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Review article

Invited review: Pancreatic exocrine insufficiency following pancreatic resection

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ABSTRACT

Background/objectives: Untreated pancreatic exocrine dysfunction is associated with poor quality of life and reduced survival, but is difficult to diagnose following pancreatic resection. Many factors including the extent of the surgery, the health of the residual pancreas and the type of reconstruction must be considered. Patients remain undertreated, and consequently there is much debate to whether or not pancreatic enzyme replacement therapy should be routinely prescribed following pancreatic resection.
Methods: A review of the literature was undertaken to establish the incidence of PEI and factors identifying treatment.
Results: Forty two to forty five percent of patients undergoing pancreatico-duodenectomy (PD) experience pancreatic exocrine insufficiency pre-operatively, whilst the post-operative incidence is 56–98% in PD, and 12–80% following distal and central pancreatectomy.
Conclusions: Routine use of pancreatic enzyme replacement should be considered at a starting dose of 50 to 75,000 units lipase with meals and 25,000 to 50,000 units with snacks in this patient group. Patients who have had a central or distal pancreatectomy should be individually assessed for pancreatic exocrine insufficiency in the post operative period, with those undergoing extensive resection most likely to experience insufficiency.
Patients who fail to respond to pancreatic enzyme replacement therapy should be referred to a specialist dietitian, be advised on dose adjustment, and undergo investigation to exclude other gastro-intestinal pathology, including small bowel bacterial overgrowth and bile acid malabsorption.

Introduction

Pancreatic exocrine insufficiency (PEI) is multifactorial following pancreatic resection. The degree of insufficiency is influenced by the quantity and quality of the pancreatic remnant [1], the resection of the stomach and duodenum with resultant changes in gut pH [2] and delayed gastric emptying [2]. Other factors include the formation of a pancreatico-jejunostomy and hepatico-jejunostomy on a roux loop, causing potential asynchrony in the delivery of pancreatic secretions and bile [3,4], abnormal cholecystokinin (CCK) secretion [5], obstruction of the pancreatic duct anastomosis [6] and the use of exocrine inhibitory medications such as Octreotide [7]. Consequently the exact type of resection and reconstruction must be considered when assessing patients for PEI.

In addition, pancreatic resection predisposes patients to other gastrointestinal conditions with symptoms that may mimic those of PEI: this in combination with the limitations of current methods of assessing pancreatic function, results in the potential for misdiagnosis and therefore sub-optimal symptom management.

Under-treatment is associated with poor quality of life [8], micronutrient deficiencies [9–11] and in some cases reduced survival [12]. Many units do not have adequate access to specialist dietitians [13], and this is associated with under treatment, and inappropriate dietary restrictions [14].

Assessment of pancreatic insufficiency

There are many pancreatic function tests available, however the accuracy of these tests following pancreatic resection is poor, and have been discussed in detail by other authors [15–18].

Function tests can be divided into two categories, those that assess the ability of the pancreas to secrete digestive enzymes, and

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those that assess the efficacy of this by quantifying the nutrients that are not absorbed. This is particularly relevant in assessing malabsorption following pancreatico-duodenectomy (PD) as extra-pancreatic factors are present.

Assessment of the ability of the pancreas to produce pancreatic enzymes maybe influenced by the reduction in, or removal of, pancreatic stimulatory mechanisms. It could also be hypothesized that the asynchrony of enzyme delivery might result in malabsorption despite an apparently normal secretion of enzymes. The concept of asynchrony of delivery of pancreatic and biliary secretions was first described in the 1950's as a consequence of the Polya gastrectomy with pancreatic enzymes reaching the small bowel sometime after partially digested food particles [19], animal studies confirmed that the degree of steatorrhoea was related to the length of the afferent limb [20]. Thus the quantity and quality of pancreatic tissue does not necessarily reflect absorption following PD. This may in part explain the poor specificity of faecal elastase (FE) following pancreatic resection. Indeed, studies have found significant differences between coefficient of fat absorption (CFA) and FE in patients following PD [8,21].

Coefficient of fat absorption (CFA) and ^{13}C- mixed triglyceride (MTG) breath tests assess fat malabsorption, but cannot quantify the influence of extra-pancreatic factors, nor can they quantify nitrogen and carbohydrate malabsorption. Nitrogen malabsorption occurs in PEI [22], and consequently will also contribute to malnutrition. Whilst compensatory mechanisms exist for carbohydrate malabsorption, by way of colonic fermentation of malabsorbed substrate to short chain fatty acids which the colon can absorb [23], this mechanism would not be present in those with colonic resection, which can be carried out concurrently [24], or as the result of a co-morbidity.

Many studies use the onset of steatorrhoea to diagnose PEI, and consequently show a much lower incidence than those using less subjective methods [25,26]. It is widely accepted that the onset of steatorrhoea is a late symptom of PEI, and many patients can exhibit significant malabsorption with an absence of abdominal symptoms [22,27]. Furthermore steatorrhoea will only be apparent in patients consuming adequate dietary fat, and many patients restrict their fat intake in an attempt to help reduce symptoms, or in response to inappropriate advice promoting fat restriction [14]. The use of opiates, iron supplements and anti-diarrhoeals may also mask abdominal symptoms.

Consequently, symptom assessment alone is not sufficient to exclude PEI, and a combination of abdominal symptoms, nutritional status and pancreatic function tests must be used to assess pancreatic exocrine function. Specialist dietitians can assess anthropometric and dietary factors in combination with clinical symptoms to assist in the evaluation of exocrine insufficiency. Hence a multidisciplinary approach is likely to provide the most comprehensive assessment of PEI.

Incidence of PEI prior to resection

In patients with operable pancreatic cancer there is often a narrow time frame for assessment in the pre-operative period, with insufficient time to carry out most pancreatic function tests.

There is limited data analysing the incidence of PEI prior to pancreatic surgery, with 16% of pre-operative patient's found to have FE < 200 μg/g in a mixed cohort of patients due to undergo distal pancreatectomy [28]. The incidence of PEI was higher in those with pancreatic adenocarcinoma and chronic pancreatitis, compared to those with other benign and pre-malignant disease [28].

There is a significant incidence of PEI prior to pancreatico-duodenectomy documented at 38–45% [3,29,30], with some variation according to underlying disease [30]. The presence of disease in the head of the pancreas, and the presence of dilated pancreatic ducts [31] on imaging may suggest PEI, and this will be apparent on pre-operative computerised tomography (CT) or endoscopic ultrasound (EUS). The presence of pre-operative jaundice may mask symptoms of PEI, and is a significant contributory factor toward pre-operative malnutrition.

Untreated PEI prior to surgery may cause malnutrition, which in turn increases pancreatic fistula risk [32], morbidity and mortality [33].

Incidence of PEI following distal or central pancreatectomy

The incidence of PEI following distal pancreatectomy is documented at 19–80% [25,26,28,29], and 11.9% following central pancreatectomy. The majority of these data comes from a large systematic review, however the degree of resection was not specified and the method of assessment was mixed across the included studies including FE, faecal chymotrypsin, p-aminobenzoic acid (PABA), and less objective markers such as onset of symptoms and prescription of PERT [26].

One study using FE included subgroup analysis on those with resection limited to the left of the portal vein compared to that which extended beyond the portal vein. Longitudinal follow up of 70 patients with normal pre-operative pancreatic function demonstrated a return to normal exocrine function by 24 months post operatively [28]. Therefore it is anticipated that the likelihood of PEI would increase with more extensive resection, and in those with poor quality residual pancreatic tissue, but improvements may occur with time.

Incidence of PEI following pancreatico-duodenectomy

There is much more data surrounding the incidence of PEI following pancreatico-duodenectomy, with a variation in incidence between 56 and 98% in the post operative period [3,8,25,29,30]. Some studies suggest an improvement in pancreatic function over time, however the apparent increase in FE, occurs alongside a reduction in sample size in one study [8] and could be as a result of those with more extensive disease, and therefore potentially more severe pancreatic dysfunction, succumbing to their disease earlier than others. Data using a consistent patient cohort shows a reduction in FE over time, suggesting deteriorating pancreatic function during the post operative period [3] perhaps as a result of atrophy of the residual pancreas. Links with dilated main pancreatic ducts have been assessed, and lower FE was observed in these patients [30].

As with other types of pancreatic resection the incidence of PEI is recorded as lower in those studies using subjective methods of assessment [25], and the extent of pancreatic parenchyma resected is not specified in any of the studies identified.

Benefits of PERT

Symptoms of PEI have a significant impact on quality of life after pancreatic resection [2]. Patients have a prolonged recovery time, and malnutrition and dehydration are common causes of hospital readmissions [34]. Correct identification and management of PEI following pancreatic resection should promote better recovery from surgery, and improved performance status, which is particularly relevant in those due to undergo adjuvant chemotherapy. In patients with chronic pancreatitis, long term survival has been linked to the provision of PERT following pancreatic resection [12].

Management of PEI

PEI should be treated with PERT at an initial starting dose of 50–75,000 units lipase with each meal, and 20–50,000 units with

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