

## Studying the post-operatory and molecular modifications in the chronic pancreatitis and pancreatic cancer. The importance of the micronutrients and pancreatic enzyme supplementation

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### ABSTRACT

The pancreatic cancer is a disorder with an exponentially increased incidence, especially over the last few years. Moreover, it is estimated that almost 95% of the patients with this disease are presenting to the hospital in the advanced and unresectable stages. Also, over the past few decades the development and advance of the surgical methods and techniques have improved, with the most of the operatory actions in the chronic pancreatitis and pancreatic cancer being represented by the whipple duodeno-pancreatectomy, which in fact represents the standard resection for tumors of the duodenum, as well as the hepatopancreatic ampulla of Vater, distal choledocus and the head of the pancreas. Moreover, it is important to mention that in these cases, after an extended resection and reconstruction of the upper gastrointestinal tract, the digestive physiology will be disrupted. In addition, previous studies have shown that patients can maintain a body mass index after surgery but often this will be lower than its preoperative value. Thus, considering the aforementioned aspects, in the present mini-review we were mainly interested in presenting also the relevance of the micronutrients such as iron, selenium, vitamin D and E, zinc or copper in this complicated area of research, as well as aspects regarding the correlations between immune function and micronutrients or the pancreatic enzyme supplementation.

### 1. INTRODUCTION

The incidence of pancreatic neoplasm has increased steadily, especially over the last 4 decades in many parts of the world and has become the sixth or even fifth cause of death by cancer in the Western countries [1]. Moreover, in 2000 there were diagnosed 216.400 new cases and 215.500 deaths caused by this disease worldwide, while in 2004 in the United States there were predicted 31.860 new cases and 31.270 deaths, which indicate that, due to a very low survival rate, the incidence and mortality are almost similar [2].

In this way, it is estimated that almost 95% of the patients with this disease are presenting to the doctor in the advanced and unresectable stages. In fact, over the past few decades the development and advance of the surgical methods and techniques have improved only morbidity and hospital postoperative mortality, without significant impact on survival.

Thus, most of the operatory actions in the chronic pancreatitis and pancreatic cancer are represented mainly by the whipple duodenopancreatectomy, which in fact represents the standard resection for tumors of the duodenum, as well as the hepatopancreatic ampulla of Vater, distal choledocus and the head of the pancreas.

Moreover, it is important to mention that in these cases, after an extended resection and reconstruction of the upper gastrointestinal tract, the digestive physiology will be disrupted.

In addition, previous studies have shown that patients can maintain a body mass index (BMI) after surgery but often this will be lower than its preoperative value [3,4].

Thus, considering the aforementioned aspects, in the present mini-review we were mainly interested in presenting also the relevance of the micronutrients in this complicated area of research.

## 2. IRON, SELENIUM, VITAMIN D AND VITAMIN E

As mentioned, the metabolic disturbances following pancreatic resections have not been amply studied. In this way, Armstrong et al. have conducted a study to determine the consequences of surgery regarding certain micronutrients deficiency. 37 patients who underwent duodenopancreatectomy for periampullary tumors and 25 healthy subjects were included in the study. All subjects received alimentary intake in accordance with the established diet and BMI was measured [5]. It was showed that patients had elevated transferrin levels (median value 2.58 vs. 2.16 g/L,  $p=0.0143$ ) and low levels of ferritin (37.7 vs. 119.0 g/L,  $p < 0.0001$ ), which of course indicated iron deficiency, as compared to the control group of healthy subjects.

Also, the patients had have low levels of antioxidants: selenium (0.78 vs. 0.93 micromol/L,  $p < 0.0001$ ) and vitamin E (a 27.4 vs. 35.7 micromol/L,  $p=0.0017$ ) with 57% patients having with high deficiencies of selenium. Moreover, patients had lower values of vitamin D versus controls (16.3 vs. 19.6 micromoles/L,  $p=0.034$ ), and 30% of the patients had increased levels of parathyroid hormone, suggesting compensatory mechanisms that are functioning in the resected patients in order to maintain normal blood calcium values, which seems to be a consequence of malabsorption [5].

Moreover, following the duodenopancreatectomy the jejunum is used for the reconstruction of the upper gastrointestinal tract. In addition to the loss of the absorption capacity of the duodenum, the chyme entering the jejunal pouch will have an altered composition with changes in its pH and low content of pancreatic enzymes, which of course will compromise the normal digestion.

In fact, in many patients this deficiency is corrected by the use of specific medication such as gastric antacids and enzyme supplements, but none of these measures can prevent the micronutrients depletion, or at least has not been noticed by the authors of the study. Also, by using life partners as control subjects with the same dietary habits and same food intake, an important source of error was removed. Moreover, the serum levels of the studied micronutrients had the same values in men and women.

In this way, the iron ions status has also been directly measured through the assessment of transferrin and ferritin. It is known that iron binds in the blood to transferrin and the transferrin concentration increases in iron deficiency. Moreover, ferritin reflects most accurately the iron reserves of the body. Thus, the presented results are demonstrating that although serum iron is similar in patients and in the control group, however patients present clinical signs of sideropenia.

Still, this effect does not result in iron-deficiency anemia, but several studies have shown that long-term survivors after duodenopancreatectomy suffer from mild forms of anemia. In addition, sideropenia features fatigue and anxiety, which may contribute to the postoperative asthenia normally present in these patients. Low iron levels affect also the iron-dependent enzymes activity.

Also, two important anti-oxidants from the diet are Selenium and vitamin E, which are playing an important role in the anti-inflammatory reactions [6] and also have a protective function in infectious and heart diseases, as well as in neoplastic processes.

In fact, following duodenopancreatectomy, 57% of the operated patients exhibited selenium deficiency, which in more advanced degrees could lead to cardiomyopathy. Although the level of vitamin E was significantly lower in patients compared with the controls, however it maintained within the normal limits, with a likelihood for other anti-oxidizing mechanisms compensatory intervention.

However, since the deficiency of anti-oxidant agents contributes to the progression of the pathophysiological processes in chronic pancreatitis, the selenium and vitamin E deficiency should be avoided in patients at risk of developing obstructive pancreatitis due to anastomotic strictures.

Patients also have lower levels of vitamin D than in normal subjects, which is of course associated with an increased level of parathyroid hormone in 30% of the patients, suggesting the stimulation of both absorption and mobilization of calcium from the bones to maintain normocalcemia. Moreover, patients with chronic pancreatitis have lower bone mineral density, with low values of vitamin D, suggesting exocrine pancreatic insufficiency as a cause.

However, other researchers have shown that patients who were subjected to even the minimum of bowel resections exhibit hypovitaminosis D with elevated levels of parathyroid hormone. In this way, these observations indicated that both the pancreatic resection and duodenal resection can lead to these deficits and also compensatory mechanisms.

In regards to Vitamin A and zinc, these were within normal limits, indicating that only certain micronutrients are lacking in this group of patients.

Thus, the long-term survivors after duodenopancreatectomy generally have a good nutritional status, but with deficiencies though without clinical manifestations of iron, vitamin D and selenium. These micronutrients should be monitored; long-term postoperative follow-up of these patients should also include testing of these deficiencies and subsequent treating through appropriate diet and medications.

Also we do think that these therapeutic modalities will become much more important in the future, as they may induce a more common prolonged survival of these patients [5].

Also, in this sub-chapter we will refer to the connections between the immune functions and some micronutrients, as it has become clear lately that almost all nutrients deficiencies may influence immune function [7].

In this way, it is believed that many ingredients in food stimulate the immune system; in fact, the only exception is represented by a series of lipids such as triglycerides, cholesterol and polyunsaturated fatty acids [8].

However, the substitution of only one deficient nutrient is unlikely to produce satisfactory results, since it was showed that a synergistic effect of several ingredients seems to be important in order to obtain a complete effect. In this way, the fruits and plants contain large amounts of antioxidants, including more than 4,000 flavonoid substances and 500 carotenoids, some of them with antioxidant effects of 5-10 times higher than vitamin C or vitamin E [9].

In addition, protein-caloric malnutrition, which is a frequent cause of immunodeficiency, is also a type of malnutrition often accompanied by shortages of certain nutrients and associated with a decrease in the immune response [10].

In fact, a number of clinical studies on the use of micronutrients supplements indicated an improvement of the immune function with good clinical results. Thus, the administration of selenium, copper and zinc determined a significant reduction in the number of infections after major burns. Moreover, this supplementation has been associated with an increase in the total number of leukocytes, neutrophils and monocytes, as compared to controls. Also, the same combination modulated the response to pulmonary infections in the high-degree burns, while an after trauma additional intake of vitamins E and C determined a better mobilization of neutrophils [11].

### 3. ZINC

Zinc is a component of numerous metallo-enzymes, necessary for cellular growth and multiplication. It is also necessary in wounds healing and antioxidant defence as a key cofactor for the superoxide-dismutase. Zinc low deficiency can affect the immune system leading to specific immunological consequences such as thymic involution, thymocytes depletion and low delayed-type hypersensitivity. These features can be found in patients with enteropathic acrodermatitis, a congenital defect of the transport and absorption of zinc. Zinc plays an important role in cell-mediated immunity because it is an important factor in the conversion of pre thymulin into thymulin, and this hormone is essential in regulating the differentiation of T cells. More recent studies have shown a Zn-specific action in the monocytes through monokine induced secretion (IL1

beta, TNF alfa) and indirect stimulation of T cells. These facts may explain the high sensitivity of the cell-mediated immune response to zinc deficiency. Zinc supplement is beneficial in the treatment of septicemia with gram-negative germs [12] probably by stimulating immune function. Increased intake of zinc also improves cell-mediated immune response in the elderly population. Although low levels of serum zinc were traced following the cardiopulmonary bypass, trauma, sepsis, the zinc supplementation must be done with caution during the acute-phase response because it can evoke an increase of the cytokines response [12]. Zinc supplements in large doses can affect immunity in the elderly population.

#### 4. COPPER

Copper (Cu) is an essential element that plays an important role in the nervous system, in the formation of connective tissue and as a part of the Cu-Zn superoxide dismutase enzyme, a cytosolic antioxidant. Copper is also a component of the caeruloplasmin, an oxidative enzyme, and copper deficiency causes iron deficiency due to the fact that the iron reserves transfer is inhibited [13]. The role of copper in immune function is little known. The limited studies conducted on humans have shown the immunomodulatory effects of copper. Recently it was shown that a low intake of copper is associated with a decrease in the proliferation of lymphocytes and their IL2 receptor secretion; on the contrary, the phagocytosis of neutrophils and circulating lymphocytes number did not change. These observations did not have an impact on the rate of infections so that these amendments are not of clinical relevance.

#### 5. PANCREATIC ENZYME SUPPLEMENTATION

As previously mentioned, in the present context we will also refer to the relevance of pancreatic enzyme supplementation. In this way, the maldigestion occurring after gastroduodenal and pancreatic resections represents a major therapeutic challenge. Mini-microspheres containing pancreatic enzymes are used in the elective therapy in chronic pancreatitis maldigestion. The efficacy of enzyme replacement oral therapy was assessed. The distal portion of the stomach being resected, it has also been assessed whether such therapy can be improved by opening the enzymatic capsules or by inhibiting gastric acid secretion. A prospective, randomized, comparative, open study was conducted on 18 patients (12 men with an average age of 55 years, limits between 34-76 years) over a period of 32 months (limits 3 to 164 months) following duodenopancreatectomy.

Thus, the maldigestion patients were randomized to receive 4 capsules containing 10,000 U lipase in the form of mini-microspheres (Kreon ®), either open or closed, for two consecutive periods of 10 days. Esomeprazole 40 mg once a day has been associated for a further 10 days period in the patients with persistent maldigestion after the enzymatic therapy.

Moreover, lipid digestion before (basal) and on the last day of each of the three periods of treatment was assessed by a C13- triglycerides respiratory test. The cumulative recovery rate of  $^{13}\text{CO}_2$  was regarded as the result of the test. 15 patients (83%) who were suffering from lipids maldigestion were included in the study. One of them was excluded from the study due to non-compliance with the protocol. The basal rate of  $^{13}\text{CO}_2$  recovery was 36%. Oral pancreatic enzymes therapy significantly improved the digestion of fats ( $^{13}\text{CO}_2$  recovery of 57%) regardless of whether there were taken open or closed capsules. 8 patients (57%) normalized their fats digestion under the enzymatic therapy. The addition of Esomeprazole in patients with persistent maldigestion significantly increased the effectiveness of pancreatic enzymes replacement oral therapy ( $^{13}\text{CO}_2$  recovery from 40% to 52%) and the following 3 patients normalized the digestion of fats. This indicates that maldigestion occurs in most patients after a Whipple type resection. The treatment with oral pancreatic enzymes in the form of mini-microspheres is very effective in this protocol. Despite the partial gastrectomy, opening of the enzyme capsules is not required. Inhibition of gastric acid secretion is very helpful in the patients with inadequate response to oral enzyme therapy, as showed by Tampere group in 2006.

In this way, it is obvious that the major pancreatic resections can result in steatorrhea due to insufficient functioning of the exocrine parenchyma, which was observed in both short-term and long-term monitoring. In the case of chronic pancreatitis, the secretory reserve capacity of the gland can compensate for up to 90-95% of the exocrine pancreatic tissue reserve before appearing steatorrhea. The degree of pancreatic impairment is not caused by the resection itself only, as there are other factors that contribute to the pathological process, such as fibrosis. On the other hand, the antrum and/or with the pylorus resection and duodenum resection may decrease the food digestion and absorption. In particular maintaining enzymatic activity in the intestinal lumen during the duodenal transit of the chyme determines the enzymatic digestion duration and thus it is another key factor, which controls the degree of micronutrients deficiency. It has also been reported that 2 months after the DPC, the cholecystikinin is no longer discharged exciziei, probably due to the excision of the duodenum, which is the main center of the cells that stimulate the release of this enzyme. On the other hand, the postprandial elevation of the plasma secretin concentration after DPC-PP was reported to be similar to that of healthy subjects. However, the test of acid PABA show that the values decrease after the operation and return to normal values during the long-term development. These observations suggest that postoperative impairment of the pancreatic exocrine function is transitory and reversible. It has been documented in a case that the low level of postprandial cholecystikinin normalized 8 years after the DPC [14].

In chronic pancreatitis misconstrued the presence of increased bacterial populations, diagnosed through duodenal aspirate culture is associated with exocrine pancreatic insufficiency. The mechanisms responsible for regulating digestion are complex and the relationship between them is incompletely known including the interplay between endocrine and exocrine pancreas with food and the other components of the gastro-intestinal tract. In the digestion process are participating the stomach with its efferents, as well as the ingested aliments with their intrinsic properties: the volume, osmolarity, pH and nutrient content that affect gastric evacuation. This may explain why malnutrition pathogenesis after the DPC is not fully understood, because in addition to the surgical procedure per se, there are other factors that interact with each other.

Duodenal sparing motility dysfunction may be caused by resection of the duodenal pacemaker and disruption of gastro-duodenal nervous connections or iatrogenic injury of Latarjet nerve with its branches. Furthermore, certain patients may be diabetic and diabetics may have maldigestion (especially the insulino-dependent ones) and peripheral neuropathy, although gastric function is normal in patients with exocrine pancreatic insufficiency. DPC can disrupt peristalsis in particular if the duodenal pacemaker is resected or affected; the pacemaker is located at approximately 5 mm distal to the pylorus and should thus remain morphologically intact in the DPC-PP but not in Whipple DPC.

There is still discussion about the optimal time of administering the enzymes. Taylor et al. studied the gastric evacuation and the intestinal transit of pancreatic preparations and discovered discrepancies between the gastric evacuation and the pancreatic enzymes intestinal transit in relation to food consumption/dietary intake. Both the amount and the time period seem to be of importance in the use of enzymes. Despite these observations, in a study conducted on 50 patients with cystic fibrosis 84% took enzymes before meals and only 46% took the enzymes more than once, both prior to, during or after meals. Over 1/3 of patients (37%) did not have any change of dosage depending on the fat content of the food intake; 16% modified the enzyme dose for both main meals and light meals, 12% modified it only for meals and 35% only for light meals.

The loss of pancreatic and duodenal hormones that affect gastrointestinal motility and pancreatic secretion can have unpredictable effects. Of greatest interest is likely the cholecystikinin, CCK, which, along with the vague is the determining factor of the amount of secreted pancreatic enzymes. CCK is released in response to ingested food at the duodenum entrance which means that after the digestive resections or bypasses that are short-circuiting the duodenum there will be a distinct risk of impaired release of this hormone. At any rate, the CCK not only adjusts the secretion

of pancreatic juice and bile but also increases the frequency of potential in the distal stomach and delays the normal gastric discharge [15].

Moreover, CCK also participates in the regulation of the pancreatic polypeptide PP which is mainly controlled by vagal cholinergic nervous mechanisms (blocked by loxiglumide, respectively atropine) which have been found to affect digestion. Duodenectomy abolishes the plasma PP interdigestive cycles and decreases the PP postprandial release. Theoretically, the DPC influences the digestion by reducing the excess of inhibitory peptides such as secretin, gastric inhibitory peptide and glucagon. How much of these observations, that are more of an academical interest, can be confirmed, is debatable, but it should be noted that in one prospective study, Buchler et al. found that plasma CCK after alimentary stimulation was normal for classic DPC and with preservation of the duodenum. This means that in fact the pancreatic body can compensate to a certain degree the loss of pancreatic head and duodenum, as sources of hormones. Exocrine pancreatic insufficiency may follow partial gastrectomy per se – as a part of the Whipple operation. The post-operative symptoms occurring after a surgery so complex are difficult to distinguish from steatorrhea symptoms [16].

After ingestion, the microspheres mix with the chyme in the stomach, but not dissolve because of the protective sheath, resisting to the normal acid pH. If the anatomy is normal, the microspheres pass through the duodenum, and if the pancreas is intact and releases bicarbonate, the coating is destroyed, and the enzymes are released for digestion. Following the major pancreatic resections, there are lost not only the pancreatic tissue producer of enzymes and bicarbonate, but also the duodenum is resected or bypassed (according to the bypass procedures) which leads to an insufficient release of the CCK-releasing factor and of other hormones and nervous stimuli important for the secretion of pancreatic enzymes. In addition, the production of acid in the stomach can be disrupted and the transit through the small intestine may become too fast for the release of enzymes and effective nutritional principles absorption. Accordingly, the content, quantity and activation site of the pancreatic enzymes can be crucial for these patients.

After pancreatic resections, as in cystic fibrosis and chronic pancreatitis, the supplementary/substitution treatment with pancreatic enzymes should be lifelong administered. This means the medications must be easy to manage and have good bioavailability, as the patient prefers to take fewer drugs, sometimes under the optimal limit. Since many patients would have to ingest a large number of enzymatic capsules per day to ensure proper digestion, new formulas with high concentration of enzymes per capsule have been designed.

The exocrine pancreas has a high reserve capacity for enzyme secretion. The malabsorption of fats appears if pancreatic lipase drops to less than 10% under its normal secretion, and clinically translates by steatorrhea. This is caused by the lack at the level of intestinal cilia and microvilli of enzymes to digest the triglycerides and the insufficient intraluminal digestion of lipids carried out by other extra pancreatic enzymes such as salivary and gastric lipase. Consequently, the loss of pancreatic lipase in humans cannot be effectively compensated by other endogenous mechanisms, unlike proteases and amylases which can be fully compensated by the extrapancreatic enzymatic systems.

The supplementation with lipase is mandatory in the patients with surgery, such as pancreatic resection, major gastric resection, or duodenal bypass, as well in the patients with chronic pancreatitis. Also, the enzymatic preparations with high content of lipase are well supported and appropriate for the patients with chronic pancreatitis and cystic fibrosis, as suggested by well documented observations.

A number of fibrosing colonopathy cases associated with the administration of large quantities of enzymes have been reported in children. Although the colonopathy could be due to some other component in certain microspheric preparations, it is generally much more prudent for the enzyme dose to be increased only after a prior assessment of the digestion. On the basis of evidence from the literature data, the maximum dose of enzymes established by the Commission on safety of the Medicinal Products is 10,000 lipase units/kg body weight per day.

Currently, there are sufficient studies asserting the frequency of pancreatic exocrine insufficiency after major pancreatic resections, on the basis of which the enzymatic medicinal supplementation is recommended. Nevertheless, the absence of acid in the stomach of these patients is an aspect to be highly considered [17].

Recommendations on enzymatic substitution are difficult to make since the number of studies concerning this issue is low, but, at any rate, the enteric coated microspheres are recommended after Whipple operations, drainage operations or distal resections. In addition, in the case of Whipple surgery, medications to reduce the intestinal transit may improve the effect of these enzymes. Following the resection of the pancreas without antrectomy, the cephalic pancreatectomy with the preservation of duodenum, or the DPC-PP, the conventional enzymatic preparations in the form of granules and PPI (proton pump inhibitors) are also recommended, while after total pancreatectomy the enzymatic supplementation must be adapted to the needs of each patient.

In a study on 10 patients without recurrence of the tumor for 6 to 46 months after DPC for cancer, for one week the diet was measured quantitatively and compared the 8 weeks later diet. The patients required pancreatic enzyme supplementation but had no benefit of dietary assessment in terms of symptoms and quality of life. In another study conducted on 14 patients the morphologic changes, but also the changes concerning the endo- and exocrine function of the restant pancreas were investigated for a period of over 10 years after the operation. Pancreatic parenchymal atrophy and diffuse dilatation of the main pancreatic duct have been observed in all cases. 10 years after the operation, there were 8 diabetes mellitus patients treated with insulin, and pancreatic function tests were abnormal in 12 patients. The fat in the stools were of 7.5 g or exceeded this quantity in all patients except one. Also, the more pronounced the degree of diabetes was, the higher the volume of fats in the stool. Determine the quantity of fats in the stool is considered a very important method for evaluating the suitability of commencement of the enzyme supplementation.

In a study on 9 different types of pancreatic enzyme preparations for human use, 7 had excess enzymatic activity. For example, 2 Solvay preparations had the amylase activity of 163-179%, the protease 113% and the lipase activity of 114-120 %.

In a prospective study on 26 patients who underwent CPD between 2000 and 2001, 61% of patients have had steatorrhea during the trial and 20% have had steatorrhea 12 months after completion of the study. The median values of fats in the stools were 8.9 g/day, 6.3 g/day, 7.1 g/day and 6.7 g/day at 6 weeks, 6 months and 12 months respectively. Significant correlations were found between the amount of fat in the stools, the frequency of the stools, their consistency and the BMI. On the other hand, there was no significant correlation between the QoL measured using the EORTC QLQ-C30 scale and abdominal pain and fats from the stool. The authors concluded that the enzyme supplementation might be beneficial in these patients in terms of quality of life.

Following a study on 31 patients with severe chronic pancreatitis and exocrine insufficiency, the authors stated the oral enzymatic preparations supplementation cannot be correctly adjusted on the basis of clinical evaluations only, because the fat-soluble vitamins serum level often remains low below normal, despite an enzymatic supplementation theoretically adequate [18].

## 6. CONCLUSIONS

Thus, in the present report we mainly reviewed the relevance of some micronutrients such as iron, selenium, vitamin D and E, zinc or copper in chronic pancreatitis and pancreatic cancer, as well describing aspects regarding the correlations between immune function and micronutrients or the pancreatic enzyme supplementation.

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