Chronic pancreatitis

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Chronic pancreatitis describes a wide spectrum of fibro-inflammatory disorders of the exocrine pancreas that includes calcifying, obstructive, and steroid-responsive forms. Use of the term chronic pancreatitis without qualification generally refers to calcifying chronic pancreatitis. Epidemiology is poorly defined, but incidence worldwide seems to be on the rise. Smoking, drinking alcohol, and genetic predisposition are the major risk factors for chronic calcifying pancreatitis. In this Seminar, we discuss the clinical features, diagnosis, and management of chronic calcifying pancreatitis, focusing on pain management, the role of endoscopic and surgical intervention, and the use of pancreatic enzyme-replacement therapy. Management of patients is often challenging and necessitates a multidisciplinary approach.

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Definition and forms

Chronic pancreatitis describes a wide range of progressive fibro-inflammatory diseases of the exocrine pancreas that eventually lead to damage of the gland. If widespread, this damage causes failure of exocrine and endocrine pancreatic function and needs treatment. Chronic pancreatitis encompasses a number of disease entities and can be broadly classified into three forms: chronic calcifying pancreatitis, chronic obstructive pancreatitis, and steroid-responsive pancreatitis (chronic autoimmune pancreatitis; figure 1). The natural history and clinical presentation of chronic pancreatitis vary depending on the form and causal mechanism, although abdominal pain is present in most patients.[1]

The early stages of chronic calcifying pancreatitis are characterised by clinically apparent acute pancreatitis. As the disease progresses, there is development of intraductal stones (in the main pancreatic duct or its side branches), pancreatic ductal distortion, strictures, and pancreatic atrophy (figure 2A). Extensive destruction of the pancreatic parenchyma leads to steatorrhoea (excess fat in faeces) and diabetes. Compared with chronic calcifying pancreatitis, the other forms of chronic pancreatitis (obstructive, autoimmune) very rarely include calcification. We use the term chronic calcifying pancreatitis because it describes the most common disease phenotype associated with this form of chronic pancreatitis and its use is widespread in the literature.

Chronic obstructive pancreatitis is a term used for chronic pancreatitis that results from primary injury to the duct or is due to partial or complete ductal obstruction.[2–4] Obstructive pancreatitis occurs upstream from a pancreatic duct stricture caused by pancreatic duct injury (during endoscopic or surgical procedures, after necrotising acute pancreatitis, or following blunt injury to the abdomen); narrowed pancreatico-enteric anastomoses; and tumours obstructing the pancreatic duct (eg, ductal adenocarcinoma and intraductal papillary mucinous tumour). Ductal obstruction due to strictures and stones can also complicate chronic calcifying pancreatitis. In the pure form of chronic obstructive pancreatitis, only the organ upstream from the obstruction is affected, with the downstream pancreas being healthy. Chronic obstructive pancreatitis is often asymptomatic; however, partial obstruction can lead to recurrent bouts of clinically acute pancreatitis involving the obstructed part of the gland.

Steroid-responsive pancreatitis (chronic autoimmune pancreatitis), better known as autoimmune pancreatitis, is a unique form of chronic pancreatitis in which the inflammation responds rapidly to corticosteroids. Autoimmune pancreatitis has been classified into two subtypes: type 1 and type 2, which seem to be two distinct diseases. Since the term autoimmune pancreatitis is generally associated with the clinical profile of type 1 autoimmune pancreatitis, some people have suggested that the term autoimmune pancreatitis be used only to describe type 1 autoimmune pancreatitis and that type 2 autoimmune pancreatitis should instead be called idiopathic duct-centric chronic pancreatitis.[5]

Type 1 autoimmune pancreatitis is the pancreatic manifestation of a multiorgan fibro-inflammatory syndrome known as immunoglobulin G4 (IgG4)-related disease, which is characterised by increased serum IgG4 concentrations, multiorgan involvement, typical histological signs, and a rapid response to corticosteroids and B-cell depletion therapy. IgG4-related disease affects several organs, including the pancreas, bile duct, salivary glands, retroperitoneum, kidneys, and lymph nodes.[6] Pancreatic disease in type 1 autoimmune pancreatitis (figure 2B) resembles that seen in other organs affected in IgG4-related disease and is characterised by a dense lymphoplasmacytic infiltrate around medium-sized ducts, a peculiar swirling (storiform) fibrosis, an intense

Search strategy and selection criteria

We searched Medline via the Ovid interface with use of MeSH terms (chronic pancreatitis/) and keyword "chronic pancreatitis". We limited the search to English language articles indexed between Jan 1, 2010, and Feb 18, 2015. On Feb 24, 2015, we searched the abstracts of Digestive Disease Week published from 2010 to 2014 . We reviewed the bibliography of selected articles and abstracts to identify additional relevant studies. We also cite high-impact articles from before 2010 when necessary for a complete understanding of the subject.

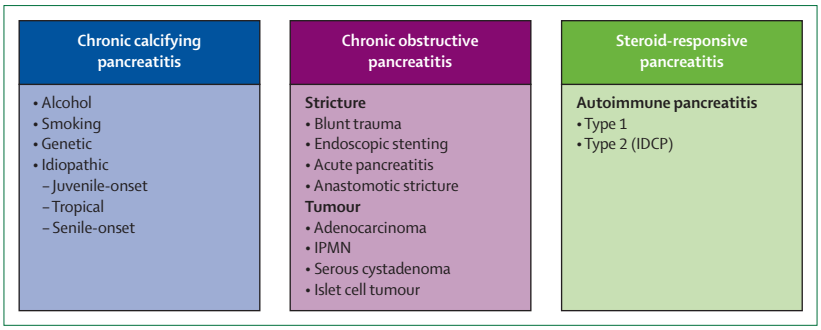

Figure 1: **Classification of chronic pancreatitis**
IPMN=intraductal papillary mucinous neoplasm. IDCP=idiopathic duct-centric pancreatitis.

inflammation that surrounds veins (obliterative phlebitis) and spares adjacent arteries, and abundant (>10 per high-power field) IgG4-positive plasma cells. The most common clinical presentation of type 1 autoimmune pancreatitis is obstructive jaundice mimicking pancreatic cancer; it less commonly presents with clinically acute pancreatitis.[7] Pain is not a prominent feature and, if present, resolves quickly with steroid treatment. Pancreatic calcification is uncommon in type 1 autoimmune pancreatitis and usually occurs in relapsing disease.[7]

Idiopathic duct-centric chronic pancreatitis (type 2 autoimmune pancreatitis) differs substantially from type 1 autoimmune pancreatitis (table). Histologically, idiopathic duct-centric chronic pancreatitis (figure 2C) is characterised by neutrophilic infiltrate in the pancreatic duct epithelium (a granulocyte epithelial lesion), which can lead to ductal obliteration. Idiopathic duct-centric chronic pancreatitis tends to present with pancreatitis, which is often recurrent.[8] In a 2015 review, Hart and colleagues[5] discuss management of both autoimmune pancreatitis and idiopathic duct-centric chronic pancreatitis.

Pancreatic fibro-atrophy is also commonly seen in autopsies of people without clinical pancreatic disease (Figure 2D). Such pancreatopathy can be associated with intense bland fibrosis, which is typically non-inflammatory, and is not associated with the pancreatic ductal changes commonly seen in chronic pancreatitis. In this Seminar, we discuss only chronic calcifying pancreatitis, referring to it as chronic pancreatitis.

Epidemiology

The epidemiological characteristics of chronic pancreatitis are not well defined. Few population-based studies have been reported and studies based on administrative data are often limited by a lack of verification of diagnosis. Compared with older studies, more recent epidemiological studies report a higher incidence of chronic pancreatitis.[9] Reported incidence in European countries varies from four cases per 100 000 people in the UK to 13·4 cases per 100 000 in Finland.[10,11] A recent population-based study from Mayo Clinic identified 106 incident cases of chronic pancreatitis in Olmsted County, MN, USA, from 1977 to 2006;[12] analysis revealed an age-adjusted and sex-adjusted incidence rate of 4·05 per 100 000 person-years (95% CI 3·27–4·83) and a prevalence rate of 41·76 per 100 000 population (95% CI 30·21–53·32). Men have a higher incidence than do women.[13,14] Black people seem to have a higher risk of chronic pancreatitis than do white people, although the reasons for this racial disparity are unclear.[13]

Risk factors

Alcohol

Alcohol has traditionally been thought of as the most common risk factor for chronic pancreatitis. Epidemiological studies from the USA have noted alcohol as the causative agent in nearly 50% of cases of chronic pancreatitis.[12] A multicentre Italian study assessing 893 patients with chronic pancreatitis showed alcohol to be the major risk factor in 43% of cases, either alone (34%) or in combination with ductal obstruction (9%).[15] Analysis of the North American Pancreatitis Study-2 (NAPS-2) cohort showed alcohol as the cause of chronic pancreatitis more frequently in men (59%) than in women (28%).[16] Recently, genetic variants in the *CLDN2* gene loci have been identified that influence the risk for alcohol-related pancreatitis.[17] The frequency of homozygosity for this genetic variant was higher in men than in women (0·26 *vs* 0·07), providing a probable explanation for the sex variation in the incidence of alcoholic chronic pancreatitis. Alcohol increases the risk of chronic pancreatitis in a dose-dependent manner. Results of a case-control study and a recent meta-analysis suggest that the risk of chronic pancreatitis doubles or trebles at a threshold of four or five drinks per day.[18,19] Although the incidence of chronic pancreatitis in people who regularly consume excess alcohol is relatively low (5–15%), it is unclear whether there is truly any safe threshold of alcohol intake in relation to chronic pancreatitis.[20] The pathogenesis of alcoholic chronic pancreatitis is poorly understood but it is thought that chronic alcohol consumption sensitises the acinar cell to injury by interfering with mechanisms in the acinar cell that protect against stress induced by the endoplasmic reticulum.[21]

Smoking

Cigarette smoking is an independent risk factor for chronic pancreatitis. In a recent meta-analysis, the pooled risk estimate for chronic pancreatitis was 2·5 (95% CI 1·3–4·6) for current smokers when compared with never smokers, after adjustment for alcohol use.[18,22] Similar to alcohol, the association between smoking and chronic pancreatitis was also dose-dependent, with a pooled risk estimate of 3·3 (95% CI 1·4–7·9) for people smoking one or more packs per day, compared with 2·4 (95% CI 0·9–6·6) for those smoking less than one pack per day.[22] Ever smokers (all people who do or have smoked) also seem to be at a higher risk of recurrent acute pancreatitis than never smokers (hazard ratio 1·59; 95% CI 1·19–2·12).

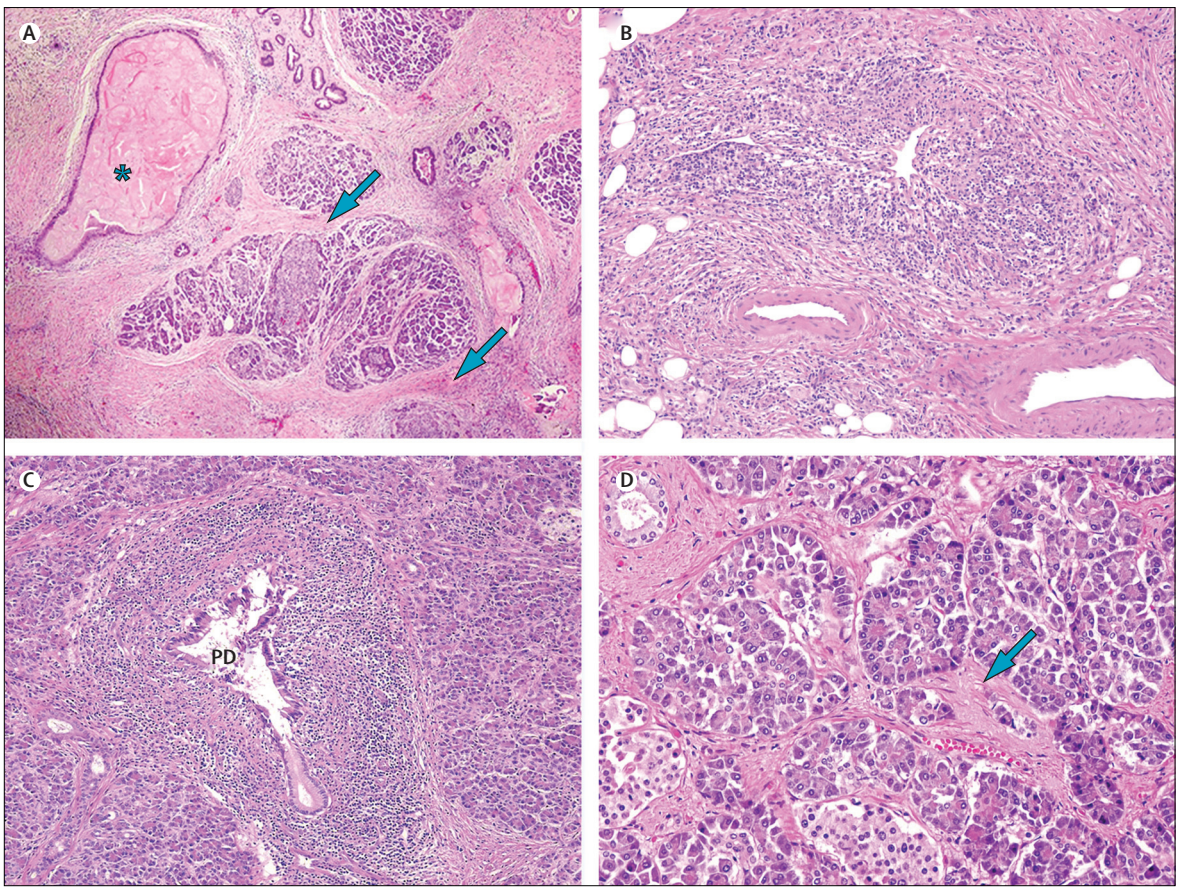

Figure 2: **Histopathological features of different forms of fibroatrophy of the pancreas**
Chronic calcifying pancreatitis (A) is characterised by large bands of interlobular fibrosis (arrow), acinar atrophy, and intraductal concretions (star). Autoimmune pancreatitis (B) with periductal lymphoplasmacytic infiltrates and storiform fibrosis. Idiopathic duct-centric chronic pancreatitis (C) with intense periductal infiltrate and characteristic granulocytic epithelial lesion involving pancreatic duct epithelium. Pancreatopathy (D), a term used for symptomatic interlobular fibrosis (arrow) without stromal cellular infiltrate representing bland fibrosis, seen at autopsy in people who smoke and overuse alcohol. PD=pancreatic duct.

The risk estimate for chronic pancreatitis for former smokers (1·4, 1·1–1·9) was reduced compared with that for current smokers, implicating a possible role of smoking cessation in reducing the risk of chronic pancreatitis.[22] The detrimental effects of smoking seem synergistic with alcohol use. A Danish study identified smoking as the strongest risk factor for progression from acute to chronic pancreatitis.[23] In-vitro studies show that nicotine induces oxidative stress in the pancreatic acinar cells.[24] The nicotine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) has been implicated in the pathogenesis of smoking-related pancreatitis.[25]

Genetic factors

In the past two decades several studies have identified specific genes that predispose to chronic pancreatitis either by premature activation of trypsinogen or failure to inactivate trypsin during pancreatic inflammation. Investigators have identified gain-of-function mutations in the cationic trypsin gene (*PRSS1*) that lead to premature trypsinogen activation as the cause of hereditary pancreatitis.[26] Inheritance is autosomal-dominant with high penetrance, and affected individuals often show signs. The serum protease inhibitor, *SPINK1*, is expressed on pancreatic acinar cells during an inflammatory response and codes for a trypsin inhibitor. Although a

	Type 1	Type 2
Median age of onset	Seventh decade	Third decade
Sex difference	Male predominant (3:1)	Equal predisposition (1:1)
Other organ involvement	Common (60%)	None
Inflammatory bowel disease	Less than 10%	About 30%
Serum IgG4 increase (>1·40 g/L)	Commonly present (>80%)	Usually absent (<10%)
Histological hallmarks		
Granulocyte epithelial lesion	Absent	Present
IgG4 staining	Prominent	Scant
Response to corticosteroid treatment	Universal	Universal
Relapse after corticosteroid treatment	Common (30–60%)	Rare (<10%)

IDCP=idiopathic duct-centric pancreatitis. IgG4=immunoglobulin.

Table: **Comparison of type 1 autoimmune pancreatitis and type 2 autoimmune pancreatitis (IDCP)**

mutation in *SPINK1* is not an independent risk factor for chronic pancreatitis, it has disease-modifying properties and has been implicated in the progression of recurrent acute pancreatitis to chronic pancreatitis.[27] *SPINK1* mutations have been strongly associated with tropical calcific pancreatitis.[28] Mutations in *CFTR* cause cystic fibrosis, a disease commonly associated with chronic pancreatitis. Mutations in *CFTR* have also been identified in patients with idiopathic chronic pancreatitis without pulmonary manifestations of cystic fibrosis, and co-inheritance with *SPINK1* can increase the risk of chronic pancreatitis.[29,30] *CTRC*, *CASR*, and most recently *CLDN2* on the X chromosome, are associated with chronic pancreatitis.[17,31–33] Hereditary pancreatitis secondary to *PRSS1* mutation is associated with a markedly increased risk of pancreatic adenocarcinoma.[34]

Ductal obstruction

Ductal obstruction due to inflammatory strictures, benign tumours, or malignancies leads to chronic obstructive pancreatitis upstream from the obstruction. Occasionally chronic pancreatitis might be confined to the dorsal pancreas in patients with pancreas divisum, suggesting a causative role of ductal obstruction in the development of chronic pancreatitis in these patients.[35] However, a higher frequency of pancreas divisum has been noted in patients with *CFTR* mutation-associated pancreatitis[36] and the pathophysiological contribution of ductal obstruction and genetic factors to the development of chronic pancreatitis in pancreas divisum is poorly understood.

Idiopathic

In a large proportion of cases of chronic pancreatitis an underlying cause is not found. Before labelling chronic pancreatitis as idiopathic, thorough investigation to identify the presence of common causes is warranted. Tropical pancreatitis, also referred to as fibrocalculous pancreatic diabetes, is a form of idiopathic early-onset chronic pancreatitis in the tropics. Southern India has the highest prevalence of this form of chronic pancreatitis, which is characterised by early-onset pain, large main pancreatic duct calcification, and rapid onset of ketosis-resistant diabetes. Although genetic (*SPINK1*), nutritional, and inflammatory factors have been implicated, the pathogenesis of this disease remains largely unknown.[37]

Pathogenesis

There are many gaps in knowledge about the pathogenesis of the different forms of chronic pancreatitis. Several theories have been proposed but few have been validated and contradictory data have added to the confusion. Generally, it is believed that protein-rich plugs form in the interlobular and intralobular ducts secondary to a failure in the compensatory increase of ductal bicarbonate secretion, which results in a viscous ductal micro-environment.[38] The exact cause of this protein–bicarbonate imbalance is not known. Ductal obstruction results in inflammation, which subsequently leads to pancreatic parenchymal fibrosis. Obstruction of the ducts might also lead to pancreatic ductal hypertension with resultant hypoperfusion and ischaemic injury of the acinar cells. Some researchers believe that a sentinel event of acute pancreatitis is a key element in the pathogenesis of chronic pancreatitis.[39] The role of pancreatic stellate cells has been studied with great interest.[40] Pancreatic stellate cells can be activated by chemokines such as transforming growth factor β (TGFβ) and platelet-derived growth factor (PDGF) released as a result of pancreatic inflammation. These activated pancreatic stellate cells form collagen and extracellular matrix, which causes pancreatic parenchymal fibrosis. However, the exact molecular pathways along which inflammation leads to fibrosis have not been delineated. Moreover, autopsy studies have shown that bland pancreatic parenchymal fibrosis is common and associated with similar risk factors to chronic pancreatitis, such as smoking and alcohol.[41,42]

Clinical features

Patients do not usually present with signs associated with classic chronic pancreatitis. More often, patients present with recurrent clinically acute pancreatitis. Over a varying time-interval (ranging from years to decades) progressive changes appear in the pancreas. Initially such changes are visible only on endoscopic ultrasound. Eventually, patients with chronic pancreatitis develop the clinical triad of abdominal pain, exocrine pancreatic insufficiency, and diabetes. Pain is often the over-riding symptom and is present in up to 85% of patients.[43] Exocrine insufficiency manifests as steatorrhoea and, in severe cases, weight loss, malnutrition, and fat-soluble vitamin deficiency. Endocrine insufficiency results in pancreatogenous diabetes, a disorder that has been referred to as type 3C diabetes mellitus to distinguish it from type 1 and type 2 diabetes.[44]

Pain in chronic pancreatitis is usually post-prandial, located in the epigastric area with radiation to the back, often associated with nausea and vomiting, and partially relieved by sitting or leaning forward. However, the location, severity, character, and intensity of pain are highly variable. The mechanism of pain in chronic pancreatitis is poorly understood. Traditional theories focused on a mechanical cause of pain related to pancreatic ductal hypertension and pancreatic parenchymal hypertension.[45] More recently, the activation of intrapancreatic nociceptors, hypertrophy, and inflammation of intrapancreatic nerves and abnormal pain processing in the central nervous system have been implicated.[46] Intrapancreatic neural remodelling and similar changes in the viscerosensory cortex seem to be key factors contributing to the pathogenesis of the chronic pain associated with this disease.[47] The poor correlation between structural changes in the pancreas and the severity of pain, and the persistence of pain in patients who have had a total pancreatectomy, lend credibility to this central sensitisation hypothesis.[48]

The clinical hallmark of pancreatic exocrine insufficiency is steatorrhoea. The pancreas has a tremendous functional reserve, and pancreatic steatorrhoea does not usually occur until pancreatic lipase output drops below 10–15% of normal levels.[49] Thus, maldigestion and steatorrhoea are features of advanced stages of chronic pancreatitis. The appearance of the patient's stool is an unreliable predictor of steatorrhoea and a 72 h faecal fat estimation, done when the patient is taking a diet restricted to 100 g of fat per day, is often required to establish diagnosis. Steatorrhoea can be associated with diseases other than chronic pancreatitis, such as small intestinal bacterial overgrowth, coeliac disease, and irritable bowel syndrome. In the absence of other clinical and radiological features, isolated steatorrhoea is almost never secondary to chronic pancreatitis.

Most patients with chronic pancreatitis eventually develop type 3C diabetes due to progressive beta cell loss.[44] However, chronic pancreatitis can occur in patients with type 1 and type 2 diabetes. A history of long-standing chronic pancreatitis before the onset of diabetes is usually typical for diagnosis of type 3C diabetes. Studies of the prevalence of type 3C diabetes are scarce and show wide variability.[50] Patients are at a higher risk of hypoglycaemia due to concomitant loss of counter-regulatory hormones such as glucagon and pancreatic polypeptide.

Common complications in patients with long-standing chronic pancreatitis include pseudocysts; common bile duct stricture; duodenal stenosis; pleural effusion; portal vein thrombosis; splenic vein thrombosis with formation of gastric varices; pseudoaneurysm affecting the splenic, hepatic, gastroduodenal, and pancreaticoduodenal arteries; and pancreatic ascites. Patients with chronic pancreatitis are also at a higher risk (relative risk 13·3, 95% CI 6·1–28·9) of pancreatic adenocarcinoma and this risk seems to be greatest for early-onset disease in patients with hereditary and tropical pancreatitis.[51]

Diagnosis

The diagnosis of chronic pancreatitis is often obvious in advanced cases. In early stage of the disease diagnosis is challenging and often based on a combination of clinical presentation, imaging (figure 3), and pancreatic function testing. In the absence of established diagnostic criteria, early chronic pancreatitis remains an elusive diagnosis. Apart from fibrosis and consequent parenchymal loss, lobular inflammation and ductal changes are key diagnostic histological features (figure 2A). In late burnt-out chronic pancreatitis, pancreatic inflammation might be absent. However, autopsy studies show that pancreatic fibrosis is common in asymptomatic people and our recent study confirms these findings in patients with diabetes mellitus,[49,52,53] suggesting that fibrosis alone is insufficient to diagnose chronic pancreatitis. Sampling error is a major limitation for surgical and endoscopic biopsies and might lead to false-negative results.[54] There is also a risk of causing pancreatitis by doing endoscopic ultrasound fine needle aspiration.[55] Overall, histology is rarely used to establish a diagnosis of chronic pancreatitis in clinical practice.

CT and magnetic resonance cholangiopancreatography (MRCP) are reasonably sensitive for detection of advanced chronic pancreatitis, but sensitivity is low.[56,57] Intravenous administration of secretin during MRCP increases sensitivity to detect ductal changes in chronic pancreatitis.[58,59] Formerly the Cambridge classification, based on ductal changes noted on endoscopic retrograde pancreatogram, was considered the most reliable imaging test for diagnosis of chronic pancreatitis with sensitivity up to 90%.[60] However, with the advent of endoscopic ultrasound, endoscopic retrograde pancreatogram is no longer used for diagnosis. The Rosemont endoscopic ultrasound criteria for diagnosis combine ductal and parenchymal features and divide all patients into four categories: consistent with chronic pancreatitis, suggestive of chronic pancreatitis, indeterminate for chronic pancreatitis, and healthy.[61] The Japanese endoscopic ultrasound criteria for chronic pancreatitis were revised in 2010 to include a category of early chronic pancreatitis.[62] Sensitivities and specificities of higher than 80% to diagnose pancreatic fibrosis have been reported for endoscopic ultrasound; the concomitant presence of four or more endoscopic ultrasound criteria has a sensitivity of up to 91%.[63] However, pancreatic changes on endoscopic ultrasound can also be seen in patients with no symptoms of pancreatic disease; therefore, findings should always be interpreted in the appropriate clinical context and are rarely diagnostic of chronic pancreatitis in isolation.

Pancreatic function tests are classified as direct and indirect. Direct pancreatic function tests have been

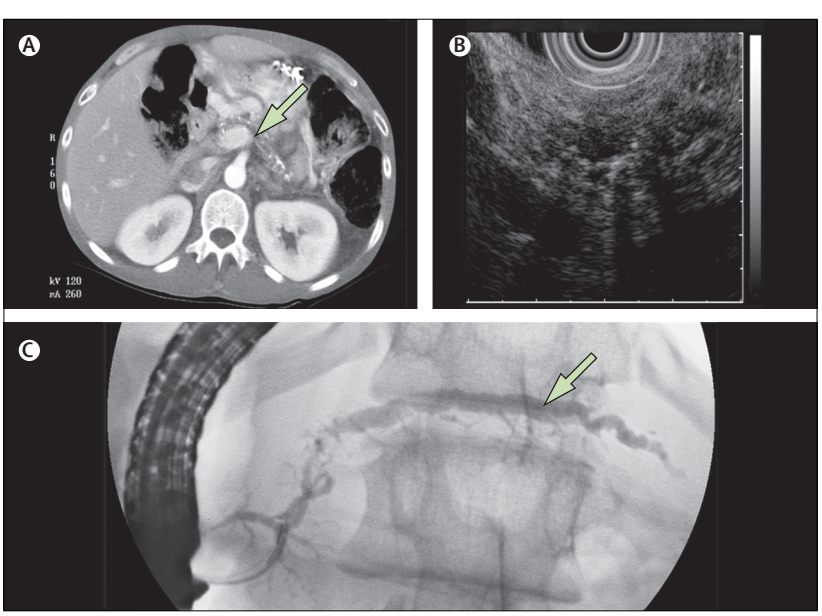

Figure 3: **Radiographic and endoscopic images for the diagnosis of chronic pancreatitis**
CT scan of abdomen showing pancreatic ductal dilation (arrow) and parenchymal calcification in an atrophic pancreas (A). Image from endoscopic ultrasound showing hyperechoic foci with shadowing (B). Endoscopic retrograde pancreatogram showing an irregular pancreatic duct (arrow; C).

phased out of clinical practice. At some centres the secretin function test has been combined with endoscopic ultrasound in which pancreatic fluid is collected endoscopically after secretin stimulation, allowing for a structural assessment of the pancreas at the same time.[64] This technique is not yet widely used.

Indirect pancreatic function tests include measurement of faecal elastase 1 concentration and of levels of faecal fat. A faecal elastase 1 concentration higher than 100 µg/g of stool is used as a marker of pancreatic exocrine dysfunction. The test result can be erroneously low in patients with diarrhoea. Since faecal elastase 1 can be checked easily and is not affected by concomitant pancreatic enzyme replacement therapy, it is commonly used in clinical practice. However, the test has low sensitivity and specificity in patients with early disease and can have high false-positive rates with up to 10% of control participants having a positive test in one study.[65] The 72 h faecal fat estimation diet is cumbersome and not available at most centres. Despite its inherent limitations the test is fairly reliable when done properly. At present no single test in isolation is diagnostic of early chronic pancreatitis. Abnormalities on endoscopic ultrasound and pancreatic function tests in the absence of clinical signs and symptoms of pancreatic inflammation are not specific and should not be used to diagnose chronic pancreatitis.

Treatment

Medical

The medical management of chronic pancreatitis can be broadly classified into management of pain, exocrine and endocrine insufficiency, and complications (biliary obstruction, bleeding, or malignancy). Nutrition and lifestyle modification are key components of a successful management plan. Endoscopic and surgical interventions can have a role in some carefully selected patients.

Pain control is the most difficult challenge in the management of patients with chronic pancreatitis. Long-term use of opioids in this setting is best avoided because it leads to tolerance and dependence. Adjunctive pain medication such as tricyclic antidepressants, gabapentin, pregabalin, and selective serotonin-reuptake inhibitors have been used either alone or in combination with opioids with variable results. A 3 week placebo-controlled randomised trial found pregabalin to be more effective for the control of pain than placebo.[66] Tramadol seems to have a similar efficacy to equivalent dose morphine with a better side-effect profile.[67] Other medical therapies for pain including pancreatic enzyme-replacement therapy, octreotide, montelukast, and allopurinol are not effective in the treatment of pain in chronic pancreatitis.[68] Two large randomised trials assessing the role of antioxidants have shown conflicting results and their use continues to be debated.[69,70] However, because of the perceived harmless nature of pancreatic enzyme-replacement therapy and antioxidants they are commonly used for pain management. Both forms of treatment involve substantial cost and their routine use in patients with chronic pancreatitis for pain control cannot be justified at this time. Alcohol and smoking cessation can reduce pain in patients with chronic pancreatitis.[71] In patients in whom the use of opioids is unavoidable, use of the lowest possible dose with as-needed dosing is preferred to daily use. In patients with suboptimum pain control, additional contributing causes should be looked for, such as pseudocysts, duodenal strictures, or treatment-related complications such as opioid-induced bowel dysfunction or postoperative intra-abdominal adhesions.

Endoscopic treatment

Not all patients with poorly controlled pain refractory to medical therapy will benefit from endoscopic procedures and a detailed risk–benefit discussion and careful patient selection should precede any intervention. The common clinical scenarios that warrant endoscopic intervention in patients with chronic pancreatitis are intraductal stones in the region of the pancreatic head, main pancreatic duct stricture, and symptomatic pseudocyst. Large stones usually need extracorporeal shockwave lithotripsy (ESWL). Studies of ESWL plus endoscopic retrograde cholangio-pancreatography to clear the pancreatic duct stone fragments have not shown any added benefit compared with ESWL alone.[72] Dominant strictures in the main pancreatic duct are managed by endoscopic pancreatic duct stent placement. Guidelines support the use of a single stent placed long term.[73] Approaches that use several stents or self-expanding metal stents are under investigation. Although endoscopic ultrasound-guided coeliac plexus neurolysis relieves pain in about 50% of patients, the effect lasts a maximum of a few weeks and this approach is not recommended for patients with painful chronic pancreatitis in the absence of a concomitant pancreatic malignancy.[74,75] In patients with pancreas divisum and recurrent pancreatitis, risks of minor papilla sphincterotomy (especially risks of papillary stenosis and thermal injury to the duct) should be weighed against the potential prevention of recurrence. In cases of pancreas divisum, the procedure is less helpful in patients with established chronic pancreatitis compared with those with recurrent acute pancreatitis.[76] Long-term pancreatic duct stenting induces morphological changes in the main pancreatic duct and parenchymal changes resembling chronic pancreatitis and should be avoided in patients with pancreas divisum.[76]

Surgical

Surgical intervention is effective in carefully selected patients. Common indications for surgical intervention in chronic pancreatitis include poorly controlled pain; duodenal, biliary and pancreatic duct obstruction; symptomatic pseudocysts; and suspicion of cancer. Surgery for chronic pancreatitis can be broadly classified into three categories: drainage procedures, partial pancreatic resection, and total pancreatectomy.

In drainage procedures a dilated pancreatic duct is cut open and anastomosed to bowel (most often to jejunum). For long-term patency of the pancreatico-jejunostomy anastomosis the pancreatic duct should be dilated to 6 mm or wider. There is significant variability in this practice depending on surgical expertise and experience. Modified surgical techniques such as the longitudinal V-shape excision of the ventral pancreas have been described for patients with a non-dilated duct, but are not widely accepted as being helpful.[77] The most common drainage procedures are the modified Puestow procedure, also known as lateral pancreatico-jejunostomy. and the Frey procedure, which in addition to a pancreatico-jejunostomy includes coring of the pancreatic head. Both procedures are relatively safe (mortality <1%) and effective. In a study involving 146 patients, there was only one in-hospital mortality during the index procedure.[78]

In patients with persistent inflammation of the pancreatic head without upstream ductal dilatation, a resective surgery such as pancreaticoduodenectomy (Whipple) or a duodenum-preserving head resection (Beger) can be done. A meta-analysis showed better postoperative pain relief and improved quality of life with the Beger procedure compared with conventional pancreaticoduodenectomy.[79,80] However, the studies included had much heterogeneity and prospective randomised controlled trials are needed before a definitive advantage can be established. Distal pancreatectomy is rarely done and is reserved for patients with disease limited to the pancreatic tail region.

A Dutch study of 146 patients who underwent surgery for chronic pancreatitis reported complete or near-complete resolution of pain in 100 (68%) patients after 63 (range 14–268) months of follow-up.[78] 18 (12%) patients reported persistent severe pain (visual analogue pain score >7) after surgery and predictive factors included preoperative daily opioid use (odds ratio 3·04; 95% CI 1·09–8·49) and high numbers of endoscopic procedures preceding index surgery (3·89; 1·01–14·9).[78] A 2015 meta-analysis of 23 studies compared outcomes of the Frey procedure to pancreaticoduodenectomy and the Berger procedure.[81] Postoperative mortality was 0·4% for patients who underwent the Frey procedure and pain-relief was achieved in 89%. Compared with pancreatoduodenectomy and the Berger procedure, the Frey procedure led to shorter operation time and overall morbidity. Quality of life and pancreatic function outcomes were more favourable in patients who had the Frey procedure than in those who had pancreatico-duodenectomy.[81] Long-term follow-up data from a randomised controlled trial comparing the Frey and Berger procedures in chronic pancreatitis showed no significant difference in survival, endocrine, or exocrine insufficiency more than a decade after surgery.[82] In patients with established chronic pancreatitis and disabling pain who have not improved with other therapeutic modalities and have diffuse disease, total pancreatectomy with islet autotransplantation can be used. A systematic review of total pancreatectomy with islet autotransplantation for chronic pancreatitis included five studies reporting outcomes in 296 patients.[83] Two studies included in this review reported a decrease in postoperative opiate use. Insulin independence decreased over time, ranging from 64% of patients at 5 year mean follow-up to only 10% at 8 year follow-up. Poor pain outcomes after total pancreatectomy with islet autotransplantation is observed in patients with heavy preoperative narcotic use and long-standing history of pain with central sensitisation. The cost-effectiveness of the procedure has been questioned and the risks, which include surgical morbidity, mortality, insulin dependence, and refractory pain in the postoperative period, must be weighed carefully and patients selected judiciously.

Randomised controlled trials comparing endoscopic and surgical management for chronic pancreatitis pain are sparse.[84,85] One of the randomised controlled trials comparing surgery to endotherapy in 39 symptomatic patients with chronic pancreatitis and pancreatic ductal obstruction reported better pain-free survival in the surgery cohort (80% *vs* 38%; p=0·042) at 5 year follow-up.[86] A Cochrane review found three trials eligible for comparison of outcomes of surgical and endoscopic interventions in the management of painful chronic pancreatitis. They similarly concluded that surgery was superior to endotherapy for pain relief in patients with a dilated pancreatic duct. The authors also stated that early surgical intervention might be preferable to conservative treatment in this cohort of patients, but methodological limitations and small sample size mean further studies are needed.[87]

The management of pain in chronic pancreatitis is challenging and often necessitates the active participation of a pain management expert as part of a multidisciplinary team. Although the optimum timing of surgery in chronic pancreatitis is widely debated, evidence favours early intervention before the onset of insulin dependence.[88] Appropriately timed surgery tailored to anatomic abnormalities in properly selected patient leads to optimum functional outcomes.[78]

Pancreatic exocrine insufficiency

Pancreatic exocrine insufficiency occurs when pancreas enzyme output is not sufficient to maintain normal digestion and is treated with pancreatic enzyme-replacement therapy. About 90 000 USP units of lipase are needed with each meal for effective fat absorption. Patients with advanced chronic pancreatitis might need up to 90 000 USP units with each meal.[89] Treatment is often started at a much lower dose with 40 000–50 000 USP units of lipase with each meal and half that amount with snacks. Lower doses of 25 000–40 000 units per meal might be effective.[90] Pancreatic enzyme-replacement therapy should be started in patients with pancreatic exocrine insufficiency. Moreover, treatment should be started at a low dose and titrated on the basis of clinical response. To optimise

digestion calories should be equally divided across three to five meals per day and the enzyme pills distributed through the meal. Since the enzymes have to be released from the pill and well mixed with food to affect digestion, taking smaller pills spread through the meal seems more logical than one or two large pills. If there is no improvement in steatorrhoea at maximum doses, then alternative causes of diarrhoea should be explored once compliance with recommended dosing has been established. Common causes of failure of enzyme replacement in compliant patients include small intestinal bacterial overgrowth and inactivation by gastric acid. Pancreatic enzyme-replacement therapy is expensive and proper patient education about its use and benefits is essential. The monitoring of serum concentrations of fat-soluble vitamins A, D, and E and appropriate supplementation is important in treatment of pancreatic exocrine insufficiency.

Pancreatic endocrine insufficiency

Metformin is often the firstline drug in management of diabetes in chronic pancreatitis, especially in patients who are not overtly malnourished and have mild hyperglycaemia. However, metformin seems poorly tolerated in this cohort.[50] In time most patients need insulin therapy. Patients with type 3C diabetes are also more prone to hypoglycaemia and need closely monitored therapy with appropriate dose adjustment. In patients with brittle diabetes the use of an insulin pump under the supervision of an expert endocrinologist is often the safest and most effective management strategy.[91]

Lifestyle modification is a key component of treatment. The importance of smoking and alcohol abstinence, healthy eating habits, and daily exercise is often under-emphasised. Referral to formal structured de-addiction programmes and a nutritionist with experience in pancreatic diseases should be considered when appropriate.

Conclusion

Chronic pancreatitis continues to be a poorly understood disease and many research questions and controversies remain (panel). Increased understanding of genetic risk factors and the effect of smoking have opened up potential avenues of research in risk prediction and for the development of preventive strategies. Management of chronic pancreatitis involves patient education, a multidisciplinary team approach to pain management, judicious use of pancreatic enzyme-replacement therapy, and timely endoscopic and surgical intervention in carefully selected patients.

Panel: **Outstanding research questions and controversies**

- How to identify factors that contribute to initiation and progression of recurrent pancreatitis to chronic pancreatitis?
- How to differentiate between bland pancreatic fibrosis and early chronic pancreatitis?
- How to identify patients with chronic pancreatitis at high risk for pancreatic ductal adenocarcinoma and screening for asymptomatic cancer?

Contributors

Both authors searched the literature, wrote the text, and designed the tables and figures. SM did the data collection. STC critically appraised the draft of the final manuscript.

Declaration of interests

We declare no competing interests.

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