

Chronic Pancreatitis

See also separate article [Acute Pancreatitis](#).

Description

Chronic pancreatitis is the result of chronic inflammation of the pancreas which results in irreversible damage. It is associated with severe abdominal pain and endocrine or exocrine dysfunction. It is a difficult illness to diagnose and manage, making it a challenge for all involved.

It is unclear if acute and chronic pancreatitis are related, although the damage to the pancreas in acute pancreatitis is reversible. At present there is no method to detect early chronic pancreatitis and calcification of the pancreas may not develop until 5-10 years after initial symptoms.

Epidemiology

- The worldwide prevalence is estimated as 4-5%.^[1]
- Few studies have been carried out in the UK but figures suggest there has been a dramatic increase in prevalence over time.^[2]
- One study reported a male:female ratio of approximately 4:1 and a median patient age of 51.^[3]

Pathophysiology

The underlying mechanism of chronic pancreatitis is unclear. There have been many theories:

- The most common thought is that there is obstruction or reduction of bicarbonate excretion. This in turn leads to activation of pancreatic enzymes, which leads to pancreatic tissue necrosis with eventual fibrosis. Abnormalities of bicarbonate excretion can be the result of functional defects at the level of the cellular wall, as in [cystic fibrosis](#), or mechanical, such as trauma.
- [Alcohol](#) causes proteins to precipitate in the ductular structure of the pancreas. This leads to local pancreatic dilatation and fibrosis. However, this is not seen in patients with recurrent attacks of acute pancreatitis associated with alcohol use.^[4]
- There may be direct toxic effects of alcohol on the pancreas. However, it has been noted that patients who drink 'normal' amounts of alcohol can also develop chronic pancreatitis, ie a dose-response relationship does not exist. It may be that there is excessive free radical formation which leads to pancreatic damage. Some trials have looked at the role of antioxidants (eg, selenium and methionine) and pain relief with promising results.^[5]

Whatever the cause, the end result is pancreatic fibrosis which can take several years to develop.

Large duct pancreatitis versus small duct pancreatitis^[4]

It is thought that there are two pathological subtypes of chronic pancreatitis: **large duct pancreatitis** and **small duct pancreatitis**. These two entities may represent two ends of the same spectrum but they have different pathological and radiological features and the management varies. They are usually applied to all causes of chronic pancreatitis.

Large duct pancreatitis is characterised by dilatation and dysfunction of the large ducts and is easily seen on imaging. It tends to occur more in men and there is also diffuse pancreatic calcification. Steatorrhoea is common and replacement of pancreatic enzymes does not reduce pain and patients usually require surgery to alleviate symptoms.

On the other hand, small duct pancreatitis occurs more in women and is not associated with pancreatic calcification. Imaging is usually normal, making it difficult to diagnose and, therefore, a high index of suspicion is needed. Steatorrhea is a rare feature and patients respond to replacement of pancreatic enzymes.

Some specific types of chronic pancreatitis

Hereditary pancreatitis:^[6]

- Rare and similar to chronic pancreatitis.
- Most cases are thought to result from genetic mutation-induced changes in human cationic trypsinogen (PRSS1) which lead to increased auto-activation by altering chymotrypsin C (CTRC)-dependent trypsinogen activation and degradation.^[7]
- It presents at a younger age with epigastric pain.
- Exocrine and endocrine dysfunction are also present and there is a high incidence of **pancreatic carcinoma** (10% at age 50, 18.7% at age 60, 53.5% at age 75).^[6]

Tropical chronic pancreatitis:^[8]

- This was first described in the 1960s.
- It is seen in developing countries with a tropical climate and affects patients at a younger age.
- It has similar presentation to alcoholic chronic pancreatitis.
- It is associated with large intraductal calculi and development of insulin-requiring **diabetes mellitus**, although ketosis is rare.
- Once diabetes mellitus has developed, it is often called fibrocalculous pancreatic diabetes.
- It affects 10-15 per 100,000 population in Western countries but is much higher in Japan - 45 per 100,000.^[9]
- One study reported a prevalence of 0.36% (1:276) of all self-reported diabetes and 0.019% (1:5,200) of the general population in Chennai in South India.^[10]
- The aetiology of tropical pancreatitis is not clearly understood but may relate to malnourishment and dietary toxins - eg, in cassava.
- Tropical pancreatitis is associated with SPINK1 and/or CFTR gene mutations in approximately 50% of patients.^[11]
- There is an increased risk of developing pancreatic carcinoma.^[12]

Autoimmune chronic pancreatitis:

- This is chronic pancreatic inflammation which results from an autoimmune process.
- There is a high prevalence in Japan.
- It is recognised that there are two types of the condition. Type 1 is more common in Eastern countries whilst type 2 is more common in the Western world. There are significant histological differences between the two types.^[13]
- The presentation is very similar to other forms of chronic pancreatitis.
- There are elevated levels of serum gammaglobulins and immunoglobulin G (IgG) levels
- Autoantibodies may also be increased - eg, **antinuclear antibody** and rheumatoid factor.^[14]
- Autoimmune chronic pancreatitis is steroid-responsive and reversible.^[15]
- There may be an association with pancreatic carcinoma but further research is needed.^[16]

Predisposing factors

One study reported that in the Western world 60-70% of patients with chronic pancreatitis have a 6- to 12-year history of alcohol abuse.^[1]

Smoking is an independent risk factor.^[1]

There has also been research into the role of genetic abnormalities in chronic pancreatitis. Genetic variation in the gamma-glutamyltransferase 1 (GGT1), CFTR and SPINK1 genes is associated with chronic pancreatitis.^[17]^[18] Chronic pancreatitis is emerging as a multifactorial condition which is the result of a complex interplay between genetically induced metabolic changes at the level of the pancreatic cell.^[19]

Other causes

There are many other causes and they are similar to those for acute pancreatitis:

- Biliary tract disease
- Iatrogenic - eg, **endoscopic retrograde cholangiopancreatography (ERCP)**
- Metabolic disorders - eg, hypertriglyceridaemia, hypercalcaemia
- Trauma
- Congenital disorders - eg, cystic fibrosis
- Drugs - eg, azathioprine, sulfonamides, loop diuretics
- Idiopathic - thought to be early- and late-onset subgroups
- Abdominal radiotherapy

Presentation

Chronic pancreatitis may present with episodes of exacerbation with intervening remission or continuous pain in patients.

- **Abdominal pain.** Classically, epigastric pain radiating into the back. The pathogenesis of this pain is not understood but pancreatic duct obstruction from one of the complications of chronic pancreatitis may be one cause.^[1] Usually the pain is very severe, which often requires opiates in the acute setting. In some cases pain may not be the major feature.
- **Nausea and vomiting.**
- **Decreased appetite.**
- **Exocrine dysfunction.** Malabsorption with weight loss, diarrhoea, steatorrhoea (pale, loose, offensive stools that are difficult to flush) and protein deficiency.
- **Endocrine dysfunction.** Diabetes mellitus and its associated morbidity and mortality.

Examination can be largely unremarkable apart from tenderness in the abdomen.

Differential diagnosis

Of abdominal pain:

- Acute **cholecystitis**
- **Peptic ulcer disease**
- Acute hepatitis
- **Abdominal aortic aneurysm**
- Pyelonephritis
- **Acute pancreatitis**
- Non-abdominal causes - eg, **myocardial infarction** and **pneumonia**

Of pancreatic calcification on abdominal imaging:

- Severe protein malnutrition
- Hereditary pancreatitis
- **Hyperparathyroidism**

Investigations and diagnosis^[20]

Early diagnosis is difficult, as no biochemical markers exist and abdominal radiology may show normal pancreatic appearances. Investigation may reveal aetiology or complications.

- Blood tests: FBC, U&E, creatinine, LFTs, calcium, amylase (usually normal), glucose, HbA1C.
- Secretin stimulation test: a positive result occurs if 60% or more pancreatic exocrine function is damaged. The use of endoscopic techniques has made what was once a lengthy and invasive procedure more accessible.^[21]
- Serum nutritional markers are being evaluated as potential diagnostic factors. Low levels of magnesium, haemoglobin, albumin, prealbumin and retinol binding protein and a high level of HbA1c are characteristic of chronic pancreatitis.^[22]
- Serum trypsinogen and urinary D-xylose or faecal elastase if malabsorption is present.

- Imaging: classically there is pancreatic calcification; however, some may have a normal pancreatic appearance on ultrasonography. Ultrasonography is first-line but CT scanning and ERCP may also be required. In severe cases, a plain AXR may show pancreatic calcification.
- Magnetic retrograde cholangiopancreatography (MRCP) may also be used. This is similar to ERCP but involves MRI scanning and not an endoscope. However, it only provides images and not a method to deal with identified problems - eg, strictures. Therefore, patients may need to go on to have ERCP.
- Pancreatic biopsy - this usually shows chronic inflammation and irregularly placed fibrosis. However, pancreatic biopsy is associated with a significant risk and is therefore rarely performed.
- Endoscopic ultrasound (EUS) - this is a newer technique. It involves passing a probe down the oesophagus and stomach and visualising the pancreas. Features like irregular duct walls, duct dilatation and cysts can be detected. However, there are varying rates of sensitivity and specificity and the diagnostic criteria need to be more closely defined, particularly in early and intermediate cases.^[11]

Management^[1]

Management principles

- Pain and malabsorption need to be managed.
- Patients may also need assessment and counselling regarding alcohol intake and illicit drug use - eg, **CAGE questionnaire**.
- Look for the presence of psychiatric conditions - eg, depression.
- History - symptoms of abdominal pain, diarrhoea, weight loss. Look for red flags such as bowel change which may indicate neoplastic disease.
- Alcohol intake, smoking status, family history.
- Examination - mostly to rule out other causes of abdominal pain - eg, cholecystitis.
- Investigations - abdominal ultrasound, baseline blood tests including liver function to look for biliary tract obstruction, refer on for possible secretin test and ERCP or CT scan.
- Management - if there is severe pain, the patient may need to be referred urgently for assessment. If there is mild-to-moderate pain, consider whether the patient can manage at home with simple analgesia, and then refer as an outpatient to gastroenterologists.

Supportive measures

- Lifestyle advice regarding alcohol intake, smoking cessation, dietary advice - high in protein and low in carbohydrate.
- If there is opiate dependence then this may need to be reviewed and managed.
- Advise abstinence from alcohol.

Pain relief^[1]

- Pain relief commonly requires opiates and there is a risk of opiate dependency. Simple analgesics should be used initially - eg, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), provided there are no contra-indications.
- Opiates may also lead to gastroparesis.
- ERCP may help to reduce pain by dilating strictures of the pancreatic ducts. Stenting is appropriate for single benign strictures but the stent may require changing every three months. The stricture often recurs if the stent is removed completely.
- Coeliac plexus block via a gastric approach under EUS guidance has a technically high success rate with low complications. Unfortunately, its effects wear off eventually (only 10% of patients experience long-term pain relief after 24 weeks) so it is reserved as a temporary measure or where no other option is available.

It is important to make sure that there is not another cause for the pain - eg, pseudo-cyst, duct obstruction or dysmotility.

Some of these procedures may result in acute pancreatitis and other complications.

Patients who remain in pain despite the above measures may need to be referred for a surgical opinion (see 'Surgical management', below) and if there is likely to be a delay or they are unsuitable for surgery, they should be referred to local pain clinics.

Malabsorption

Malabsorption is treated by replacing pancreatic enzymes. Diarrhoea can improve but does not usually resolve completely. Lipase is the treatment of choice but it is degraded in the stomach so that high doses have to be given. The results of using enteric coated forms has thus far been disappointing.

Pancreatic enzymes

Replacement of pancreatic enzymes can help malabsorption and also reduce pain - eg, Creon®. It is thought that the pancreatic enzymes provide negative feedback on pancreatic exocrine function. Randomised trials have shown this method to be effective in 30% of patients, especially patients with small duct disease.^[1]

Cholecystokinin (CCK) also stimulates the pancreas and is released from the small intestine by CCK-releasing peptide. The CCK-releasing peptide is broken down by proteases. Pancreatic enzymes that reach the small intestine can break down the CCK-releasing peptide, thereby halting pancreatic stimulation.

Pancreatic enzymes are administered orally and are degraded by stomach fluid reducing the bioavailability. Acid-suppressing medications can be administered at the same time with varying results.

Pancreatic enzymes are usually given as a trial for one month and, if they are effective, they are continued for six months and then they are withdrawn. 50% of patients will have long-term resolution of pain.^[4] However, if patients fail to respond then they should be considered for surgical procedures.

Octreotide

Octreotide is a somatostatin analogue and inhibits pancreatic enzyme secretion and CCK levels. It has been used with varying success rates - but this is limited by the subcutaneous route of administration.^[4]

Surgical management^[1]

- Surgery may be required for the management of complications - eg, pseudo-cyst decompression. An endoscopic approach under ultrasound guidance is increasingly being used.
- Pancreatic duct stones may pass spontaneously, may dislodge with ERCP or may require endoscopic shock wave lithotripsy or laser lithotripsy.
- Surgical decompression of duct dilatation can be performed if this cannot be achieved by ERCP alone. Furthermore, if duct dilatation is large (eg, more than 6 mm), a lateral pancreaticojejunostomy can be performed. Surgical drainage has proved superior to endoscopic techniques for patients with dilated ducts and chronic severe pain (1.5 years or more) unresponsive to opiates.^[18]
- Local surgical resection may also relieve pain in selected cases.^[23]
- Most children and young adults with hereditary pancreatitis can be managed with endoscopic therapy but more invasive surgery is sometimes required.^[24]

Pancreatic resection^[25]

- Pancreatoduodenectomy has been used in chronic pancreatitis and pancreatic cancer.
- Other forms of surgery used include Beger's procedure (duodenal preserving resection of the pancreatic head) and Frey's procedure (extended lateral pancreaticojejunostomy).
- Radical surgery is used for relief of intractable pain not responding to other methods.
- This procedure has been shown to be effective in providing long-term pain relief in patients.
- Recurrence of pain can occur and is often related to alcohol use.
- However, patients will require pancreatic enzyme supplementation, as they lose a large majority of exocrine function.
- A meta-analysis reported that pancreaticoduodenectomy and duodenum-preserving pancreatic head resection were equally effective with regard to pain relief and preservation of pancreatic function. However, at long-term follow-up, duodenum-preserving procedures resulted in a better quality of life and improved long-term outcome in several measures including weight gain, diarrhoea and fatigue.
- Combining surgery with pancreatic enzyme replacement not only provides pain relief but is also associated with weight gain.

Newer management strategies

- Pancreatectomy, followed by autologous islet cell transplantation, has been used in chronic pancreatitis. As islet cells are replaced there is no, or less, endocrine dysfunction. The autologous cells are infused into the portal vein. It is a lengthy operation and is associated with major complications. However, it is associated with reduced pain scores and a reduction in insulin requirements. [4] [26]
- Radiofrequency treatment and spinal cord stimulation are being evaluated as potential pain management options. [4]

Complications

- Cobalamin deficiency.
- Diabetes mellitus - usually brittle and associated with complications.
- **Pericardial**, peritoneal or **pleural** effusions.
- Pseudo-cyst - localised collections of pancreatic fluid which require drainage and bowel rest. [1]
- Gastrointestinal tract haemorrhage - eg, from a pseudo-cyst invading the duodenum.
- Pancreatic carcinoma - it is postulated that chronic inflammation leads to an adenocarcinoma change in pancreatic tissue. [27]

Prognosis

Chronic pancreatitis is associated with increased mortality and morbidity - one third of patients will die within 10 years. Furthermore, for those who continue to drink alcohol, this risk is further increased. The exception is autoimmune pancreatitis which responds well to steroids, even if relapses occur. [28]

Further reading & references

- Paulo JA, Kadiyala V, Banks PA, et al; Mass Spectrometry-Based (GeLC-MS/MS) Comparative Proteomic Analysis of Endoscopically (ePFT) Collected Pancreatic and Gastroduodenal Fluids. *Clin Transl Gastroenterol*. 2012 May 3;3:e14. doi: 10.1038/ctg.2012.7.
1. Oza VM, Kahaleh M; Endoscopic management of chronic pancreatitis. *World J Gastrointest Endosc*. 2013 Jan 16;5(1):19-28. doi: 10.4253/wjge.v5.i1.19.
 2. **Chronic Pancreatitis**, British Society of Gastroenterology, 2009
 3. Lewy P, Barthelet M, Mollard BR, et al; Estimation of the prevalence and incidence of chronic pancreatitis and its complications. *Gastroenterol Clin Biol*. 2006 Jun-Jul;30(6-7):838-44.
 4. Puylaert M, Kapural L, Van Zundert J, et al; 26. Pain in chronic pancreatitis. *Pain Pract*. 2011 Sep-Oct;11(5):492-505. doi: 10.1111/j.1533-2500.2011.00474.x. Epub 2011 Jun 16.
 5. Tandon RK, Garg PK; Oxidative stress in chronic pancreatitis: pathophysiological relevance and management. *Antioxid Redox Signal*. 2011 Nov 15;15(10):2757-66. doi: 10.1089/ars.2011.4115.
 6. Rebours V, Lewy P, Ruzsiewicz P; An overview of hereditary pancreatitis. *Dig Liver Dis*. 2012 Jan;44(1):8-15. doi: 10.1016/j.dld.2011.08.003. Epub 2011 Sep 9.
 7. Schnur A, Beer S, Witt H, et al; Functional effects of 13 rare PRSS1 variants presumed to cause chronic pancreatitis. *Gut*. 2013 Mar 1.
 8. Kibirige D, Kibudde S, Mutebi E; Fibrocalculous pancreatic diabetes in a young Ugandan patient, a rare form of secondary diabetes. *BMC Res Notes*. 2012 Nov 5;5:622. doi: 10.1186/1756-0500-5-622.
 9. Barman KK, Premalatha G, Mhan V; Tropical chronic pancreatitis.; *Postgrad Med J*. 2003 Nov;79(937):606-15.
 10. Mhan V, Farooq S, Deepa M; Prevalence of fibrocalculous pancreatic diabetes in Chennai in South India. *JOP*. 2008 Jul 10;9(4):489-92.
 11. DiMugno MJ, DiMugno EP; Chronic pancreatitis. *Curr Opin Gastroenterol*. 2011 Sep;27(5):452-9. doi: 10.1097/MOG.0b013e328349e333.
 12. Raimondi S, Lowenfels AB, Morselli-Labate AM, et al; Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Pract Res Clin Gastroenterol*. 2010 Jun;24(3):349-58. doi: 10.1016/j.bpg.2010.02.007.
 13. Dettlefsen S, Lohr JM, Drewes AM, et al; Current concepts in the diagnosis and treatment of type 1 and type 2 autoimmune pancreatitis. *Recent Pat Inflamm Allergy Drug Discov*. 2011 May;5(2):136-49.
 14. Kim KP, Kim MH, Kim JC, et al; Diagnostic criteria for autoimmune chronic pancreatitis revisited.; *World J Gastroenterol*. 2006 Apr 28;12(16):2487-96.
 15. Liu B, Li J, Yan LN, et al; Retrospective study of steroid therapy for patients with autoimmune pancreatitis in a Chinese population. *World J Gastroenterol*. 2013 Jan 28;19(4):569-74. doi: 10.3748/wjg.v19.i4.569.
 16. Gupta R, Khosroshahi A, Shinagare S, et al; Does Autoimmune Pancreatitis Increase the Risk of Pancreatic Carcinoma?: A Retrospective Analysis of Pancreatic Resections. *Pancreas*. 2012 Dec 26.
 17. Brand H, Diergaarde B, O'Connell MR, et al; Variation in the gamma-Glutamyltransferase 1 Gene and Risk of Chronic Pancreatitis. *Pancreas*. 2013 Mar 4.
 18. DiMugno MJ, DiMugno EP; Chronic pancreatitis. *Curr Opin Gastroenterol*. 2012 Sep;28(5):523-31. doi: 10.1097/MOG.0b013e3283567dea.

19. Bhanot UK, Moller P; Mechanisms of parenchymal injury and signaling pathways in ectatic ducts of chronic pancreatitis: implications for pancreatic carcinogenesis. *Lab Invest.* 2009 May;89(5):489-97. doi: 10.1038/labinvest.2009.19. Epub 2009 Mar 23.
20. Freedman S, Chronic Pancreatitis, Merck Manual, 2012
21. Stevens T, Parsi MA; Update on endoscopic pancreatic function testing. *World J Gastroenterol.* 2011 Sep 21;17(35):3957-61. doi: 10.3748/wjg.v17.i35.3957.
22. Lindkvist B, Dominguez-Munoz JE, Luaces-Regueira M, et al; Serum nutritional markers for prediction of pancreatic exocrine insufficiency in chronic pancreatitis. *Pancreatology.* 2012 Jul-Aug;12(4):305-10. doi: 10.1016/j.pan.2012.04.006. Epub 2012 May 4.
23. Andersen DK, Frey CF; The evolution of the surgical treatment of chronic pancreatitis. *Ann Surg.* 2010 Jan;251(1):18-32.
24. Ceppa EP, Pitt HA, Hunter JL, et al; Hereditary Pancreatitis: Endoscopic and Surgical Management. *J Gastrointest Surg.* 2013 Feb 23.
25. Lu WP, Shi Q, Zhang WZ, et al; A meta-analysis of the long-term effects of chronic pancreatitis surgical treatments: duodenum-preserving pancreatic head resection versus pancreatoduodenectomy. *Chin Med J (Engl).* 2013 Jan;126(1):147-53.
26. Garcea G, Pollard CA, Illouz S, et al; Patient satisfaction and cost-effectiveness following total pancreatectomy with islet cell transplantation for chronic pancreatitis. *Pancreas.* 2013 Mar;42(2):322-8. doi: 10.1097/MPA.0b013e318264d027.
27. Kudo Y, Kamisawa T, Anjiki H, et al; Incidence of and risk factors for developing pancreatic cancer in patients with chronic pancreatitis. *Hepatogastroenterology.* 2011 Mar-Apr;58(106):609-11.
28. Hart PA, Kamisawa T, Brugge WR, et al; Long-term outcomes of autoimmune pancreatitis: a multicentre, international analysis. *Gut.* 2012 Dec 11.

Disclaimer: This article is for information only and should not be used for the diagnosis or treatment of medical conditions. EMIS has used all reasonable care in compiling the information but make no warranty as to its accuracy. Consult a doctor or other health care professional for diagnosis and treatment of medical conditions. For details see our [conditions](#).

Original Author: Dr Gurvinder Rull	Current Version: Dr Laurence Knott	Peer Reviewer: Dr Helen Huins
Last Checked: 09/04/2013	Document ID: 1528 Version: 23	© EMIS

View this article online at www.patient.co.uk/doctor/chronic-pancreatitis-pro.

Discuss Chronic Pancreatitis and find more trusted resources at www.patient.co.uk.

EMIS is a trading name of Egton Medical Information Systems Limited.