

Post-pancreatectomy management

This week's Update looks at the management of pancreatic enzyme insufficiency post-pancreatectomy.

Introduction

PANCREATIC cancer is the fourth most common cause of cancer death in our society, with an overall survival of less than 5% at five years.^{1,2,3} Pancreatic cancer most commonly presents at an advanced stage, and as a consequence surgical resection is only possible in about 20% of patients. Surgery offers the only possibility of cure or long-term survival, which, with chemotherapy, is 20%-25% at five years.

There are now modern approaches to pancreatic surgery, a better understanding, and more appropriate treatment of precursor lesions of pancreatic cancer such as mucinous cystic neoplasms. These factors are improving overall outcomes for pancreatic cancer and increasing the number

of patients that require nutritional monitoring and support in the community.

The most common operative techniques used for carcinoma in the pancreatic head are the classic Whipple's pancreaticoduodenectomy² (see Figure 1) and the pylorus-preserving pancreaticoduodenectomy procedure.^{4,5} Left-sided resection (e.g. distal pancreatectomy) is performed for tumours of the body and tail of the pancreas. Although operative mortality rates are relatively low (about 3%) in specialised units,^{1,6,7} significant morbidity still occurs in about 30% of patients who undergo pancreaticoduodenectomy.^{8,9,10}

The pancreas plays a vital role in food digestion and glucose homeostasis; patients who have had pancreatic

resections are at risk of pancreatic (exocrine and endocrine) insufficiency and malabsorption.¹¹

Symptoms of diarrhoea, flatulence, tenesmus and fatty stools may substantially affect quality of life.¹² Gastrointestinal dysmotility leading to delayed gastric emptying and enterogastric reflux can also be a significant long-term clinical problem in a small proportion of patients.^{13,14}

Pancreatic insufficiency and gastrointestinal dysmotility after major pancreatic resection can adversely affect oral intake and gastrointestinal absorptive function, and can lead to malnutrition with associated long-term sequelae. GPs can play an important role in the prevention and treatment of these conditions.

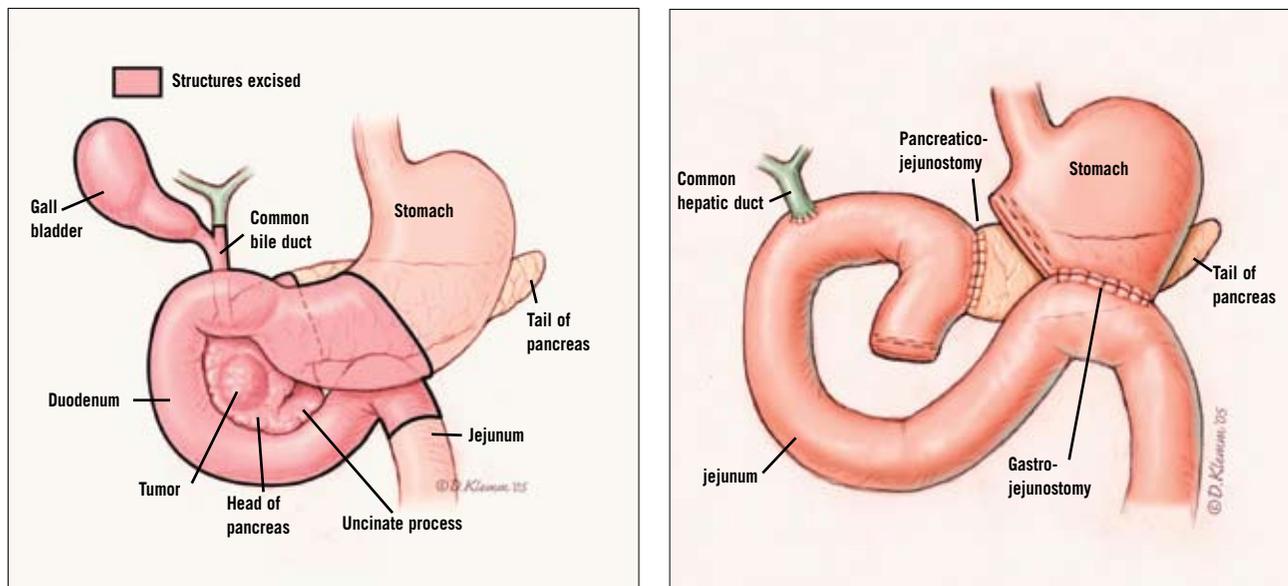


Figure 1. The Whipple's procedure (A). Before the procedure (B). After the procedure; note the anastomosis of the hepatic duct and the remaining pancreas and stomach to the jejunum.

Pancreatic insufficiency

The impact of pancreatectomy on digestive function is in general terms dependent on the extent of the resection and the functional state of the residual pancreas.

Compared to patients with a relatively

normal residual pancreas, those with chronic pancreatic disease (e.g. chronic pancreatitis) before resection are more likely to develop pancreatic insufficiency, and thus early and more aggressive treatment may be required.¹¹

As with exocrine insufficiency, diabetes is a well-recognised sequelae in 20%-50% of patients who undergo major pancreatic resections for malignancy,^{11,15} the management of which is beyond the scope of this article.

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Declaration of interest:
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Pancreatic enzyme replacement

Most patients who have major pancreatic resections have a degree of exocrine insufficiency. Pancreatic enzyme replacement may be an important part of the long-term management of some of these patients. The key clinical issue is identifying patients that require enzyme replacement. Symptoms of pancreatic insufficiency may not be obvious, and sequelae of malnutrition such as osteoporosis due to deficiency of the fat-soluble vitamin, vitamin D, may not become apparent for many years.

In patients where pancreatic exocrine insufficiency is identified or suspected, adequate enzyme-replacement therapy reduces malnutrition, normalises biochemical indices of malnutrition, assists a patient to recover much of their original body weight, and improves their overall quality of life.^{16,17} There is limited information concerning the routine use of pancreatic enzyme-replacement therapy, nor is there data which defines a threshold for the requirement of replacement therapy.

Furthermore, objective measures of pancreatic insufficiency have not proven to be accurate or clinically useful at this point in time.

Patients can have different degrees of exocrine pancreatic insufficiency. The dosage of pancreatic enzymes should therefore be titrated to the individual patient's symptoms.^{16,18,19} All patients should be monitored and screened for symptoms and signs of inadequate replacement (see Figure 2 below).

Figure 2: Signs and symptoms of inadequate pancreatic enzyme replacement.

Weight loss
Diarrhoea
Steatorrhoea
Dyspeptic symptoms with bloating
>15g/day stool fat excretion

Adapted from Braga M, *et al.* Pancreatic enzyme replacement therapy in post-pancreatectomy patients. *Int J Pancreatol* 1989;5(Suppl):37-44.

Figure 3. An overview of pancreatic enzyme-replacement preparations in Australia.

	Creon	Cotazym-S Forte	Panzytrat 25000
Enzyme content ^{30,31,32}	Creon 5000 5000 BP U lipase, 300 Ph.Eur U protease, 4000 BP U amylase Creon 10000 10,000 BP U lipase, 600 Ph.Eur U protease, 8000 BP U amylase Creon Forte 25,000 BP U lipase, 1000 Ph.Eur U protease, 18,000 BP U amylase	10,000 BP U lipase; 750 BP U protease, 7700 BP U amylase	25,000 BP U lipase, 1250 Ph.Eur U protease, 22,500 BP U amylase
Particle size The optimum particle size to leave the stomach with food is 1.4+0.3 mm; those with a diameter of 1.8 mm show a delay in onset of duodenal activity. ³³	Most mini-microspheres in Creon are 1-1.2 mm. ³³	28% of particles are 1.2-1.7 mm; 63% are 1.7-2 mm diameter. ³⁴	2 mm in diameter, with a thickness 1.9-2.1 mm. ³²
Dissolution characteristics Duodenal pH is normally 6-7; after a meal it drops to 5-5.5. The pH of the duodenum in patients with pancreatic disease may be lower than normal due to bicarbonate deficiency. ³⁵	Steep enzyme release of more than 90% at pH 5.5 or above after 45 minutes. ³³ At pH 6, 82% of lipase released after 15 minutes, more than 90% at 30 minutes.	In a fluid with a pH of 6, simulating the condition in the duodenum, Cotazym-S Forte releases almost all of its enzymatic activities within 30 minutes. ³¹	At pH of 6, at least 50% of the labelled lipase activity being released within 30 minutes. ³⁶

Despite apparently adequate dosage regimens, symptoms may still persist due to inadequate delivery of active enzymes to the small intestine. Of all pancreatic enzymes, lipase is the most sensitive to acidic and proteolytic denaturation, and is therefore the most affected.^{16,20} As the digestion of fat by lipase is important and cannot be easily compensated by non-pancreatic mechanisms, the key to successful pancreatic enzyme replacement is to achieve sufficient lipase activity in the intestine.²⁰

Contrary to general belief, the relationship between the dose of pancreatic enzymes required and symptoms of maldigestion is not linear. In general, the required amount of lipase to be delivered to the small intestine with each meal is 25,000 to 50,000 units.^{16,20,21}

As unprotected enzyme is rapidly

destroyed by gastric acid, the use of acid-suppression therapy may be a useful adjunct therapy and is recommended, especially if severe steatorrhoea continues with adequate dosing of pancreatic enzyme.^{16,20,22}

pH-sensitive pancrelipase microsphere preparations have become increasingly popular and have been recommended as the treatment of choice.^{18,19,20,23} However, this preparation may be ineffective in patients who underwent pylorus-preserving pancreaticoduodenectomy because the microspheres are retained in the stomach.²⁴ In these patients, conventional powdered pancreatin enzyme preparations may improve the efficacy of treatment.²⁴

It should be noted that this is not available in Australia.

If symptoms and signs of maldigestion

persist despite these therapeutic measures, a trial of pH-sensitive enteric-coated microspheres, restricting the amount of dietary fat and/or replacing fat with medium-chain triglycerides, should be considered.^{16,25,26,27}

Factors influencing the effects of pancreatic enzyme replacements include:²⁸

- Variations in enzyme content
- Size of the enzyme particles and their rate of exit from the stomach
- Dissolution characteristics of the preparation

An overview of pancreatic enzyme replacement preparations available in Australia is shown in Figure 3.

Timing related to meals can also influence the effectiveness of pancreatic enzymes. Dosing during or towards the end of the meal may optimise mixing and enhance the effectiveness of enzymes.²⁹

Dietary and nutritional management

Apart from pancreatic exocrine insufficiency, poor oral intake from factors such as chronic abdominal discomfort, gastrointestinal dysmotility and persistent steatorrhoea can also lead to malnutrition in these patients. Specific modification to the carbohydrate, protein and fat moieties of the diet, therefore, is an essential adjunct therapy to adequate replacement of pancreatic enzymes.^{37,38} Frequent small meals with high carbohydrate and protein (1-1.5 g/kg) content are recommended to achieve an adequate intake. Up to 30% of calories of the meal can be given as fat. Management of the patient may include

the advice of a dietitian.

In patients who fail to gain or maintain adequate body weight, and/or have persistent steatorrhoea, the amount of dietary fat should be minimised and medium-chain triglycerides (MCT) can be trialled because of the lipase-independent absorption property of MCT.^{37,39} However, MCTs are poorly tolerated by most patients and may induce side-effects such as abdominal pain, nausea and diarrhoea.³⁹ In addition, a low-fibre diet can be implemented as dietary fibre absorbs enzymes, further decreasing active enzyme delivery.



Summary

In summary, major pancreatic resections not only impair pancreatic function, but also the function of the entire upper gastrointestinal tract. This may adversely affect the nutritional status and the overall

quality of life of these patients.

Current literature suggests that with advances in surgical techniques and post-operative care (including optimal pancreatic enzyme replacement), most of these

patients will have good outcomes with minimal gastrointestinal symptoms, will be able to maintain adequate weight and achieve a high quality of life.

However, it is important that pancreatic

enzyme insufficiency after pancreatectomy is suspected, and a patient's nutritional status (including serum levels of vitamins and minerals) is closely monitored so that appropriate treatment can be provided.

Practical application to general practice

Case study

A 40-YEAR-old man presented with fluctuating symptoms of abdominal cramps and diarrhoea for nine months. Eight years previously he underwent a Whipple pancreaticoduodenectomy for a benign insulinoma. He denied any symptoms of significance previous to the past nine months.

He was intensively investigated for these symptoms with ultrasound, CT scanning, gastroscopy, colonoscopy and capsule endoscopy, all of which did not reveal a cause. He did not describe any classic symptoms of fat malabsorption such as floating and difficult-to-flush

stools. All routine blood analyses were normal.

He was started on enzyme-replacement therapy at a dose of two pancrelipase (Creon Forte) capsules or 50,000 IU lipase with meals, and had minimal change in his symptoms over a four-week period. This dosage was increased to three capsules or 75,000 IU lipase with meals, with substantial improvement in his cramping and diarrhoea, but intermittent symptoms persisted. Addition of one capsule (25,000 IU lipase) replacement with snacks led to complete resolution of this

patient's symptoms.

This case illustrates that symptoms of pancreatic exocrine insufficiency may manifest a significant period of time after pancreatic resection; that symptoms of fat malabsorption are not always consistent with classical descriptions; and that a dosage of 50,000 IU had no effect, whereas a 50% increase had a dramatic response. Complete resolution of symptoms occurred when 25,000 IU lipase was given in conjunction with snacks. This, therefore, reinforces the importance of individually titrating doses to obtain maximal symptom control.

Diagnosing pancreatic enzyme insufficiency can be difficult, but should be suspected after pancreatectomy. As no accurate objective measures of insufficiency are regularly used, a trial of replacement therapy is appropriate.

The dose of enzymes should be titrated to the symptoms of an individual patient. A starting dose of 25,000 to 50,000 IU per meal, with 25,000 IU with snacks, is generally recommended.²¹ The dose should be increased if symptoms continue; doses of up to 80,000 IU of lipase may be required.⁴⁰

Dietary adjustment, checking if patients adhere to medications, and further investigations for other possible diagnoses (such as bacterial overgrowth, giardiasis or coeliac disease) may be required if symptoms are not adequately controlled.²⁹

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Pancreatic cancer

WHAT IS THE PANCREAS?

THE pancreas is an important gland located in the abdomen, slightly behind your stomach and in front of your spine. The pancreas is about 25 cm long and is shaped like a tadpole. It produces digestive enzymes, which are secreted into the duodenum (the first part of your small intestine) to help break down the food you have eaten. It also produces the hormones insulin and glucagon, which balance the sugar levels in your blood and body cells.

WHAT IS PANCREATIC CANCER?

'Pancreatic cancer' is a broad term used to describe as many as 20 different types of tumour that can occur in the pancreas. Each type requires a different treatment and has a different prognosis.

The pancreas is part of both the endocrine and exocrine systems of the body. The endocrine system includes the glands that secrete hormones directly into the bloodstream. The exocrine system consists of glands that secrete outwards through ducts onto the surface of the gut or the skin.

Pancreatic cancer is often categorised as being either non-endocrine (that is, it does not affect the hormone-producing cells of the pancreas) or endocrine (where it can have dramatic effects on the amounts of hormones produced). Non-endocrine tumours make up the majority of pancreatic cancers (more than 90 per cent). Endocrine tumours are much less common.

WHAT ARE THE SYMPTOMS OF PANCREATIC CANCER?

Unfortunately, the symptoms of pancreatic cancer do not usually occur until the disease is well advanced, making early diagnosis difficult. Because the pancreas is located deep within the abdomen, it is difficult for your doctor to feel any abnormalities in the pancreas itself. Also, the symptoms often do not appear until the tumour has grown big enough to interfere with the function of nearby organs, such as the liver and stomach, or to invade the nerves.

When they do develop, the symptoms of pancreatic cancer may include:

- Jaundice

- Development of diabetes
- Nausea or vomiting
- Lack of appetite
- Weight loss accompanied by abdominal pain
- Dark urine, light-coloured stools, diarrhoea, bloating or gas
- Ongoing back pain, especially when lying down or eating.

HOW IS PANCREATIC CANCER TREATED?

The options for treating pancreatic cancer include surgery, radiation, chemotherapy or a combination of these techniques. Surgery is generally only undertaken if the cancer has not spread.

The surgical removal of most pancreatic cancers is done using a technique known as the 'Whipple procedure' or 'pancreaticoduodenectomy'. This complex operation often involves not only removing part or all of the pancreas, but also the gallbladder, part of the bile duct, part of the stomach, parts of the small intestine, and all of the regional lymph nodes (the lymph nodes that drain lymphatic fluid from the region of

the tumour). Sometimes, treatment may involve a combination of surgery plus radiotherapy and/or chemotherapy.

Unfortunately, many pancreatic cancers cannot be surgically removed, and in these cases radiotherapy and/or chemotherapy are used to help manage the symptoms. Several other pain-management techniques may also be employed. These include palliative surgery to perform nerve blocks or to clear blockages to the bile duct and stomach, as well as the administration of pain-relieving medications.



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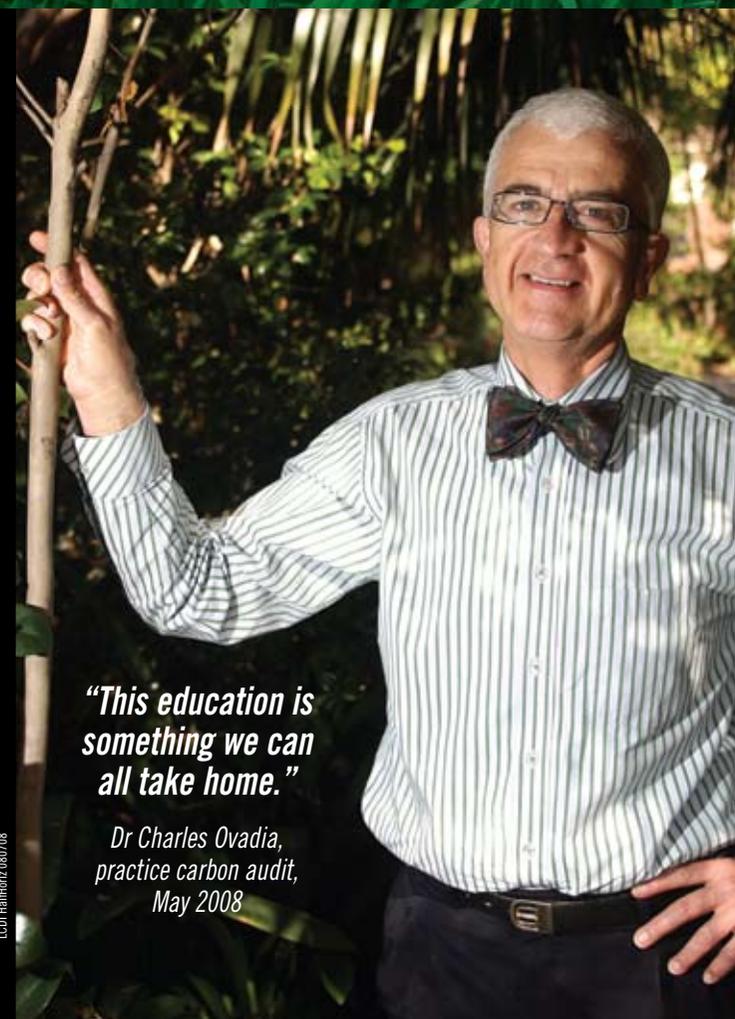


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