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Management of Nutritional Issues After Major Pancreatic Resections

Nam Q. Nguyen, Neil D. Merrett and Andrew V. Biankin

Pancreatic resection is associated with a number of long term gastrointestinal complications that can lead to malnutrition and a consequent reduction in the quality of life. These are predominantly the manifestation of exocrine and endocrine insufficiency, gastrointestinal dysmotility, biliary dysfunction and bacterial overgrowth. Such sequelae can lead to reduced oral intake, macro- and micronutrient malabsorption, and impaired glucose homeostasis, which adversely impact on the patient's well-being. In order to minimise these complications after major pancreatic resection, it is imperative to identify these deficiencies and closely monitor the patient's energy consumption, symptoms and nutritional status. The management needs to be coordinated using a multi-disciplinary approach and in each case treatment individualised and based on an understanding of the anatomical, physiological and nutritional sequelae caused by the loss of pancreatic parenchyma through surgical resection.

Keywords: Pancreatic cancer, pancreatectomy, pancreatic insufficiency, gastrointestinal dysmotility, malabsorption, nutritional management, quality of life.

1. Introduction

Surgical resection offers the only possibility of cure for patients with peri-ampullary and pancreatic cancer.[1–3] The classic Whipple's procedure[2] and the pylorus-preserving pancreatico-duodenectomy (PPPD)[4,5] are the two most common operative techniques used for carcinoma in the pancreatic head. For tumours located toward the body/tail of the pancreas, left-sided pancreatectomy is preferable. Although the operative mortality rate of these procedures is below 5% in high-volume surgical centres,[1,6,7] the operative morbidity related to pancreatic fistulae, sepsis, and delayed gastric emptying (DGE) remains high at 30 to 40%.[8–10] Furthermore, as the pancreas plays a vital role in food digestion and glucose homeostasis, long-term survivors after pancreatoduodenectomy are at risk of pancreatic exocrine insufficiency and malabsorption.[11] The presence of symptoms such as diarrhoea, flatulence, tenesmus, and steatorrhoea may substantially affect the quality of life of these individuals, and can lead to progressive weight loss and malnutrition.[12,13] Gastrointestinal dysmotility can also be a significant clinical problem in a small proportion of patients and may lead to symptoms such as DGE, early satiety and entero-gastric reflux.[14,15] Together, these long-term complications of exocrine insufficiency and GI dysmotility after major pancreatic resection can adversely affect the oral intake and GI absorptive function of these patients and predispose them to significant malnutrition.

Although the morbidity and mortality benefits of pre-operative nutritional support have been well demonstrated,[16,17] especially in malnourished patients, the impact of nutrition on long term outcomes of patients who have had a pancreatic resection are yet to be defined. Overall, current data suggest that pancreatic resection causes a notable reduction in global quality of life.[18,19] The current chapter reviews the anatomical and physiological impact of major pancreatic resection on gastrointestinal (GI) function, subsequent nutrition and discussed relevant issues in the management of these patients.

2. Management of Pancreatic Insufficiency After Pancreatectomy

2.1 *Exocrine insufficiency*

The degree of alteration in the digestive function of the pancreas after resection depends on the amount of pancreatic parenchyma resected and the functional capacity of the residual pancreas (Table 1). Clinically, this relates to the type of surgical procedure carried out and the presence of underlying pancreatic atrophy or pancreatitis. In a cohort of approximately 700 patients, pancreatic parenchymal volume was strongly correlated with body weight, exocrine and endocrine function.[20] The presence of partial gastrectomy or antrectomy further disrupts post-prandial synchrony of digestion, by impairing the release of gastrin, pancreatic polypeptide and cholecystokinin.[21,22] The type of pancreatico-enterostomy is also important and can influence post-operative exocrine function.

Due to the early deactivation of pancreatic enzymes by gastric acid, deterioration in pancreatic exocrine function in patients who

Table 1. Impact of major pancreatic resection on upper gastrointestinal tract function.

Pancreatic function
• Pancreatic exocrine insufficiency from reduced function.
o Degree of insufficiency correlates with extent of parenchymal resection and functional state of the residual pancreas.
• Diabetes mellitus from reduced endocrine function.
Gastric function
• Delayed gastric emptying; most improve within six months.
• Inadequate acid buffering leading to peptic ulceration.
Biliary function
• Recurrent cholangitis from either strictures or bacterial overgrowth.
Small intestinal function
• Disturbed jejunal migrating motor complex (MMC) phase III and reduced feed pattern.
• Entero-gastric reflux.
• Diarrhoea and malabsorption from bacterial overgrowth (blind loop syndrome).

have undergone PPPD with pancreatico-gastrostomy is greater,[11,23] and can be overcome with the administration of acid suppressive therapy.[24] Compared to patients with a normal residual pancreas, pancreatic function of those with chronic pancreatic disease such as chronic pancreatitis or atrophy is often impaired, even before any type of resection is carried out. In these patients, exocrine and endocrine pancreatic function deteriorates progressively after a major resection and aggressive replacement is required.[11]

Management

As pancreatic enzymes play a major role in food digestion and absorption, appropriate replacement to correct exocrine insufficiency is essential and reduces malnutrition, normalises biochemical indices of malnutrition, assists patients in recovering much of the original body weight and improves quality of life.[25,26] Because patients have different degrees of exocrine insufficiency, the dosage of pancreatic enzymes has to be adjusted to the individual.[25,27,28] All patients should be monitored and screened for symptoms and signs of inadequate replacement, which includes loss of body weight, diarrhoea or steatorrhoea, dyspeptic symptoms with gaseous distension and a stool fat excretion greater than 15 g/day.[25]

Amongst the pancreatic enzymes, lipases have significantly shorter intra-luminal survival time because they are most susceptible to acidic and proteolytic denaturation[25,29] and the aim of successful pancreatic enzyme replacement is to achieve sufficient lipase activity in the intestine.[29] Contrary to general belief, there is not a linear relationship between the dose of pancreatic enzymes and the symptoms of mal-digestion. In general, the required amount of lipase to be delivered to the duodenum with each meal is of the order of 25,000 to 40,000 units to achieve lipase activity of 40–60 units/ml of chyme.[25,29] As the unprotected enzyme is rapidly destroyed by gastric acid, co-administration of acid suppression therapy is a useful adjunct therapy and is recommended especially if severe steatorrhoea continues with adequate dosing with pancreatic enzymes.[25,29,30]

More recently, pH-sensitive pancreatic lipase microsphere preparations have become increasingly popular and have been recommended by some authors as the treatment of choice.[27–29,31] This preparation however may be ineffective in patients who underwent PPPD because the microspheres are retained in the stomach.[32] In these patients, conventional powdered pancreatic enzyme preparations may improve the efficacy of treatment.[32] If symptoms and signs of mal-digestion persist despite the above therapeutic measures, trials of pH-sensitive enteric-coated microspheres, restricting the amount of dietary fat and/or replacing fat with medium chain triglycerides should be considered.[22,25,33,34]

2.2 *Endocrine insufficiency*

Approximately 20 to 50% of patients who have major pancreatic resection for malignancy develop diabetes mellitus,[11,35] and the incidence is significantly higher in patients who have a left-sided pancreatectomy than after a Whipple's procedure (57% versus 36%, respectively).[36] Similar to exocrine insufficiency, a greater degree of endocrine insufficiency is seen in patients with a compromised residual pancreas from pre-existing chronic pancreatitis or atrophy.[36–38]

Management

It is important to note that the glucose homeostasis and response to insulin treatment in these patients with secondary diabetes mellitus is different to those with idiopathic diabetes mellitus. As glucagon secretion is simultaneously reduced in these patients, they are 'hyper-sensitive' to the effects of insulin, exposing the patients to higher risk of recurrent attacks of hypoglycaemia and a substantial number of deaths and brain-injury.[11,39] Previously, this complication was considered to be a major issue for these patients, having been reported, especially in those who with alcoholic chronic pancreatitis.[40] Until recently, short-acting insulin preparations given repeatedly before meals and according to pre-prandial glucose levels have been the mainstay of therapy. This required intensive monitoring with slow dosage titration, to avoid hypoglycaemic complications. The recent advances in long-acting formulations of insulin have substantially reduced this problem, improving overall glycaemic control.

3. Management of Upper Gastrointestinal Dysfunction After Pancreatectomy

3.1 *Upper gastrointestinal dysfunction*

Although delayed gastric emptying (DGE) occurs in up to 50% of patients during the early post-operative period, only a small proportion of patients have persistent symptoms beyond six months post-operatively.[41–43] In more recent studies, the incidence of DGE fell to less than 10% and this improvement is most likely related to the advances in surgical technique, increased surgical experience, and improvements in post-operative intensive care management.[44–52] Currently, known risk factors for delayed gastric emptying after pancreatic resection include: pre-operative cholangitis, post-operative leakage and sepsis, pancreatico- and biliary-enteric anastomosis via the retro-mesenteric route and radical pancreatico-duodenectomy.[44–52] Whilst there has been much debate surrounding the higher incidence of DGE after PPPD compared to the classical Whipple's procedure, the most recent meta-analysis failed to demonstrate a difference in the rate of DGE between the two procedures[2] and the current rates of DGE following pancreatic resection are significantly lower (3–7%) than historically reported.[44–52] The reasons that underlie the controversy are multi-factorial and are most likely related to the variation in the definition of DGE between trials,[53] increased surgical experience and advances in post-operative intensive care management.[44–52]

Dysmotility of the upper jejunum with slower phase III of the migrating motor complex (MMC) and a reduced feed pattern are also frequently observed, leading to problems with entero-gastric reflux and bacterial growth in a small proportion of patients.[15,54,55] Entero-gastric reflux is more frequently observed in patients after Whipple's resection compared to those with PPPD, as the retained pylorus is competent to prevent entero-gastric reflux.[15] Recent data, however, suggest the use of undivided Roux-en-Y reconstruction following Whipple's procedures may decrease the incidence of entero-gastric reflux and thus, eliminating problems due to bile reflux gastritis and ulceration.[56]

Division of the vagus nerve and removal of the duodenal pacemaker by duodenectomy have been proposed as neurohormonal mechanisms involved in the pathogenesis of upper gastrointestinal dysfunction after major pancreatic resection, leading to a loss of coordination of gastrointestinal motility and an alteration in plasma concentrations of gastrointestinal peptides and hormones important for regulation of normal gastric motility such as motilin, pancreatic polypeptide, glucagon-like peptide-1, and peptide YY.[54,57–60]

Peptic ulceration occurs infrequently after pancreatic surgery (5%), particularly with Whipple's resection,[43] and is related to inadequate acid buffering from the fall in pancreatic bicarbonate secretion and the impaired mixing of bicarbonate secreted into the ascending loop with the 'acidic' chyme.[11,43]

Management

It is important to treat delayed gastric emptying promptly and effectively as this post-operative complication significantly increases the length of hospital stay, the number of days with a naso-gastric tube, and the number of days until solid food is tolerated.[52] More importantly, measures such as meticulous care during the operation to prevent post-operative leakage and sepsis, as well as avoiding the retro-mesenteric route for pancreato- or biliary-enteric anastomosis should be taken to reduce the risk of DGE.[61–63] Centralisation of pancreatic resections in high-volume centres with recent advances in operative techniques and post-operative care have not only reduced the need for re-operation but also lowered the incidence of DGE to an extremely low level.[1,15,64]

Prokinetic therapy should be the initial treatment for upper gastrointestinal tract dysmotility. The currently used prokinetic agents to improve upper gastrointestinal dysmotility in clinical practice are erythromycin, metoclopramide and domperidone. Low doses of erythromycin (a motilin agonist, 1 mg/kg/d) induce antral contraction and initiate premature gastric phase 3 activity of the MMC that migrates through the small intestine,[65–67] and has been shown to reduce the incidence of DGE by 50–75% with a shorter duration of naso-gastric drainage, and earlier resumption of eating.[68,69] Although no major adverse effects of erythromycin were observed in these trials,[68,69] care must be taken to avoid drugs that can interact and cause a prolonged QT interval and related cardiac arrhythmias. Despite their frequent uses in clinical practice, efficacy data of dopamine antagonists such as metoclopramide and domperidone for improving

delayed gastric emptying in patients with pancreato-duodenectomy are lacking. Although cisapride (a 5-HT4 receptor antagonist) has been shown to accelerate gastric emptying in patients with DGE after PPPD with a Billroth I type duodeno-jejunostomy,[70,71] its clinical use has been restricted to highly specialised centres for refractory cases, because of the risk of cardiac arrhythmia when used in combination with other prokinetic agents such as erythromycin.[72,73]

Approximately 2–6% of patients experience prolonged upper gastrointestinal dysmotility despite prokinetic therapy,[71,74–78] and treatment of these persistent cases proves challenging, with the role of prokinetic agents being controversial. Although switching to another prokinetic agent or adding a second agent with a different mechanism of action is frequently adopted in clinical practice, the efficacy data for these approaches in these persistent cases are lacking. Furthermore, the major concern of prolonged uses of these prokinetic agents is associated tachyphylaxis. Recently, the role of electrical stimulation or pacing was investigated and preliminary data in patients with gastroparesis from Roux-en-Y gastric bypass suggested that electric gastric pacing improved both gastric emptying as well as nausea and vomiting in the majority of patients.[79]

3.2 *Biliary dysfunction*

Motility changes in the small bowel loop used for the entero-biliary anastomosis may result in bacterial overgrowth and hence recurrent bouts of cholangitis without any evidence of anastomostic stricture. Recurrent attacks of cholangitis may also occur in the small subset of patients who develop entero-biliary anastomostic strictures.

Management

Entero-biliary anastomostic strictures need to be excluded in all patients, as these strictures can be promptly treated with the combination of antibiotic therapy and endoscopic intervention. Occasionally, radiological and/or surgical interventions are required when endoscopic intervention has failed due to alteration in the upper gastrointestinal anatomy.[80] If recurrent cholangitis occurs in the absence of anastomotic stricture, combinations of prokinetic and long term, low dose antibiotic prophylaxis may prevent recurrence.[11]

3.3 *Bacterial overgrowth*

Bacterial overgrowth is common after both types of pancreatic resection, especially in the entero-pancreatico-biliary loop. The presence of excessive bacteria results in de-conjugation of bile acids with consequent failure of micelle formation and decreases lipid uptake further impairing fat absorption and causing more steatorrhoea,[15,54,55] leading to malabsorption of both macro- and micro-nutrients.[11] The syndrome should be considered if steatorrhoea persists despite adequate pancreatic enzyme replacement with appropriate acid suppressive therapy.

Management

The diagnosis should be confirmed by hydrogen breath tests prior to treatment with a combination of intermittent antibiotic therapy such as ciprofloxacin or metronidazole and prokinetic agents.[11]

4. Management of Other Nutritional-Related Issues After Pancreatectomy

Loss of muscle mass, impairment of voluntary muscle function and respiratory function can be seen as early as the third post-operative day.[81] Dual energy X-ray absorptiometry (DEXA) detects a small, but significant reduction in mid-arm circumference and total body fat during the first post-operative week.[82] Patients who have undergone a Whipple's resection are more likely to restrict their intake of fat, and to a lesser extent, carbohydrate due to heartburn, dyspepsia and steatorrhoea.[13] Consequently, up to one-third of these patients were found to have deficiencies in the intake of micronutrients and minerals such as iron, zinc, calcium, vitamin D and selenium.[11,13,82] Although the body mass index (BMI) of most patients is often well below their pre-illness level,[64] the overall body weight remains stable and ongoing weight loss is more often a sign of recurrent disease.[11]

Management

In addition to pancreatic enzyme replacement and treatment of upper gastrointestinal dysfunction,[83,84] specific dietary modification

Table 2. Key issues in the management of patients after major pancreatic resection.

- Understanding the nature of the surgical resection.
- Individualising the dosage of pancreatic enzymes, as patients have different degree of exocrine pancreatic insufficiency.
- The presence of weight loss, diarrhoea or steatorrhoea, dyspeptic symptoms with strong meteorism and a stool fat excretion greater than 15 g/day indicates inadequate replacement.
- Co-administration of acid suppression therapy is recommended, especially if severe steatorrhoea continues with adequate dosing of pancreatic enzyme.
- In patients with endocrine insufficiency, glucagon secretion is simultaneously reduced and the dosage of insulin needs to be titrated slowly to avoid hypoglycaemic complications.
- Specific dietary modification to a high carbohydrate, protein and fat moieties meals is recommended.
- Temporary enteral nutritional support is recommended for patients with debilitating gastric stasis, significant abdominal pain or ongoing weight loss despite apparently adequate dietary intake.
- Neither short or long term parenteral nutritional support are recommended.
- Correct the associated upper GI dysmotilities with prokinetic therapy to improve oral intake.
- If steatorrhoea persists despite adequate pancreatic enzyme replacement with appropriate acid suppressive therapy, intestinal bacterial overgrowth should be considered and treated if present.

is essential to ensure that the intake of both macronutrients and micronutrients is adequate (Table 2). Frequent small meals with high carbohydrate and protein (1.0–1.5 g/kg) content are recommended, and up to 30% of calories of the meal can be given as fat in these patients. Aggressive post-operative nutritional support reduces loss of muscle mass, enhances voluntary muscle and respiratory function during the first few weeks after the surgery,[85] and facilitates normalisation of these parameters at six months following surgery.[12,13]

In patients who fail to gain or maintain adequate body weight, and/or experience persistent steatorrhoea, the amount of dietary fat should be minimized. Medium chain triglycerides (MCT) can be trialed because of the lipase independent absorption property of MCT.[83,86] However, MCTs are poorly tolerated by most patients and may induce side effects such as abdominal pain, nausea and diarrhoea.[86] In addition, the amount of fibre in the diet should be low, as fibres absorb enzymes and this may lead to reduce intake of nutrients. In view of recent data on micronutrients and mineral deficiencies,[87,88] it is important to replace these essential vitamins and micronutrients adequately in this group of patients.

In patients who have debilitating gastric stasis, significant abdominal pain or ongoing weight loss despite apparently adequate dietary intake, enteral nutrition is indicated and is best delivered temporarily via a jejunal feeding tube to correct the malnourishment prior to definitive treatment of any underlying cause.[16,84,89] Enteral formulae that are peptide or amino acid based are recommended and may be given overnight. However, enteral infusion of fat and protein activates neurohumoral feedback mechanisms that can potentially impair gastric emptying and prolong post-operative gastroparesis. Cyclic enteral feeding is preferable and is associated with a shorter period of enteral nutrition, a faster return to a normal diet and a shorter hospital stay than those fed continuously.[90] Currently, the role of immuno-nutrition in these patients remains controversial. Whilst earlier studies suggested that immune-enhanced enteral nutrition decreases infectious complications by 13%,[91,92] this has not been reproduced.[93] Data on long-term enteral nutritional therapy is not available.

Routine use of parenteral nutrition is not recommended post-operatively, either short term or long term usage, due to the concerns of septic complications.[16] Overall, administration of post-operative parenteral nutrition in these patients is associated with a greater intestinal permeability, an increased infective complication rate, with no improvement in mortality and higher health care costs.[94–99] Recent studies failed to show any differences in the rate of diarrhoea, abdominal distension or vomiting, whether post-operative parenteral or enteral nutrition was used.[95,96,98]

5. Summary and Conclusions

In summary, major pancreatic resection impairs not only the pancreatic exocrine and endocrine function, but also the function of the gastrointestinal tract. A better understanding of the anatomical and physiological sequelae after pancreatectomy is imperative to ensure optimal nutritional support in these patients. Given the adverse impact of malnutrition on well-being and health related

quality of life, nutritional status should be closely monitored and treated appropriately.

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Management Decisions in Primary and Secondary Liver Cancer

Mark E. Brooke-Smith and Robert T. A. Padbury

Abstract

Management of liver neoplasia is a multidisciplinary endeavour. In the non-cirrhotic liver resectional surgery has a well-defined place in the management of primary liver tumours. In the cirrhotic liver, the approach to treatment of hepatocellular carcinoma depends on the severity of underlying liver disease and the size of the tumour. The best long term results are achieved with transplantation regardless of severity of liver failure, but the number and size of lesions is important. Liver resection can be used in any size lesion, but the extent of resection possible is dependent on the severity of liver disease. As with ablative methods, the tumour volume is an important prognostic factor. Colorectal cancer is the most common secondary liver cancer with a chance of cure following surgical resection. Surgical resection is becoming more aggressive, as more sophisticated techniques and increasing chemotherapeutic options allow removal of more advanced tumours. The role and timing of surgery, local ablation, chemotherapy and adjuvant chemotherapy are explored in the setting of both synchronous and metachronous disease. Surgical resection and the chance of cure is possible