Chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a progressive, disabling, fibro-inflammatory disease of the pancreas of variable clinical course and is usually associated with permanent loss of exocrine and endocrine function over a period of time. The incidence is increasing. There are various aetiological risk factors that cause CP, chronic alcoholism being the most common risk factor. The TIGAR-O classification identifies all the risk factors and aetiology. Most susceptible patients have a sentinel acute pancreatitis event which initiates chronic progressive inflammation, scarring and fibrosis, though some may present insidiously with symptoms of functional loss – diabetes or steatorrhoea. Intractable abdominal pain, steatorrhoea, weight loss and (type 3c) diabetes mellitus are late manifestations of the disease. Diagnosis is made with a combination of clinical history, examination, cross sectional imaging combined with pancreatic function tests (in equivocal cases). Complications include gastric and biliary obstruction, pseudocyst formation, pancreatic ascites, pseudoaneurysms and venous thrombosis. Patients with CP have increased risk of developing pancreatic adenocarcinoma. Management includes making the diagnosis, identifying the aetiology, instituting life-style changes to abstain from alcohol and smoking, and involving the specialist multidisciplinary team (including pain team, dietician, clinical psychologist, endoscopist, gastrointestinal physician and pancreatic surgeon) if initial steps do not control the symptoms.

Keywords Chronic pain; chronic pancreatitis; exocrine insufficiency; pancreas

Background

Chronic pancreatitis (CP) is a progressive irreversible inflammatory disease where pancreatic parenchyma is gradually replaced by fibrosis. CP is typically characterized by abdominal pain associated with variable loss of exocrine and endocrine function depending on the extent of the parenchymal damage over a period of time. A US study reported an age and sex adjusted prevalence rate of 42 cases/100,000 population and an incidence of 4/100,000 person years. The incidence is increasing due to alcohol consumption, increased awareness of the disease and improved access to diagnostic facilities. Symptomatic patients often require repeated hospital admissions for intravenous opiate analgesia, various investigations and may require medical or surgical intervention for complications that have a significant impact on their quality of life. In an observational study, CP was reported to be associated with an overall mortality rate of 30% and 55% at 10 and 20 years, respectively, from the time of diagnosis, significantly more than the background population. Given the rise in incidence and prevalence of CP, the potential complications and high mortality rate, it is important that the pathophysiology, risk factors, disease process and management of this disease is understood.

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Pathophysiology

The majority of patients with CP have a protracted course of illness with varying degrees of symptoms over the years. The natural course is very variable and there is no tool available to predict the disease progress for an individual patient. In the majority of patients, the onset is an acute episode of abdominal pain followed by recurrent episodes, although in some patients there may be an insidious onset. The exact mechanism of development of CP is unknown but there are various theories regarding the underlying pathophysiology.

Oxidative stress

It has been proposed that the root cause of pancreatic inflammatory disease is the overactivity of hepatic mixed-function oxidases. These enzymes are useful in the detoxification of harmful blood-borne substances in the liver. The reactive molecules, which are the by-products of their activity, can cause oxidative damage to the tissues. The pancreas is exposed to this 'oxidative stress' either through the systemic circulation or through the reflux of bile into the pancreatic duct, leading to inflammation and tissue damage. There are critics to this theory who feel that oxidative stress may have a role in the pathogenesis of CP but does not initiate it.

Toxic metabolites

Alcohol is directly toxic to the pancreatic acinar cell. Alcohol consumption can lead to accumulation of lipid within the acinar cells and can lead to fatty degeneration, cellular necrosis and fibrosis. However, as only 5–10% of people who consume alcohol develop clinically apparent chronic pancreatitis, this alone does not explain alcohol as a single aetiological factor.

Duct obstruction and stone formation

Alcohol increases lithogenicity of pancreatic juice leading to the formation of protein plugs and stones. The presence of stones in the pancreatic duct results in irritation, inflammation, ulceration, stricture formation and pancreatic duct obstruction.

Necrosis-fibrosis

This hypothesis proposes that the development of CP occurs as a consequence of recurrent episodes of acute pancreatitis. Inflammation and necrosis from acute pancreatitis produces fibrosis or scarring in the periductular areas. This scarring and fibrosis may cause obstruction of the ducts, stasis and stone formation resulting in atrophy of the gland.

Primary duct theory

This proposes that CP represents a primary autoimmune or inflammatory condition beginning in the pancreatic duct, similar to primary sclerosing cholangitis. This theory assumes that the primary pathogenic factor leading to duct destruction is an immunogenic attack of the duct epithelium, destroying the duct, leading to inflammation and scarring of the ductal architecture.

Sentinel acute pancreatitis event (SAPE) theory

This hypothesis combines the knowledge about molecular and cellular mechanisms of CP pathogenesis in an effort to put previous hypotheses together. This SAPE hypothesis attempts to explain the 'final pathway' for various aetiologies of CP. A 'sentinel' attack of acute pancreatitis is essential in a susceptible person (due to genetic or other mechanism) with risk factors (like toxins, alcohol, infections) to trigger the process of fibrosis, calcification and atrophy.

Aetiology and risk factors

There is no one aetiology for chronic pancreatitis but a better understanding of the pathophysiology has led to a realization that the presence of multiple risk factors in a susceptible person makes them prone to develop CP. The major risk factors associated with development of CP are categorized according to the TIGAR-O classification (Figure 1).

Toxic and metabolic

Alcohol remains the commonest risk factor associated with CP, with 5–10% of alcoholic patients developing clinically apparent CP, though at autopsy 10–20% of alcoholics are found to have evidence of CP. The quantity and duration of alcohol consumption is very variable among patients with CP. In most patients, a large quantity of alcohol (>60 g/day) over several years is needed to develop CP but in some patients, a smaller amount may be sufficient to produce pancreatic damage suggesting a genetic susceptibility.

Smoking is considered an independent risk factor for CP. It is possible that smoking is an isolated factor in some patients, whereas in others it could be a co-factor potentiating the toxic effects of alcohol.

Hypercalcemia causes premature trypsinogen activation, direct damage to acinar cells and modifies pancreatic secretion leading to protein plug formation and chronic pancreatitis.

Idiopathic

Up to one-third of patients with CP have no known risk factors, i.e. idiopathic. There are two groups of patients – early onset and late onset. Patients with early onset CP tend to present with abdominal pain before the age of 20 years. Patients with late onset CP usually present in their 5th decade of life without pain but with associated poor pancreatic function related symptoms.

Genetic

Hereditary pancreatitis is associated with CP. There are a few gene mutations described – gain-of-function mutation (e.g. PRSS-1 mutation associated with premature activation of trypsinogen to trypsin) or loss-of-function mutation (e.g. SPINK1 or CTRC mutation associated with lack of inhibition of trypsin, or CFTR mutation causing impairment of secretary function of duct cells and inhibition of pancreatic enzyme flow). Inheritance occurs as an autosomal dominant trait with variable expression. These groups of patients have a high risk of developing pancreatic ductal adenocarcinoma.

Autoimmune

Autoimmune pancreatitis is a rare form of pancreatitis which is immune mediated and responds well to steroid treatment. It is classified as type 1 or type 2. Type 1 autoimmune pancreatitis is part of a multiorgan fibro-inflammatory syndrome known as IgG4 disease, and is characterized by increased serum IgG4 concentrations, multiorgan involvement, typical histological findings with lymphocytic infiltration, and a rapid response to steroids. Type 2 is distinctly different in that it is mainly duct centric with acute recurrent episodes and has neutrophilic infiltration without response to steroids.

Recurrent severe

Acute severe necrotic pancreatitis may result in scarring, fibrosis and permanent dysfunction of the pancreas. Recurrent acute pancreatitis of any cause may lead to CP through necrosis-fibrosis and SAPE.

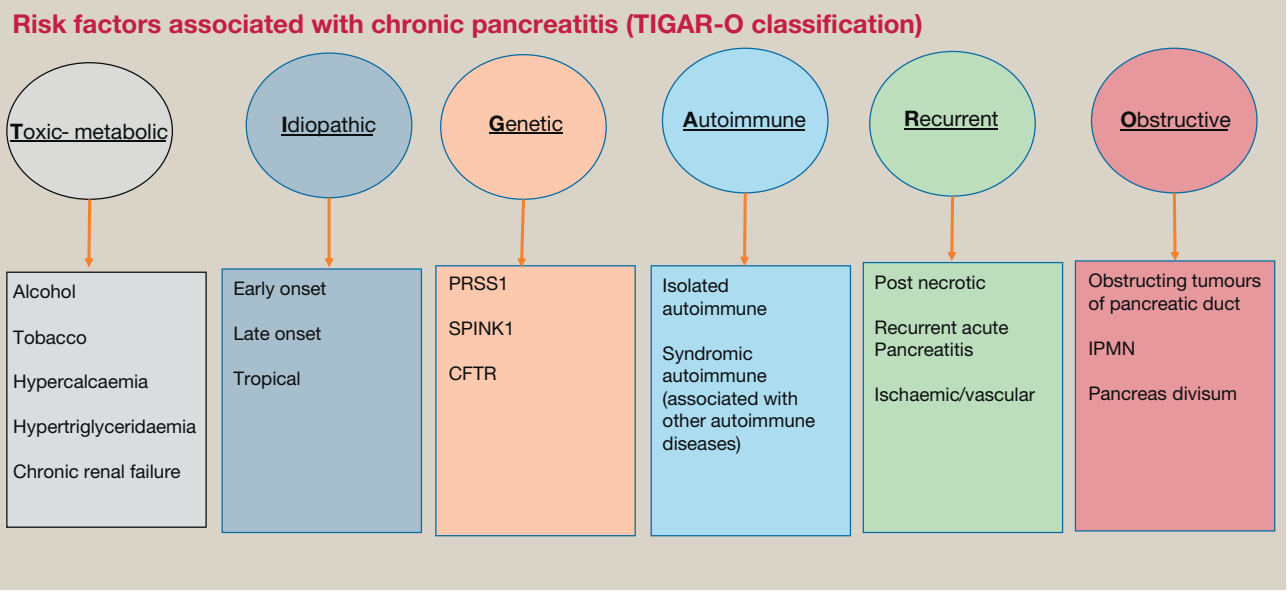


Figure 1

Obstructive

Ductal obstruction secondary to pancreatic malignancy, trauma or inflammatory strictures can cause chronic obstructive pancreatitis. There is ongoing debate as to whether pancreas divisum and sphincter of Oddi dysfunction can cause CP.

Clinical features

Patients rarely present with classical symptoms of CP initially. Typically, they present with repeated episodes of upper abdominal pain consistent with recurrent acute pancreatitis. Over a period of years, this leads to morphological and functional changes in the pancreas. With time, patients develop the classical triad of abdominal pain, exocrine pancreatic insufficiency (with weight loss) and diabetes.

Pain in CP usually occurs after a meal, mainly in the epigastric area with radiation to the back, often associated with nausea and vomiting. Pancreatic ductal hypertension, pancreatic parenchymal hypertension (like 'compartment syndrome'), activation of intrapancreatic nociceptors, hypertrophy and inflammation of intrapancreatic nerves, abnormal pain processing in the central nervous system, and onset of local or remote complications of CP are all reasons that may cause severe persistent pain in patients with CP. There is often little correlation between the severity of pain and demonstrable abnormal vital signs or morphological changes of the pancreas on cross-sectional imaging. This often results in undertreatment of pain in patients with CP.

Pancreatic enzymes, bile salts and an intact intestinal mucosa are essential for the complex process involved in fat digestion and absorption. Pancreatic exocrine enzyme insufficiency due to CP is one of the causes of steatorrhoea, i.e. excess maldigested and mal-absorbed fat in the stool. The pancreas has a large functional reserve and it takes up to 90% of the gland to be destroyed before a patient develops symptoms of pancreatic enzyme deficiency.

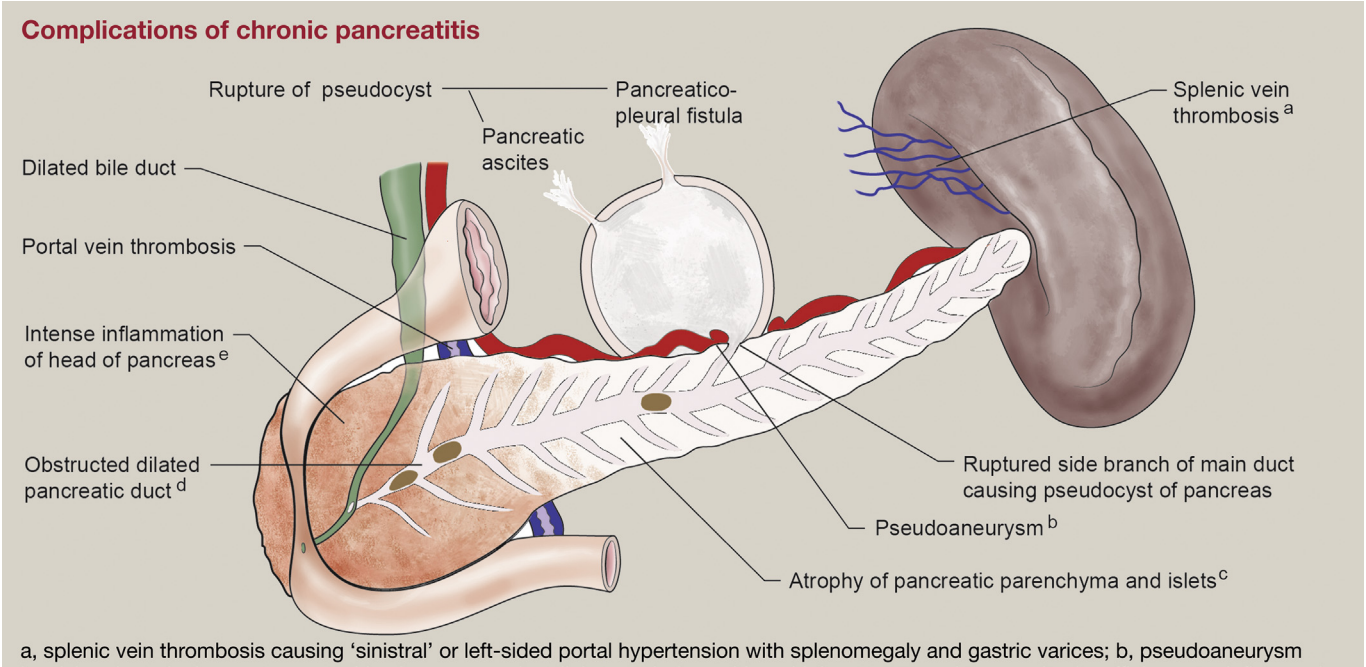
Progressive fibrosis with loss of endocrine cells in the pancreas leads to development of type 3C (or pancreatogenic) diabetes mellitus. These patients loose not only beta cells (as a result of scarring/fibrosis) resulting in hyperglycaemia, but are at a higher risk of developing hypoglycaemia due to loss of alpha and delta cells resulting in lack of counter hormones such as glucagon and vasoactive intestinal polypeptide.

Some patients develop complications from CP. Pancreatic duct rupture with recurrent inflammation may lead to formation of pseudocysts, pancreatic ascites or pancreato-pleural fistula; scarring and fibrosis may lead to duodenal or biliary duct obstruction; portal and splenic vein thrombosis may lead to left sided ('sinistral') portal hypertension and formation of gastric varices; erosion of the peripancreatic arteries may lead to pseudoaneurysm and bleeding from splenic, gastroduodenal, superior and inferior pancreatico-duodenal arteries (Figure 2).

Diagnosis

The diagnosis of CP is based on thorough clinical history, physical examination, appropriate cross-sectional imaging with or without additional pancreatic function tests. Diagnosis is very obvious in patients with advanced disease. It can be challenging in early stages and suspicion of CP in the correct clinical context is the key to making the diagnosis.

In addition to the main clinical symptoms of abdominal pain, weight loss, steatorrhoea and diabetes mellitus, patients may present with symptoms related to local complications (Figure 2). These symptoms may present in various combinations with different severity during evolution of the disease. Abdominal pain is the most common symptom, but may be absent in 15% of patients with



a, splenic vein thrombosis causing 'sinistral' or left-sided portal hypertension with splenomegaly and gastric varices; b, pseudoaneurysm involving the splenic artery; c, atrophic changes causing diabetes; d, duct with multiple stones causing exocrine insufficiency; e, inflammation with biliary and duodenal stenosis and upstream dilatation

Figure 2

alcohol-related CP (and in up to 23% of patients with non-alcoholic pancreatitis). Patients can have a bloating sensation, abdominal pain or a change in bowel habit due to impaired pancreatic exocrine secretion, and steatorrhoea usually develops late.

Physical examination may reveal signs of malnutrition, erythema ab igne, jaundice, ascites, splenomegaly, signs of liver failure or it may be normal.

The most accurate method for diagnosing CP is histologic examination of the pancreatic gland. It is not always practical to obtain pancreatic tissue due to the difficulty in accessing the pancreas and the risks associated with biopsy of the pancreas. Although endoscopic and percutaneous biopsy options are available, sample error (resulting in false negative diagnosis) and adverse effects (from complications like acute pancreatitis) are the main limitations in obtaining pancreatic tissue for diagnosis.

Other diseases can present with a similar clinical picture and it is important to consider pancreatic cancer as a main differential diagnosis, particularly when there is a mass lesion in the pancreas or if the patient presents with obstructive jaundice. Other causes to be considered are peptic ulcer disease, gallstone disease, chronic mesenteric ischaemia and irritable bowel syndrome.

Figure 3 Plain X-ray of the abdomen showing diffuse calcification of the pancreas with advanced chronic pancreatitis.

Plain abdominal X-ray

Focal or diffuse calcification in the distribution of the pancreas gland area is a definite indication of advanced chronic pancreatitis (Figure 3). Absence of this does not rule out the diagnosis.

Ultrasound

Abdominal ultrasound is usually done as a first step in investigation of abdominal pain. However, abdominal ultrasound is not very useful in the investigation of pancreatic pathology due to its retroperitoneal location and the presence of gas-containing viscera anterior to the pancreas interfering with the penetration of ultrasound waves to get meaningful information.

Computed tomography (CT)

CT is sensitive in demonstrating both pancreatic parenchymal and pancreatic duct changes in CP and is widely available (Figure 4). CT is very sensitive to identify (ductal and parenchymal) calcification, pancreatic mass, pancreatic parenchymal atrophy and CP associated complications (such as pseudocysts, ascites, pseudoaneurysms, venous thrombosis and biliary obstruction). Limitation of CT is its lack of sensitivity and specificity in picking up early mild forms of CP. It has an inherent risk of radiation (particularly with repeated examination) and can induce contrast associated nephropathy.

Magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP)

MRCP is a non-invasive procedure and does not use radiation. It has high sensitivity for identifying strictures and dilatations in (main and side branch) pancreatic ducts. Dynamic MRCP or secretin MRCP captures series of images in rapid sequence for up

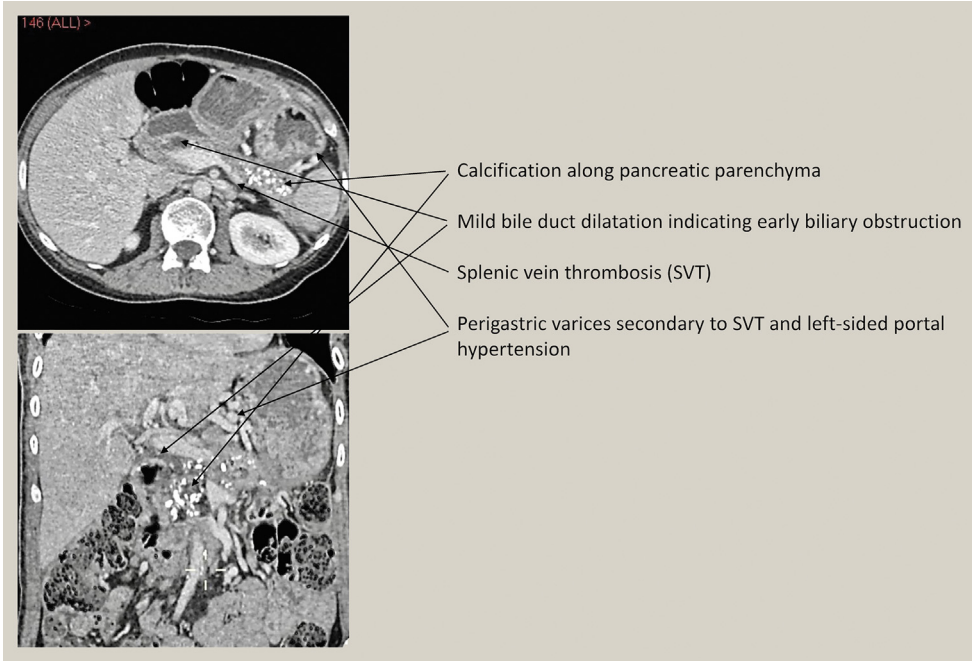


Figure 4 Axial and coronal reconstruction of a CT scan of a patient with chronic pancreatitis.

to 10 minutes after intravenous administration of secretin hormone and provides excellent spatial resolution and functional information regarding exocrine pancreatic function. Intravenous contrast agent is not used routinely and this limits identification of other pancreatic parenchymal abnormalities and vascular complications. Secretin is expensive, hence secretin MRCP examination is not widely available and is restricted to specialist practice.

MRI examination of the pancreas usually uses intravenous contrast and gives better information of the pancreatic parenchyma compared to MRCP. However, CT is more sensitive in picking up small calcifications and vascular abnormalities than MRI. Advanced MRI for estimation of tissue stiffness, quantification of fibrosis in pancreas and pancreatic fluid flow dynamics are under evaluation.

Endoscopic retrograde cholangiopancreatography (ERCP)

ERCP was the gold standard investigation to diagnose CP in the past. Ductal changes noted on ERCP were previously considered the most reliable imaging test for diagnosis of chronic pancreatitis with sensitivity up to 90%. Due to wider availability of non-invasive MRCP and its capacity to obtain good quality images of the pancreatic duct, ERCP use is now restricted to therapeutic purposes only.

Endoscopic ultrasound (EUS)

EUS can be used to diagnose CP. The 'Rosemont' classification was developed in an attempt to define criteria for diagnosis of CP. It is uncertain which EUS features are normal age-related findings or due to non-diagnostic asymptomatic fibrosis, particularly in an asymptomatic patient with the absence of endocrine or exocrine dysfunction. Interobserver variation is well known to occur in EUS reporting. Though it is a useful tool to obtain biopsy of a pancreatic mass (identified on CT or MRI) when malignancy is suspected in patients with known CP, it remains under evaluation for use as a diagnostic tool for CP.

Tests of pancreatic function

There are tests to measure exocrine and endocrine function of the pancreas gland. The pancreatic gland has to lose 90% of its function before clinical symptoms of steatorrhoea occur. However, there are direct and indirect methods to assess pancreatic exocrine function.

The direct pancreatic function tests include duodenal intubation using fluoroscopy or endoscopy to collect the pancreatic juice. The pancreatic juice is collected after stimulation of the pancreas with secretin. The total volume and biochemical content of the juice for bicarbonate level are measured. This procedure is invasive and cumbersome with poor patient compliance due to the requirement of duodenal intubation, but can be considered in a symptomatic patient with suspected CP and equivocal CT/MRI images.

Non-invasive indirect pancreatic function tests are available. A 72-h our quantitative faecal fat determination can be used to diagnose fat maldigestion resulting in steatorrhoea. It is not specific for CP and can give false-positive results in patients with biliary obstruction, small bowel mucosal disease and bacterial overgrowth. Measurement of faecal elastase-1 enzyme, which is produced by the pancreas and remains unchanged in the gastrointestinal tract, is a commonly used test in clinical practice. It is not sensitive or helpful in patients with mild or moderate pancreatic exocrine insufficiency. However, faecal elastase-1 has been shown to be more specific, with a sensitivity approaching 100% and specificity reported as 93% in patients with severe insufficiency.

Treatment

Non-operative management

The aim of treatment in patients with CP is mainly to control pain, address exocrine and endocrine insufficiency, and deal with complications such as biliary obstruction, bleeding, etc. Life-style changes including abstaining from alcohol and stopping smoking will reduce the risk of recurrent episodes of CP and will preserve existing pancreatic function.

Pain control is the main problem in this difficult group of patients. They often do not show all the objective signs of pain and their analgesic requirement is often underestimated. Some patients will develop opioid addiction and become frequent attenders to hospital seeking narcotic analgesics. It is important to make sure that there are no underlying CP associated complications by undertaking cross sectional imaging prior to escalating doses of narcotics. Pain control should follow the principles of the WHO 'pain relief ladder'. Antidepressants (e.g. amitriptyline), anticonvulsants (e.g. gabapentin and pregabalin) and selective serotonin reuptake inhibitors sometimes work along with conventional analgesics in a synergistic way. It is important to involve a specialist pain team and clinical psychologist in management of complex pain associated with CP. During acute episodes, patients with CP may benefit from short duration intravenous morphine administered using a patient-controlled analgesia (PCA) device. Pancreatic enzyme supplementation or antioxidants for treatment of pain in CP are not recommended. Invasive procedures like coeliac plexus block and thoracoscopic splanchnicectomy may provide short term benefit for intractable pain but invariably the pain returns and these techniques are therefore not advocated for treatment of pain in patients with CP.

Exocrine failure leads to fat malabsorption and results in steatorrhoea and weight loss. This is associated with deficiency of fat-soluble vitamins. Pancreatic enzymes can be administered orally along with snacks and meals. The dosage is measured in lipase units. Adequacy of dosage is determined by reduction in frequency of steatorrhoea and weight gain. The usual starting dose is 25,000 lipase units with snacks and 50,000 lipase units with meals. These dosages can be titrated based on the response. Adding a proton pump inhibitor may enhance the efficacy of pancreatic enzyme supplementation. However, if the response to pancreatic enzymes is poor, once compliance is assured, alternate causes need to be explored.

Endocrine failure leads to type 3c diabetes mellitus. Although this may initially be treated with oral hypoglycaemic drugs, usually these patients will require insulin supplementation.

Life style modification (smoking and alcohol abstinence, daily exercise and healthy eating habits etc) is a key component of non-operative treatment.

Endoscopic treatment

Endoscopic treatment is considered in symptomatic CP with:

- pancreatic duct stricture and upstream dilatation

- pancreatic duct stones with obstruction
- pancreatic pseudocyst
- bile duct stricture with deteriorating obstructive liver function tests.

Large symptomatic pancreatic duct stones associated with strictures can be treated by pancreatic duct dilatation and removal of the stones, usually combined with extracorporeal shockwave lithotripsy (ESWL). Though endoscopic stenting of the obstructed pancreatic duct is an option, it is reserved for less fit patients as early surgery may preserve pancreatic parenchymal function in the long term. Symptomatic pancreatic pseudocysts can be drained (once matured) by transmural drainage using EUS or by transpapillary pancreatic duct stent at ERCP. With the advent of fully covered self-expanding metal stents (FCSEMS), bile duct strictures secondary to CP can be successfully treated. A prospective multicentre case series showed endoscopic FCSEMS as a viable treatment option for CP patients with benign lower common bile duct strictures, with a stricture resolution rate of 79.4% at 1 year and a stricture recurrence rate of 10.5% after a mean follow-up of 20 months.

Surgical treatment

Surgery in selected patients is associated with good results. Surgery is typically indicated in patients with duodenal, pancreatic or biliary obstruction, those with a symptomatic large pseudocysts, if a pancreatic mass is present (on the background of CP) and malignancy cannot be excluded and in patients with intractable pain. Though invasive surgical procedures may be justified as a treatment for complications of CP (like duodenal or biliary obstruction or suspected neoplasm), the risks versus benefits in offering major surgery for intractable pain in patients with CP should be considered carefully, the rationale being that

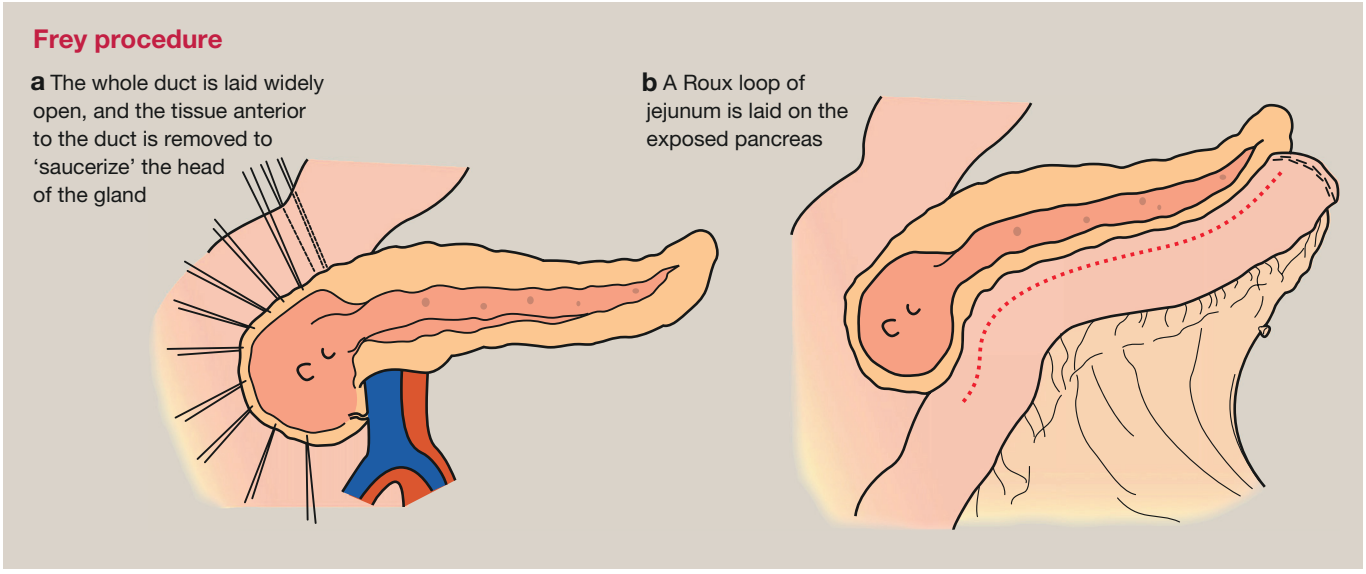


Figure 5

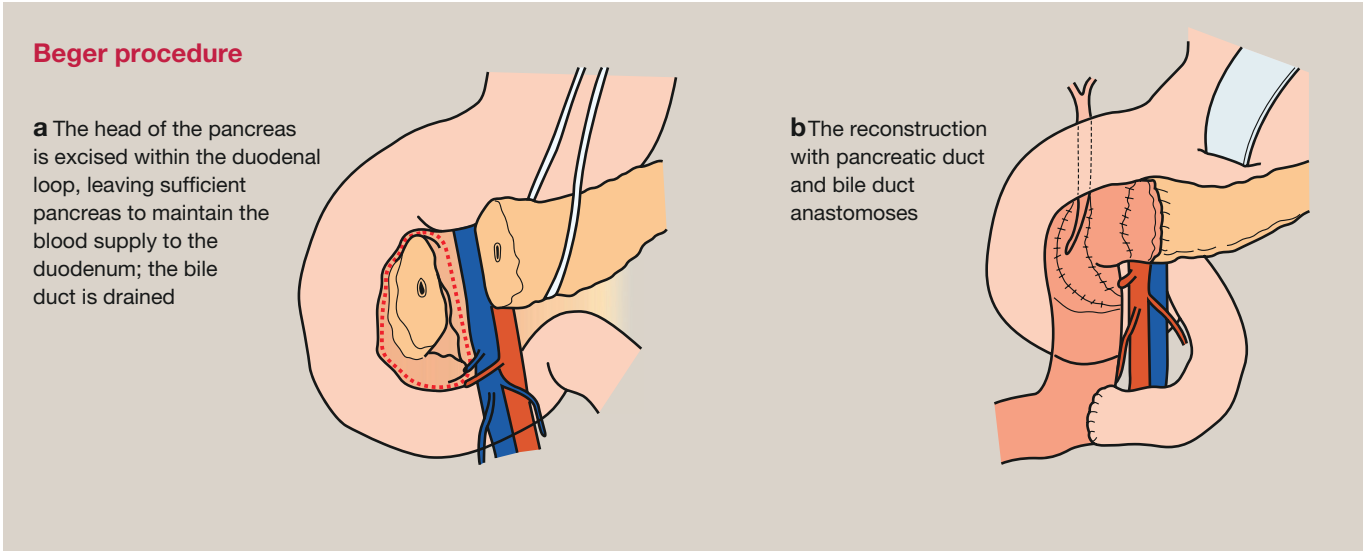


Figure 6

pain may be caused by pancreatic ductal obstruction or increased intrapancreatic pressure (like 'compartment syndrome') or by ongoing inflammation associated with a mass lesion usually located in the head of the pancreas. None of the described operations are sham controlled in trials and it is not possible to assess the placebo effect of surgery or the natural course of the disease. However, in most studies, operative intervention (with pain as an indication) in selected patients is associated with significant long-term pain relief (up to 70–90%).

Most clinicians consider surgical treatment in patients with severe pain who have failed to respond to maximal medical treatment and also have a surgical target in the form of dilated pancreatic duct or a mass lesion. Surgical procedures for CP are mainly divided into three categories:

- drainage or decompression (e.g. Peustow's longitudinal pancreaticojejunostomy)
- resection (e.g. Whipple's pancreaticoduodenectomy, distal pancreatectomy)
- combination of both (e.g. Frey's procedure, Beger's procedure).

A commonly performed procedure for CP is longitudinal pancreaticojejunostomy (Peustow's operation). This involves exposing the anterior part of the pancreas and opening the entire length of the pancreatic duct longitudinally from the ampulla along the head, body and tail of the pancreas. After removal of all the stones from the opened duct, a Roux loop of jejunum is anastomosed to the opened pancreatic duct longitudinally to establish adequate drainage. This operation often does not address an enlarged, inflamed pancreatic head which can cause persistent symptoms after the procedure. However, a Frey's procedure (Figure 5), where the tissue in the head of the pancreas anterior to the pancreatic duct is cored out, gives better symptom control in the long run. Alternatively, the whole of the pancreatic head can be removed with preservation of the duodenum as in a Beger's procedure (Figure 6). A formal resection of the head of the pancreas, i.e. a Whipple pancreaticoduodenectomy should be performed when malignancy associated with CP cannot be excluded. Distal pancreatectomy is occasionally undertaken in selected patients where disease is confined to the distal pancreas. Total pancreatectomy is associated with postoperative brittle diabetes and 50% of patients will have persistent pain. Total pancreatectomy with islet autotransplantation is a viable option (in specialized centres) for patients with hereditary chronic pancreatitis, due to an increased risk of pancreatic cancer in this group.

In summary, CP is disabling disease that sometimes can be difficult to diagnose. Management is often conservative with life style changes, but some patients with intractable pain or disease-specific complications will require the expertise of a multidisciplinary team and specialist therapeutic interventions. ◆

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