Diagnosis and management of pancreatic exocrine insufficiency

Mayur Kumar MRCP and Mark Wilkinson MD, FRCP

Managing pancreatic exocrine insufficiency effectively is challenging for both specialist and primary-care physicians. This review summarises current methods employed to diagnose and treat PEI effectively and prevent complications.

Pancreatic exocrine insufficiency (PEI) develops when less than 10 per cent of functioning pancreas remains. It is characterised by deficiency or absence of pancreatic enzymes – amylase, lipase and proteases. Clinical symptoms include chronic abdominal pain, cramps and steatorrhoea, eventually leading to malnutrition and weight loss. Despite several tests available to diagnose this condition, none is 100 per cent specific and sensitive.

Epidemiology
In the UK about 11 000 patients develop PEI each year from various causes. The overall prevalence of chronic pancreatitis (CP) in the Western world is 27.4 cases per 100 000 population. Some 50–80 per cent of patients with CP develop PEI with an average interval of 5–10 years from diagnosis of alcoholic CP. In nonalcohol-related pancreatitis the progression to PEI is slower.

Causes
The most common cause of chronic pancreatitis in industrialised nations is excess alcohol consumption. Other less common causes include untreated coeliac disease, small bowel Crohn’s disease, hereditary pancreatitis, IgG4-related systemic disease, so-called tropical pancreatitis, obstructive chronic pancreatitis, hyperlipidaemia, chronic renal failure, hyperparathyroidism and postradio/chemotherapy pancreatitis.

Rare causes include Shwachman-Diamond syndrome, Johanson-Blizzard syndrome, Pearson syndrome and HIV/AIDS.

Clinical features
The most common clinical symptom of PEI is steatorrhoea. The pancreas has a large reserve capacity and more than 90 per cent of the pancreatic acini must be destroyed...
Pancreatitis

PERT remains the mainstay of treatment; high doses are employed: starting doses in adults are usually 25,000–40,000 IU per main meal. PERT remains the mainstay of treatment and secretin MRCP tests can diagnose PEI more accurately and may become more widely available.

Diagnostic tests

Several diagnostic tests exist to diagnose chronic pancreatitis and PEI, but none is 100 per cent sensitive or specific for the condition.

Direct tests

Direct hormone-stimulated pancreatic function tests (PFTs) are the most sensitive and specific tests for assessing pancreatic exocrine function and provide a gold standard. They involve gastric and duodenal intubation (Dreiling tubes) and iv injection of secretin or cholecystokinin followed by collection and analysis of the resulting pancreatic secretions.

Direct tests are most useful in patients in whom radiological investigations are inconclusive. Unfortunately, they are invasive, unpleasant, take about two to three hours and the laboratory techniques required for fluid analysis are not universally available. Direct PFTs are therefore rarely performed.

Indirect tests

Several indirect tests have been developed to diagnose chronic pancreatitis and PEI to overcome the complexity, lack of availability and discomfort of direct tests. These tests can measure pancreatic enzymes in blood or stool. A general criticism of these tests is low sensitivity for mild/moderate disease. They include: faecal chymotrypsin, faecal elastase, serum trypsin and 13C breath test.

Faecal chymotrypsin assay has a sensitivity for advanced disease of 50–80 per cent, increasing to 80–90 per cent in cystic fibrosis, with a specificity of 50–100 per cent.

Faecal elastase Pancreatic elastase-1 is a pancreas-specific protease that is minimally degraded during intestinal transit. The concentration of faecal elastase in stool is measured by ELISA (enzyme-linked immunosorbent assay) and a faecal elastase less than 100µg per g of stool indicates severe PEI. Values over 200µg are normal. Sensitivity varies between 0 and 65 per cent for mild disease to between 33 and 100 per cent for severe CP.

Faecal elastase requires only a single stool sample without the need for prolonged urine collections and is recommended by the British Society of Gastroenterology as the test of first choice in patients with steatorrhoea. Most centres in the UK now perform a faecal elastase test to diagnose PEI.

Serum trypsin test The serum trypsin assay is a simple and convenient test. Low levels – <20ng per ml – are specific for CP, but are sensitive only for advanced disease. This is a radioimmunoassay test and takes a few days for results to be available.

13C breath tests Breath tests using 13C isotopes are available to diagnose PEI. Sensitivities of 85–100 per cent have been reported with specificity >90 per cent with high fat intake. 13C breath tests can be used to measure response to pancreatic enzyme replacement therapy (PERT).

These tests, which require a mass spectrometer, are however inappropriate in patients with diabetes, liver disease or obesity and are not widely available in the UK.

Endoscopic pancreatic function tests (ePFT)

Recently, simplified tests of pancreatic function have been developed to improve accessibility in patients undergoing endoscopy. These include the secretin ePFT and aspiration of pancreatic fluid at endoscopic retrograde cholangiopancreatography (ERCP).

The ePFT is most useful in patients with a suspicion of CP but with minimal or equivocal radiographic abnormalities. A disadvantage is the requirement for endoscopy and/or ERCP, with their attendant costs and risks.

Combined endoscopic ultrasound EUS/ePFT A combination of structural and functional testing can be performed using EUS. This involves EUS following secretin stimulation, with collection of duodenal fluid and analysis of bicarbonate and pancreatic enzymes.

Combined EUS/ePFT is a novel diagnostic tool and provides complementary functional and structural information for the evaluation of CP and pancreatic function in one session, but routine use needs validation in larger studies.

Secretin MRCP

Conventional CT (see Figure 1) and magnetic resonance cholangiopancreatography (MRCP) can diagnose chronic pancreatitis reliably but cannot assess pancreatic function. Hence secretin MRCP has been introduced to measure the functional status of the pancreas.

Secretin-stimulated pancreatic secretion with measurement of duct dilatation and filling of the duodenum is used to assess exocrine function and correlates well with faecal elastase-1 and urinary pancreolauryl levels in diagnosing PEI. Both

Table 1. Causes of pancreatic exocrine insufficiency

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<td>postnecrotising acute pancreatitis</td>
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<td>cystic fibrosis</td>
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<td>pancreatic cancers/tumours</td>
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<td>IgG4 autoimmune pancreatitis</td>
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<th>Extrapancreatic diseases</th>
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<tr>
<td>coeliac disease</td>
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<tr>
<td>inflammatory bowel disease</td>
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<td>diabetes mellitus</td>
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<td>Zollinger-Ellison syndrome</td>
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<th>Postsurgical states</th>
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<tr>
<td>gastric resection</td>
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<td>Whipple’s pancreaticoduodenectomy</td>
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<td>short bowel syndrome</td>
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<td>bariatric surgeries</td>
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structural and functional components of the pancreas are assessed noninvasively.

All of the above tests have some value in diagnosing PEI but none is of the required specificity or sensitivity for reliable diagnosis, so a combination of tests is used in clinical practice to diagnose and manage PEI.

### Management of pancreatic exocrine insufficiency

Effective management of PEI remains a challenge and needs a multidisciplinary approach involving dietitians, primary-care physicians and specialist gastroenterologists.

#### Lifestyle modifications

Patients should refrain from drinking alcohol and stop smoking. This improves both CP pain and PEI. Dietary fat restriction to <20g per day is the initial approach to managing steatorrhoea, but this may lead to restricted consumption and deficiency of fat-soluble vitamins. Diet should be reviewed regularly and nutritional status assessed by experienced dietitians.

Currently the mainstay of treatment is PERT.

#### Pancreatic enzyme replacement therapy

Patients with steatorrhoea, weight loss and faecal fat excretion of greater than 15g per day need PERT. PERT (non-enteric coated preparations) may also be beneficial in reducing pain in CP patients through a negative feedback mechanism by inhibiting cholecystokinin release, although the evidence is mixed. A few small randomised controlled trials have shown benefit in pain reduction, but a meta-analysis of six randomised controlled trials showed no benefit. Our experience suggests that using non-enteric coated enzyme preparations has a role in pain reduction in CP patients with PEI.

The main aim of PERT is to simulate the physiological response of the pancreas to food and thus aid normal digestion, especially of fats. PERT is also believed to improve quality of life.

Porcine pancreatin preparations are the most widely used, but other preparations are available by special order if there are cultural or religious issues with pig-related products. Table 2 summarises the various preparations available in the UK. Most products have a similar enzyme constitution, but the formulations differ in strength. The dosage of pancreatic enzyme preparations is individually tailored. A reasonable starting dose for adults is 25 000–40 000IU of lipase per main meal. The dosage for light meals or snacks depends on their size but should be at least 10 000IU. In children, doses are calculated based on body weight or on amount of fat intake. The maximum daily dose in children is limited to 10 000IU of lipase per day to prevent fibrosing colonopathy, which is reported with higher doses. To ensure that they are well mixed with the food in the stomach, pancreatic preparations should be taken during or immediately after meals.

Unsuccessful responses can be managed by dose escalation or the addition of proton pump inhibitors (PPIs) or H2-antagonists to prevent acid inactivation of lipase. Success to therapy is usually measured by improvement in patient symptoms; however, faecal fat measurement and 13C breath tests can be used to measure success objectively.

Patient education is vital for success with this therapy. The following advice should be provided to patients who are started on PERT:

1. Enzymes to be taken with all meals and snacks; sporadic intake should be avoided.
2. Doses should be titrated according to response.
3. Concomitant PPI/H2-antagonist use if inadequate response
4. Do not crush or chew enteric-coated enzymes preparations to avoid mouth irritation and sores.
5. Avoid antacids containing magnesium and calcium as they can reduce effectiveness.
6. Warn against potential side-effects such as bloating, abdominal cramps, diarrhoea, headache, dizziness and mouth and perianal soreness. These symptoms are usually transient and treatable with simple measures discussed above.

Fibrosing colonopathy has been reported in paediatric CF patients taking high doses of pancreatic enzymes. This is thought to be secondary to the methacrylic acid co-polymer used in some brands of enteric-coated preparations, although an autoimmune process has been postulated too. Newer products such as enzyme granules and mini-microspheres have not been associated with this complication.

The US Cystic Fibrosis Foundation consensus guidelines recommend that dosages should be limited to 500–2500 lipase units per kg per meal, <10 000 lipase units per kg per day or <4000 lipase units per g dietary fat per day. Hypersensitivity reactions such as skin allergy, allergic rhinitis and rarely anaphylaxis have been reported, but these are uncommon.

PERT is generally considered safe, even in high doses.

### Fa-soluble vitamin deficiency in PEI

Malabsorption of fat-soluble vitamins (A, D, E and K) is frequently present in patients with PEI but often undiagnosed. Vitamin D deficiency is common in CF patients with...
pancreatic insufficiency. Latent vitamin A and E deficiency is reported even in patients on PERT.\textsuperscript{15,16} Monitoring of fat-soluble vitamin levels and adequate replacement are essential in the management of PEI patients.

**Conclusion**

PEI develops in almost all patients with CP and the average time to develop symptoms can vary from 5 to 10 years. Diagnosing PEI accurately remains a challenge and none of the currently available tests is 100 per cent sensitive or specific, leading to delayed diagnosis in some cases. Indirect tests are currently used to diagnose PEI, but newer tests such as ePFT and secretin MRCP may be more widely available in future and diagnose PEI more accurately.

The main aim of treatment is to reduce steatorrhoea and prevent malnutrition and weight loss. PERT remains the mainstay of treatment.

**References**


**Declaration of interests**

None to declare.

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