METABOLIC DISORDERS IN PATIENTS OPERATED FOR PANCREATIC CANCER

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(Abstract): Adenocarcinoma of the pancreas presents a major threat with a 5-years survival rate of 5%. Whipple pancreaticoduodenectomy (PD) is the standard procedure for cephalo-pancreatic neoplasm. After an extended resection and reconstruction of superior gastrointestinal tract the digestive physiology might be heavily disrupted. A literature review of metabolic alterations of patients who suffered a major pancreatic resection is performed, regarding micronutrients, lipid absorption and pancreatogenic diabetes. Long-term survivors following PD generally have a satisfactory nutritional status although with subclinical iron, vitamin D and selenium deficiency. These patients should be followed-up also regarding these micronutrients and properly dietary supplemented when necessary, also considering the increased life expectancy. Approximately 17-25% of patients will develop insulin-dependent diabetes but pancreatogenic diabetics have elevated levels of serum insulin and minimal or absent response to food intake, as opposed to a type I diabetics, where insulin serum is normal or elevated and there is an exaggerated response to ingestion of sugar. Keywords: PANCREATIC CANCER, SURGERY, METABOLIC, NUTRITIONAL, DIABETES

Adenocarcinoma of the pancreas is a major threat to survival, worse than most other forms of gastrointestinal cancer (1). Compared to other gastrointestinal malignancies, exocrine pancreatic cancer is a fairly common malignancy, outnumbered only by colorectal cancer and – slightly – by stomach cancer. Pancreatic ductal adenocarcinoma is the most common malignancy of the pancreas, most frequently arising from the ductal epithelium of the pancreas (2). The age adjusted incidence rates peaks between 60 and 80 years which implies that many of the patients are not fit enough for extensive surgery (3).

Until 1970s, pancreaticoduodenectomy (PD) was a seldom performed procedure, which should be understood against a backdrop of in-hospital mortality of 20-25 percent. However, during the 1980s and 1990s,
experience in performing PD increased steadily and high-volume centers reported low treatment-related morbidity and mortality. One rationale for the increased rate of TP may be an increased diagnosis of diffuse ductal disease in all patients undergoing pancreatic resection. Improved radiographic and endoscopic surveillance during preoperative testing as well as close attention to intra-operative frozen section pathologic analysis of the pancreatic duct margin may contribute to this.

Recently the mortality in high-volume centers is usually close to zero, whereas major morbidity has decreased to 30% or less – even though the procedures have been extended (4). Depending on the stage, the treatment options include chemotherapy, radiation, and surgery. Surgical resection has offered the only hope for cure in the treatment of exocrine pancreatic cancer. Even so, pancreatic cancer still remains a major, unsolved therapeutic challenge and is the most lethal type of gastrointestinal cancer with a 5-year survival rate of 5%. Adjunct chemotherapy remains to be gemcitabine alone, though fluorouracil offers the same survival and role of radiation remains controversial. Nevertheless, only a few patients survive for at least 5 years after R0 resection and adjuvant therapy (5). Generally, one of the reasons for the bad prognosis of pancreatic cancer is the late diagnosis despite the development of new technologies. This delay in diagnosis is mainly due to the fact that there is no early symptom or sign. Moreover, the initial presenting symptoms of pancreatic carcinoma are generally vague and non-specific.

The two important antioxidants in the diet, selenium and vitamin E, have an important role in anti-inflammatory reaction and also are protective factors in heart diseases, infectious diseases and in neoplastic processes. After PD 57% of the patients had selenium deficiency which in advanced stages can lead to cardiomyopathy. Although vitamin E level was significantly lower in operated patients, it remained at normal values. It’s already

for neoplasm of duodenum, ampulla of Vater, distal coledochus and the head of pancreas. After an extended excision and reconstruction of superior gastrointestinal tract, the digestive physiology might be heavily disrupted. Previous studies have shown that patients might maintain a normal body mass index (BMI) after surgery for pancreatic cancer, although frequently lower than preoperative values (6, 7, 8).

Metabolic disorders consecutive to pancreatic resections have not been widely studied. Compared to healthy individuals, these patients may have measurable reduced concentrations of trace elements and vitamins (selenium, vitamin B12, vitamin D) in whole blood and serum by the time cancer is diagnosed and long before clinically relevant changes in nutritional status are seen (9). Armstrong et al. showed that long-term survivors of duodeno-pancreatectomy are relatively deficient in several micronutrients compared to non-operated controls taking the same diet. Patients had elevated transferrin and low ferritin levels indicating relative iron deficiency. Patients also showed lower levels of the antioxidants - selenium and vitamin E- with 57% of patients with significant selenium deficiencies. Lower levels of vitamin D than controls were found and 30% of patients had a high parathyroid hormone level, suggesting compensatory mechanisms operate to maintain normocalcaemia (10).

The development of sophisticated surgical procedures, improved postoperative care, and the capacity for early diagnosis of disease has prolonged life expectancy after pancreatic resection.

Whipple PD is the standard procedure
known that the deficit of antioxidant agents contributes to the progression of pathophysiological processes in chronic pancreatitis so we consider that low values of selenium and vitamin E should be avoided in patients operated for pancreatic cancer. Other micronutrients such as copper and zinc which are part of many metalloenzymes and normally play an important role in cell mediated immunity have low values in patients operated for pancreatic cancer. These observations did not have an impact on infection rates so that these changes have no clinical relevance.

In addition to improved endocrine control, exocrine insufficiency may be improved by modern pancreatic enzyme formulations, proton pump inhibitor therapy and the use of the duodenum-preserving pancreatic head resections. In a report from Japan, the pylorus-preserving technique was noted to be associated with significantly improved albumin levels and weight loss over the standard total pancreatectomy (21).

Lipid malabsorption after major pancreatic resections is the result of several mechanisms contributing to early occurrence of steatorrhea compared malabsorption of other nutrients. For various reasons impairment of pancreatic lipase activity cannot be sufficiently compensated by other mechanisms. Digestion of fats in the small intestine is mainly due to the combined effects of lipase and its cofactors, especially bile acids. Intestinal mucosa does not express enzymatic systems that digest triglycerides and lipolytic activity performed by other extrapancreatic sources (salivary and gastric) cannot compensate lipid digestion by pancreatic lipase (11).

The loss of pancreatic parenchyma resulting from pancreatic resection causes an extreme disruption of glucose homeostasis known as pancreateogenic diabetes.

Pancreateogenic diabetes is attracting attention as the primary factor influencing quality of life in patients who have undergone this procedure, but is difficult to predict the effect on carbohydrate metabolism because metabolic changes are from mild to major. The incidence of new-onset diabetes mellitus after pancreatic resection increases as the follow-up period after surgery becomes longer and is related to the progression of underlying disease, the type of surgery, and the extent of resection. In general, postoperative changes are usually moderate to severe and approximately 17-25% of patients will develop insulin-dependent diabetes.

Studies on pancreatic endocrine function after resection are few and controversial. This is probably due to the fact that long-term metabolic consequences may differ even if for the same type of pancreatic resection or surgical indication and depend mainly of the quality of the remaining pancreas tissue (tab. I).

### TABLE I

**Postoperative consequences after different types of resection and drainage procedures for pancreatic cancer**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>New diabetes (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal pancreatectomy</td>
<td>21-40%</td>
<td>Morrow (12)</td>
</tr>
<tr>
<td>Cefalic pancreatectomy with preservation of the duodenum</td>
<td>2-15%</td>
<td>Beger (13)</td>
</tr>
<tr>
<td>Cephalic pancreatectomy with preservation of the pylorus</td>
<td>12%</td>
<td>Traverso (14)</td>
</tr>
<tr>
<td>Whiple duodenopancreatectomy</td>
<td>17%</td>
<td>Schwarz</td>
</tr>
<tr>
<td>Total pancreatectomy</td>
<td>Brittle diabetes 100%</td>
<td>Andrén-Sandberg (15)</td>
</tr>
</tbody>
</table>
Metabolic disorders in patients operated for pancreatic cancer

The pathophysiology of pancreatogenic diabetes is related to pancreatic hormone deficiency and the altered responses of the liver and peripheral organs to lower than normal hormone levels. Experimental results suggest that insulin-independent glucose metabolism after pancreatic resection is done for a large proportion of absorbed glucose. This may explain why patients with pancreatogenic diabetes behave differently than other diabetics sensitive to insulin therapy. These patients with unmanageable diabetes - "brittle diabetics" - may become unpredictable hypoglycemic during treatment with insulin, unrelated to food intake or to physical effort. Diabetes resulting after pancreatic resection differs in several ways from type I (juvenile, or insulin-dependent) and the type II (adult, or non-insulin-dependent).

Hyperglycemia occurs when the amount of insulin produced or administered is insufficient because of unsuppressed hepatic glucose production secondary to a deficiency in pancreatic polypeptide. In contrast, patients lapse into hypoglycemia when insulin is barely excessive because of enhanced peripheral insulin sensitivity and glucagon deficiency. Nutritional state, pancreatic exocrine function and intestinal function also affect glycemic control. Unlike type I diabetes, patients with pancreatogenic diabetes rarely develop ketoacidosis and the degree of hyperglycemia is mild in most cases. Compared with type II diabetes highly resistant to insulin, resected patients are really sensitive to insulin and iatrogenic hypoglycemia episodes are common. These patients have an increased serum level of gluconeogenic precursors such as lactate and alanine.

Hyperglycemia has been attributed to pancreatic glucagon secretion deficits (17). Pancreatogenic diabetics have elevated levels of serum insulin and minimal or absent response to food intake, as opposed to a type I diabetics, where insulin serum is normal or elevated and there is an exaggerated response to ingestion of sugar (18) (tab. II).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Type I diabetes</th>
<th>Type II diabetes</th>
<th>Pancreatogenic diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoacidosis</td>
<td>frequent</td>
<td>rare</td>
<td>rare</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>severe</td>
<td>mild</td>
<td>mild</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>frequent</td>
<td>rare</td>
<td>frequent</td>
</tr>
<tr>
<td>Peripheral insulin sensitivity</td>
<td>normal/elevated</td>
<td>low</td>
<td>elevated</td>
</tr>
<tr>
<td>Liver insulin sensitivity</td>
<td>normal</td>
<td>elevated</td>
<td>low</td>
</tr>
<tr>
<td>Insulin level</td>
<td>low</td>
<td>elevated</td>
<td>low</td>
</tr>
<tr>
<td>Glucagon level</td>
<td>normal/elevated</td>
<td>normal/elevated</td>
<td>low</td>
</tr>
<tr>
<td>Pancreatic peptide level</td>
<td>elevated</td>
<td>elevated</td>
<td>low</td>
</tr>
</tbody>
</table>

As pointed out by Frey et al., the incidence of diabetes is directly related to the extension of the resection of pancreatic tissue (19). Patients requiring total or near-total pancreatectomy pay a significant price represented by altered secretion of glycemic regulating hormones. In these patients requiring distal pancreatectomy or only a
limited excision of the pancreas diabetes develops far less frequently than those that require PD or total or near-total pancreatectomy.

It has been noticed an increased sensitivity of extrahepatic tissue to physiological hyperinsulinemia and increased amounts of insulin bound to receptors from red blood cells in patients with pancreateogenic diabetes. Thus, there is an increase of peripheral insulin receptors in response to insulin deficiency that makes these patients susceptible to hormone replacement.

Patients with PD have a good metabolic status and a significant number of them require insulin replacement therapy, due to failure to control blood sugar with oral antidiabetic agents. Insulin replacement is considered to be the main treatment option for insulin dependent pancreateogenic diabetes. Improvements in glucose monitoring systems, insulin delivery systems and insulin formulations may contribute to superior glycaemic control for these patients. (25)

Surgeons, gastroenterologists and endocrinologists alike may be more comfortable with the management of the apancreatic state that was so feared in the past. Jethwa et al. (22) reported that there were no observed mortalities as a result of diabetic complications or metabolic consequences of pancreatic resection during long-term follow-up of 47 patients undergoing TP. They concluded that diabetic control after TP is less difficult and associated with fewer glycaemic complications than generally assumed. Similarly, in the largest single institution review of 124 elective TPs, a group from Germany found TP was performed with the same morbidity rate as partial pancreatectomy, and quality of life was not significantly different in the two groups. (23) This confirmed a previous report from 2005 where the significant metabolic derangements of the apancreatic state may not become immediately apparent in the post-operative inpatient recovery phase. Most of these elderly patients do not have baseline endocrine or exocrine insufficiency before surgery and have difficulty adjusting to complex diabetic and nutritional changes seen after TP. Multidisciplinary management is mandatory for improved outcomes and intensive diabetic and nutritional counselling are essential. Providing extended care by discharge to a skilled nursing facility with diabetic education and nutrition capabilities appears appropriate. Additionally, consideration should be given for providing all patients with supplemental enteral feeding for several weeks post-operatively. A strict follow-up protocol should be available for these patients who include close endocrine and nutrition supervision, strict adherence to proton pump inhibitor (PPI) and pancreatic enzyme replacement therapy and adequate hydration and protein intake. These measures may avoid readmission in the majority of the patients, particularly for the diagnosis of dehydration, diabetic complications and failure to thrive (26).

CONCLUSIONS

Mortality and long-term morbidity associated with TP appear to be lessening over the past decade, indicating that the risks of TP appear acceptable compared with the benefits of resection, especially for those patients with premalignant disease. Overall, survival is generally based on the underlying disease process, not a consequence of the surgery.

The goal of the treatment of pancreatic
cancer should be to balance the quantity and quality of life according to individual preferences. Long-term survivors following PD generally have a satisfactory nutritional status although with subclinical iron, vitamin D and selenium deficiency. These patients should be followed-up also regarding these micronutrients and properly dietary supplemented when necessary, also considering the increased life expectancy.

REFERENCES


**SYNDROME-ASSOCIATED SOFT TISSUE TUMOURS**

Soft tissue neoplasms may be associated with a variety of genetic disorders and malformation syndromes, especially when they arise in children, adolescents and early adulthood. While many soft tissue tumours are sporadic and without a known pathogenesis or established risk factors, in recent years there has been an increasing awareness that certain types of benign, intermediate and malignant soft tissue neoplasms may be a manifestation of a genetic or malformation syndrome and that specific syndromes carry with them a higher risk of sarcoma. This is a particular concern for children, adolescents and young adults because of the relatively increased frequency of sarcomas in younger patients. Li–Fraumeni syndrome (including those with germline p53 mutations), hereditary retinoblastoma and neurofibromatosis type are the prototypical syndromes associated with soft tissue tumours, but many other syndromes and genetic conditions have soft tissue tumours as a manifestation, including Gorlin–Goltz syndrome, familial adenomatous polyposis (FAP) and pleuropulmonary blastoma syndrome. Vascular masses, usually malformative in nature, are characteristic of a variety of other disorders, including Maffucci, Sturge–Weber, Klippel–Trénaunay–Weber, Proteus and von Hippel–Lindau syndromes. In children, malformation syndromes, congenital anomalies and genetic disorders are among the major risk factors for development of soft tissue sarcoma. In this review, the authors summarize the principal histopathological types of soft tissue tumours which occur in various syndromes, with an emphasis on pathological features, genetic aspects and considerations for the diagnostic pathologist (Coffin C M, Davis J L & Borinstein S C. Syndrome-associated soft tissue tumours. *Histopathology* 2014, 64, 68–87).