Chronic pancreatitis

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Chronic pancreatitis is a progressive fibroinflammatory disease primarily caused by a complex interplay of environmental and genetic risk factors. It might result in pancreatic exocrine and endocrine insufficiency, chronic pain, reduced quality of life, and increased mortality. The diagnosis is based on the presence of typical symptoms and multiple morphological manifestations of the pancreas, including pancreatic duct stones and strictures, parenchymal calcifications, and pseudocysts. Management of chronic pancreatitis consists of prevention and treatment of complications, requiring a multidisciplinary approach focusing on lifestyle modifications, exocrine insufficiency, nutritional status, bone health, endocrine insufficiency, pain management, and psychological care. To optimise clinical outcomes, screening for complications and evaluation of treatment efficacy are indicated in all patients with chronic pancreatitis.

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Introduction

Chronic pancreatitis is a pathological fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, or other risk factors, who develop persistent, pathological responses to parenchymal injury or stress, causing loss of function, local complications, and pain. It is often multifactorial, but the precise pathophysiology is not fully understood. Common features of established and advanced chronic pancreatitis include pancreatic atrophy, fibrosis, pain syndromes, pancreatic duct distortion and strictures, calcifications, pancreatic exocrine and endocrine dysfunction, and dysplasia.[1] The global estimate of chronic pancreatitis incidence is approximately ten cases per 100 000 person-years.[2] Incidence is twice as high in men as in women, and epidemiological data published in the past 5 years indicate an upward trend.[3–5] There is high heterogeneity between patients, and the course of the disease can be difficult to predict. Various complications might occur, including exocrine and endocrine insufficiency, nutritional deficiencies, morphological complications, and chronic pain. Secondary prevention and management of complications are essential to improve clinical outcomes. In this Seminar, we aim to provide a practical overview of current evidence on risk factors, diagnosis, and management of chronic pancreatitis, and we discuss uncertainties and key areas for future research.

Risk factors

There are multiple risk factors contributing to the development of chronic pancreatitis. Established risk factors are summarised in the M-ANNHEIM classification, including alcohol consumption, nicotine consumption, nutritional factors, hereditary factors, efferent duct factors, immunological factors, and miscellaneous and rare metabolic factors.[6] Chronic pancreatitis is often caused by a combination of risk factors.[7] Alcohol and smoking have been recognised as the most prevalent risk factors of chronic pancreatitis, both being present in more than 50% of patients.[7–9] Relative risk for developing chronic pancreatitis increases with the amount of alcohol consumed and number of pack-years smoked. Furthermore, there appears to be a cumulative effect when both risk factors are present to develop chronic pancreatitis after an initial attack of acute pancreatitis.[10–14] Genetic predisposition is another established risk factor. In hereditary pancreatitis, mutations in the cationic trypsinogen (*PRSS1*) gene cause recurrent acute pancreatitis or chronic pancreatitis in 80% of affected family members. However, besides hereditary pancreatitis, multiple genetic variants, primarily in the *PRSS1*, *SPINK1*, *CTRC*, and *CFTR* genes, have been identified to increase the risk for development of chronic pancreatitis, especially in the presence of other risk factors.[15–17] More modest risk factors include anatomical variants, such as pancreatic divisum, hypertriglyceridemia, and chronic kidney disease.[15] A detailed overview of known risk factors and associated odds ratios has been published previously.[15,18] Autoimmune pancreatitis might lead to chronic pancreatitis when disease progresses; however, diagnostic criteria and treatment differ substantially compared with classic chronic pancreatitis and is beyond the scope of this Seminar.[19] Finally, approximately 25% of patients are diagnosed with idiopathic chronic pancreatitis.[7,20]

Disease course

Role of recurrent acute pancreatitis as a precursor to chronic pancreatitis

Chronic pancreatitis is frequently described as a pancreatic disease resulting from recurrent inflammatory episodes, suggesting that acute pancreatitis must precede chronic pancreatitis. This suggestion aligns with

Search strategy and selection criteria

Data for this Seminar were identified by searches of PubMed and Embase with the term "chronic pancreatitis". When applicable, we included meta-analyses and randomised controlled trials to obtain the highest quality of data. We mainly focused on articles published Jan 1, 2010 to April 10, 2024. For older research that remains essential to current knowledge, we included the original references. The literature was updated manually on July 20, 2024, after the revision process of this Seminar. Recent, but as yet unpublished, international treatment guidelines were also included.

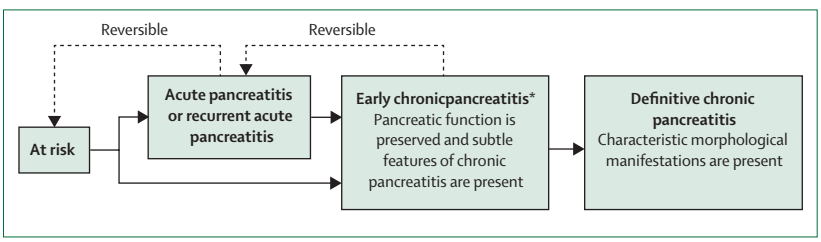

Figure 1: **Stages of disease progression in chronic pancreatitis**
*Early chronic pancreatitis is a disputable disease entity and terminology.

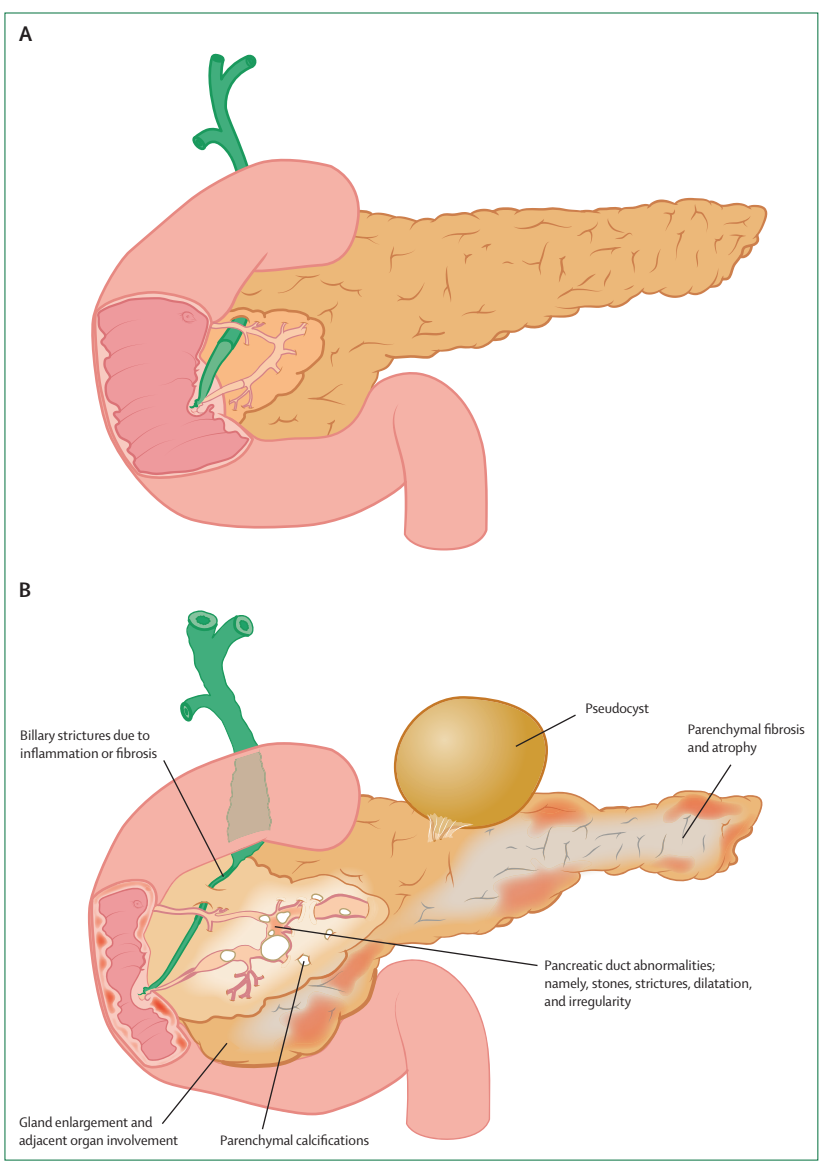

Figure 2: **Morphological changes and complications in chronic pancreatitis**
Healthy pancreas (A) and morphological changes and complications caused by chronic pancreatitis (B). Morphological changes and complications caused by chronic pancreatitis include parenchymal fibrosis and atrophy, gland enlargement during acute inflammation, pseudocyst, pancreatic duct obstruction, dilatation and irregularities, and duodenum and common bile duct obstruction.

the widespread and accepted Sentinel Acute Pancreatitis Event model.[21] This model presumes that a first episode of acute pancreatitis activates pancreatic stellate cells, whereafter recurrent or continuous acinar cell injury stimulates stellate cells to produce collagen.[21] Therefore, common causes of acute pancreatitis (eg, biliary, including microlithiasis) might also be seen as a cause of chronic pancreatitis (figure 1). However, chronic pancreatitis without a previous episode of acute pancreatitis has been described in 30–65% of patients with chronic pancreatitis.[22–24] The reason for the discrepancy between theory and clinical practice remains partly obscure, but might be explained by variances in pain perception or the existence of subclinical acute pancreatitis.[23,25]

Early chronic pancreatitis

Chronic pancreatitis is a progressive disease in which characteristic changes of the pancreas might occur as the disease advances. An early disease stage, before definite chronic pancreatitis, has been suggested (figure 1). An international Consensus Statement proposed that the term early chronic pancreatitis describes the initial stage of definite chronic pancreatitis.[26] In early chronic pancreatitis, pancreatic function is preserved and morphological changes are potentially reversible. However, early chronic pancreatitis is still a disputable disease entity without clearly defined diagnostic criteria or global consensus on terminology.[26,27]

Morphological manifestations

During the course of the disease, typical morphological manifestations of chronic pancreatitis might develop. These morphological manifestations include pancreatic duct stones and strictures, parenchymal calcifications, pancreatic duct dilatation with irregularity, abnormal side branches of the pancreatic duct, pancreatic pseudocysts, and parenchymal fibrosis and atrophy (figure 2).[28]

Diagnostic approach

Diagnosing chronic pancreatitis involves a clinical evaluation, laboratory testing to evaluate pancreatic function, and imaging. The disease is confirmed in patients with a typical history of chronic pancreatitis (panel 1), combined with the presence of morphological manifestations characteristic for chronic pancreatitis.[28]

Various conventional imaging modalities can be used in the diagnosis of chronic pancreatitis, including CT, MRI with magnetic resonance cholangiopancreatography, endoscopic ultrasound, and endoscopic retrograde pancreatography (ERP). Between these imaging modalities, sensitivity (75–82%) and specificity (90–98%) for the diagnosis of chronic pancreatitis are similar.[29] Therefore, a stepwise approach based on invasiveness, availability, and intrarater reproducibility is recommended, consisting of CT, followed by magnetic

resonance cholangiopancreatography, and—if the results are inconclusive—endoscopic ultrasound. Due to the invasiveness and risk of post-ERP pancreatitis, ERP is not considered a diagnostic tool for chronic pancreatitis.[30–32]

Role of endoscopic ultrasound

Endoscopic ultrasound enables the visualisation of more subtle pancreatic changes compared with CT and MRI, which are primarily features of pancreatic fibrosis. Endoscopic ultrasound can, therefore, be used in the diagnostic path for early chronic pancreatitis.[33] Although endoscopic ultrasound has the capability to identify subtle pancreatic changes, these observations are not highly specific for chronic pancreatitis, as they might also reflect normal variations that could normalise over time, or they are associated with pancreatic fibrosis related to ageing or diabetes.[34] Also, interobserver agreement for these subtle findings is modest.[35]

Symptoms and complications

Exocrine insufficiency

In chronic pancreatitis, exocrine insufficiency is caused by loss of, or damage to, acinar cells or by obstruction of pancreatic outflow (eg, pancreatic duct strictures or stones).[36,37] The presence of exocrine insufficiency in patients with chronic pancreatitis is strongly associated with disease duration and smoking.[20,38] 5 years after disease onset, exocrine insufficiency is present in approximately 20% of patients, which increases to approximately 70% after 20 years.[20]

Pancreatic exocrine insufficiency is a clinically defined syndrome in which pancreatic exocrine secretion or intraluminal activity of pancreatic enzymes, or both, are reduced below a level that permits normal digestion of nutrients. This syndrome is associated with malabsorption and, therefore, it might cause intestinal symptoms, including steatorrhea, diarrhoea, bloating and flatulence, and nutritional deficiencies.[39] Clinical signs and symptoms of pancreatic exocrine insufficiency are, however, non-specific and highly variable among individuals.[40] Intestinal symptoms might also be caused or worsened by conditions such as small intestinal bacterial overgrowth, and nutritional deficiencies might arise not only from exocrine insufficiency but also from abdominal pain, leading to food avoidance, poor diet, diabetes, alcohol misuse, and smoking.[37,41–43]

Recognition of intestinal symptoms is crucial as it has been identified as an important factor that negatively affects both physical and mental quality of life in patients with chronic pancreatitis.[44,45] Besides overt symptoms, exocrine insufficiency might cause reduced absorption of both macronutrients (including fat, carbohydrate, and protein) and micronutrients (including fat-soluble vitamins A, D, E, and K; magnesium; and zinc).[46,47] Consequently, exocrine insufficiency might lead to several long-term complications, including osteopenia, osteoporosis, and low-trauma fractures. It might also be associated with cardiovascular diseases, infections, and an increased risk of mortality, although these associations are less well established (table).

Panel 1: **Typical history of chronic pancreatitis**

A combination of symptoms must be present to suspect chronic pancreatitis.

- History of intermittent abdominal pain (typically after meals) or chronic pain
- History of recurrent acute pancreatitis
- History of excessive alcohol consumption or long-term smoking, or both
- Steatorrhea (primarily after fatty meals)
- Unintentional weight loss
- New-onset diabetes

Endocrine insufficiency

In patients with endocrine insufficiency due to chronic pancreatitis, all cell subtypes of the islets of Langerhans are affected, resulting in a deficiency of insulin, glucagon, and pancreatic polypeptide, contributing to rapid fluctuations in glucose levels (so-called brittle diabetes).[61,62] Because this distinct pathophysiology differentiates it from other types of diabetes, it is classified as type 3c diabetes (also termed pancreatic diabetes or pancreatogenic diabetes).[63,64] Observational studies indicate that patients with type 3c diabetes show poorer glycaemic control, a higher incidence of diabetes-related complications, and a greater need for antidiabetic medications, compared with those with type 2 diabetes.[65,66] In clinical practice, differentiation between types of diabetes is complex; therefore, the term new-onset diabetes after pancreatitis is frequently used to cover this complication.[67] The incidence of new-onset diabetes after pancreatitis is estimated to be up to 50% among patients with chronic pancreatitis 10 years after diagnosis, and is associated with disease duration, smoking, pancreatic calcifications, and pancreatic surgery.[62,66–70]

Pain

Pain is the most prominent symptom of chronic pancreatitis. Pain might manifest in different pain patterns, including continuous pain, either with or without pain attacks, and intermittent pain, when pain-free episodes in between pain attacks exist.[71] Typically, pain is initiated or worsened after meals and is localised in the epigastric region, irradiated to the back or the flanks. Pain is usually a dull ache, but might be sharp and stabbing.[72] Episodes of acute pancreatic inflammation in patients with chronic pancreatitis (also known as acute-on-chronic pancreatitis) are common but the exact incidence is unknown.[73] Longitudinal data show that pain is present at some point during the clinical course in 84–90% of patients with chronic pancreatitis.[74,75]

	Prevalence	Risk	Study design
Osteopathy			
Overall	58–65%[48,49]	..	Meta-analysis of 17 cohort and case-control studies (1659 patients);[48] meta-analysis of 11 case-control, cross-sectional studies and retrospective reviews (555 patients with chronic pancreatitis and 214 controls);[49] meta-analysis of 21 cohort and cross-sectional studies (20 155 patients with chronic pancreatitis and 2 007 278 controls);[50] meta-analysis of 19 cohort and cross-sectional studies (20 460 patients with chronic pancreatitis and 2 007 304 controls);[51] retrospective cohort study (2594 patients with chronic pancreatitis and 847 099 controls);[52] retrospective cohort study (3192 patients with chronic pancreatitis and 1 461 207 controls)[53]
Osteopenia	37–41%[48–51]	..	..
Osteoporosis	18–21%[48–51]	OR 2·8 in patients with chronic pancreatitis compared with healthy controls[51]	..
Osteoporotic fractures	5–6%[50,53]	OR 2·2–2·4 in patients with chronic pancreatitis compared with healthy controls[52,53]	..
Other complications			
Cardiovascular events	11–14%[54,55]	OR 1·5 in patients with chronic pancreatitis compared with healthy controls;[54] OR 5·0 in patients with chronic pancreatitis with exocrine insufficiency who do not have diabetes compared with patients with chronic pancreatitis without exocrine insufficiency or diabetes;[55] OR 6·5 in patients with chronic pancreatitis with exocrine insufficiency and diabetes compared with patients with chronic pancreatitis without exocrine insufficiency and diabetes[55]	Retrospective cohort study (63 230 patients with chronic pancreatitis and 28 778 980 controls);[54] prospective longitudinal cohort study (430 patients with chronic pancreatitis)[55]
Underweight	26%[56]	OR 3·4 in patients with chronic pancreatitis compared with healthy controls[56]	Cross-sectional study (166 patients with chronic pancreatitis and 160 controls)[56]
Sarcopenia	17%[57]	OR 3·8 in patients with chronic pancreatitis with exocrine insufficiency compared with patients with chronic pancreatitis without exocrine insufficiency[57]	Prospective cohort study (182 patients with chronic pancreatitis)[57]
Mortality	NA[58–60]	HR 4·3–5·0 in patients with chronic pancreatitis compared with healthy controls;[58,60] HR 2·6 in patients with chronic pancreatitis with exocrine insufficiency compared with patients with chronic pancreatitis without exocrine insufficiency[59]	Prospective longitudinal cohort study (290 patients with chronic pancreatitis and controls from nationwide registries);[58] prospective longitudinal cohort study (430 patients with chronic pancreatitis);[59] retrospective cohort study (11 972 patients with chronic pancreatitis and 119 720 controls)[60]

OR=odds ratio. HR=hazard ratio. NA=not applicable.

Table: **Prevalence and risk of complications associated with malnutrition and pancreatic exocrine insufficiency in patients with chronic pancreatitis**

Interestingly, patient-reported pain intensity and pattern correlate poorly with morphological abnormalities of the pancreas and often change over time.[76,77]

In patients with chronic pancreatitis, various mechanisms contribute to the pathophysiology of pain. Initially, a mechanical cause of pain related to increased ductal and interstitial pressures (plumbing theory) was assumed. However, as interventions aiming to improve pancreatic drainage often had limited success in relieving pain, more sophisticated neurobiological mechanisms were postulated.[78,79] Pancreatitis is associated with so-called wiring modifications, with altered, abnormal peripheral pain perception (peripheral sensitisation) and central pain processing of nociceptive input (central sensitisation) similar to patients with neuropathic pain and other forms of chronic pain.[80] Proinflammatory, pronociceptive signalling pathways and neurotrophic factors are upregulated in chronic pancreatitis.[81] Sensitisation of the peripheral nervous system, CNS, cerebral cortex restructuring, and modifications in pain control systems might serve as a basis for this abnormal pain processing.[82,83] Additionally, some patients present with generalised hyperalgesia, in which denervation does not occur, and pain perpetuates, independently of peripheral nociceptive input.[84] Pancreatic neuroplasticity, reflecting modifications of the intrapancreatic innervation, caused by activation of glia and immune cells, sprouting and neuritis of pancreatic nerves, and enhanced density and hypertrophy of neural structures, seems to be relevant for the cause of chronic pancreatitis pain.[85] In addition, pain can arise from local complications of the disease (eg, pseudocysts, duodenal and bile duct obstruction, and splenic vein thrombosis) or unwanted side-effects from treatment (eg, opioid-induced hyperalgesia).[83] Finally, increased concentration of cholecystokinin and enhanced sympathetic drive might also lead to pain in chronic pancreatitis. In line with the biopsychosocial model of pain, the individual's experience of pain, including biological profile, psychiatric disorders, and neurological factors, contribute to pain perception.[86] Previously, pain due to chronic pancreatitis was thought

to diminish over time as the pancreas undergoes progressive fibrosis, thereby reducing its capacity to generate pain—a concept known as the burn-out theory, dating back to 1984.[71] However, multiple cohort studies conducted since the 1990s have produced conflicting results, leading experts to largely abandon the burn-out theory.[74,75,87]

Quality of life and psychological burden

Patients with chronic pancreatitis have a substantially reduced quality of life, strongly associated with pain—particularly continuous pain—as well as disability or unemployment, and mental health disorders, including anxiety and depression.[44,86,88,89] Symptoms of depression are prevalent in up to 40% of patients with chronic pancreatitis.[90] The relationship between pain and mental disorders is complex, as pain might induce mental disorders; however, mental disorders might also worsen pain. Genetic variations associated with severe pain in patients with chronic pancreatitis were found to resemble those in patients with anxiety or post-traumatic stress disorder. Therefore, mental disorders in patients with chronic pancreatitis should not only be seen as a result of chronic pancreatitis or pain, but patients with chronic pancreatitis might also have a pre-existing risk for the development of mental disorders.[91]

Obstruction of common bile duct and duodenum, pseudocysts, and vascular complications

Chronic inflammation, particularly in the pancreatic head, can cause compression on, or involvement of, the duodenum or common bile duct. Obstruction of the duodenum might lead to gastric outlet obstruction, whereas obstruction of the common bile duct might lead to abdominal pain, jaundice, or cholangitis. These complications are primarily seen in groove pancreatitis: a specific form of chronic pancreatitis affecting the groove between the pancreatic head, duodenum, and common bile duct.[92] Another pancreatic complication in chronic pancreatitis is the development of pancreatic pseudocysts. Pancreatic pseudocysts are collections of enzyme-rich pancreatic fluid surrounded by a well defined wall, primarily within the peripancreatic tissue.[93] Finally, vascular complications might develop, including splenic vein thrombosis and pseudoaneurysms, which are often associated with the presence of pseudocysts.[94]

Pancreatic cancer

For patients with chronic pancreatitis, the risk of developing pancreatic cancer is approximately 7-times that of unaffected individuals.[60,95] Despite the elevated risk, the absolute risk of developing pancreatic cancer is still low and does not justify screening.[22,96] Although new-onset diabetes is a common complication of chronic pancreatitis, it might also precede pancreatic cancer. Therefore, it is suggested that older patients with sudden weight loss and severe hyperglycaemia might warrant abdominal imaging.[97,98] In patients with hereditary pancreatitis with *PRSS1* gene mutations, the risk of developing pancreatic cancer is approximately 60-times higher than the general population.[99,100] Therefore, surveillance is recommended for patients with hereditary pancreatitis due to *PRSS1* mutation at a pancreatic specialist centre, although there is no standard screening method for the detection of early pancreatic cancer.[96,101]

Screening for complications

Evaluation of pancreatic exocrine function and nutritional status

Considering the high incidence of pancreatic exocrine insufficiency and the associated negative clinical consequences, in patients with chronic pancreatitis it is advisable to screen for pancreatic exocrine insufficiency at the time of diagnosis, annually thereafter, and upon the onset of symptoms.[30,43]

Diagnosing pancreatic exocrine insufficiency can be challenging, as symptoms are often non-specific and pancreatic function tests have poor sensitivity and specificity, and can be impractical for routine use. Therefore, the diagnostic approach consists of multiple aspects, including evaluation of intestinal symptoms, pancreatic function tests, and nutritional evaluation (figure 3).[104] To measure pancreatic exocrine function, the faecal elastase-1 test is most frequently used, as it is a practical, accurate, and non-invasive diagnostic test that evaluates pancreatic secretion by measuring the faecal elastase concentration in the stool.[105] Low concentrations of faecal elastase-1 (<200 μg/g) are highly suggestive of exocrine insufficiency, whereas faecal elastase-1 concentrations greater than 500 μg/g can help to exclude exocrine insufficiency. Nonetheless, precise cutoff thresholds for faecal elastase-1 concentrations remain uncertain, complicating the diagnosis of mild-to-moderate exocrine insufficiency.[106,107] Other pancreatic function tests that are less frequently used or limited in availability are the coefficient of fat absorption, 13C-labelled mixed triglyceride breath test, and the endoscopic pancreatic function test.[104] Nutritional evaluation can also clarify the presence of exocrine insufficiency: low BMI or unintentional weight loss, and deficiencies of fat-soluble vitamins, minerals, or plasma proteins are indicative of pancreatic exocrine insufficiency (figure 3).[47]

Evaluation of bone health

Due to the high risk of osteoporosis in patients with chronic pancreatitis, assessment of bone mineral density, by the use of dual-energy x-ray absorptiometry, should be performed in all patients. Although the optimal frequency of osteopathy screening has not been investigated, guidelines from the past 5 years suggest performing dual-energy x-ray absorptiometry at diagnosis and once every 2 years.[45,108]

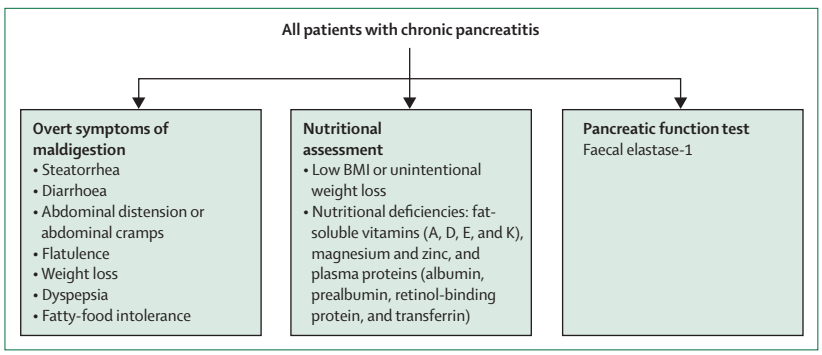

Figure 3: **Diagnostic approach to pancreatic exocrine insufficiency**
Biomarkers of fat-soluble vitamins include serum retinol (vitamin A), 25-hydroxyvitamin D (vitamin D), alpha-tocopherol (vitamin E), and phylloquinone (vitamin K). In addition, functional tests, such as prothrombin time or international normalised ratio, can be used to evaluate vitamin K-dependent coagulation.[102,103]

Evaluation of pancreatic endocrine function

As part of chronic pancreatitis management, pancreatic endocrine function should be evaluated by examining fasting plasma glucose (≥7·0 mmol/L) and HbA_{1c} (≥48 mmol/mol; 6·5%) at diagnosis and annually thereafter.[30,109] When diagnosis of diabetes is uncertain, an oral glucose tolerance test should be performed.[30]

Treatment

Lifestyle modifications

Independent from the cause of chronic pancreatitis, abstinence from alcohol and smoking is strongly recommended to prevent further destruction of pancreatic parenchyma and reduce the intensity and frequency of pain attacks.[30] The impact of physical exercise on patients with chronic pancreatitis has been scarcely studied.[110] However, considering the positive effects of physical activity in other chronic conditions, such as potential benefits to mental wellbeing, bone mineral density, and blood glucose regulation in patients with diabetes, exercise might offer similar advantages in this population.[30,110,111]

Treatment of pancreatic exocrine insufficiency

In the presence of exocrine insufficiency, treating patients with pancreatic enzyme replacement therapy is indicated, which can reduce intestinal symptoms, optimise nutritional status, reduce the risk of long-term complications, and improve quality of life (figure 4).[44,112–114] Despite the evident positive effects of enzyme replacement therapy, studies investigating guideline adherence found that inadequate screening, and non-treatment or undertreatment of exocrine insufficiency are common.[115,116]

Suppletion of nutritional deficiencies and nutritional management

Vitamin D deficiency is strongly associated with osteopenia and osteoporosis. Adequate diet, calcium and vitamin D intake, and regular weight-bearing exercise are recommended in all patients with chronic pancreatitis; vitamin D replacement therapy is indicated in patients with vitamin D deficiency.[30,117] The necessity of supplementing vitamins A, E, and K, and minerals in case of a deficiency is uncertain, as no randomised controlled trials to evaluate the effect of suppletion on clinically relevant outcome parameters have been performed in this population.[118] Therefore, the recommendation to start replacement therapy in case of deficiency is primarily based on expert opinion. The latest guideline from the European Society for Clinical Nutrition and Metabolism[43] states that fat-soluble (eg, vitamins A, D, E, and K) and water-soluble (eg, vitamin B12, folic acid, and thiamine) vitamins, and minerals (eg, magnesium, iron, selenium, and zinc), should be administered if low concentrations are detected in patients with chronic pancreatitis or in case of clinical signs of deficiency. The primary clinical manifestations of fat-soluble vitamins include night blindness and xerophthalmia (vitamin A); osteopathy, muscle weakness, and fatigue (vitamin D); peripheral neuropathy (vitamin E); and increased bleeding tendency (vitamin K).[119] Alongside pancreatic enzyme replacement therapy, optimisation of nutritional status is an important element of treatment.[30] A well

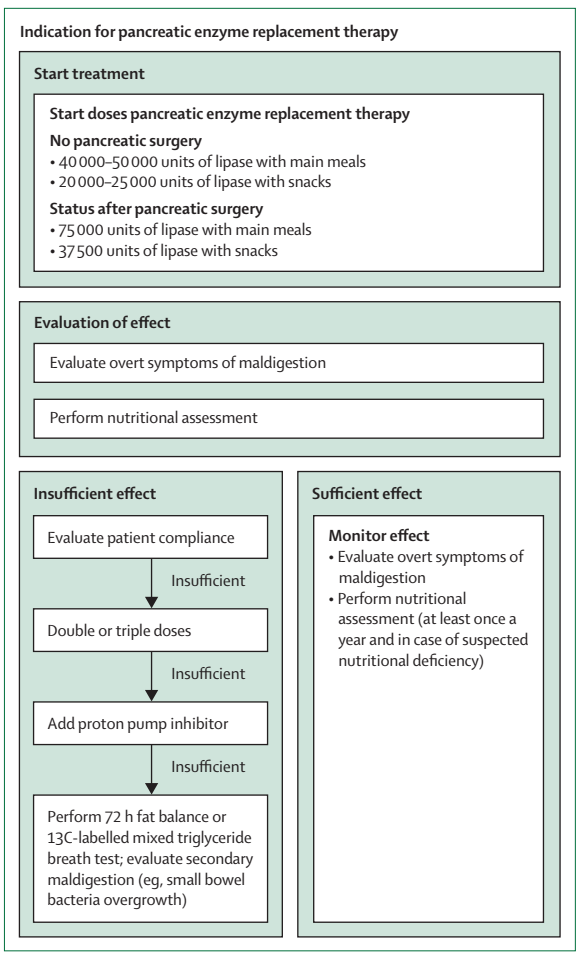

Figure 4: **Treatment approach for pancreatic exocrine insufficiency**

balanced diet is recommended in patients with a normal nutritional status. A low-fat diet should only be considered in patients with persistent steatorrhea, which cannot be controlled by optimal pancreatic enzyme replacement therapy. In patients who are malnourished, first-line treatment includes frequent (five to six meals daily), high protein and high energy meals.[43,47] The use of oral nutritional supplementation in patients with chronic pancreatitis has rarely been investigated.[118] A randomised controlled trial studied the effect of oral nutritional supplementation compared with dietary counselling.[120] Both interventions improved nutritional status without significant differences between the interventions, concluding that oral nutritional supplementation should be considered solely in patients who do not respond to first-line treatment. In selected patients with persistent malnutrition, enteral and parenteral (in cases of intolerance or contraindications to enteral feeding) nutrition are recommended.[43]

Glycaemic control in patients with pancreatic endocrine insufficiency

To date, optimal pharmacological treatment of diabetes in patients with chronic pancreatitis has not been extensively studied.[30] Insulin therapy is effective in short-term blood glucose control in secondary diabetes and is often the first-choice therapy in patients who are malnourished due to the anabolic effect of insulin.[30,121] Nevertheless, the use of metformin in patients with new-onset diabetes after pancreatitis was associated with considerable survival benefit in observational studies.[122,123] Therefore, it is suggested that metformin should be prescribed in all patients with new-onset diabetes after pancreatitis, independent from insulin usage. In patients with mild hyperglycaemia, and when concomitant insulin resistance is suspected, metformin as a monotherapy might be considered.[30,62,64] Other oral hypoglycaemic agents, which are frequently prescribed in type 2 diabetes, should be avoided due to adverse effects in patients with new-onset diabetes after pancreatitis, or patients with chronic pancreatitis and diabetes (eg, glucagon-like peptide-1 agonists due to the risk of pancreatitis, and sulfonylureas due to the risk of hypoglycaemia).[62,124] Although sodium–glucose co-transporter-2 inhibitors effectively lower blood glucose without causing hypoglycaemia, they are associated with an increased risk of diabetic ketoacidosis, particularly in patients with impaired insulin production and poor (and irregular) carbohydrate intake, and are not recommended in this population.[125,126] Because of the rapid fluctuations of glycaemic state, which are typical in type 3c diabetes, adequate glucose control is challenging. Closed-loop glucose control systems providing continuous monitoring and automated hormone delivery might offer a promising solution.[127]

Besides pharmacological therapy, optimal nutritional management is essential in the treatment of diabetes. To improve glycaemic control, patients should be educated on the importance of regular, healthy meals and appropriate pancreatic enzyme replacement therapy in cases of concurrent exocrine insufficiency.[97,128]

Medical therapy for painful chronic pancreatitis

When pain is present, consultation with a pain specialist is recommended in both early stage and advanced disease to optimise medical pain treatment alongside invasive therapy. Optimisation of pain treatment can prevent or delay the progression to neuropathic pain.

Medical therapy adheres to the so-called pain ladder principle outlined by WHO, which is based on the principle of initiating treatment with the lowest analgesic potency and scaling up when necessary.[30] Unfortunately, no randomised controlled trials have been performed to investigate the effect of class one analgesics (eg, paracetamol, non-steroidal anti-inflammatory drugs, and dipyrone) in patients with chronic pancreatitis. Caution should be taken when prescribing short-acting opioids. Although they are effective in managing acute pain episodes in chronic pancreatitis, they come with multiple side-effects, and their long-term use can exacerbate central sensitisation by altering pain pathways. In chronic pancreatitis, analgesic therapy is often required over a longer period, increasing the risk of dependency and hyperalgesia.[129,130] In opioid-induced hyperalgesia, opioids paradoxically enhance pain sensitisation, necessitating higher opioid doses to reduce pain. As a result, pain management might be even more complex for patients on prolonged opioid therapy, compared with those not receiving long-term opioids.

Adjuvant analgesics, such as tricyclic antidepressants, gabapentinoids, selective serotonin inhibitors, and esketamine, have proven to be efficacious in the treatment of chronic pain (not specifically chronic pancreatitis) in multiple placebo-controlled trials.[131] In clinical practice, adjuvant analgesics also seem promising in the treatment of pain associated with chronic pancreatitis. In patients with chronic pancreatitis, pregabalin has been the most intensively investigated. Three placebo-controlled trials showed the superiority of pregabalin (two of the trials in combination with antioxidants) over placebo.[132–134]

Studies investigating the ability of antioxidant therapy to reduce pain by decreasing oxidative stress show inconsistent findings and only minimal positive effects; therefore, this is not recommended as a standard treatment.[135,136] A randomised placebo-controlled trial studied the effect of camostat—a serin protease inhibitor widely used for treating acute pain in patients with chronic pancreatitis in Japan—but no positive effect on pain reduction was observed.[137] Although pancreatic enzyme replacement therapy is essential for treating intestinal symptoms of maldigestion and improving nutritional status, it is not effective for alleviating chronic pancreatitis pain.[30]

Interventional therapy for painful chronic pancreatitis

Although pain in chronic pancreatitis is often multifactorial, in some patients increased ductal and parenchymal pressure is thought to be the main driver of pain. These patients might benefit from endoscopic or surgical drainage of the main pancreatic duct. Over the past 5 years, the landscape of interventional therapy for painful chronic pancreatitis and dilated main pancreatic duct is changing from an endoscopy-first approach to a more surgical approach.[138,139] Two randomised controlled trials showed that surgery results in better long-term pain relief and quality of life for patients, fewer reinterventions, and was more cost-effective than endoscopy as a first-line treatment.[140,141] However, these results must be interpreted cautiously, as in both trials the clinical success of endoscopy—defined as ductal clearance—was low, and new endoscopic techniques (ie, pancreatoscopy-directed lithotripsy) to improve ductal clearance have not yet been implemented. Exploratory subgroup analyses of one of these trials (ESCAPE trial) revealed that superiority of surgery over endoscopy was no longer evident when total ductal clearance was obtained within the endoscopy group.[140] Despite the recommendation for early surgical evaluation in patients with painful chronic pancreatitis, the less-invasive endoscopic approach is often preferred in clinical practice before considering surgery.[139] The choice of intervention should be considered on an individual basis. Factors to consider include whether local complications of chronic pancreatitis other than obstructive main pancreatic duct might contribute to pain, the invasiveness and feasibility of the procedure (eg, location of pancreatic duct obstruction and anatomical factors complicating surgery), comorbidity, and patient preference.

Endoscopic therapy for treating patients with painful chronic pancreatitis, with a dilated main pancreatic duct due to a concrement in the pancreatic duct, consists of stone removal by ERP. ERP is primarily suitable for obstruction in the head or neck of the pancreatic duct, and is less successful in distal pancreatic duct obstructions. Stones 5 mm or smaller can be treated solely by ERP. For larger stones, shockwave lithotripsy, either as standalone treatment or combined with ERP, is recommended.[138,142] State-of-the-art techniques fragment stones under direct visualisation (pancreatoscopy-direct lithotripsy) by use of electrohydraulic shockwaves or laser. A consecutive case series showed that electrohydraulic shockwaves were technically successful in 71% of cases, and lower pain scores were noted in 58% of cases after a median follow-up period of 35 months.[143,144] A randomised sham-controlled trial was conducted to evaluate pain relief following extracorporeal shockwave lithotripsy combined with endoscopic retrograde pancreatography.[145] In the intervention group, pain relief was slightly better than in the control group after short-term follow-up, but this difference was not maintained at 24 weeks. However, significant benefits were observed in secondary outcomes, such as the number of pain-free days and days requiring opioids, in favour of combined extracorporeal shockwave lithotripsy with endoscopic retrograde pancreatography compared with sham procedures.

Pancreatic duct strictures can be treated by endoscopic stenting. Due to the fibroinflammatory nature of the disease, strictures are often rigid, and achieving continuous drainage is challenging. When symptoms are improved after insertion of a single plastic stent, long-term (12 months), uninterrupted stenting is required to accomplish remodelling of the pancreatic duct.[138] In patients with persistent stricture and pain, surgical treatment or insertion of multiple side-by-side plastic stents should be considered.[142] Fully covered, self-expandable metal stents have not been shown to be superior to multiple plastic stents in the treatment of pancreatic duct strictures.[146]

Tailored surgery—the least extensive procedure based on pancreatic morphology—is recommended as a surgical approach for chronic pancreatitis.[147] Surgical therapy can be divided into drainage procedures (eg, lateral pancreatojejunostomy), resection procedures (eg, partial pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy), and a combination of both (eg, duodenum-preserving pancreatic head resection, including Frey and Berne procedures). Drainage procedures are primarily indicated in patients with ductal disease (dilated main pancreatic duct >5 mm), whereas resection procedures are indicated when the disease is primarily characterised by extensive inflammation of pancreatic parenchyma (presence of enlarged pancreatic head >40 mm and involvement of adjacent organs). Less extensive procedures might be marginally favourable due to short-term advantages and longer survival after surgery, but no differences in patient-reported outcomes such as pain and quality of life.[148] Alternatively, the ChroPac trial,[149] a large, randomised, controlled, double-blind study, showed that patients who received partial pancreatoduodenectomy required fewer reinterventions for chronic pancreatitis and there were no differences in adverse events. This finding suggests that resection procedures might offer a more definitive solution for treating chronic pancreatitis pain. Overall, when tailored surgery is adhered to, different surgical approaches exhibit similar clinical outcomes.[150] Therefore, in clinical practice, type of procedure is also affected by a surgeon's preference and local expertise.

A more invasive surgical approach to painful chronic pancreatitis is a total pancreatectomy, optionally with concomitant autologous islet cell transplantation to improve glycaemic control.[151] A meta-analysis of observational studies showed an opioid-free rate of 63% in patients with chronic pancreatitis who received total pancreatectomy with concomitant autologous islet cell

transplantation, compared with 0–15% before surgery, and an insulin-free rate of 30% compared with 90–100% before surgery.[152] There is, however, a high variability in outcomes of total pancreatectomy with autologous islet cell transplantation, which is probably due to considerable differences in the study population. Specific indication and optimal timing of total pancreatectomy is, therefore, still under debate. Due to the extensiveness of the procedure and high risk of iatrogenic diabetes, total pancreatectomy is primarily considered in patients exhibiting extensive and diffuse disease, and with an inadequate response to endoscopic or less extensive surgical interventions.[153]

Adjuvant pain interventions

In selected patients with refractory pain, adjuvant pain interventions performed in an experienced pain centre can be considered, including celiac plexus or splanchnic blockade, transcutaneous electrical nerve stimulation, and spinal cord stimulation. However, current data on their efficacy are not compelling and further research is needed.[138,154–156]

Treatment of local complications: pseudocysts and common bile duct strictures

The management of pancreatic pseudocysts is initially conservative as pseudocysts can spontaneously resolve; this is, however, less likely when pseudocysts are present for more than 12 weeks.[157] The presence of complications, such as compression of surrounding organs, pain, infection, bleeding, or splenic involvement, are indications for endoscopic drainage with plastic stents to create a connection between the cyst and the gastrointestinal lumen.[30,142,158] Stents can be removed after cyst resolution (after a minimum of 8 weeks).[30,142] Pancreatic pseudocysts might reoccur, which is more common when there is loss of continuity of the main pancreatic duct. Therefore, placement of long-term indwelling plastic stents after cyst resolution is indicated when a disconnected duct is suspected.[142,159] Percutaneous drainage or surgical procedures for the treatment of pseudocysts are indicated if endoscopic drainage is not technically feasible.

Common bile duct strictures can lead to abdominal pain, jaundice, or cholangitis. Initially, conservative treatment is indicated, given that the obstruction might stem from swelling of the pancreatic head or pseudocyst, applying external pressure on the common bile duct. When present for 4 weeks or longer, endoscopic treatment, either by use of multiple side-by-side plastic stents or a fully covered metal stent, is recommended.[30,142] When endoscopic treatment is not feasible or has failed, surgically connecting the hepatic duct to the jejunum (hepaticojejunostomy) can be considered. When there is a concomitant indication for resection of the pancreatic head, a duodenum-preserving pancreatic head resection or pancreatoduodenectomy can be performed.[160]

Future directions and conclusion

To date, definite chronic pancreatitis can only be diagnosed at an advanced stage, when multiple complications have developed, and the disease and its symptoms are often irreversible. Current treatment options are, therefore, based on treatment of complications rather than treatment of the disease itself. We must aim to diagnose chronic pancreatitis at an earlier stage. Novel, endoscopic ultrasound-based diagnostic modalities are currently being investigated to support the diagnosis of early chronic pancreatitis.[161] The prospect of identifying chronic pancreatitis at an earlier stage, when the disease might still be reversible, substantially enhances the impact of advancements in lifestyle modifications. Furthermore, the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatitis Cancer is currently investigating the physiological effect of indometacin on pancreatic function in patients with chronic pancreatitis, with the long-term goal of investigating its use as a potential therapy to reverse or slow disease progression (the PAIR trial).[162]

In painful chronic pancreatitis with morphological complications, interventional treatment modalities provide good clinical outcomes. However, adequate patient selection is crucial, as a proportion of patients do not respond to interventional therapy, and pain remains present. This persistent pain after interventional therapy might be due to the existence of neuropathic pain and central sensitisation. Besides early recognition of the disease and its complications, it is crucial to consider interventional therapy early in the treatment process. Pancreatic quantitative sensory testing, a minimally

Panel 2: **Key unsolved research questions in chronic pancreatitis**

Early chronic pancreatitis and diagnosis

- How can chronic pancreatitis be diagnosed in its early stage, before irreversible complications develop?
- What are the diagnostic criteria for identifying so-called early chronic pancreatitis?

Treatment

- Can treatment be developed that cures chronic pancreatitis or slows disease progression?

Pain management

- Can quantitative sensory testing be used in clinical practice to predict who will benefit from interventional therapy and who will not?
- What is the role of adjuvant pain interventions, including celiac plexus or splanchnic blockade, transcutaneous electrical nerve stimulation, and spinal cord stimulation?

Improving patient-reported outcomes

- How can patient-reported outcomes, including quality of life, be improved?

invasive technique whereby patient-reported pain intensity caused by standardised pain stimuli is compared with normal pain thresholds to identify central sensitisation, might be helpful in identifying patients who would benefit from interventional treatment. Whether this test can predict treatment response in patients with chronic pancreatitis undergoing endoscopic or surgical intervention is currently being investigated (panel 2).[163]

Clinical studies typically concentrate on individual aspects of the disease. In these isolated interventions, improvements to quality of life are often limited. Recognising the need for a more comprehensive approach, the Dutch Pancreatitis Study Group is currently performing a stepped-wedge, cluster-randomised, controlled trial to evaluate the effect of a multimodal management algorithm based on the 2017 HaPanEu guideline,[30] consisting of multiple treatment domains including lifestyle, pain management, exocrine and endocrine pancreatic insufficiency, nutrition, and bone health (COMBO trial).[164]

To conclude, chronic pancreatitis is a multisystemic disorder for which a holistic and multidisciplinary approach is required to obtain optimal clinical outcomes for patients. Future research should focus on early recognition of chronic pancreatitis, exploration of treatment modalities to reverse or slow disease progression, secondary prevention by optimisation of lifestyle, adequate patient selection for interventional therapy, and the added value of combined interventions.

Contributors

NDET coordinated the project under the direct supervision of RCV and SAWB. NDET did the literature search and drafted the manuscript. JML, HCvS, and JEvH coauthored the writing of the manuscript. All authors approved the final manuscript.

Declaration of interests

JML is president of the United European Gastroenterology; holds stock options for Centogene, a company unrelated to pancreatitis; acted as a consultant for iCellate and Falk Pharmac; and has received honoraria from Abbott and Viatris. JEvH is chair of the Dutch Pancreatitis Study Group; acted as a consultant for Olympus; and has received honoraria from Cook Medical, Boston Scientific, and Falk. All other authors declare no competing interests.

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