

Carol Rees Parrish, M.S., R.D., Series Editor

# Pancreatic Resection: Nutritional Implications and Long Term Follow Up



Mary E. Phillips

Pancreatic resection is carried out for benign and malignant diseases of the pancreas, duodenum and distal common bile duct. These operations contribute significantly to both macro-nutrient and micro-nutrient malabsorption. Pancreatic enzyme supplements are underused and should be administered routinely to all patients who have had a pancreatic head resection. Patients suffer both short term and long term deficiencies and are prone to other gastro-intestinal conditions with similar symptoms. Thus, identifying the cause of their symptoms is challenging and requires careful follow up in a multi-professional setting. Vitamin and mineral deficiencies are common and weight loss, abdominal symptoms and diabetes have a significant impact on quality of life and survival. Patients should have access to specialist dietetic support and endocrine function should be assessed routinely following all pancreatic resection. Assessment of vitamin and mineral status should be carried out in patients who have undergone curative resection or who have benign disease.

## INTRODUCTION

Types of pancreatic resections vary considerably; each having a different impact on the digestive system and therefore on the patient's nutritional status. Poor nutritional status is associated with poor quality of life,<sup>1</sup> and reduced survival.<sup>2</sup> Pancreatic exocrine insufficiency (PEI) is common and undertreated<sup>3</sup> and there is a lack of funding for dietetic support for this patient group.<sup>4</sup>

Survival with malignant pancreatic disease remains

poor, but some pancreatic resections are carried out for benign disease, and long term implications must be considered in all patients with benign disease, and those who have had surgery with curative intent.

Fat, carbohydrate and protein malabsorption all occur in PEI;<sup>5-7</sup> yet historical treatment has focused on fat malabsorption. This results in many patients following unnecessary dietary fat restrictions and not receiving appropriate enzyme supplementation or dietary advice. Pancreatic cancer and chronic pancreatitis are both progressive diseases, and consequently the severity of both exocrine and endocrine dysfunction can worsen with time.

Pancreatico-duodenectomy (PD), can be pylorus

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**Table 1. Aetiology of PEI and Subsequent Malabsorption Following Pancreatic Resection<sup>10</sup>**

- ◆ Asynchrony of delivery of enzymes and bile<sup>35,36</sup>
- ◆ Calibre of the pancreatic remnant
- ◆ Abnormal cholecystokinin (CCK) secretion<sup>37</sup>
- ◆ Pancreatic inhibitory medication such as Sandostatin / Octreotide
- ◆ Obstruction of the pancreatic anastomosis<sup>38</sup>
- ◆ Changes in gut pH due to concurrent resection of the duodenum and distal stomach<sup>39</sup>
- ◆ Gastric and duodenal resection cause secondary pancreatic exocrine insufficiency through lack of pancreatic stimulation<sup>40</sup>

preserving in nature, or include a distal gastrectomy. There is a high incidence of PEI following this resection, documented in as many as 98% of patients.<sup>1,8-10</sup> Furthermore, the presence of a blind loop of bowel predisposes the patient to small intestinal bacterial overgrowth (SIBO). The asynchrony of the delivery of bile, precipitation of bile salts and resection of the gallbladder results in a higher risk of bile acid malabsorption (BAM). A lower incidence of PEI (12-80%)<sup>11-13</sup> is reported in central pancreatectomy and distal pancreatectomy, but there is massive variation between studies.<sup>10</sup>

Procedures carried out in patients with chronic pancreatitis to relieve ductal obstruction and remove calcification within the gland, such as Frey, Beger, Peustow and longitudinal pancreatico-jejunostomy (LPJ) procedures are associated with damage due to obstruction of the pancreatic duct prior to surgery. Consequently there is a high incidence of PEI and type 3c diabetes, and this has an impact on survival.<sup>2, 3, 14</sup>

## Malabsorption

Pancreatic exocrine insufficiency is common after all pancreatic resections.<sup>10</sup> and often undertreated. Diagnostic tests have low sensitivity in this setting<sup>1</sup> and markers of nutritional status have links with PEI, but are not diagnostic in their own right.<sup>15</sup>

The aetiology of PEI and malabsorption is multifactorial with the type of surgery, reconstruction, and concurrent use of inhibitory medications, all contributing to malabsorption (Table 1). Thus, the quantity of residual pancreas may not predict the

severity of PEI.

Clinical symptoms of malabsorption are listed in Table 2. Severe malabsorption can occur in the absence of abdominal symptoms.<sup>5</sup> Due to the high cost of pancreatic enzymes in the United States, patients need to demonstrate a clinical need. Assessment takes place in the form of coefficient of fat absorption, the presence of weight loss in the setting of adequate oral intake or non-infective diarrhoea.

Other tests available include the faecal elastase (FE1) or C13 mixed triglyceride breath tests. The prescription of pancreatic enzyme replacement therapy (PERT) is occasionally challenged due to the lack of a reliable measure of exocrine function. FE1 is poorly correlated with fat malabsorption after PD,<sup>1</sup> but coefficient of fat malabsorption is an unpleasant test requiring a 48-72 hour stool collection whilst consuming a 100g fat per day diet. Some clinicians empirically will start PERT and monitor clinical response; others consider this test controversial for diagnostic purposes.<sup>17</sup> C<sup>13</sup> mixed triglyceride breath tests are not routinely available in the United States or the United Kingdom.

Studies that use symptoms of steatorrhoea to determine PEI report a much lower incidence compared to those using formal diagnostic tests.<sup>8,12</sup> It is widely accepted that steatorrhoea is a late symptom of malabsorption.<sup>18</sup> This, along with the influence of low fat diets, constipating medication, and the poor specificity of diagnostic tests, means that sometimes the only option to confirm the diagnosis may be a trial on PERT.

These issues and the lack of ability to definitively

Table 2. Symptoms of Malabsorption

<b>Abdominal Symptoms</b>	<ul style="list-style-type: none"> <li>◆ Bloating, distension and flatulence</li> <li>◆ Steatorrhoea (pale, oily, floating stool)</li> <li>◆ Diarrhoea (loose, large volume stool)</li> <li>◆ Faecal urgency</li> <li>◆ Reflux</li> <li>◆ Cramping abdominal pain and abdominal gurgling</li> </ul>
<b>Endocrine Function</b>	<ul style="list-style-type: none"> <li>◆ Hypoglycaemia</li> <li>◆ Reduced insulin requirements in those already on insulin therapy</li> </ul>
<b>Systemic / Biochemical</b>	<ul style="list-style-type: none"> <li>◆ Vitamin A deficiency night blindness</li> <li>◆ Vitamin D deficiency</li> <li>◆ Low serum selenium, zinc, magnesium, calcium, phosphate, potassium, Vitamin E</li> <li>◆ Elevated parathyroid hormone (secondary to vitamin D deficiency)</li> <li>◆ Osteopenia / Osteoporosis</li> </ul>
<b>Nutritional</b>	<ul style="list-style-type: none"> <li>◆ Unexplained weight loss</li> <li>◆ Sarcopenia</li> <li>◆ Weakness / fatigue</li> <li>◆ Food avoidance (due to concern over link with bowel symptoms)</li> </ul>

determine the need for PERT, can make it difficult to obtain the funding for the use of these medications.

### Pancreatic Enzyme Replacement Therapy (PERT)

Pancreatic enzyme replacement therapy takes many forms. Enteric coated mini-microspheres are most commonly used, but tablets, granules and powdered forms are available in some countries.

PERT should be prescribed with all meals and snacks. The dose varies and should be adjusted to each individual patient. The PERT dose also needs to be higher with higher energy meals, and should be prescribed alongside nutritional supplements and sip feeds (Table 4).

Patients requiring enteral feeding should be prescribed a semi-elemental peptide, medium chain triglyceride based feed, and PERT may need to be administered alongside enteral feeds. However, depending on the tube size, this may result in clogging

if the patient does not receive clear information.<sup>19</sup> Alternatively, a strict elemental formula can be used without the need for pancreatic enzymes.

PERT should be swallowed with a cold drink and stored out of extreme heat. Storage temperatures vary between products, but range from 15-25 degrees centigrade. Patients should be taught how to adjust their own enzyme dose, specifically to increase their dose with larger meals and to spread their capsules out throughout their meals. This is especially important for long duration meals, such as meals with several courses. Patients should also be advised on managing potential side effects, which include nausea and constipation.

Gastric acid suppression may be of benefit to prevent acid denaturing of the enzymes,<sup>20</sup> which require a pH of > 5.5 for activation, but are irreversibly denatured in very acidic environments. Bicarbonate secretion from the pancreas is reduced in pancreatic failure, which may result in a change in pH within the gut. A more acidic

*(continued on page 23)*

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environment in the proximal small bowel can result in delayed enzyme release from the enteric-coated PERT and destabilize bile salts altering micelle formation.

Each PERT product differs in efficacy at different acidity levels and have different activation times, varying from 30 to 120 minutes at pH's from 4.5 to 5.6.<sup>22,23</sup> So it may be assumed that some products may work better in some patients than others. There are no trials directly comparing products in different clinical situations such as delayed gastric emptying or dumping syndrome, but theoretically there could be a benefit to trialling different products in different clinical situations. Consequently, if a patient does not see significant benefit with the first brand of enzyme prescribed, a trial on an alternative product is recommended.

### Nutritional therapy

Historically malabsorption has been treated with low fat diets. This will minimize symptoms of steatorrhoea, but will not correct malabsorption of nutrients, merely mask it. Experienced clinicians recommend that low fat diets are not used in the management of PEI due to the negative impact on nutritional status.<sup>24</sup>

Patients who are nutritionally compromised should be encouraged to consume high energy meals with food fortification advice including the use of nutritional

supplements and sip feeds as deemed necessary by a specialist dietitian.

### Constipation

Constipation can occur alongside PERT therapy, and often complicates management, as PERT doses are often reduced in an effort to control constipation. The concurrent use of laxatives and other methods of correcting constipation are more appropriate than inducing malabsorption in an effort to control bowel function.

### Vitamin and Minerals

Data on vitamin and mineral status is limited, however deficiencies in zinc, selenium, iron and vitamins A, D, E, and K in both resection of pancreatic cancer and in chronic pancreatitis are reported.<sup>25,26</sup> The duodenum plays a key role in absorption of vitamins and minerals, and is removed in PD resections. This, in combination with malabsorption and increased metabolic demand, results in increased risk of micronutrient deficiencies. Routine supplementation of fat soluble vitamin and trace elements are recommended following resection.<sup>25</sup>

### Differential Diagnosis of Failure to Thrive

Reoccurrence of tumor and benign strictures can cause narrowing of the gastro-jejunostomy resulting in

**Table 3. Considerations When Using Fecal Elastase-1 (FE-1) Stool Test**

- ◆ Protease enzymes secreted by pancreatic cells concentrated in stool
- ◆ Stable during intestinal transit and correlates with levels of other pancreatic enzymes
- ◆ Simple, non-invasive and inexpensive test
- ◆ Does not require special diet or specific fat intake
  - The monoclonal test is not altered by pancreatic enzyme supplementation
  - Polyclonal FE-1 tests require patients to discontinue their PERT
- ◆ FE-1 < 200 µg/g consistent with pancreatic exocrine insufficiency
- ◆ **Key limitations** of using FE-1:
  - Difficulties in diagnosing mild to moderate pancreatic insufficiency
  - Sensitivity is poor following pancreatic resection
  - Differentiating pancreatic from non-pancreatic malabsorption
    - Watery stool /high volume diarrhea dilutes FE-1 giving an artificially low result

**Table 4. A Stepwise Approach to Managing Pancreatic Enzyme Replacement Therapy**

<b>Step 1</b>	<ul style="list-style-type: none"> <li>◆ Commence pancreatic enzyme replacement therapy at a dose of:                             <ul style="list-style-type: none"> <li>○ 50,000 – 75,000 units lipase with meals,</li> <li>○ 25,000 – 50,000 units lipase with snacks and nutritional supplements/sip feeds.</li> <li>○ Patients should distribute capsules throughout their meals, and swallow with a cold drink.</li> <li>○ Check glucose levels within 2 weeks of commencing enzymes</li> </ul> </li> </ul>
<b>Step 2</b>	<ul style="list-style-type: none"> <li>◆ Add a proton pump inhibitor or H2 antagonist</li> <li>◆ Refer to a specialist pancreatic dietitian</li> </ul>
<b>Step 3</b>	<ul style="list-style-type: none"> <li>◆ Double the dose of enzymes with meals, snacks and supplements</li> <li>◆ 100-150,000 units lipase with meals</li> <li>◆ 50-100,000 units lipase with snacks and nutritional supplements / sip feeds</li> </ul>
<b>Step 4</b>	<ul style="list-style-type: none"> <li>◆ Increase dose further</li> <li>◆ 150-200,000 units lipase with meals</li> <li>◆ 100-125,000 units lipase with snacks and nutritional supplements / sip feeds</li> <li>◆ Consider adding anti-diarrhoeal medication to reduce transit speed</li> </ul>
<b>Step 5</b>	<ul style="list-style-type: none"> <li>◆ Change product to an alternative preparation</li> </ul>
<b>Step 6</b>	<ul style="list-style-type: none"> <li>◆ Investigate to exclude other conditions such as: infectious diarrhoea; bile acid malabsorption; small intestinal bacterial overgrowth; coeliac disease; lactase deficiency; disease reoccurrence; delayed gastric emptying</li> </ul>
<b>Step 7</b>	<ul style="list-style-type: none"> <li>◆ Ensure nutritional intake is optimized, using supplements, sip feeds and if necessary, peptide, medium chain triglyceride based enteral nutrition, and if necessary, an elemental formula</li> </ul>
<b>Step 8</b>	<ul style="list-style-type: none"> <li>◆ If malabsorption cannot be controlled and nutritional status is poor, parenteral nutrition should be considered</li> </ul>

delayed gastric emptying or gastric outflow obstruction. Tumors can infiltrate the mesentery, including the portal vein. This or the development of liver metastases can cause ascites. All of these issues reduce oral intake and worsen gut function.

Bile acid malabsorption (BAM) and SIBO are common in chronic pancreatitis, pancreatic cancer and following pancreatoduodenectomy<sup>27-29</sup> and the symptoms of these are difficult to distinguish from

PEI. Patients who do not respond to PERT should be investigated for BAM and SIBO.

### Diabetes

Type 3c or pancreaticogenic diabetes occurs in patients with pancreatic disease.<sup>14</sup> This type of diabetes is more brittle than type 1 or type 2 diabetes; patients often require insulin therapy and are prone to significant episodes of hypoglycaemia due to the reduction in



glucagon secretion.<sup>30</sup> There are specific hormonal differences between type 1, 2 and 3c diabetes, including low pancreatic polypeptide, insulin and glucagon levels in type 3c diabetes.<sup>31</sup>

When PERT is commenced in a patient with pre-existing diabetes, blood glucose levels should rise and oral hypoglycaemic agents or insulin therapy may need to be adjusted accordingly. Similarly, commencing PERT may unmask diabetes in a patient not yet diagnosed.<sup>32</sup> Consequently, glucose levels should be checked before and after commencing PERT, as well as periodic glycosylated hemoglobin levels.

### Annual Screening

Nutritional status should be assessed regularly, and PERT doses adjusted as required. All patients with pancreatic disease should be regularly screened for diabetes, regardless of underlying pathology. Vitamin and mineral screening and bone density scans should take place in all patients with benign pancreatic disease<sup>26,33,34</sup> and those who have had surgery with curative intent.

### CONCLUSION

PEI is common before and after pancreatic resection, but remains difficult to diagnose and undertreated. Patients should be referred to a specialist dietitian and undergo regular screening for diabetes in addition to vitamin and mineral deficiencies. Adequate doses of PERT are an essential part of patient management, and doses should be reviewed regularly as they may need to be increased over time. Failure to respond to PERT should result in investigations for other gastrointestinal pathology (Table 4). ■

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