Chronic pancreatitis and exocrine pancreatic insufficiency

Søren Schou Olesen

Abstract

Chronic pancreatitis is a fibro-inflammatory disease of the pancreas characterized by inflammation and fibrosis. It is associated with excessive alcohol consumption and smoking, although a number of other risk factors are increasingly recognized, including genetic predisposition. Patients typically present with upper abdominal pain, weight loss and changes in bowel habits caused by exocrine pancreatic insufficiency. Additionally, chronic pancreatitis is frequently complicated by secondary diabetes mellitus (type 3c diabetes) and a number of other conditions, including common bile duct stenosis and duodenal obstruction. Because of malabsorption, patients also have an increased risk of osteoporosis and low-energy fractures. Alcohol abstinence and smoking cessation are key elements of management. Pain is often the most prominent symptom and has a multifactorial aetiology that requires a multidisciplinary treatment approach, including specialized endoscopic and surgical expertise. Exocrine pancreatic insufficiency is treated by enzyme replacement therapy with careful monitoring of patients' macro- and micronutritional state, including systematic assessment of bone health. Diabetes secondary to chronic pancreatitis requires special therapeutic considerations because of a high risk of hypoglycaemia. Most patients obtain an acceptable life quality when adhering to modern treatment recommendations.

Keywords Alcohol; chronic pancreatitis; diabetes mellitus; exocrine pancreatic insufficiency; MRCP; pain; smoking

Key points

- Chronic pancreatitis is a prevalent disease that must be considered in patients with abdominal pain, weight loss or diarrhoea
- Patients with chronic pancreatitis have an increased mortality and risk of developing pancreatic cancer
- Alcohol and smoking are independent risk factors, and counselling against their use is a key element of patient management
- Pain is the most prominent symptom and has a multifactorial aetiology that requires a multidisciplinary treatment approach
- Exocrine pancreatic insufficiency is treated by enzyme replacement therapy with careful monitoring of patients' macro- and micronutritional state, including systematic assessment of bone health
- Diabetes mellitus secondary to chronic pancreatitis requires special therapeutic considerations because of the heightened risk of hypoglycaemia

Introduction

Chronic pancreatitis is a fibro-inflammatory disease of the pancreas characterized by inflammation and a gradual replacement of the exocrine and endocrine cells with fibrotic tissue.[1] The aetiological risk factors most frequently associated with it are alcohol abuse and smoking. However, recent studies emphasize the complexity of disease pathogenesis, which in most cases involves interactions between environmental risk factors (e.g. smoking, alcohol) and biological predisposition (e.g. mutations in tryptase or anti-tryptase genes). Hence, most patients have more than one aetiological risk factor, which explains why only a minority of heavy drinkers and smokers develop pancreatitis — a biological predisposition is usually required in combination with adequate exposure to environmental risk factors (Table 1).[2]

Recurrent episodes of acute pancreatitis often precede the development of chronic pancreatitis, and continued smoking and alcohol consumption accelerate this process. The incidence of chronic pancreatitis is approximately 10 cases per 100,000 persons per annum in Western European countries, and the prevalence has been estimated at 120–140 cases per 100,000 persons. Patients with chronic pancreatitis have a 5-fold increased mortality rate compared with the background population, and the disease is associated with severely reduced life quality, stigmatism and high resource usage.[1]

Clinical presentation and complications to chronic pancreatitis

The clinical presentation of chronic pancreatitis is highly variable and determined by the presence of pancreatic and extrapancreatic complications that occur with varying prevalence and severity (Table 2). Pain is the dominant symptom in most patients and frequently presents before the patient develops pancreatic insufficiency or typical morphological changes. The pain is typically described as a constant, dull ache in the mid-epigastrium, which often radiates to the back. It may be worsened by food intake, and pain attacks can last for days or develop into a chronic pain state. These classic pain characteristics are not universal, and the location, character and quality of pain can vary between patients and within patients over time. The past observation that the pain would 'burn out' over time as disease progressed is not substantiated by recent studies, and most patients have pain for decades.[3]

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The M-ANNHEIM multiple risk factor classification of chronic pancreatitis

Aetiological risk factor	Comment
Alcohol consumption	No safe thresholds have been established; there is an increased risk of chronic pancreatitis with alcohol consumption >5 units/day
Nicotine consumption	No safe thresholds have been established; there is an increased risk of chronic pancreatitis with increasing number of daily cigarettes
Nutritional factors	Hypertriglyceridaemia
Hereditary factors	Mutations in tryptase and anti-tryptase genes Mutations in the cystic fibrosis transmembrane conductance regulator gene Different disease phenotypes: • Hereditary pancreatitis (with or without known mutations) • Early- and late-onset idiopathic chronic pancreatitis • Tropical chronic pancreatitis
Efferent duct factors	Pancreas divisum, pancreas annulare and other congenital abnormalities of the pancreas Pancreatic duct obstruction (e.g. tumours, cysts) Post-traumatic pancreatic duct scars Sphincter of Oddi dysfunction (controversial)
Immunological factors	Autoimmune pancreatitis
Miscellaneous and rare metabolic factors	Hypercalcaemia and hyperparathyroidism Drugs Toxins

Table 1

Long-standing disease predisposes to the development of pancreatic exocrine insufficiency, which typically presents as steatorrhoea, weight loss and malnutrition. Malabsorption of vitamins and trace elements increases the risk of osteoporosis, and patients have a high risk of low-energy fractures. Diabetes mellitus is another common complication of chronic pancreatitis. In addition, a number of more infrequent complications can develop during the course of disease. These include obstruction of neighbouring organs such as common bile duct stenosis, with patients presenting with jaundice and/or symptoms of cholangitis. Duodenal obstruction typically presents as nausea and vomiting after meals. Vascular complications include splenic or portal vein thrombosis and the development of portal hypertension with gastric and/or oesophageal varices. A rare vascular complication is pseudoaneurysm of the splenic artery or adjacent vessels; this has a high risk of spontaneous rupture and can cause fatal bleeding.[3]

Complications of chronic pancreatitis and their treatments

Complication	Treatment
Upper abdominal pain	Treatment of secondary causes of pain (e.g. pseudocyst, peptic ulcer) Pain medication including adjuvant analgesics Endoscopic therapy Surgery Handling in a multidisciplinary team is recommended
Exocrine pancreatic insufficiency	Pancreatic enzyme replacement therapy Vitamin and trace element supplements
Secondary diabetes (type 3c)	Antidiabetic agents (metformin, insulin) *Cave*: incretin-based therapies
Osteoporosis	Vitamin D supplements Calcium supplements Bisphosphonates or other antiresorptive therapy
Common bile duct stenosis	Endoscopic therapy and stenting Surgery in refractory cases
Duodenal obstruction	Conservative management Endoscopic dilation Surgery in refractory cases
Mesenteric venous thrombosis	Anticoagulation therapy if it can be substantiated that the thrombosis is newly developed (absence of collaterals on cross-sectional imaging) Upper gastrointestinal endoscopy to reveal and treat varices

Table 2

Diagnosis

Chronic pancreatitis should be suspected in patients presenting with upper abdominal pain, steatorrhoea, weight loss or newly developed diabetes. In particular, patients with preceding attacks of acute pancreatitis and/or a history of alcohol abuse and smoking have a high pre-test probability of chronic pancreatitis. The diagnosis is confirmed by contrast-enhanced computed tomography and/or magnetic resonance cholangiopancreatography, with evidence of a dilated main pancreatic duct and abnormal side branches, as well as parenchymal atrophy and calcifications (Figure 1).[4] In addition to establishing a diagnosis, thorough imaging, such as with contrast-enhanced computed tomography, it is key to ruling out the differential diagnoses of chronic pancreatitis, including pancreatic cancer, and to reveal the presence of treatable complications (e.g. pseudocyst, biliary obstruction).

The diagnosis of chronic pancreatitis is straightforward for patients with typical symptoms and imaging findings, but can be difficult in those with early disease, as these patients often present with isolated pain complaints and normal pancreatic morphology. In these patients, secretin-enhanced magnetic resonance cholangiopancreatography or endoscopic ultrasonography can be helpful to elucidate findings compatible with a

diagnosis of 'early chronic pancreatitis', including side-branch abnormalities and discrete parenchymal changes.[4]

Pancreatic functional testing is used to characterize pancreatic exocrine function. The most common test is the faecal elastase test, which has largely replaced direct pancreatic function tests and faecal fat quantification. Faecal elastase is unaffected by use of enzyme replacement therapy and is sensitive for detecting moderate to severe exocrine insufficiency, albeit less accurate for mild exocrine dysfunction. In addition, the elastase test can be falsely positive in patients with diarrhoea unrelated to pancreatic disease and, as such, abnormal test results must be interpreted in a clinical context and preferably in conjunction with imaging findings.

The ^{13}C mixed triglyceride (triacylglycerol) breath test is a functional test of duodenal fat digestion and measures the digestion of a radioactively labelled substrate (mixed triglycerides) provided in a test meal. The test is time-consuming but highly accurate in detecting fat maldigestion and can be used to monitor the response to enzyme replacement therapy.[4]

Management

The aim of management is to prevent further disease progression and to alleviate symptoms once complications have developed.[4]

Prevention of disease progression – smoking cessation and alcohol abstinence is pertinent to all patients with chronic pancreatitis. Continued smoking and alcohol consumption worsen the natural history of the disease and lead to an increased frequency of fibrosis-related complications and development of pancreatic insufficiency.

Pain management – the most troublesome complication of chronic pancreatitis is pain. It is important to recognize that the cause of pain is highly variable between patients, and treatable causes of pain can often be identified after a detailed clinical work-up. Patients with significant changes in their pain symptoms should therefore undergo systematic clinical investigation, including blood testing and imaging, to rule out treatable complications.

Pseudocysts are often amenable to endoscopic drainage (cyst-gastrostomy). Newly developed strictures or stones in the pancreatic duct can obstruct pancreatic outflow and cause pain (Figure 2); these can be treated by endoscopic stone removal and/or stenting of pancreatic strictures. Surgical intervention is reserved for patients who do not respond to endoscopic intervention. The risk of peptic ulcers is increased in chronic pancreatitis, and oesophago-gastro-duodenoscopy should be considered to rule this out. Although treatable sources of pain can be identified in many patients, a significant number continue to have pain without any recognizable source (genuine pancreatic pain).

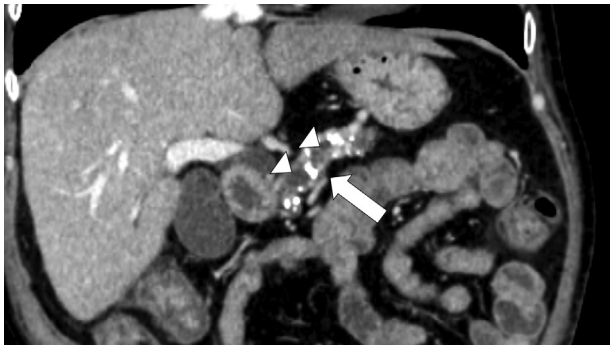

Figure 1 A 65-year-old woman presented with upper abdominal pain, weight loss and diarrhoea. There was a past history of excessive alcohol consumption and smoking. CT revealed end-stage chronic pancreatitis (Cambridge grade 4) with evidence of numerous pancreatic calcifications and gland atrophy (arrow) as well as a dilated main pancreatic duct (arrow heads).

The symptomatic treatment of pain for these patients follows the general treatment recommendations for non-malignant pain provided by the World Health Organization. These are based on the pain relief ladder and serial introduction of analgesics with increasing potency until adequate pain relief is obtained. Importantly, adjuvant analgesics, including anticonvulsants and antidepressants, should be considered at an early stage to treat neuropathic pain components, which have been increasingly recognized as important in this context. Many patients require opioids to achieve adequate pain relief. These medications should be prescribed with caution and monitored regularly to avoid dose escalation and dependency. Concomitant prescription of a laxative is important to prevent opioid-induced bowel dysfunction or opioid-induced constipation. Most patients taking opioid-based treatment achieve an acceptable life quality when adhering to these recommendations.[5]

Management of exocrine pancreatic insufficiency – exocrine pancreatic insufficiency is managed by pancreatic enzyme replacement therapy. Enteric-coated enzyme preparations are recommended, with a starting dose of 50,000 units of lipase with main meals, and 25,000 units of lipase with snacks. Enzymes should only be taken with food, and should be titrated individually to correct abnormal digestion and nutritional deficits. In some patients, concomitant prescription of a proton pump inhibitor enhances the efficacy of pancreatic enzymes.[4]

Management of diabetes – diabetes secondary to pancreatic diseases (type 3c diabetes) is a distinct type of diabetes characterized by general destruction of endocrine pancreatic tissue, including insulin-producing β-cells, as well as glucagon-producing α-cells and pancreatic polypeptide producing δ-cells. This has important clinical implications as patients lack mechanisms to counterregulate hypoglycaemia (glucagon) and type 3c diabetes is frequently complicated by recurrent episodes of hypoglycaemia ('brittle diabetes'). An adequate and balanced food intake, together with pancreatic enzyme replacement therapy and abstinence from alcohol, is therefore crucial to minimize the risk of hypoglycaemia and obtain adequate glycaemic control. Metformin can reduce the long-term risk of pancreatic cancer but is generally inadequate in achieving glycaemic control on its own in most patients. The majority of patients are treated with insulin in combination with metformin. Incretin-based antidiabetic agents, such as glucagon-like peptide agonists and dipeptidyl peptidase 4 inhibitors, are not recommended because of a suspected link with pancreatitis.[4]

Management of malnutrition and bone health – patients with malnutrition are recommended to take frequent, high-energy meals during the day, whereas patients with a normal nutritional state should follow normal healthy eating advice. Modern guidelines have removed restrictions on fat ingestion. Many patients develop micronutritional deficiencies, so supplements of fat-soluble vitamins and minerals should be prescribed

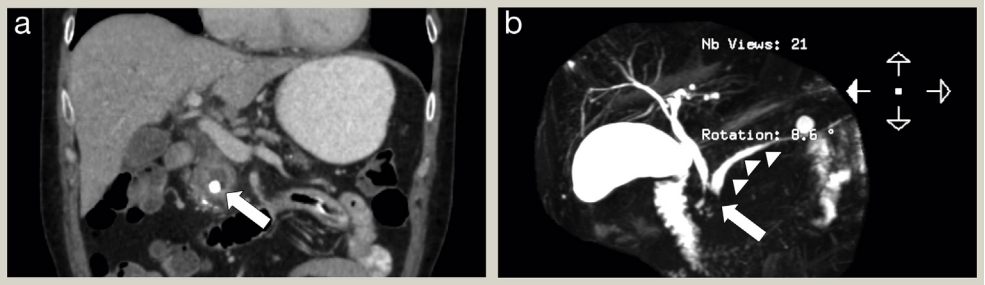

Figure 2 A 66-year-old man presented with upper abdominal pain. CT (**a**) and subsequent magnetic resonance cholangiopancreatography (**b**) revealed an impacted stone in the pancreatic duct (arrows) with dilation of the distal pancreatic duct (arrow heads). The pain was relieved by endoscopic therapy with stone removal and stenting.

if deficiency is present. Dual-energy X-ray absorptiometry is recommended in all patients with chronic pancreatitis at the time of diagnosis and every 3 years to monitor bone health and screen for osteoporosis.[4]

Management of obstructive complications – common bile duct stenosis is treated by endoscopic therapy with placement of multiple plastic stents or self-expanding metal stents. A prolonged treatment period is often necessary to obtain sufficient and sustained effects. Duodenal obstruction is managed conservatively or by endoscopic dilation. In cases of endoscopic treatment failure, most obstructive complications can be treated surgically.[4]

Follow-up

Patients should be regularly followed up, preferably at specialized centres with a multidisciplinary set-up. This should include biochemical assessment of vitamins and trace elements, monitoring of bone health and endocrine and exocrine pancreatic function. With worsening abdominal pain or unexplained weight loss, cross-sectional imagining and endoscopy must be considered to exclude the development of complications. Continued counselling against smoking and alcohol is a key element of patient management. ◆

KEY REFERENCES

1 Kleeff J, Whitcomb DC, Shimosegawa T, et al. Chronic pancreatitis. *Nat Rev Dis Prim* 2017; **3:** 17060.

2 Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007; **42:** 101–19.

3 Braganza JM, Lee SH, McCloy RF, McMahon MJ. Chronic pancreatitis. *Lancet* 2011; **377:** 1184–97.

4 Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United Eur Gastroenterol J* 2017; **5:** 153–99.

5 Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatol* 2017; **17:** 720–31.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 43-year-old man presented with a 5-month history of upper abdominal pain and a 6 kg weight loss. There was no change in bowel habit and no significant past medical history. He drank an average of 45 units of alcohol a week and had done so for many years. He had a 25 pack–year history of smoking.

On clinical examination, there was some tenderness in the epigastrium.

Investigations

- Haemoglobin 162 g/litre (130–180)
- White cell count 5.6 × 10^9/litre (4.0–11.0)
- C-reactive protein 6 mg/litre (<10)
- Bilirubin 15 micromol/litre (1–22)
- Alanine aminotransferase 23 U/litre (5–35)
- Alkaline phosphatase 64 U/litre (45–105)
- Amylase 70 U/litre (60–180)
- HbA_{1c} 57 mmol/mol (20–42)
- Ultrasound of the abdomen showed a normal liver and bile duct. There was an insufficient view of the pancreas because of gas in overlying bowel, but there was an impression of hyperechoic pancreatic parenchyma

What is the next best step (if any) to confirm the likely diagnosis?

A. No further diagnostic work-up is needed
B. F-elastase and computed tomography of the pancreas
C. F-elastase but no further imaging needed
D. Re-examination with abdominal ultrasound
E. Upper gastrointestinal endoscopy and F-elastase

Question 2

A 57-year-old woman presented with a 2-year history of intermittent upper abdominal pain, worsening over the previous 2 months. She had a 12-year history of alcohol-related chronic pancreatitis, complicated by exocrine pancreatic insufficiency and diabetes. Opioids had had a limited effect.
Clinical examination was normal.

Investigations

- Haemoglobin 142 g/litre (115–165)
- White cell count 5.6 × 10^9/litre (4.0–11.0)
- C-reactive protein 15 mg/litre (<10)
- Bilirubin 15 micromol/litre (1–22)
- Alanine aminotransferase 23 U/litre (5–35)
- Alkaline phosphatase 64 U/litre (45–105)
- Amylase 230 U/litre (60–180)

What is the next best step for the management of her pain?

A Request a CT scan of pancreas
B Advise a proton pump inhibitor
C Advise laxatives
D Refer to the pain clinic
E Advise a cautious increase in opioid dosage

Question 3

A 65-year-old man presented with a 2-month history of weight loss and changes in bowel habit with frequent daily bowel actions and foul-smelling stools that were often difficult to flush. He had a 3-year history of idiopathic chronic pancreatitis.

Investigations

- Haemoglobin 152 g/litre (130–180)
- White cell count 5.9 × 10^9/litre (4.0–11.0)
- C-reactive protein 15 mg/litre (<10)
- Biliruin 18 micromol/litre (1–22)
- Alanine aminotransferase 33 U/litre (5–35)
- Alkaline phosphatase 74 U/litre (45–105)
- Amylase 50 U/litre (60–180)
- F-elastase <10 microgram/g (>200)
- CT of the pancreas showed chronic calcific pancreatitis with a slightly dilated pancreatic duct but no evidence of malignancy
- Colonoscopy was normal

What is the next most appropriate diagnostic step to perform?

A. Faecal fat assay
B. ^{13}C mixed triglyceride breath test
C. Upper gastrointestinal endoscopy
D. Dual-energy X-ray absorptiometry
E. Bowel motility studies