar both in healthy subjects and in these patients [11].

Truncal vagotomy, on the other hand, disrupts the entire stomach. These effects on gastric emptying are complicated. In most patients gastric emptying of solids is initially accelerated, but this initial fast process is followed by a slow evacuation phase. In up to 50% of patients slow evacuation is prevalent, which makes the total gastric evacuation to be delayed. Still, the shredding process is not affected by this procedure [14].

In addition, gastric surgery might affect not only the postprandial gastric emptying, but also the profound effects of gastrointestinal motility during dietary fasting could be affected. In this way, it was showed that after truncal vagotomy the migration of the motor complex myoelectric is either very low or absent [15]. Consequently, these patients are highly susceptible to develop bezoar, which is a mass found trapped in the gastrointestinal system [16].

Also, many of the problems appearing after the postprandial gastric surgery can be easily understood by the accelerated gastric emptying. For example, the lactose intolerance occurring after gastric surgery is related to the rapid occurrence of lactose in the small intestine. In this way, due to a limited capacity to hydrolyse lactose in adults, this massive appearance of lactose exceeds the hydrolytic capacity of lactase [17].

By analogy, postprandial hyperglycaemia after gastric surgery causes rapid entry of glucose in the small intestine, with a fast absorption of carbohydrates [18]. That is way many patients are losing weight after gastric surgery and as consequence to malnutrition and other nutritional deficiencies.

Also, mild steatorrhea is common after gastric surgery, but the daily amount of fat in the faeces rarely exceeds 15% of the ingested fat [19,20]. Factors contributing to this effect are considered to be the alterations in pancreatic and biliary secretion responses, biliopancreatic normal secretions and an unfavourable rate of food intake and digestive juices.

Moreover, there is an accelerated transit of the chyme through the small intestine, which generates an insufficient digestion, and as a result, undigested food reaches the colon. Also, after distal gastrectomy, food fragments larger than 1 mm pass from the stomach into the small intestine. These "big" fragments can only be digested slowly. Thus, with an accelerated transit, time for digestion is insufficient.

In addition, pancreatic enzymes and bile salt concentrations are significantly decreased in the small intestine immediately after the ingestion of liquids in patients with subtotal gastrectomy [21]. This marked reduction is more likely the result of a dilution of the biliary and pancreatic secretions through the study of gastric emptying after the liquid lunch. Also, these results refer to liquid meals and are not observed in solid lunches.

Thus, the exocrine function of the pancreas appears to be close to normal after gastric surgery. On the other hand, several clinical studies have documented impaired exocrine pancreatic function after various gastric surgery procedures [22]. Alteration of exocrine pancreatic function was demonstrated both by analysing the fat in stools, as well as by indirect pancreatic function tests. Thus, it is preferable to use the term of impaired digestion rather than impaired exocrine pancreatic secretion, since the pancreas secretion is normal, but probably the digestion process was altered as we described above.

It also has to be mentioned that the most common clinical problems after gastric surgery are postprandial symptoms like precocious satiety, postprandial vomiting, alkaline or bile reflux gastritis and abdominal discomfort. In addition, the diarrhea, weight loss, maldigestion, anaemia and bone disease may be present. In this way, the weight loss can be caused by several factors and some conditions after gastric surgery, but an inadequate diet may be considered in patients with weight loss. Moreover, digestive insufficiency, with or without exocrine pancreatic insufficiency, and in excess multiplication of the bacterial flora in the small intestine could be another two factors contributing to weight loss [23].

Also, anaemia can occur after gastric surgery. In fact, in the absence of other complications, anaemia occurs after a period of several years after surgery. Thus, in a classic study of the 50' [24] anaemia developed gradually over the years with faster appearance of anaemia in patients which have lost blood. Anaemia can also develop as a result of iron deficiency, vitamin B12 and folate or a combination of these. In this way, the iron deficiency is the most common cause of postoperative anaemia. In addition, it has mentioned that two factors are the most important in regards to the high prevalence of postoperatively iron deficiency: a decrease in the availability of iron salts to be absorbed due to reduced post-surgical acid production and a disturbance of food digestion (especially meat), which is the main iron source for most of the people [25].

Bone Demineralization, Dumping and Re-resection

Other aspects that could be described in the present context could be represented by the bone demineralization, dumping and re-resection processes.

In this way, the appearance of metabolic bone disease as a late complication after gastrectomy is well known [26]. For a long time, it was accepted that in patients with total or subtotal gastrectomy, a disturbance in calcium absorption and low levels of vitamin D occurs, without a plausible explanation.

As a consequence, the bone disease may develop over time. In this way, the bone demineralization is a physiological process that occurs with age and progresses faster in women than in men [27,28].

It seems that total gastrectomy accelerates bone demineralization more than a physiological process. Moreover, total gastrectomy induces a faster mineralization, as compared to the partial gastric resection [29]. In this way, in a study on 39 patients with total gastrectomy, as

compared with 59 patients with partial gastrectomy, the first group had higher incidence of bone demineralization (56% vs. 23%). The decline in bone mineral content was also related to age and more pronounced in women.

In addition, 10 years after surgery, many partially resected patients showed a marked decrease in bone mineralization, while in patients with total gastrectomy these changes occurred in 5 years. Also, approximately 30% of patients had abnormalities in serum minerals (calcium and phosphorus), alkaline phosphatase and 25-hydroxyvitamin D [26].

Even more, the importance of bone changes after gastric surgery is best illustrated by the observation that in the postoperative period fractus rate is 2-3 times higher, as compared to the healthy population of the same age and sex [30].

Regarding the dumping processes, it is considered that because part of the stomach is resected in standard Whipple operation, approximately 10% of patients suffer from the so called dumping syndrome (e.g. occurs when food, especially sugar, moves from the stomach into the small bowel too quickly) [31].

Also, in regards to the re-resection, our group found in the literature 4 documented cases [32] of reanastomosis for anastomotic stenosis after PCD, which had as symptoms upper abdominal pain, diarrhea and impaired results at the glucose tolerance test. Moreover, after the reanastomosis symptoms have disappeared. Moreover, there are descriptions for a repeated surgery for local recurrence or hepatic metastasis in pancreatic cancer after an initial cephalic duodenopancreatectomy [33].

Postoperative Gastrointestinal Physiology after a Pancreatic Resection

Exocrine pancreatic insufficiency which is installed after pancreatic surgery may be due to a pre-existing preoperative pathological process, such as chronic pancreatitis, which is aggravated by the pancreatic resection leading to the loss of functional parenchyma [34].

Also, the insufficiency may result from the lack of activation for the pancreatic enzymes in the small intestine. It is also important to mention that the general assumption that once the pancreatic insufficiency is installed, pancreatic function is deteriorating rapidly over the years; it is not entirely true, at least for a substantial number of patients. In this way, pancreatic insufficiency in these patients may remain stable or may even improve due to alcohol abstinence and /or due to a pre-existence of a mild or moderate preoperative insufficiency [34].

Clinically, the evolution stages of exocrine pancreatic insufficiency can be divided into compensated and uncompensated. Moreover, the substantial reserve capacity of the pancreas enables an alteration of the exocrine pancreatic secretion of up to 90%, without clinical signs of malabsorption. In addition, steatorrhea and azotorrhea occur when the amount of lipase and trypsin drops to less than 10% of normal [35].

Still, in the literature we could find some contradictory observations to other two groups of patients: those who had exocrine secretions of the pancreatic higher than 10%, but had diarrhea and those with almost no lipase in the pancreatic juice, but with the daily excretion of fat being normal [36].

While the first situation can be explained by a wide variability in the exocrine secretory capacity of the pancreas, the second may be due to effective the action of the non-pancreatic lipases. These may originate in the serous salivary glands and in the gastric mucosa, while lipase activity is higher in the upper portion of the great curvature of the stomach, as compared to the proximal one. According to this finding, patients with exocrine pancreatic insufficiency can absorb more than 50% of ingested fat despite the absence of a measurable lipase activity.

In fact, it has been found that the pancreatic insufficiency was associated with significantly increased activity of the non-pancreatic lipolytic in the duodenum in fasting conditions. However, no significant difference was found between the tested groups regarding the postprandial non-pancreatic lipolysis activity. This situation was present in 90% of patients with total lipolytic activity at the level of Treitz ligament in patients with exocrine pancreatic insufficiency, in contrast to the healthy controls. This fact may explain why some patients do not require enzyme replacement even after total pancreatectomy.

In the case of pancreatic carcinoma, pancreatic insufficiency rapidly occurs and usually coincides with ductal obstruction in the pancreatic head. However, 40% of the otherwise healthy proximal pancreatic part is able to maintain the necessary secretion of enzyme. Although theoretically all pancreatic function tests may be performed after the operation, direct testing which involves duodenal intubation, such as the secretin-pancreozymin Lundh test, are not possible after right conventional resection of the pancreas with antrectomy (Whipple operation).

Looking at things in a pragmatic manner, postoperative testing for steatorrhea as a sign of exocrine pancreatic insufficiency is sufficient. The problem is to appreciate at what level of steatorrhea, enzyme replacement therapy should be initiated. As a rule, the administration of enzymes is initiated only when the excretion of fat exceeds 15 g/day or the patient loses weight or has diarrhea or dyspepsia [37].

There are also studies showing that the pancreatic function in chronic pancreatitis does not deteriorate over time in all patients. In this way, Sato et al. after a follow-up of 7 years observed in 4 of 11 patients who had performed different surgical procedures and secretin-pancreozymin test pre- and postoperatively, that it improves postoperative exocrine pancreatic function. Moreover, Dohi et al. observed the same facts 12 months after pancreatic resection or pancreatic-jejunal anastomosis. Malfertheiner et al. diagnosed the exocrine pancreatic insufficiency when steatorrhea occurred. In this way, postoperative steatorrhea occurred in 24 patients after resection surgeries, but only in 4% after drainage procedures. Similar results were also reported by Gooszen et al. In this way, exocrine pancreatic function deteriorated in 44% of 23 patients after partial pancreatic resection, but in none of 22 patients who received surgical drainage.

Moreover, Frey et al. have demonstrated that postoperative steatorrhea depends on the type of operation and the extent of the resection. After the Whipple operation the percentage of patients with steatorrhea increased from 5% to 55%, from resecting 80-95% of the left pancreatic, steatorrhea has increased from 9% to 38%, and after resecting of 40% - 80% of the left pancreas steatorrhea increased from 4% to 19%. In addition, Prinze and Greenlee have carried out drainage procedures on 87 patients with chronic pancreatitis. 20% of them have required preoperative enzyme replacement due to severe exocrine pancreatic insufficiency and 33% postoperatively.

Moreover, in a study of Lankisch et al. on exocrine pancreatic function, 25 patients were investigated for 25 months after surgery. 44% had an improvement in exocrine function after different types of surgery; another 44% had a steady trendand 12% deterioration. Also, monitoring these patients for a median period of 37 months showed that 46% of 26 patients had an improvement of exocrine function. In addition, this was more frequent after drainage operations, than after resections. 35% had a steady evolution, while in 19% a deterioration was observed.

In fact, only one study attempted to assess which preoperative condition of the exocrine function is necessary to be met to expect an improvement in postoperative evolution. In this way, the authors

reported that pancreaticojejunostomy performed on patients with Wirsung duct and late emergence of pathological changes as well as exo-and endocrine insufficiency, determines a belated damage mixed insufficiency, regardless if the patient gives up alcohol or not. These results are consistent with those found by Miyake et al. which also reported unoperated patients presenting an improvement in exocrine insufficiency, if this was mild or moderate at the time of diagnosis. In conclusion, experience in the postoperative exocrine pancreatic function is limited, but lately there seems to be an improvement. Moreover, postoperative exocrine function deterioration appears to be more common after resection operations, rather then after surgical drainage [38,39].

Testing Pancreatic Function

It is known that exocrine pancreatic insufficiency causes malabsorption, the main symptoms being steatorrhea (fat in stool > 7 grams/day), abdominal pain and weight loss [40]. Moreover, exocrine insufficiency mechanism can be an isolated or a general reduction of the pancreatic enzymes or on the contrary, these could be quantitative normal, but no longer active in the small intestine [37].

In this way, there are two different ways to test the exocrine pancreatic function in non-operated patients, but this test is also necessary after surgery, especially in pancreatic carcinoma to assess what is left of exocrine pancreatic function. Moreover, both tests (e.g. pancreozymin secretin test (SPT) and Lundh test) require intubation of the duodenum and thus are not possible after Whipple operation. The SPT test measures the concentration of bicarbonate and the secreted amount as well as the enzymes such as amylase, lipase and trypsin in duodenal liquid after the stimulation of the pancreas with secretin and cholecystokinin-pancreozymin, CCK-PZ or caerulein, a pancreatic peptide that stimulates the secretion of isolated secretin from the frog skin with a structure similar to CCK. Also, the performance of the test was not standardized and each centre has its own procedures and different benchmarks.

On the other side, in Lundh test [41] stimulation is made by a well-defined lunch. However, even in this case, each centre has its own values. While CPS test gives the values of the submaximal response to exocrine pancreas stimulation, at the Lundh test we obtained a physiological response. Also, there are some false results in celiac disease and after vagotomy or gastric resection.

Regarding the indirect testing of the pancreas, there are urine tests, faeces tests and faecal fat analysis. The only urine test remained in use is PLT (pancreolautyl test). In fact, patients are receiving the test lunch along with acid test and dialuric- fluorescein, which is cleaved by pancreatic arilesterases. Also, part of the substance (fluorescein) is absorbed and then excreted through urine. Two days later the test is repeated with fluorescein to exclude individual absorption impairments or metabolic liver disease or kidney failure. In this way, the final result is obtained by making excretion rate on the testing day compared to control day. In addition, the administration of pancreatic enzymes should be interrupted 5 days before the test. Also, we should note that false results can occur in patients with Billroth II operation.

Postoperative Weight Loss and Remnant Pancreatic Fibrosis

Regarding the postoperative weight loss, in a prospective study on a group of 26 resected patients between 2000 and 2001, 61% presented steatorrhea during the study and 20% at 12 months after surgery. There was also a significant increase in median Body Mass Index (BMI) from 6 weeks (22.9 ± 4.4) and 12 months (26.5 ± 4.3) after surgery. Median value of stool fat was 8.9 grams/day, 6.3 g/day, 7.1 g/day and 6.7g/ ay at 6 weeks, 3 months, 6 months and 12 months, respectively. Also, there were significant correlations between fat stools and their frequency, stool consistency and BMI. In this way, the authors concluded that there

might be a role for enzyme substitution in these patients after pancreatic resection to relieve symptoms and quality of life [41]. Moreover, in a study of 35 patients which received cephalic duodenopancreatectomy with preservation of the pylorus, gastric emptying was delayed shortly after surgery (1-2 months) and then returned to preoperative values in the long term (6-12 months). Moreover, body weight returned to normal if both faecal chymotrypsin and fasting blood sugar were preoperative normal, but this effect was not present if any of them was modified before the operation [41].

With regards to remnant pancreatic fibrosis, it is believed that the fibrosis of the pancreatic remnant after PCD at 12-18 months after surgery can be better evaluated using the time- signal intensity curve of dynamic MRI. Also, mucosa-to-mucosa pancreaticojejunal anastomosis was found to be more advantageous, with a low risk of fibrosis of the pancreatic remnants, as compared to pancreaticojejunal end-to-side anastomosis, in a study on 36 consecutive patients.

Conflict of interest

The authors are stating that they do not have any conflict of interest to disclose.

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