Chronic pancreatitis

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Abstract | Chronic pancreatitis is defined as a pathological fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathological responses to parenchymal injury or stress. Potential causes can include toxic factors (such as alcohol or smoking), metabolic abnormalities, idiopathic mechanisms, genetics, autoimmune responses and obstructive mechanisms. The pathophysiology of chronic pancreatitis is fairly complex and includes acinar cell injury, acinar stress responses, duct dysfunction, persistent or altered inflammation, and/or neuro-immune crosstalk, but these mechanisms are not completely understood. Chronic pancreatitis is characterized by ongoing inflammation of the pancreas that results in progressive loss of the endocrine and exocrine compartment owing to atrophy and/or replacement with fibrotic tissue. Functional consequences include recurrent or constant abdominal pain, diabetes mellitus (endocrine insufficiency) and maldigestion (exocrine insufficiency). Diagnosing early-stage chronic pancreatitis is challenging as changes are subtle, ill-defined and overlap those of other disorders. Later stages are characterized by variable fibrosis and calcification of the pancreatic parenchyma; dilatation, distortion and stricturing of the pancreatic ducts; pseudocysts; intrapancreatic bile duct stricturing; narrowing of the duodenum; and superior mesenteric, portal and/or splenic vein thrombosis. Treatment options comprise medical, radiological, endoscopic and surgical interventions, but evidence-based approaches are limited. This Primer highlights the major progress that has been made in understanding the pathophysiology, presentation, prevalence and management of chronic pancreatitis and its complications.

The term chronic pancreatitis is traditionally used to describe a syndrome of chronic inflammation of the pancreas, which is most often seen in alcoholics and smokers, and, rarely, in genetically predisposed individuals, that results in progressive scarring of the pancreatic tissue, pain, endocrine pancreatic gland dysfunction (mainly owing to the loss of the islets of Langerhans), exocrine pancreatic insufficiency (deficiency of the digestive enzymes produced by the pancreas resulting in impaired digestion) and increased risk of pancreatic ductal adenocarcinoma[1]. Clinically, chronic pancreatitis typically presents as recurrent bouts of acute pancreatitis in its early stages and as pain, sclerosis, calcification, diabetes mellitus and/or steatorrhoea (excess fat in the stool owing to the impaired digestion of lipids) in its later stages.

Chronic pancreatitis represents an array of different disorders and complications that converge over time along common pathological pathways, resulting in the same end-stage syndrome. Classic chronic pancreatitis involves recurrent or sustained injury to the exocrine parenchyma that is most often induced by alcohol abuse and tobacco smoking, and that is characterized by an inflammation, resolution and regeneration sequence followed by recurrence of the sequence with progressive destruction of the gland and the development of various complications[1]. The injury-driven inflammatory response distinguishes chronic pancreatitis from fibrosis associated with normal ageing and diabetic pancreatopathy or the desmoplastic reaction that often accompanies pancreatic cancer. Thus, it is important to determine the aetiology of chronic pancreatitis-like features observed using imaging. It has been proposed to use an umbrella term — 'chronic inflammatory diseases of the pancreas' — to include all forms of chronic pancreatitis and to list all the known aetiological factors in each patient, as patients often have several risk factors (BOX 1). A mechanistic definition of chronic pancreatitis subclassifies the chronic inflammatory disease of the pancreas into the classic form that is driven by acinar and duct cell injury or stress, whether it is caused by alcohol, smoking, hypercalcaemia, genetic factors

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or a combination of factors[1], and distinguishes classic chronic pancreatitis from autoimmune pancreatitis (which is reversible upon steroid treatment), obstructive pancreatitis, and, rarely, infectious aetiologies. Classic chronic pancreatitis can be further subdivided into typical chronic pancreatitis, which is dominated by fibrosis, and atypical chronic pancreatitis, which is dominated by atrophy. In this Primer, we focus mainly on classic chronic pancreatitis, unless otherwise specified.

In the past, diagnosis was based on the triad of steatorrhoea, diabetes mellitus and pancreatic calcifications visible on abdominal radiography. However, diagnosis based on these criteria could only be made in end-stage disease, after the pancreas was essentially destroyed. From a clinical perspective, pain is a common symptom and is often the most debilitating factor. With better imaging techniques, the development of pancreatic function tests and careful epidemiological studies, it has become clear that chronic pancreatitis is more prevalent and heterogeneous than previously thought. However, many of the features of chronic pancreatitis, such as pancreatic atrophy and fibrosis, exocrine pancreatic insufficiency, pancreatitis-like pain and diabetes mellitus overlap with those of other disorders, making biomarkers of chronic pancreatitis nonspecific and precluding early diagnosis.

Once the disease is well established, the disease process probably cannot be reversed, although the rate of progression and symptoms can be modified by interventions. In this respect, chronic pancreatitis differs from acute pancreatitis, in which the pancreas returns to normal after resolution of the attack. The exception to this rule is when there are long-term sequelae from necrotizing pancreatitis, which occurs in a minority of patients with severe acute pancreatitis and which may lead to chronic pancreatitis. Over the past two decades, new discoveries and concepts based on novel genetic and biomarker data and carefully designed cohort studies have revolutionized the field of chronic pancreatitis, opening the door to a new understanding of the pathogenesis of chronic pancreatitis and to the development of novel approaches to manage the disorder[1,2].

In this Primer, we present our current understanding of the pathophysiology, presentation, prevalence and management of chronic pancreatitis, with a focus on classic chronic pancreatitis and its complications. For comprehensive evidence-based recommendations of the medical and surgical management of chronic pancreatitis in Europe, the reader is referred to REF. 3.

Epidemiology

Only a few population-based epidemiological studies on the incidence, prevalence and natural history of chronic pancreatitis have been conducted. Thus, much of the epidemiological knowledge of this disorder is derived from studies that are based on data obtained from health insurance records or hospital charts, which are often limited by data quality and the lack of an appropriate confirmation of the diagnosis.

Overall, chronic pancreatitis is a major source of morbidity in the United States and Europe[4]. Acute pancreatitis (including acute pancreatitis attacks in chronic pancreatitis) is the most common gastrointestinal discharge diagnosis (that is, the final diagnosis after all diagnostic tests have been performed) in the United States, whereas chronic pancreatitis is not in the top 15 gastrointestinal discharge diagnoses[5]. The annual incidence rates reported worldwide are roughly similar in all countries and range from 5 to 14 per 100,000 individuals, with a prevalence of approximately 30–50 per 100,000 individuals[6–12] (FIG. 1a). However, prevalence may be as high as 120–143 per 100,000 individuals, owing to a long survival (with a median survival of 15–20 years) and an underestimation of the true number of cases for various reasons, including patient compliance, disease definition and quality of diagnosis[8]. The most recent studies seem to indicate an increasing incidence of chronic pancreatitis in the past decade. As alcohol consumption and smoking levels have been relatively stable or have declined[10], this observation most likely reflects an improvement in diagnosis and changes in disease definition. The prevalence of chronic pancreatitis increases with age, and the median age at diagnosis ranges between 51 and 58 years[7,12–15] (FIG. 1b). Younger ages of onset, including childhood, are mostly related to genetic risk factors[16,17]. The incidence of early chronic pancreatitis has been estimated as 1 per 100,000 individuals[18], whereas the incidence of established chronic pancreatitis is thought to be 14 per 100,000 individuals[19] (although the diagnostic criteria are debated[20]). A precise estimation of the proportion of patients progressing from early to definite chronic pancreatitis remains elusive.

Chronic pancreatitis has traditionally been considered to be a disease of men, especially of those with a high alcohol intake[7,12], and has been reported to be up to five-times more frequent in men than in women[7,12].

Box 1 | **Aetiologies of chronic pancreatitis according to the TIGAR-O system***

- Toxic-metabolic: chronic pancreatitis caused by alcohol abuse, tobacco smoking, hypercalcaemia, hyperlipidaemia, chronic kidney failure, medications or toxins.
- Idiopathic: chronic pancreatitis that is not associated with any known gene mutations, such as early-onset chronic pancreatitis, late-onset chronic pancreatitis and tropical chronic pancreatitis (an early-onset form of non-classic chronic pancreatitis that is almost exclusively observed in tropical countries in the developing world and that is characterized by an aggressive course).
- Gene mutations: chronic pancreatitis caused by Mendelian diseases involving the pancreas, complex genetics or modifying genes (for example, *PRSS1*, *CFTR* and *SPINK1*).
- Autoimmune: steroid-responsive chronic pancreatitis, which can be isolated or syndromic.
- Recurrent and severe acute pancreatitis: chronic pancreatitis that is associated with necrosis (severe necrotizing acute pancreatitis), vascular disease (including ischaemia) and post-irradiation damage.
- Obstructive: chronic pancreatitis that is associated with pancreas divisum (a congenital abnormality of the pancreas), sphincter of Oddi disorders, duct obstruction (for example, from a tumour) and post-traumatic pancreatic duct scars.

*See REF. 216.

However, other studies suggest that the prevalence of chronic pancreatitis in women may be more common than previously believed[6,21,22] (FIG. 1a). Analyses of the North American Pancreatitis Study 2 (NAPS2) cohort, the largest multicentre study of prospectively ascertained patients with chronic pancreatitis in the United States, revealed that, in 2000–2014, 45% of all patients with chronic pancreatitis were women[14]. However, the aetiology of chronic pancreatitis differs between men and women, with alcohol abuse and tobacco smoking being the major causes in men, but idiopathic and obstructive aetiologies being more common in women.

Chronic pancreatitis is more common in black individuals than in white individuals[9,23]. Analysis of the NAPS2 cohort revealed that in comparison to white patients, chronic pancreatitis in black individuals was almost twice as likely to be associated with alcohol abuse and tobacco smoking and was more often severe, with morphological abnormalities of the pancreas, constant and/or severe pain, a higher prevalence of endocrine pancreatic gland dysfunction and a greater degree of disease-related disability[13]. Whether these differences reflect differences in socioeconomic status between black and white individuals remains to be addressed.

The standardized incidence ratio of developing pancreatic cancer in patients with sporadic pancreatitis with a minimum 5-year follow-up is estimated to be 14.4 (95% CI: 8.5–22.8). The cumulative proportion of patients with pancreatic cancer in this population 20 years after diagnosis is 4% (95% CI: 2–5.9%)[24]. Longer follow-up data are available for patients with hereditary chronic pancreatitis. In this case, the cumulative proportion of patients with pancreatic cancer is 1.5% (95% CI: 0–3.6%) at 20 years, 8.5% (95% CI: 1.4–15.7%) at 40 years and 25.3% (95% CI: 2.5–48.1%) at 60 years after symptom onset[24–26].

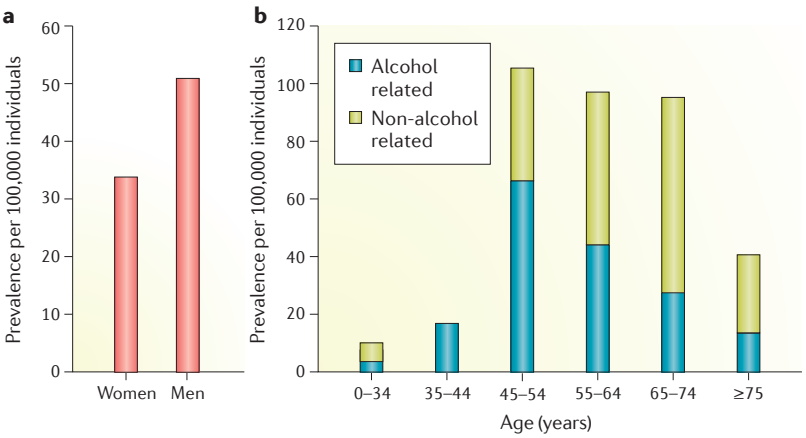

Figure 1 | **Prevalence of chronic pancreatitis.** The prevalence of chronic pancreatitis in Olmsted County, Minnesota, USA, in 2006, stratified by sex (part **a**) and age and aetiology (part **b**) per 100,000 individuals. Data from REF. 6.

Mechanisms/pathophysiology

Risk factors

The most prevalent cause of chronic pancreatitis remains chronic alcohol abuse (FIG. 1b). In Western countries, 40–70% of all cases of chronic pancreatitis are attributed to alcohol abuse, and similar rates have been reported for Japan[12,18,21,22,27,28]. The mechanisms are poorly understood, but direct toxicity of alcohol metabolites to acinar cells via the inhibition of endoplasmic reticulum activity and subsequent increased oxidative stress seems to play an important part[23,29–31]. Alcohol increases susceptibility to acute pancreatitis, especially during alcohol withdrawal, and may alter the inflammatory response to recurrent pancreatitis (reviewed in REF. 32). Of note, in the NAPS2 study, alcohol did not confer a risk of chronic pancreatitis until a threshold of 5 drinks per day (60–80 grams of ethanol) was exceeded, with an odds ratio of 3.10 (95% CI: 1.87–5.14)[33]. However, the risk of chronic pancreatitis clearly increases with higher levels of alcohol consumption[34]. Furthermore, cessation of alcohol after acute pancreatitis decreases the likelihood of progressing to recurrent acute or chronic pancreatitis[35].

Tobacco smoking is an independent risk factor of chronic pancreatitis[21], and smoking increases the risk of chronic pancreatitis in a dose-dependent manner[33,36]. For current smokers, the pooled relative risk of developing chronic pancreatitis is estimated to be 2.8 (95% CI: 1.8–4.2). The relative risk significantly decreases after smoking cessation, and the estimated relative risk for former smokers is 1.4 (95% CI: 1.1–1.9)[37]. In a rat model, tobacco inhalation resulted in an increase in extracellular matrix synthesis and fibrosis in the pancreas, a decrease in acinar structures and abnormal lobular architecture, associated with infiltration by inflammatory cells[32,38,39].

Non-alcohol-associated and non-tobacco-associated chronic pancreatitis accounts for 20–50% of cases in Western countries. The inflammatory process can be due to genetic predisposition[25,26,40–42]; chronic obstructive causes (pancreatic tumours and variations in pancreatic ductal anatomy)[43]; metabolic disorders such as hypercalcaemia (the most common cause of

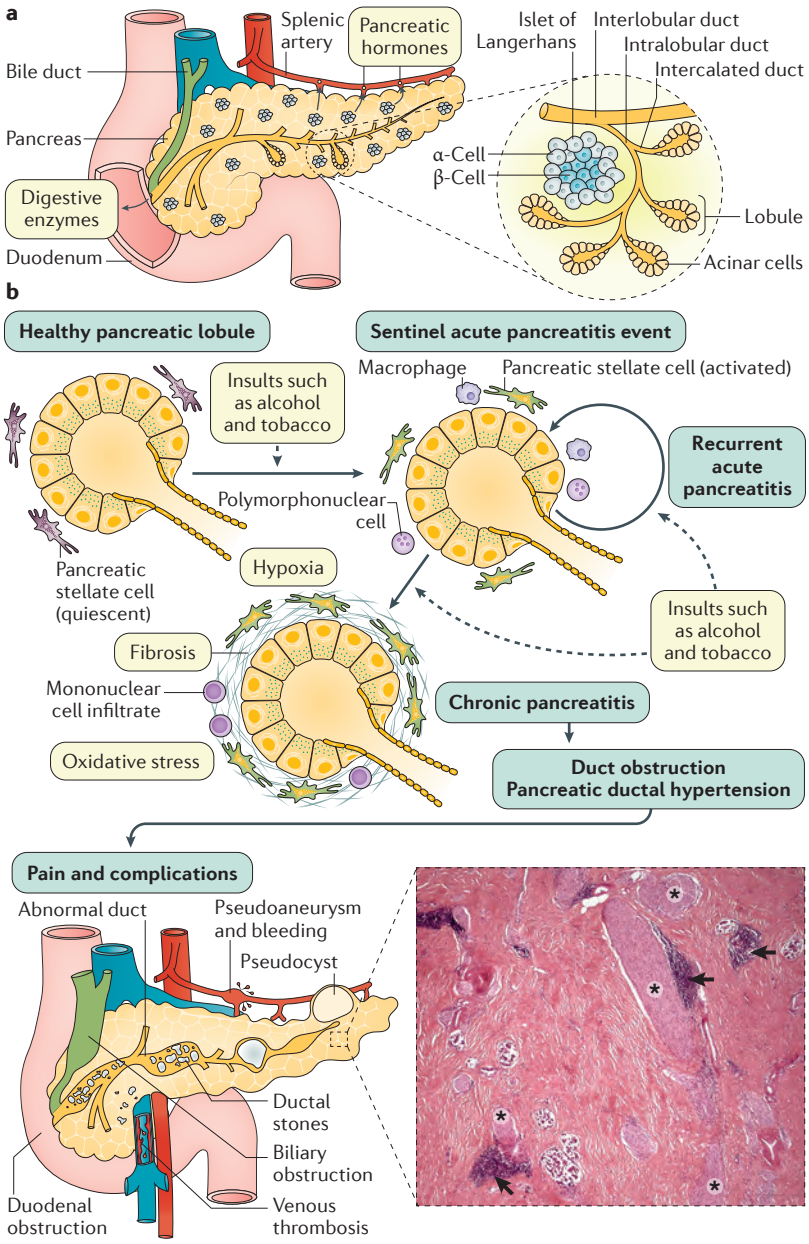

Figure 2 | **Pathophysiology of chronic pancreatitis. a** | Anatomy of the pancreas. The pancreas consists of an exocrine and an endocrine compartment. The exocrine tissue is composed of acini, which are involved in the secretion of digestive enzymes, and ducts, which transport these enzymes to the intestine and which secrete large volumes of alkaline fluid, whereas the endocrine compartment contains the islets of Langerhans (which are involved in the secretion of pancreatic hormones including insulin, glucagon and somatostatin). Anatomically, the pancreas is divided into the head, neck and body. **b** | Pathophysiology of chronic pancreatitis. Insults such as alcohol and tobacco initiate the first episode of acute pancreatitis, which is characterized by the recruitment of inflammatory cells. Continued insults lead to recurrent attacks of acute pancreatitis, which activate pancreatic stellate cells and initiate pancreatic fibrogenesis, ultimately resulting in chronic pancreatitis in most individuals. Notably, these insults cause histopathological changes in the pancreas in a substantial proportion of individuals, most of whom remain asymptomatic and only a few of whom develop clinical disease[218,219]. Organ complications include biliary obstruction, duodenal obstruction, portal vein thrombosis, vascular aneurysms and bleeding. Pseudocysts can also develop in the course of the disease, causing further symptoms. Potential causes of pain in chronic pancreatitis include increased pressure in the ductal system and/or neuroplastic changes. A pancreatic resection specimen of a patient with chronic pancreatitis (inset) shows hypertrophy and dystrophy of the nerves (asterisks) surrounded by extensive fibrotic tissue and lymphocyte infiltrates (arrows).

hypercalcaemia-related pancreatitis is primary hyperparathyroidism) and hypertriglyceridaemia; or autoimmune disorders (autoimmune pancreatitis type 1 or type 2)[44–46] (BOX 1).

Hereditary pancreatitis is a rare cause of chronic pancreatitis and is most commonly due to mutations of *PRSS1*, which encodes trypsin 1 (also known as cationic trypsinogen) — with trypsinogen being the precursor of the serine protease trypsin 1, a digestive enzyme that is secreted by the pancreas. The prevalence of hereditary pancreatitis is approximately 0.3 per 100,000 individuals in Western countries[47] and Japan[48] and has not yet been reported in Africa or in people of African ancestry. The inheritance pattern is autosomal dominant, with an incomplete penetrance (up to 80% of individuals carrying *PRSS1* mutations are affected)[47]. Since 1996, >35 mutations in *PRSS1* have been found to be associated with hereditary pancreatitis. The four most common mutations are R122H, R122C, N29I and A16V[40,49,50] (see also http://www.pancreasgenetics.org). *In vitro*, *PRSS1* mutations increase autocatalytic conversion of inactive trypsinogen to active trypsin 1, or diminish the hydrolysis of active trypsin 1 to degradation products[50]. Premature conversion of trypsinogen to trypsin 1 and reduced inactivation of trypsin 1 are believed to cause pancreatic injury through autodigestion of pancreatic proteins causing injury, an inflammatory response and recurrent acute pancreatitis, leading to chronic pancreatitis[40,51]. Furthermore, some mutations may cause chronic stress and pancreatic inflammation through the activation of the unfolded protein response[52].

Variants in other genes have been found to increase susceptibility to classic chronic pancreatitis, with either familial or sporadic patterns. Mutations in two genes encoding proteins involved in controlling intrapancreatic trypsin 1 activity are strongly associated with recurrent acute and chronic pancreatitis: *SPINK1* and *CTRC*. *SPINK1* encodes serine protease inhibitor Kazal-type 1, a pancreatic secretory trypsin 1 inhibitor and acute-phase protein that is upregulated by inflammation, and synthesized and secreted by the acinar cell in parallel to trypsinogen[53]. Numerous studies have shown an association between mutations in *SPINK1* (that is, the common N34S high-risk haplotype) and the risk of developing recurrent acute and chronic pancreatitis from multiple trypsin 1 activation-associated aetiologies, including alcohol and tropical pancreatitis[54]. Variants of *CTRC*, encoding chymotrypsin C (involved in the degradation of prematurely activated trypsin 1), were associated with a significantly increased risk of chronic pancreatitis[55], also through the loss of trypsin 1 degradation[55–57]. The *CTRC* G60G high-risk haplotype increases the risk of classic chronic pancreatitis in adults, especially in smokers[58].

The most important molecule for proper functioning of the pancreatic duct is cystic fibrosis transmembrane conductance regulator (CFTR). CFTR is an anion channel that is used by the pancreatic duct cells to secrete bicarbonate, which flushes pancreatic digestive enzymes, secreted by the acinar cells, out of

Box 2 | **Causes of pain in chronic pancreatitis**

Primary (genuine) pancreatic pain

- Duct obstruction and tissue hypertension
- Active inflammation
- Tissue ischaemia
- Altered nociception, owing to cholecystokinin-related changes in pain threshold, local nerve damage (neuropathic pain), peripheral and central sensitization of the nervous system and increased sympathetic drive

Secondary pain

- Local complications, including pseudocysts, an inflammatory mass in the pancreas, small bowel strictures and adenocarcinoma
- Remote complications, including obstruction of the bile duct and duodenum, peptic ulcer due to changes in blood flow, bacterial overgrowth due to changes in motility, mesenteric ischaemia after acute pancreatitis, small bowel strictures after acute pancreatitis and diabetes mellitus type 3c-related visceral neuropathy

Treatment-related pain

- Surgical and/or endoscopical complications
- Adverse effect to medication (opioid-induced bowel dysfunction and opioid-induced hyperalgesia)

the pancreas and into the duodenum. Two mutations in *CFTR* that severely impair the function of the protein result in cystic fibrosis; the pancreas being the location of the cysts and 'fibrosis' conferring the name of this autosomal recessive disorder. Other mutations in *CFTR* result in a less severe phenotype, known as atypical cystic fibrosis or cystic fibrosis-related disorders[59]. Recurrent acute pancreatitis and classic chronic pancreatitis are classified as cystic fibrosis-related disorders based on clinical features, genotyping and functional studies. Dysfunction of CFTR seems to be linked to the trypsin-injury pathway, as combined *CFTR* and *SPINK1* mutations markedly increase the risk of recurrent acute and chronic pancreatitis[60,61]. Patients with *CFTR* mutations that selectively disrupt bicarbonate secretion have been found to have a newly discovered syndrome of chronic sinusitis, male infertility and chronic pancreatitis[62].

Mutations in the genes encoding calcium-sensing receptor (CASR)[63,64] and carboxypeptidase A1 (CPA1)[57] were also associated with a small increase in the risk of developing chronic pancreatitis[65]. *CPA1* variants are of special importance, as chronic pancreatitis that is associated with these mutations seems to be triggered by an unfolded protein response, which activates the immune system independently of trypsin activation[66].

Finally, variants in non-coding regions of the *PRSS1/PRSS2* and *CLDN2* loci affect the risk of sporadic and alcoholic pancreatitis[67,68]. The *PRSS1/PRSS2* variants reduce the expression of trypsinogens and thereby seem to reduce the risk of pancreatitis, and the *CLDN2* variants seem to alter the immune response to accelerate the development of chronic pancreatitis, especially in individuals who are alcoholics[63]. Other genetic variants have been reported, such as blood type B[69,70], γ-glutamyltranspeptidase 1 (REF. 71) and bile salt-activated lipase (also known as carboxyl ester lipase)[72–74], with increasingly complex interactions and mechanisms.

Pathophysiology

Chronic pancreatitis is characterized by persistent damage to the endocrine and exocrine tissues of the pancreas due to recurrent episodes of acute pancreatitis and chronic inflammation, which lead to clinical manifestations such as endocrine and exocrine insufficiencies[1,3]. All types of insults that cause injury to the exocrine tissue can lead to pancreatic inflammation by increasing the intracellular levels of activated pancreatic enzymes (seen in the blood as markers of acinar cell and duct damage), inducing oxidative stress or causing duct obstruction with long-term damage to the endocrine cells as a field effect.

Five main mechanisms have been hypothesized to be involved in the pathophysiology of chronic pancreatitis (FIG. 2). First, a necrosis–fibrosis sequence hypothesis suggests that chronic pancreatitis develops through episodes of severe acute pancreatitis[75,76]. Over time and after repeated episodes of acute pancreatitis, the repair of damaged regions by inflammatory cells and pancreatic stellate cells (that is, myofibroblast-like cells) results in the replacement of necrotic pancreatic parenchyma with fibrotic tissue[77,78]. However, a history of pancreatic necrosis is uncommon in patients with classic chronic pancreatitis. Second, the 'sentinel acute pancreatitis event' hypothesis is a 'two-hit' model, in which a single episode of acute pancreatitis causes infiltration of inflammatory cells (for example, macrophages) and the activation of pancreatic stellate cells, and ongoing injury or stress drives fibrosis through activated immune cells[32,79]. This hypothesis was tested in a rat model in which multiple episodes of acute pancreatitis caused fibrosis, and a potentiating effect of continued alcohol consumption was demonstrated[80]. Third, a direct metabolic-toxic effect of environmental factors (that is, alcohol and tobacco) and their metabolites on acinar cells has been proposed[81], although most alcoholics and heavy smokers do not develop classic chronic pancreatitis despite exposure to these potential pancreatic toxins. Fourth, oxidative stress due to free radicals in acinar cells results in membrane lipid oxidation and the expression of transcription factors (for example, nuclear factor-κB (NF-κB)), with the release of cytokines (for example, tumour necrosis factor (TNF; also known as TNFα))[82]. Oxidative stress can

Box 3 | **Diagnostic criteria for chronic pancreatitis**

The diagnosis of chronic pancreatitis involves several criteria[3,125,128].

- Recurrent bouts of pain with or without ≥3-fold the normal upper limit of amylase or lipase levels and one or more of the following criteria:
- Radiological evidence comprising strictures and dilatation in side branches and/or the main pancreatic duct and/or intraductal and/or parenchymal pancreatic calcifications by contrast-enhanced CT and magnetic resonance cholangiopancreatography.
- Histological proof of chronic pancreatitis from biopsy samples undertaken by endoscopic ultrasonography or from a surgically resected specimen.

Table 1 | **Sensitivity and specificity of the available non-invasive pancreatic function tests***

Test	Marker	Mild exocrine deficiency	Moderate exocrine deficiency	Severe exocrine deficiency	
		Sensitivity (%)	Sensitivity (%)	Sensitivity (%)	Specificity (%)
Pancreatic elastase tests (faeces)	Marker for pancreatic enzyme secretion	54	75	95	85
Qualitative faecal fat test	Marker for steatorrhoea	0	0	78	70
Chymotrypsin activity in faeces	Marker for pancreatic enzyme secretion	<50	60	80–90	80–90
^{13}C (mixed triglyceride) breath test	Marker for impaired fat digestion	ND	ND	90–100	80–90

ND, not determined. *Sensitivity and specificity compared with invasive pancreatic function tests (secretin and secretin–pancreozymin-stimulated tube tests were used as reference methods)[108].

promote the fusion of lysosomes and zymogen granules[83], which leads to intravesicular protease activation, acinar cell necrosis, inflammation and fibrosis[84]. Fifth, a ductal dysfunction (for example, *CFTR* mutations are associated with a failure to secrete large volumes of alkaline fluid that contains bicarbonate[85]) leads to the formation of protein plugs and upstream ductal obstruction. Ductal protein plugs are observed in most forms of chronic pancreatitis, especially in alcoholic and hereditary pancreatitis[77], although it is not known whether these plugs cause pancreatitis or are a result of pancreatitis.

Acute pancreatic damage is initially reversible, except in severe cases with pancreatic necrosis. However, recurrent episodes evoke an irreversible state, with acinar cell and islet cell destruction that results in pancreatic exocrine insufficiency and diabetes mellitus, an immune response that leads to nerve abnormalities and chronic pain, and acinar-to-ductal metaplasia, which is one of the first steps in the development of pancreatic cancer[86,87].

Pancreatic stellate cells are key cells involved in pancreatic injury[88,89]. During pancreatitis, in response to oxidative stress, cytokines, growth factors and toxins, pancreatic stellate cells are transformed from a quiescent state to an activated myofibroblast-like phenotype in which the cells synthesize and secrete excessive amounts of extracellular matrix proteins. Numerous studies have demonstrated the key role of pancreatic stellate cells in the development of fibrosis in acute and chronic pancreatitis due to the imbalance between fibrogenesis and matrix degradation[90–92]. *In vitro* studies have confirmed the role of hypoxia in pancreatic stellate cell activation with the increased release of factors, such as type I collagen, fibronectin and vascular endothelial growth factor. Pancreatic stellate cells contribute to the fibrotic and hypoxic milieu by amplifying abnormal extracellular matrix deposition[93].

Pain

Pain is the most disabling and clinically dominant symptom in patients with chronic pancreatitis and is present in most patients. Pancreatic burn-out (improvement of pain symptoms) can occur, but this is unpredictable and not constant[3,94]. Most studies have focused on structural abnormalities and increased pressure in the ductal system or tissue as causes of pain. However, other studies have found maladaptive neuroplastic changes of the central nervous system, and in many cases, pain probably has a neuropathic origin[95–97] (FIG. 2). It is now well established that pain associated with chronic pancreatitis is multimodal, involving pancreatic and peripancreatic complications, extra-pancreatic visceral mechanisms, and abnormalities in the peripheral and central nervous systems (BOX 2). This multimodality explains some past therapeutic failure when the choice of treatment was based only on morphological abnormalities.

Intrapancreatic changes are characterized by neuronal plasticity corresponding to the increase in the number of nerves and hypertrophy (increase in size) of the neurons[95]. Sensitization of pancreatic sensory neurons and neurogenic inflammation might also have a role in the development of pain[96]. Moreover, crosstalk between pain and inflammation was described and demonstrated in animal studies. In models of pancreatitis induced by an analogue of cholecystokinin (caerulein; also known as ceruletide), which stimulates digestive enzyme secretion, inflammatory changes were associated with the increased excitability of pancreatic neurons by increased expression of nociceptors and, conversely, the activation of these nociceptors promoted immune and inflammatory cell responses[98,99] (FIG. 2).

Diagnosis, screening and prevention

Diagnosis

Often the first signs of the disease that prompt patients to seek medical attention are abdominal pain, which originates in the epigastrium and radiates to the back in a belt-like manner, loss of body weight (in 80% of patients) and steatorrhoea (in <50% of patients), and later, in approximately 26–80% of patients, diabetes mellitus[100,101]. Some patients do not experience pain despite gross pathological changes on radiology; the reason for this is unknown.

Recurrent bouts of pancreatic pain with a documented rise in amylase or lipase activity at least threefold the normal upper limit with any histological or radiographic features mentioned in BOX 3 would be diagnosed as chronic pancreatitis. In the absence of histological and/or radiological evidence, the diagnosis would be recurrent acute pancreatitis (and not chronic

pancreatitis) because consensus criteria for early chronic pancreatitis and atypical chronic pancreatitis have not been established.

The time interval between the onset of symptoms and the diagnosis of chronic pancreatitis is a median of 30–55 months in alcoholics[102,103]. In non-alcoholics, the diagnosis is even more delayed (a median of 81 months) and is frequently only established if complications of the disease occur, such as pseudocysts (cavities with a fibrous wall that are filled with turbid fluid/pancreatic juice), jaundice or gastric outlet obstruction. The main reason for this delay is the variation in the natural course of the disease. The clinical presentation varies from severely ill patients with symptoms of an acute abdomen (an emergency condition presenting with acute abdominal pain) to patients with slowly progressing cachexia.

There is ongoing discussion about the term, definition and clinical implication of early chronic pancreatitis. An earlier diagnosis and subsequent therapy might prevent irreversible destruction of the pancreas and might reduce the risk of pancreatic cancer; however, this might also result in over-diagnosis and treatment[104]. The Japanese pancreatology community established diagnostic criteria for early chronic pancreatitis[20] comprising the following four clinical symptoms: recurrent upper abdominal pain, abnormal pancreatic enzyme levels in the serum or urine, abnormal pancreatic exocrine function and continuous heavy alcohol drinking, as well as imaging findings of early chronic pancreatitis on endoscopic ultrasonography imaging or endoscopic retrograde cholangiopancreatography (ERCP). A diagnosis of early chronic pancreatitis can be made using the

Table 2 | **Morphological features of chronic pancreatitis***

Condition	Macroscopic features	Necrosis and/or pseudocyst	Inflammatory cells (localization and type)	Ductal changes	Parenchymal changes	Fibrosis
Alcoholic CP	Segmental or diffuse involvement	Present	• Sparse and perineural or perivascular distribution of lymphocytes and mast cells • Neutrophils and histiocytes in necrotic areas	Ductal irregularities, with dilatation, destruction of the epithelium, squamous metaplasia and ductal calculi	Acinar atrophy and tubular complexes	Present in the perilobular, interlobular and intralobular areas
Hereditary CP	Segmental or diffuse involvement	Sometimes present	• Sparse and periductal distribution of lymphocytes • Neutrophils and histiocytes in necrotic areas	Ductal irregularities with dilatation, necrosis, squamous metaplasia and ductal calculi	Acinar atrophy and tubular complexes	Present in the perilobular, interlobular, intralobular and periductal regions
Tropical CP	Segmental or diffuse involvement	Not present	Sparse distribution of lymphocytes, plasma cells and mast cells	Ductal irregularities with dilatation and ductal calculi	Acinar atrophy and tubular complexes	Present in the perilobular, interlobular, intralobular and periductal regions
Idiopathic CP	Segmental or diffuse involvement	Not present	Sparse distribution of lymphocytes, plasma cells and mast cells	Ductal irregularities with dilatation and sometimes ductal calculi	Acinar atrophy and tubular complexes	Present in the perilobular, interlobular and intralobular regions
Obstructive CP	Duct obstruction and diffuse involvement	Not present	Sparse distribution of lymphocytes	Ductal irregularities with dilatation; ductal calculi are not usually present	Acinar atrophy and tubular complexes	Diffuse distribution in the interlobular and intralobular areas
Paraduodenal CP (also known as groove CP)	Localized in the ectopic pancreatic tissue in the duodenal wall between the major and minor papilla[116]	Present	Sparse distribution of lymphocytes; the presence of neutrophils and histiocytes in necrotic areas	Ductal irregularities with dilatation and cysts and sometimes ductal calculi	Acinar atrophy, tubular complexes and proliferation of myoid cells	Extensive fibrosis localized in the interlobular and intralobular areas
Autoimmune pancreatitis type 1	Forms a tumour-like mass or diffuse induration, mostly in the head	Not present	Lymphocytes, plasma cells, eosinophils and neutrophils present in the periductal region of large and medium-sized ducts	Ductal stenosis	Acinar atrophy	Diffuse distribution with storiform appearance in the periductal region
Autoimmune pancreatitis type 2	Forms a tumour-like mass or diffuse induration, mostly in the head	Not present	Lymphocytes, plasma cells, eosinophils and neutrophils present in the periductal and intraductal regions (neutrophils are also present in intra-acinar regions)	Ductal stenosis	Sometimes acinar atrophy	Present in the periductal region with a diffuse or storiform distribution

Ductal calculi are small areas of calcifications in the pancreatic duct. Tubular complexes are duct-like structures with flattened cells surrounding a large lumen in response to pancreatic injury. Note that the aetiology of the chronic pancreatitis cannot be determined by histological criteria in non-autoimmune chronic pancreatitis. CP, chronic pancreatitis. *Based on data in REFS 115,117–122.

Japanese criteria if the patient meets at least two of the four clinical symptoms listed and shows signs of early chronic pancreatitis on imaging.

Exocrine pancreatic insufficiency

Exocrine pancreatic deficiency is defined as a decreased secretion of digestive enzymes and bicarbonate by the pancreas regardless of its cause and may be mild or severe. Exocrine pancreatic insufficiency implies that the reduced pancreatic enzyme secretion is insufficient to maintain the normal digestion of nutrients. The main causes of exocrine pancreatic insufficiency in adults are chronic pancreatitis, pancreatic carcinoma and a previous pancreas resection. Typical symptoms of exocrine pancreatic insufficiency include abdominal cramps, bloating, flatulence, steatorrhoea and malnutrition[105].

In patients with alcoholic chronic pancreatitis, clinically manifest exocrine pancreatic insufficiency usually develops approximately 10–15 years after the onset of symptoms; this interval might be even longer in patients with early-onset idiopathic or hereditary chronic pancreatitis. The late manifestation of exocrine pancreatic insufficiency, despite the destruction of pancreatic tissue in the early stages of the disease, is explained by the large functional reserve capacity of the pancreas of >90–95%[106].

In most patients, there is a correlation between the extent of morphological changes visualized via imaging and reduced exocrine pancreatic function[3]. MRI-based techniques allow semi-quantitative parameters to assess exocrine pancreatic function by determining fluid secretion into the duodenum during a secretin-enhanced magnetic resonance cholangiopancreatography (MRCP), in which secretin is used to stimulate pancreatic fluid secretion[107]. The secretin test can directly measure exocrine pancreatic function and is useful as a reference method to evaluate new tests. To answer clinical questions, a non-invasive function test such as the pancreatic elastase test (the measurement of enzyme in the faeces) can be used (TABLE 1). However, none of the non-invasive pancreatic function tests is sensitive enough to diagnose slight-to-moderate exocrine pancreatic insufficiency reliably, and these tests are generally unnecessary for advanced disease[108].

In addition to exocrine pancreatic insufficiency, other causes of malnutrition are pain-related reduction of food intake, continued alcohol consumption and an increased metabolic rate[3]. Some studies suggest impaired absorption of fat-soluble vitamins in patients with mild-to-moderate exocrine pancreatic insufficiency due to chronic pancreatitis. Although the prevalence of vitamin D deficiency is high in patients with chronic pancreatitis, no difference in vitamin D levels was observed compared with age-matched and sex-matched controls in several studies[103,109–111]. The increased risk of osteoporotic fractures in patients with chronic pancreatitis is likely to be multifactorial and can only partially be attributed to exocrine pancreatic deficiency and reduced absorption of vitamin D[112].

Endocrine pancreatic insufficiency

Pancreatogenic (type 3c) diabetes in chronic pancreatitis is characterized by a deficiency of insulin secretion and other hormones secreted by the cells of the islets of Langerhans[101,113]. The risk of hypoglycaemia is increased in patients with pancreatogenic diabetes, resulting in increased mortality. Episodic hypoglycaemia occurs in up to 79% of patients with pancreatogenic diabetes, and severe hypoglycaemia occurs in up to 41%. Median survival is 8.7 years after the diagnosis of pancreatogenic diabetes. Thus, diagnosis and follow-up monitoring of diabetes mellitus is important and should be performed according to international guidelines[114].

Histopathology

The morphological features of chronic pancreatitis vary depending on aetiology and stage of disease[115] (TABLE 2). Macroscopic features of the pancreas in advanced-stage classic (alcoholic) chronic pancreatitis are an irregular contour, firm consistency and loss of lobulation. Dilated and irregular ducts that sometimes contain stones can be observed. Pseudocysts can be present in the pancreas and can even extend beyond the normal pancreatic border. These changes can be patchy and may mimic a neoplasm on imaging[115].

The key histological features are interlobular, intralobular and periductal fibrosis, atrophy of the acinar parenchyma and duct distortion with intraluminal protein plugs and/or calcifications; squamous metaplasia of the duct epithelium may be observed (FIG. 3). Sparse lymphocytic infiltrates are present in the interstitial tissue, and also surrounding often enlarged peripheral nerves. Other characteristic features include the

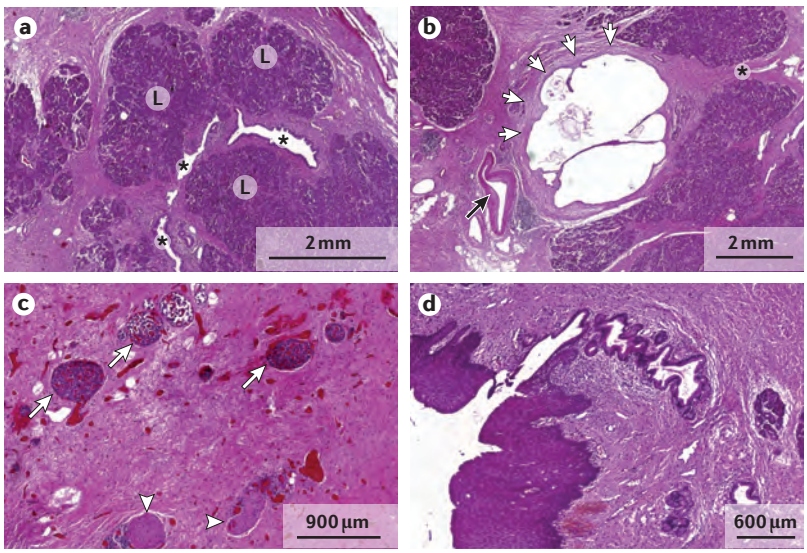

Figure 3 | **Histological characteristics of alcoholic chronic pancreatitis. a** | Early-stage disease with well-preserved pancreatic parenchyma with moderate perilobular, interlobular and periductal fibrosis, and focal intralobular fibrosis (lower left). Lobuli are represented by 'L' and ducts by asterisks. **b** | Histological image of a cystically dilated duct (centre) with flattened epithelium, periductal (white arrows) and perilobular fibrosis (asterisk), and a blood vessel with a thickened wall (black arrow). **c** | End-stage chronic pancreatitis with complete atrophy of the acinar cells, paucicellular fibrosis with prominent islets (arrows) and nerves (arrowheads). **d** | Large interlobular duct with squamous metaplasia.

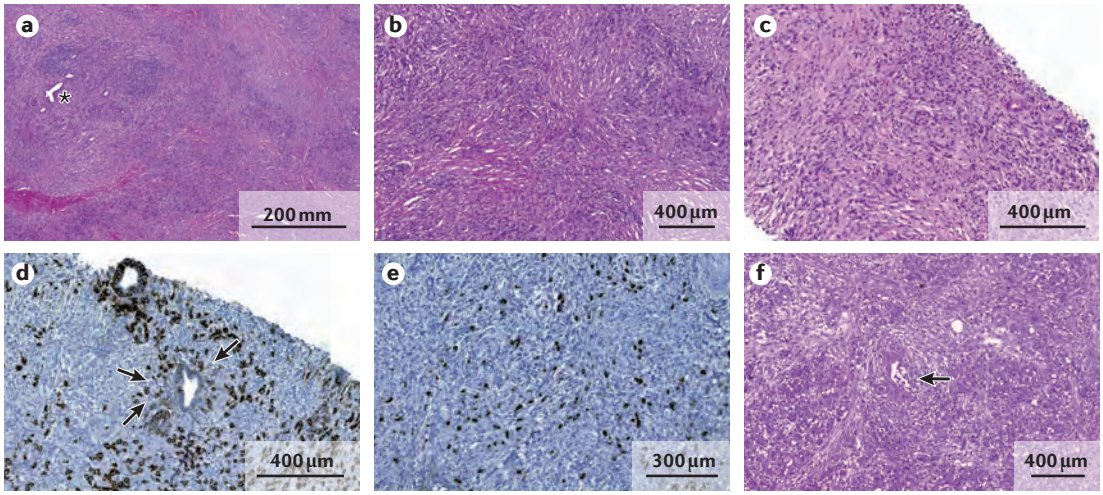

Figure 4 | **Histological characteristics of autoimmune pancreatitis. a** | Massive obliteration of the lobular architecture with diffuse fibrosis, abundant inflammatory infiltrates and stenosis of a medium-sized duct (asterisk) in autoimmune pancreatitis type 1. **b** | Detail of storiform fibrosis in autoimmune pancreatitis type 1. **c** | Core needle biopsy sample of a patient with autoimmune pancreatitis type 1 showing massive lymphoplasmacellular infiltration and fibrosis. **d** | Immunohistochemistry for CD138 showing abundant plasma cell infiltrates with periductal localization (arrows) in autoimmune pancreatitis type 1. **e** | Immunohistochemistry for IgG4 showing abundant IgG4-positive cells in autoimmune pancreatitis type 1. **f** | Granulocytic epithelial lesions of an interlobular medium-sized duct with a ruptured epithelium (arrow) in autoimmune pancreatitis type 2.

presence of irregular clusters of islets and the presence of thick-walled vessels. Owing to its recurrent nature, chronic pancreatitis may show areas of acute parenchymal and fat necrosis, especially in the earlier stages of the disease. In this case, periductal and interlobular fibrosis predominate over intralobular involvement, and acinar tissue is still well preserved. Variations of the histological features, such as those described in alcoholic chronic pancreatitis, are also observed in hereditary, metabolic, tropical, idiopathic and paraduodenal chronic pancreatitis[115–119] (TABLE 2).

Autoimmune pancreatitis is the only type of chronic pancreatitis for which the aetiology can be determined based on histological features[120–122] (FIG. 4; TABLE 2). Macroscopically, both a focal, tumour-like appearance with surrounding normal parenchyma and a diffuse induration and enlargement of the pancreas can be observed. Autoimmune pancreatitis type 1 belongs to the spectrum of IgG4-sclerosing disease and is characterized by intense periductal inflammation, high numbers of IgG4-positive plasma cells, inflammatory changes of venules, sometimes in the form of an obliterative phlebitis (inflammation of the venules typical in autoimmune pancreatitis type 1), and by the so-called storiform fibrosis consisting of swirling collagen fibres, activated fibroblasts and myofibroblasts and inflammatory cells. Dense infiltrates of eosinophils, extension of the inflammatory process beyond the borders of the pancreas, hyperplastic lymph follicles and arteritis may be additional features. Infiltrates of neutrophils within the acinar parenchyma and the ductal epithelium, sometimes with the formation of small intraductal abscesses (so-called granulocytic epithelial lesions) are the hallmarks of autoimmune pancreatitis type 2, which otherwise shares most of the above-described morphological features of type 1, except for numbers of IgG4-positive plasma cells. Notably, although it is known as autoimmune pancreatitis, type 2 has no serological findings suggesting an autoimmune aetiology[120–123].

Imaging

CT provides excellent information about morphological changes of the pancreas, such as pancreatic duct dilatation or strictures, atrophy, calcification and pseudocystic changes (FIG. 5). The main drawbacks of CT are the limited visualization of the pancreatic ductal system and the lack of sensitivity and specificity for mild forms of chronic pancreatitis, although the sensitivity for the detection of calcifications is better than that of MRI[11,124,125]. MRCP (FIG. 6) has a high sensitivity for detecting strictures and dilatation in (the side branches of) the pancreatic duct. Images obtained by MRCP are essentially identical to those obtained by ERCP (FIG. 6), which was once used for diagnosis but is now restricted to interventional procedures. Dynamic MRCP (FIG. 6), in which images are acquired every 30 or 60 seconds over a 10-minute period following intravenous secretin hormone injection, provides excellent spatial resolution and functional information on exocrine pancreatic insufficiency[124,126,127]. Thus, MRCP or dynamic MRCP can be considered as the first choice for the classification and staging of patients with chronic pancreatitis. The major limitation of MRCP is in the identification of parenchymal calcifications and small ductal calculi, which is where CT is especially sensitive. Although endoscopic ultrasonography has an important role in obtaining diagnostic biopsies and therapeutic interventions, the relatively poor interobserver agreement for endoscopic ultrasonography limits its diagnostic accuracy for chronic pancreatitis[128–130]. In addition,

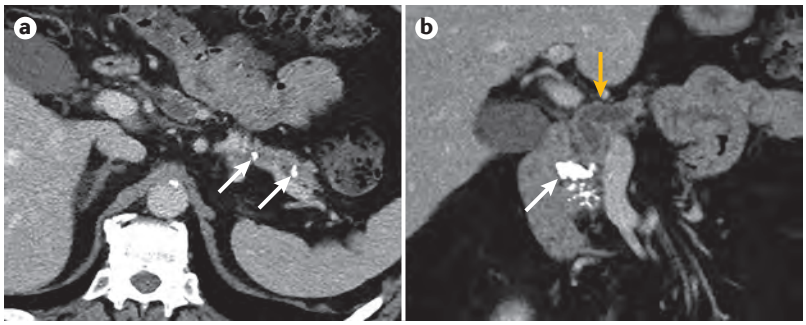

Figure 5 | **CT imaging in chronic pancreatitis.** Post-contrast CT image of severe chronic pancreatitis shows ductal stones (white arrows in part **a** and part **b**) within the dilated pancreatic duct (orange arrow; part **b**).

endoscopic ultrasonography will incorrectly overcall early chronic pancreatitis[124]. Prospective evaluation is required for emerging innovative technologies, such as MRI elastography for the evaluation of tissue stiffness[131,132], T1-mapping (MRI) for the quantification of fibrosis in the pancreas[133], diffusion-weighted MRI for the analysis of microscopic physical properties of tissues at a molecular level[134,135], and pancreatic fluid flow dynamics imaging[136].

Scoring

Several scoring systems exist to evaluate the severity of chronic pancreatitis. The Cambridge classification for severity grading using ERCP[137], and its adaptation for other types of imaging is still used for diagnosing and scoring chronic pancreatitis in adults[103,124]. The ABC system uses a classification that consists of three stages combining clinical criteria (pain, recurrent attacks of pancreatitis, local complications, steatorrhoea and diabetes mellitus) with imaging (ductal or parenchymal changes)[138]. The Rosemont classification can diagnose chronic pancreatitis using only endoscopic ultrasonography criteria[139]. The number of parameters correlates with the severity of the disease as confirmed by histopathology. The M-ANNHEIM classification attempts to characterize patients according to aetiology, clinical stage and severity[140]. The severity of the inflammatory reaction is evaluated using clinical symptoms and therapeutic interventions (for example, whether it is responsive to steroids). Rather complex classification criteria involve a points system describing the severity of chronic pancreatitis. The Chronic Pancreatitis Prognosis Score (COPPS) predicts individual short-term (12-month) prognosis using C-reactive protein levels, thrombocyte count, glycosylated haemoglobin levels (a marker of diabetes mellitus), body mass index and pain levels. It allows objective monitoring of chronic pancreatitis regarding readmission to hospital, as well as length of hospital stay[141]. Finally, several scoring systems exist for pain, such as visual analogue scales and the Izbicki pain score (see REF. 3 for a comprehensive discussion).

Prevention

Few data are available when it comes to the prevention of chronic pancreatitis. Alcohol consumption and smoking should be avoided and abstinence may slow the progression of the disease[142,143]. Earlier surgical intervention can also ameliorate the long-term consequences of pain, and endocrine and exocrine function[144,145].

Management

The aim of management is to alleviate symptoms (most commonly pain, followed by exocrine and endocrine insufficiency) and to prevent further disease progression and disease-related complications, such as bile duct obstruction, gastric outlet obstruction and portal vein thrombosis.

Pain management

The treatment options for pain associated with chronic pancreatitis are shown in BOX 4. Pain is most often genuine, but there are several secondary causes that should always be considered, as they are easier to treat than genuine pancreatic pain[97] (BOX 2). Pathology such as pancreatic duct stones and strictures are typically treated invasively, including by endoscopic stone removal and stenting, extracorporeal shock wave lithotripsy (ESWL) and surgical resections, and drainage procedures[146]. Endoscopic treatment can be combined with ESWL in the presence of large (>4 mm in size) obstructive stones[147]. Pain relief is seen in 60–80% of cases, but data must be interpreted carefully as no sham-controlled

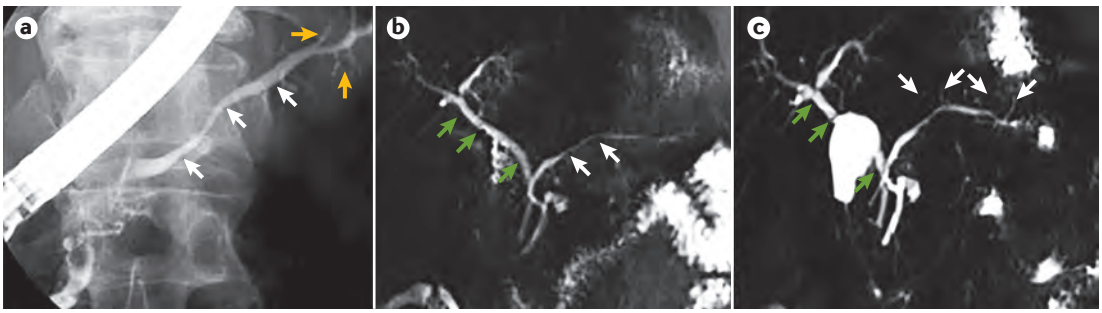

Figure 6 | **ERCP and MRCP imaging in chronic pancreatitis. a** | Endoscopic retrograde cholangiopancreatography (ERCP) showing moderate chronic pancreatitis as evidenced by a slightly dilated duct (white arrows) and visible side branches (orange arrows). **b**,**c** | Magnetic resonance cholangiopancreatography (MRCP) imaging shows abnormal pancreatic duct (white arrows; part **b**) and enables the visualization of multiple abnormal side branches after secretin injection (white arrows; part **c**). Note the bile duct in part **b** and part **c** (green arrows).

Box 4 | **Different treatment modalities for pain in chronic pancreatitis**

Before treatment is initiated, all secondary causes of pain should be considered and treated appropriately. Not all treatments have been evaluated in chronic pancreatitis, and evidence often comes from randomized trials in other chronic pain conditions.

Risk factor modification

- Alcohol abstinence
- Tobacco smoking cessation
- Dietary therapy (to improve the condition in general, including pain)

Initiatives to minimize pressure in the duct system and parenchyma

- Pancreatic rest by tube feeding into the jejunum or nutritional products that do not activate cholecystokinin
- Uncoated pancreatic enzymes that may degrade cholecystokinin-releasing factor
- Cholecystokinin inhibitors
- Proton pump inhibitors (to increase the efficacy of enzyme treatment)

Analgesics

- Simple analgesics such as paracetamol and NSAIDs (combined with proton pump inhibitors)
- Adjuvant analgesics; for example, gabapentinoids
- Weak or strong opioids plus laxatives

Invasive procedures

- Endoscopy
- Extracorporeal shock wave lithotripsy
- Surgery
- Celiac ganglion neurolysis (temporal neuronal block performed under CT) and splanchnicectomy (surgical excision of part of the greater splanchnic nerve) aimed at pain suppression
- Spinal cord stimulation aimed at pain suppression
- Intrathecal opioids aimed at pain suppression

Treatment of anxiety and depression

- Tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors; these drugs also have a direct effect on the pain system
- Cognitive–behavioural therapy, including sleep therapy
- Anxiolytics

Neuromodulation aimed at improving pain

- Acupuncture
- Transcutaneous electrical nerve stimulation
- Transcranial magnetic stimulation
- Direct current stimulation
- Physiotherapy

Experimental therapies aimed at improving pain and health status in general

- Ketamine, antipsychotics and clonidine
- Radiotherapy of the pancreas
- Nerve growth factor inhibitors
- Cannabinoids

For details and further information, the reader is referred to www.pancreapedia.org.

studies have been carried out[148]. For a detailed discussion of the different techniques, the reader is referred below and to REF. 148.

Some patients benefit from enzyme supplementation and antioxidants for pain relief, but the results are variable and inconclusive[149–152]. Analgesic treatment follows the principles of the 'pain relief ladder' provided by the WHO, with the serial introduction of drugs with increasing analgesic potency (I: simple analgesics; II: weak opioids ± adjuvants; and III: strong opioids) that are titrated until pain relief is obtained[153]. In most patients, simple analgesics such as paracetamol are not sufficient and tramadol is the preferred level II analgesic as it is in some respects superior to morphine[154]. Opioid therapy is difficult owing to adverse effects, and rotation between the drugs is often needed[155,156]. Transdermal administration of opioids can be used for patients who have trouble with tablet ingestion[157]. Adjuvant analgesics include antidepressants and anticonvulsants. In chronic pancreatitis, only pregabalin has been investigated in a placebo-controlled trial and it was found to provide moderate but significant pain relief compared with placebo[158]. In difficult cases, other treatments such as thoracoscopic splanchnic denervation, spinal cord stimulation, radiation therapy, transcranial magnetic stimulation and acupuncture may have limited benefits[159–163]. Patients who have comorbid depression and anxiety[164] may benefit from cognitive–behavioural therapy and drugs with combined effects on pain and depression such as serotonin–noradrenaline reuptake inhibitors[3,165], but multidisciplinary evaluation and follow-up is mandatory.

Exocrine and endocrine substitution

Maldigestion-related symptoms (such as diarrhoea, steatorrhoea, weight loss, flatulence and abdominal distention) and nutritional deficiencies are the main consequences of exocrine pancreatic insufficiency, which can be avoided by appropriate pancreatic enzyme replacement therapy[166,167]. Pancreatic enzymes (usually a combination of lipase, amylase and protease) should be administered orally together with each meal or snack[168]. Enteric-coated enzyme preparations in the form of microspheres or mini-microspheres improve digestion and the absorption of nutrients, relieve symptoms and improve the nutritional status of patients[169]. Enzyme dose should be adjusted based on the volume, fat and calorific content of meals. As a guide, a starting dose of 40,000–50,000 United States Pharmacopeia unit (USP) or European Pharmacopeia of lipase with main meals, and one-half of that dose with snacks is generally recommended[170]. Enzyme dose should be further individualized based on symptom response and objective evaluation of nutritional status.

Diabetes therapy in chronic pancreatitis should be individually tailored, not only to control for hyperglycaemia but also to reduce the risk of hypoglycaemia[101,113]. An adequate and balanced food intake together with oral pancreatic enzymes and alcohol abstinence are required for appropriate glycaemic control[101,113]. Pain treatment should also be optimized, as postprandial pain compromises food intake and hence glycaemic control. Insulin substitution is usually required for diabetes mellitus type 3c, and long-acting basal insulin

analogues together with on-demand short-term insulin is recommended. Controlling mild hyperglycaemia with oral hypoglycaemic agents, such as metformin, may be a valid approach[101]. Patients should be monitored for the development of retinopathy, nephropathy and neuropathy.

Endoscopy

Between 30% and 60% of patients with chronic pancreatitis will ultimately require some type of endoscopic or surgical intervention for treatment[103]. The indication for endoscopic therapy is most often intractable pain, and treatment should be considered before patients become opiate-dependent. The most common indications for endoscopic treatment are strictures of the pancreatic duct, obstruction of the common bile duct and pancreatic pseudocysts[148]. Several endoscopic procedures are available, which differ in their potential benefits and prognosis.

When increased pressure in the pancreatic duct owing to a dilated duct with strictures is assumed to be the cause of either pain or recurrent disease episodes, endoscopic sphincterotomy is performed first. This procedure, in which the muscular valve that controls the flow of bile and pancreatic juice is cut, is usually followed by the insertion of one or more plastic stents into the pancreatic duct[171]. Whether the removal of intraductal stones or their disintegration by prior ESWL is of additional benefit is still being discussed and is not necessarily supported by high-quality clinical evidence[172]. Observational studies suggest that approximately two-thirds of patients experience some pain reduction after endoscopic therapy involving sphincterotomy and/or stent placement[173]. One randomized study on stent placement with no endoscopic treatment that involved 41 patients found that, over 3 years, stent placement reduced pain by 35% compared with controls but did not affect endocrine function[174].

For the obstruction of the common bile duct, one or more plastic stents can be inserted into the bile duct after biliary sphincterotomy to restore patency[175]. More recently, fully covered (membrane-covered metal or polymer) self-expanding stents (FCSEMS) have become popular. Like stents in the pancreatic duct, stents in the bile duct need to be regularly exchanged to prevent occlusion and cholangitis (that is, infection of the bile duct system). A suggested exchange interval for plastic stents is 3 months, whereas FCSEMS remain open for 6 months or longer[176,177]. FCSEMS seem to improve outcome in case series[178], non-randomized[179] and randomized trials[180], with a stricture resolution rate of 76–93% and a recurrence rate of strictures of only 14–15%.

The third most common indication for endoscopic intervention, following increased pressure in the pancreatic duct or the obstruction of the bile duct, is pancreatic pseudocysts, which develop in 20–40% of patients. These patients should be treated when symptoms (most often infection, pain, nausea and vomiting) or complications develop (for example, compression of large blood vessels or the common bile duct, bleeding into pseudocysts or gastrointestinal tract, or pancreatic pleural fistulas). When cysts remain asymptomatic, their size and clinical course can still warrant endoscopic drainage. If they measure >5 cm in diameter and do not regress spontaneously over 6 (or 12) weeks, complications are likely and drainage should be considered[181]. Drainage can be achieved either by inserting a transpapillary plastic stent used for smaller cysts located closer to the papilla[182] or by transmural placement of pigtail or self-expanding, lumen-apposing metal stents from the stomach or the duodenum into the cyst cavity[183] (FIG. 7). Whether drainage by plastic or lumen-apposing metal stents leads to a better outcome or to fewer complications is still being debated[183]. Depending on the location, combined trans-sphincter, transmural or transabdominal ultrasound and CT-guided or laparoscopic procedures may be necessary.

Surgery

The aim of surgical intervention is to alleviate severe, constant or recurrent abdominal pain and to cure or prevent additional organ complications, including biliary compression that results in jaundice, duodenal compression that causes gastric outlet obstruction, or vascular obstruction that potentially leads to portal hypertension or portal vein thrombosis with subsequent varicose collaterals.

Evidence-based data regarding surgical versus endoscopic intervention are sparse and no studies have yet been performed that are sham controlled. Two randomized controlled trials have been carried out comparing surgery and endoscopy in a specific subpopulation of patients with chronic pancreatitis; both trials showed that surgery was superior for short-term and/or long-term pain relief than endoscopy[184–186]. However, these trials have been criticized because of their small cohorts and

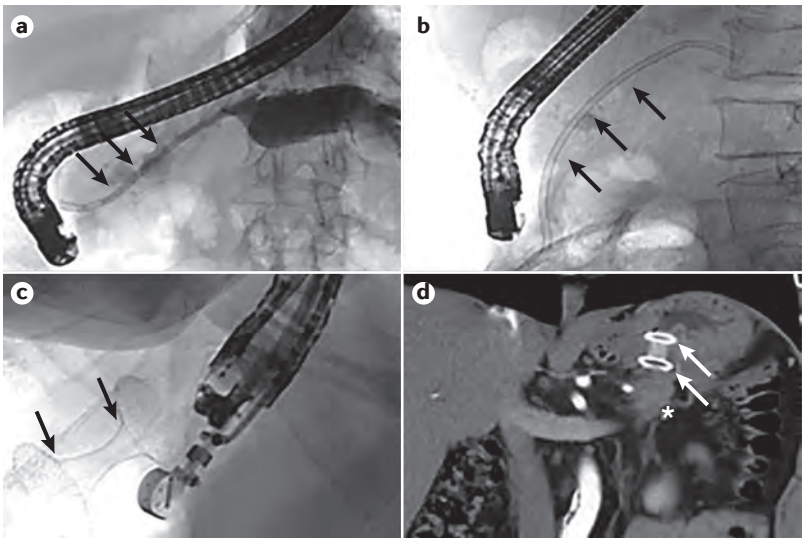

Figure 7 | **Endoscopic management of chronic pancreatitis.** Drainage of a long stenotic segment of the pancreatic main duct (arrows; part **a**), by the insertion of a plastic stent (arrows; part **b**). A pancreatic pseudocyst with solid content is drained via the posterior wall of the stomach with a self-expanding metal stent (arrows; part **c**) under the guidance of endoscopic ultrasonography. CT scan showing near-complete resolution of the pseudocyst (asterisk; part **d**) following the insertion of the stent (arrows; part **d**).

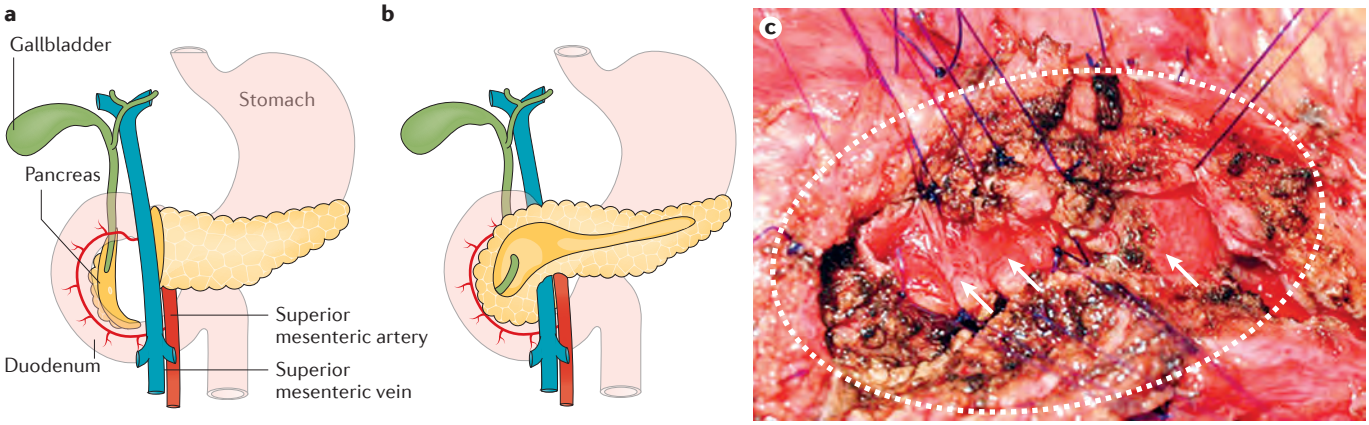

Figure 8 | **Surgical management of chronic pancreatitis. a** | Duodenum-preserving pancreatic head resection. Note that the pancreas is cut above the superior mesenteric vein and portal vein axis. **b** | Variant of the duodenum-preserving pancreatic head resection. Note that the pancreas is not cut above the superior mesenteric vein or portal vein axis and that the pancreatic duct is opened towards the pancreatic body and tail. **c** | Photograph of the intraoperative situs (surgical site) following a variant duodenum-preserving pancreatic head resection. The resection area is circled. The arrows mark the opened pancreatic duct.

specific subpopulations[187], and the results have not led to a change in general clinical practice. One could argue that surgery — if necessary — should be carried out early during the disease course to reduce further parenchymal damage and severe chronic pain syndromes[144,145,188–192]. There are better outcomes for early versus later surgery regarding pain management, and endocrine and exocrine function of the remnant pancreas, as well as better yields of islet cells (in the case of auto-transplantation) and a lower risk of cancer development (in the case of total pancreatectomy)[193–197]. As chronic pancreatitis usually presents with diverse morphological patterns, symptoms and complications[198], two main surgical principles have been suggested, which often overlap in individual surgical approaches: drainage to alleviate pancreatic duct pressure and resection to remove inflamed pancreatic tissue. Resection often focuses on the pancreatic head, as most obstructive complications arise there. Drainage-only procedures, such as the Partington–Rochelle operation, drain the opened pancreatic duct by connecting it to a small bowel loop (longitudinal pancreato-jejunostomy)[199]. Classic resectional procedures, such as the Whipple operation (partial duodenopancreatectomy), are carried out less frequently in favour of duodenum-preserving pancreatic head resections (the Beger procedure[200]) (FIG. 8a), with various variants of this operation being described[198] (FIG. 8b,c). Duodenum-preserving and spleen-preserving total pancreatectomy is indicated especially in patients with hereditary pancreatitis and/or end-stage disease[188].

In mild chronic pancreatitis, total pancreatectomy with auto-islet transplantation, a procedure in which islet cells are isolated from the resected pancreas and re-implanted in the liver, is possible[201]. This procedure can be considered in patients with hereditary pancreatitis, but is controversial in patients with non-hereditary chronic pancreatitis who show only minimal morphological alterations, as long-term graft failure remains a concern[202].

Partial or left pancreatectomies have also been carried out for segmental dominant disease. Evidence-based data regarding the optimal surgical strategy are sparse, as only a few relatively small randomized controlled trials have been carried out. Meta-analyses of these trials, as well as of prospective and retrospective studies[198,203–205], have suggested potential advantages of duodenum-preserving procedures with respect to operating time and hospital stay, whereas better postoperative weight gain and quality of life (QOL) and reduced perioperative complications have not been consistently shown. A comparison of different variants of duodenum-preserving procedures did not reveal any relevant differences.

Quality of life

Multidimensional QOL questionnaires are highly relevant to assess disease severity. Previously, various questionnaires have been used in chronic pancreatitis, including the Medical Outcomes Short-Form Health Survey (SF-36 or SF-12)[206–209] and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire[210]. Recently, the Pancreatitis Quality of Life Instrument has been introduced[211].

Studies using such questionnaires have all demonstrated that patients with chronic pancreatitis have a substantially impaired QOL[211–213]. Compared with before the development of chronic pancreatitis, 74% of patients have had their work altered and only 37% were employed with a substantial reduction in income[214]. QOL and symptom burden are strongly associated. Decreased QOL has been associated with low body weight, disease duration, unemployment, depression, fatigue, and fear of future and extra-pancreatic complications[100,213,215]. The association between QOL and pain has been the most consistent finding, but the exact findings are inconsistent and controversial. A large multicentre study showed that patients with constant pain were reported to have a lower QOL than patients

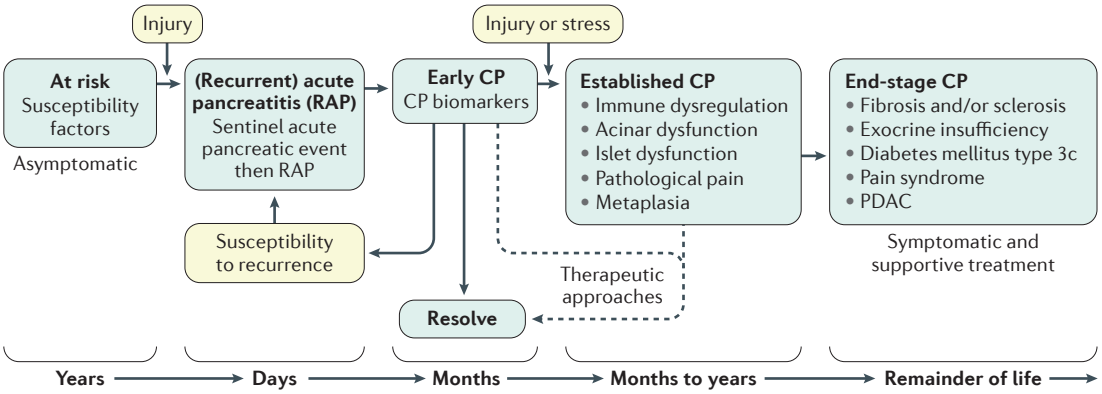

Figure 9 | **A conceptual model of disease progression linked to the mechanistic definition of chronic pancreatitis.** This model organizes the genetic and environmental risk factors, the role of recurrent injury or stress, and the normal and abnormal response to the injury–inflammation–resolution–regeneration sequence. CP, chronic pancreatitis; PDAC, pancreatic ductal adenocarcinoma. Adapted with permission from REF. 1, Elsevier.

with intermittent pain[207–209]. However, studies in Poland and Denmark showed no differences in temporal pain patterns in QOL, but the pain intensity was closely correlated with QOL[100,215].

Outlook

Definition

Although guidelines summarize the current approach to diagnosing and managing chronic pancreatitis[3], this disease needs to be redefined with a focus on essential pathways and informative biomarkers rather than relying on end-stage pathology. The goal is to develop a rational framework and approach for early diagnosis, classification and prognosis. A new mechanistic definition should include two components, as a combination of these features defines the syndrome: the essence of chronic pancreatitis and the characteristics of well-established chronic pancreatitis.

The essence of chronic pancreatitis is characterized as "a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" (REF. 1). This mechanistic definition emphasizes the fact that pancreatitis is rare and only occurs under extreme conditions, such as pathogenetic variants of key susceptibility genes, strong environmental forces, or other, rare, internal factors. Second, as most cases of chronic pancreatitis are not congenital, considerable events must occur to cause injury and/or stress to parenchymal cells, resulting in injury signals and inflammation. Third, a persistent pathological response is needed for the features of chronic pancreatitis to develop. Thus, the pathogenetic process is an aberration of the injury–inflammation–resolution–regeneration sequence.

The characteristics of chronic pancreatitis have also been defined: "common features of established and advanced chronic pancreatitis include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia" (REF. 1). Thus, the common features could be linked to the responses of specific cell types that display a normal or abnormal response to injury or stress over time. Atrophy suggests abnormal regeneration, fibrosis suggests an abnormal type or duration of the immune response, and pain can be subclassified by the type of injury, the response to injury and/or the duration of injury with normal or abnormal types of adaptation. Thus, knowledge of the underlying pathogenetic risk factors, with the stage and activity of disease, can be used to predict future outcomes and targets for intervention. Debate continues on the criteria for early chronic pancreatitis, and whether patients with multiple features of chronic pancreatitis, except fibrosis, represent an atypical form of classic chronic pancreatitis.

Conceptual model of disease progression

Regarding the mechanistic definition, a conceptual model has been proposed of the progression of an individual through five stages, beginning with at risk and progressing to end-stage disease[1] (FIG. 9). This model serves as a template to organize the genetic and environmental risk factors, the role of recurrent injury or stress, and the normal and abnormal responses to the inflammatory environment. Importantly, this model highlights the role of acute pancreatitis and recurrent acute pancreatitis in the initiation of the cascade that leads to chronic pancreatitis in the majority of patients, and the existence of early-stage disease, with some features of chronic pancreatitis before the loss of significant function or irreversible damage characteristic of more-advanced disease. Incorrect diagnosis of early chronic pancreatitis may have harmful consequences for the patient, as it can lead to radical treatments for overlapping disorders that are not true chronic pancreatitis[124]. However, imaging evidence of fibrosis alone is not diagnostic of early chronic pancreatitis. However, patients with recurrent acute pancreatitis, who have strong risk factors (for example, alcohol abuse) plus biomarkers of chronic pancreatitis (such as fibrosis), without other causes of fibrosis (such as long-standing diabetes mellitus) are likely to have true early chronic pancreatitis.

Classification

The mechanistic definition allows chronic pancreatitis to be classified by aetiology, stage and complications. Aetiology can be complex, with multiple aetiological factors converging to cause disease. The TIGAR-O system provides an accepted list of known aetiologies[216] (BOX 1).

Chronic pancreatitis can be classified by stage, as outlined in FIG. 9. No consensus currently exists on the criteria for each stage, especially as the pathological features of the later stages are not surrogates of each other. For example, one cannot predict the pain experienced by the patient using imaging studies[217]. The definition of early chronic pancreatitis is also important, and a consensus definition of this stage is needed.

The classification of chronic pancreatitis by complication remains important among researchers because accurate classification of patients is needed to define primary end points for trials in a heterogeneous cohort. As each patient seems to develop a different set of complications at different rates, each complication must be isolated and viewed according to the underlying biological system (for example, nervous system or immune response), the specific risk and aetiologies, and the mechanisms of progression. A deep understanding of these systems will be the foundation for 'personalized medicine' in the future. However, even in the absence of a complete understanding of the pathogenesis, we need to move forwards in a concerted effort to develop causal treatment strategies and to overcome the past century of symptomatic treatment. Further advances require an accurate system of defining early chronic pancreatitis, and a robust staging system that distinctly describes progressive disease that is supported by biomarkers that can categorize the stage of disease. This will only be possible with a combined effort from all the sub-specialities involved in the treatment of chronic pancreatitis.

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