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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.

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

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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.

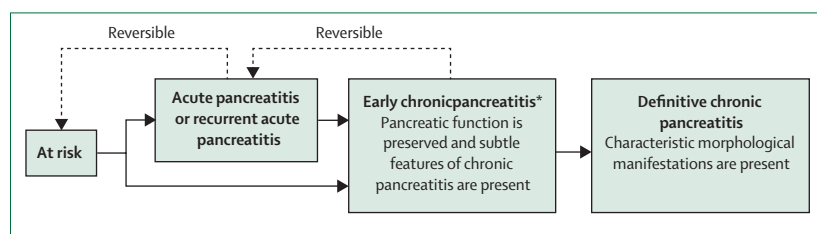


Figure 1: Stages of disease progression in chronic pancreatitis

*Early chronic pancreatitis is a disputable disease entity and terminology.

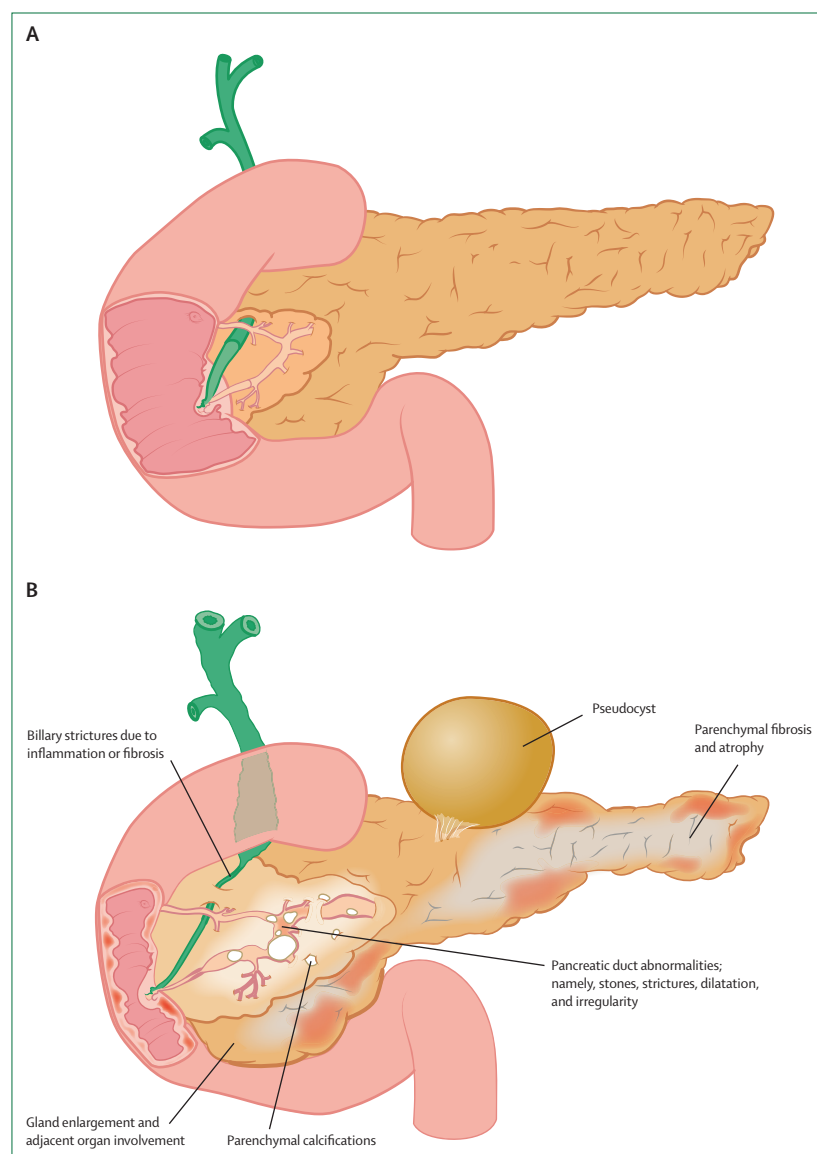


Figure 2: Morphological changes and complications in chronic pancreatitis

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,

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

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).

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}

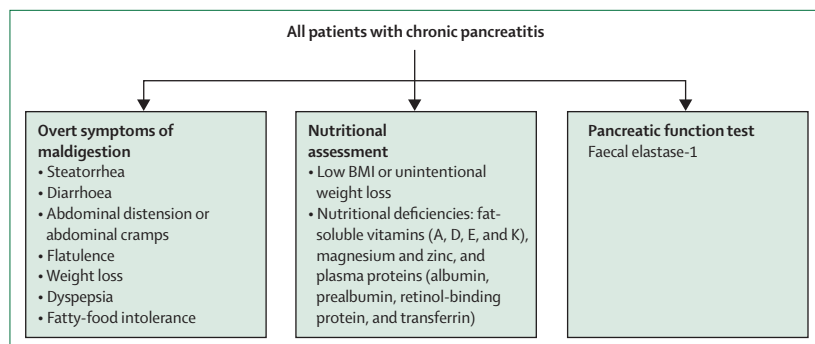


Figure 3: Diagnostic approach to pancreatic exocrine insufficiency

Biomarkers of fat-soluble vitamins include serum retinol (vitamin A), 25-hydroxyvitamin D (vitamin D), alpha-tocopherol (vitamin E), and phyloquinone (vitamin K). In addition, functional tests, such as prothrombin time or international normalised ratio, can be used to evaluate vitamin K-dependent coagulation.^{30,303}

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

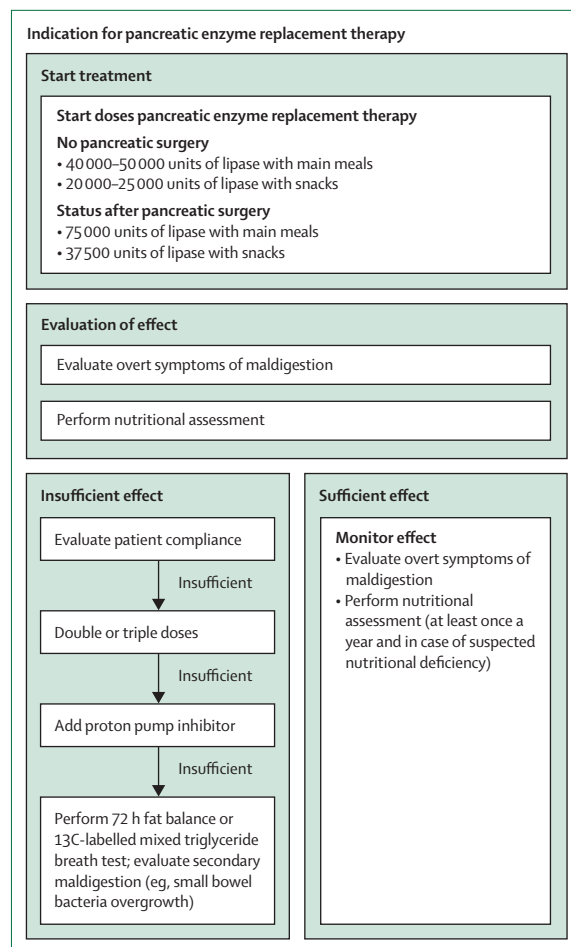


Figure 4: Treatment approach for pancreatic exocrine insufficiency

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 Metabolism⁴³ 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

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 dipyrrone) 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 pancreaticojejunostomy), resection procedures (eg, partial pancreateoduodenectomy, 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 pancreateoduodenectomy 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 Viartis. 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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References

- Whitcomb DC, Frulloni L, Garg P, et al. Chronic pancreatitis: an international draft consensus proposal for a new mechanistic definition. *Pancreatology* 2016; **16**: 218–24.
- Xiao AY, Tan ML, Wu LM, et al. Global incidence and mortality of pancreatic diseases: a systematic review, meta-analysis, and meta-regression of population-based cohort studies. *Lancet Gastroenterol Hepatol* 2016; **1**: 45–55.
- Spagnolo DM, Greer PJ, Ohlsen CS, et al. Acute and chronic pancreatitis disease prevalence, classification, and comorbidities: a cohort study of the UK BioBank. *Clin Transl Gastroenterol* 2022; **13**: e00455.
- Cai QY, Tan K, Zhang XL, et al. Incidence, prevalence, and comorbidities of chronic pancreatitis: a 7-year population-based study. *World J Gastroenterol* 2023; **29**: 4671–84.
- Olesen SS, Mortensen LH, Zinck E, et al. Time trends in incidence and prevalence of chronic pancreatitis: a 25-year population-based nationwide study. *United European Gastroenterol J* 2021; **9**: 82–90.
- Etemad B, Whitcomb DC. Chronic pancreatitis: diagnosis, classification, and new genetic developments. *Gastroenterology* 2001; **120**: 682–707.
- Conwell DL, Banks PA, Sandhu BS, et al. Validation of demographics, etiology, and risk factors for chronic pancreatitis in the USA: a report of the North American Pancreas Study (NAPS) group. *Dig Dis Sci* 2017; **62**: 2133–40.
- Olesen SS, Nøjgaard C, Poulsen JL, et al. Chronic pancreatitis is characterized by distinct complication clusters that associate with etiological risk factors. *Am J Gastroenterol* 2019; **114**: 656–64.
- Beyer G, Mahajan UM, Budde C, et al. Development and validation of a chronic pancreatitis prognosis score in 2 independent cohorts. *Gastroenterology* 2017; **153**: 1544–54.
- Irving HM, Samokhvalov AV, Rehm J. Alcohol as a risk factor for pancreatitis. A systematic review and meta-analysis. *JOP* 2009; **10**: 387–92.
- Samokhvalov AV, Rehm J, Roerecke M. Alcohol consumption as a risk factor for acute and chronic pancreatitis: a systematic review and a series of meta-analyses. *EBioMedicine* 2015; **2**: 1996–2002.
- Aune D, Mahamat-Saleh Y, Norat T, Riboli E. Tobacco smoking and the risk of pancreatitis: a systematic review and meta-analysis of prospective studies. *Pancreatology* 2019; **19**: 1009–22.
- Hansen SEJ, Nordestgaard BG, Langsted A. Smoking as the most important risk factor for chronic pancreatitis in the general population. *Eur J Epidemiol* 2023; **38**: 95–107.
- Ahmed Ali U, Issa Y, Hagenaars JC, et al. Risk of recurrent pancreatitis and progression to chronic pancreatitis after a first episode of acute pancreatitis. *Clin Gastroenterol Hepatol* 2016; **14**: 738–46.
- Beyer G, Habtezion A, Werner J, Lerch MM, Mayerle J. Chronic pancreatitis. *Lancet* 2020; **396**: 499–512.
- Mayerle J, Sendler M, Hegyi E, Beyer G, Lerch MM, Sahin-Toth M. Genetics, cell biology, and pathophysiology of pancreatitis. *Gastroenterology* 2019; **156**: 1951–68.
- Hegyi P, Parniczky A, Lerch MM, et al. International consensus guidelines for risk factors in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatologists, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatology* 2020; **20**: 579–85.
- Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: a review. *JAMA* 2019; **322**: 2422–34.
- On W, Huggett MT. European guideline on IgG4-related digestive disease: UEG and SGF evidence-based recommendations. *Frontline Gastroenterol* 2022; **13**: 171–74.
- Kempeneers MA, Ahmed Ali U, Issa Y, et al. Natural course and treatment of pancreatic exocrine insufficiency in a nationwide cohort of chronic pancreatitis. *Pancreas* 2020; **49**: 242–48.
- Whitcomb DC. Hereditary pancreatitis: new insights into acute and chronic pancreatitis. *Gut* 1999; **45**: 317–22.
- Cook ME, Bruun NH, Davidsen L, Drewes AM, Olesen SS. Multistate model of the natural history of inflammatory pancreatic diseases: a nationwide population-based cohort study. *Gastroenterology* 2023; **165**: 1547–57.
- Hori Y, Vege SS, Chari ST, et al. Classic chronic pancreatitis is associated with prior acute pancreatitis in only 50% of patients in a large single-institution study. *Pancreatology* 2019; **19**: 224–29.
- Singh VK, Whitcomb DC, Banks PA, et al. Acute pancreatitis precedes chronic pancreatitis in the majority of patients: results from the NAPS2 consortium. *Pancreatology* 2022; **22**: 1091–98.
- Olesen SS, Drewes AM, Novovic S, Nøjgaard C. The sentinel acute pancreatitis event hypothesis revisited. *Pancreatology* 2019; **19**: 614–15.

- 26 Whitcomb DC, Shimosegawa T, Chari ST, et al. International consensus statements on early chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with The International Association of Pancreatology, American Pancreatic Association, Japan Pancreas Society, PancreasFest Working Group and European Pancreatic Club. *Pancreatology* 2018; **18**: 516–27.
- 27 Ito T, Ishiguro H, Ohara H, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2015. *J Gastroenterol* 2016; **51**: 85–92.
- 28 Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. *J Gastroenterol* 2007; **42**: 101–19.
- 29 Issa Y, Kempeneers MA, van Santvoort HC, Bollen TL, Bipat S, Boermeester MA. Diagnostic performance of imaging modalities in chronic pancreatitis: a systematic review and meta-analysis. *Eur Radiol* 2017; **27**: 3820–44.
- 30 Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). *United European Gastroenterol J* 2017; **5**: 153–99.
- 31 Hoffmeister A, Mayerle J, Beglinger C, et al. English language version of the S3-consensus guidelines on chronic pancreatitis: definition, aetiology, diagnostic examinations, medical, endoscopic and surgical management of chronic pancreatitis. *Z Gastroenterol* 2015; **53**: 1447–95.
- 32 Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice guidelines in chronic pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas* 2014; **43**: 1143–62.
- 33 Shimizu K, Ito T, Irisawa A, et al. Evidence-based clinical practice guidelines for chronic pancreatitis 2021. *J Gastroenterol* 2022; **57**: 709–24.
- 34 Sheel ARG, Baron RD, Sarantis I, et al. The diagnostic value of Rosemont and Japanese diagnostic criteria for “indeterminate,” “suggestive,” “possible” and “early” chronic pancreatitis. *Pancreatology* 2018; **18**: 774–84.
- 35 Anaizi A, Hart PA, Conwell DL. Diagnosing chronic pancreatitis. *Dig Dis Sci* 2017; **62**: 1713–20.
- 36 Nordaas IK, Tjora E, Dimcevski G, et al. Structural imaging findings are related to clinical complications in chronic pancreatitis. *United European Gastroenterol J* 2022; **10**: 385–95.
- 37 O'Brien SJ, Omer E. Chronic pancreatitis and nutrition therapy. *Nutr Clin Pract* 2019; **34** (suppl 1): S13–26.
- 38 Erchinger F, Engjom T, Dimcevski G, et al. Exocrine pancreas insufficiency in chronic pancreatitis—risk factors and associations with complications. A multicentre study of 1869 patients. *Pancreatology* 2022; **22**: 374–80.
- 39 European Pancreatic Club. European guidelines on the diagnosis and therapy of pancreatic exocrine insufficiency (PEI). 2023. <https://www.europeanpancreaticclub.org/about-us/diagnosis-and-treatment-guidelines/european-guidelines-on-the-diagnosis-and-therapy-of-pancreatic-exocrine-insufficiency-pei/> (accessed Nov 7, 2024).
- 40 Whitcomb DC, Duggan SN, Martindale R, et al. AGA-PancreasFest Joint Symposium on Exocrine Pancreatic Insufficiency. *Gastro Hep Advances* 2023; **2**: 395–411.
- 41 Min M, Patel B, Han S, et al. Exocrine pancreatic insufficiency and malnutrition in chronic pancreatitis: identification, treatment, and consequences. *Pancreas* 2018; **47**: 1015–18.
- 42 Madro A. Malnutrition in chronic pancreatitis: causes, assessment methods, and therapeutic management. *Can J Gastroenterol Hepatol* 2020; **2020**: 8875487.
- 43 Arvanitakis M, Ockenga J, Bezmarevic M, et al. ESPEN practical guideline on clinical nutrition in acute and chronic pancreatitis. *Clin Nutr* 2024; **43**: 395–412.
- 44 de Rijk FEM, van Veldhuisen CL, Kempeneers MA, et al. Quality of life in patients with definite chronic pancreatitis: a nationwide longitudinal cohort study. *Am J Gastroenterol* 2023; **118**: 1428–38.
- 45 Whitcomb DC, Buchner AM, Forsmark CE. AGA clinical practice update on the epidemiology, evaluation, and management of exocrine pancreatic insufficiency: expert review. *Gastroenterology* 2023; **165**: 1292–301.
- 46 Duggan SN, Smyth ND, O'Sullivan M, Feehan S, Ridgway PF, Conlon KC. The prevalence of malnutrition and fat-soluble vitamin deficiencies in chronic pancreatitis. *Nutr Clin Pract* 2014; **29**: 348–54.
- 47 Dominguez-Munoz JE, Phillips M. Nutritional therapy in chronic pancreatitis. *Gastroenterol Clin North Am* 2018; **47**: 95–106.
- 48 Ramai D, Facciorusso A, Maida M, et al. Prevalence of osteopathy in chronic pancreatitis: a systematic review and meta-analysis. *Clin Transl Gastroenterol* 2023; **14**: e00623.
- 49 Duggan SN, Smyth ND, Murphy A, Macnaughton D, O'Keefe SJ, Conlon KC. High prevalence of osteoporosis in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; **12**: 219–28.
- 50 Chhoda A, Hernandez-Woodbine MJ, Addo NAA, et al. Burden of bone disease in chronic pancreatitis: a systematic review and meta-analysis. *World J Gastroenterol* 2023; **29**: 1374–94.
- 51 Koh A, Oyende O, Humes DJ, Lobo DN. Risk of osteopaenia, osteoporosis and osteoporotic fractures in patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Nutr* 2023; **42**: 1086–94.
- 52 Bang UC, Benfield T, Bendtsen F, Hyldstrup L, Beck Jensen JE. The risk of fractures among patients with cirrhosis or chronic pancreatitis. *Clin Gastroenterol Hepatol* 2014; **12**: 320–26.
- 53 Tignor AS, Wu BU, Whitlock TL, et al. High prevalence of low-trauma fracture in chronic pancreatitis. *Am J Gastroenterol* 2010; **105**: 2680–86.
- 54 Khan D, Abureesh M, Alkhayat M, et al. Prevalence of myocardial infarction in patients with chronic pancreatitis. *Pancreas* 2021; **50**: 99–103.
- 55 de la Iglesia D, Vallejo-Senra N, Lopez-Lopez A, et al. Pancreatic exocrine insufficiency and cardiovascular risk in patients with chronic pancreatitis: a prospective, longitudinal cohort study. *J Gastroenterol Hepatol* 2019; **34**: 277–83.
- 56 Olesen SS, Frandsen LK, Poulsen JL, Vestergaard P, Rasmussen HH, Drewes AM. The prevalence of underweight is increased in chronic pancreatitis outpatients and associates with reduced life quality. *Nutrition* 2017; **43–44**: 1–7.
- 57 Olesen SS, Buyukuslu A, Kohler M, Rasmussen HH, Drewes AM. Sarcopenia associates with increased hospitalization rates and reduced survival in patients with chronic pancreatitis. *Pancreatology* 2019; **19**: 245–51.
- 58 Nøjgaard C, Bendtsen F, Becker U, Andersen JR, Holst C, Matzen P. Danish patients with chronic pancreatitis have a four-fold higher mortality rate than the Danish population. *Clin Gastroenterol Hepatol* 2010; **8**: 384–90.
- 59 de la Iglesia-Garcia D, Vallejo-Senra N, Iglesias-Garcia J, Lopez-Lopez A, Nieto L, Dominguez-Munoz JE. Increased risk of mortality associated with pancreatic exocrine insufficiency in patients with chronic pancreatitis. *J Clin Gastroenterol* 2018; **52**: e63–72.
- 60 Bang UC, Benfield T, Hyldstrup L, Bendtsen F, Beck Jensen JE. Mortality, cancer, and comorbidities associated with chronic pancreatitis: a Danish nationwide matched-cohort study. *Gastroenterology* 2014; **146**: 989–94.
- 61 Wynne K, Devereaux B, Dornhorst A. Diabetes of the exocrine pancreas. *J Gastroenterol Hepatol* 2019; **34**: 346–54.
- 62 Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. *Lancet Gastroenterol Hepatol* 2016; **1**: 226–37.
- 63 Ewald N, Hardt PD. Diagnosis and treatment of diabetes mellitus in chronic pancreatitis. *World J Gastroenterol* 2013; **19**: 7276–81.
- 64 Viggers R, Jensen MH, Laursen HVB, Drewes AM, Vestergaard P, Olesen SS. Glucose-lowering therapy in patients with postpancreatitis diabetes mellitus: a nationwide population-based cohort study. *Diabetes Care* 2021; **44**: 2045–52.
- 65 Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): a retrospective cohort study. *Diabetes Care* 2017; **40**: 1486–93.
- 66 Dugic A, Hagstrom H, Dahlman I, et al. Post-pancreatitis diabetes mellitus is common in chronic pancreatitis and is associated with adverse outcomes. *United European Gastroenterol J* 2023; **11**: 79–91.
- 67 Petrov MS, Olesen SS. Metabolic sequelae: the pancreatitis zeitgeist of the 21st century. *Gastroenterology* 2023; **165**: 1122–35.

- 68 Kempeneers MA, Issa Y, Ahmed Ali U, et al. A classification algorithm for types of diabetes in chronic pancreatitis using epidemiological characteristics: outcome of a longitudinal cohort study. *Pancreas* 2021; **50**: 1407–14.
- 69 Zhu X, Liu D, Wei Q, et al. New-onset diabetes mellitus after chronic pancreatitis diagnosis: a systematic review and meta-analysis. *Pancreas* 2019; **48**: 868–75.
- 70 Bellin MD, Whitcomb DC, Abberbock J, et al. Patient and disease characteristics associated with the presence of diabetes mellitus in adults with chronic pancreatitis in the United States. *Am J Gastroenterol* 2017; **112**: 1457–65.
- 71 Ammann RW, Muellhaupt B. The natural history of pain in alcoholic chronic pancreatitis. *Gastroenterology* 1999; **116**: 1132–40.
- 72 Drewes AM, van Veldhuisen CL, Bellin MD, et al. Assessment of pain associated with chronic pancreatitis: an international consensus guideline. *Pancreatol* 2021; **21**: 1256–84.
- 73 Bouca-Machado T, Bouwense SAW, Brand M, et al. Position statement on the definition, incidence, diagnosis and outcome of acute on chronic pancreatitis. *Pancreatol* 2023; **23**: 143–50.
- 74 Kempeneers MA, Issa Y, Verdonk RC, et al. Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. *Gut* 2021; **70**: 1724–33.
- 75 Vipperl K, Kanakis A, Slivka A, et al. Natural course of pain in chronic pancreatitis is independent of disease duration. *Pancreatol* 2021; **21**: 649–57.
- 76 Steinkohl E, Olesen SS, Drewes AM, Frokjaer JB. Progression of pancreatic morphology in chronic pancreatitis is not associated with changes in quality of life and pain. *Scand J Gastroenterol* 2020; **55**: 1099–107.
- 77 Drewes AM, Bouwense SAW, Campbell CM, et al. Guidelines for the understanding and management of pain in chronic pancreatitis. *Pancreatol* 2017; **17**: 720–31.
- 78 Lieb JG 2nd, Forsmark CE. Review article: pain and chronic pancreatitis. *Aliment Pharmacol Ther* 2009; **29**: 706–19.
- 79 Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. *Pain Rep* 2017; **2**: e625.
- 80 Drewes AM, Krarup AL, Detlefsen S, Malmstrom ML, Dimcevski G, Funch-Jensen P. Pain in chronic pancreatitis: the role of neuropathic pain mechanisms. *Gut* 2008; **57**: 1616–27.
- 81 Fasanella KE, Davis B, Lyons J, et al. Pain in chronic pancreatitis and pancreatic cancer. *Gastroenterol Clin North Am* 2007; **36**: 335–64.
- 82 Frokjaer JB, Bouwense SA, Olesen SS, et al. Reduced cortical thickness of brain areas involved in pain processing in patients with chronic pancreatitis. *Clin Gastroenterol Hepatol* 2012; **10**: 434–38.
- 83 Poulsen JL, Olesen SS, Malver LP, Frokjaer JB, Drewes AM. Pain and chronic pancreatitis: a complex interplay of multiple mechanisms. *World J Gastroenterol* 2013; **19**: 7282–91.
- 84 Bouwense SA, Buscher HC, van Goor H, Wilder-Smith OH. Has central sensitization become independent of nociceptive input in chronic pancreatitis patients who fail thoracoscopic splanchnicectomy? *Reg Anesth Pain Med* 2011; **36**: 531–36.
- 85 Demir IE, Friess H, Ceyhan GO. Neural plasticity in pancreatitis and pancreatic cancer. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 649–59.
- 86 Olesen SS, Phillips AE, Faghhi M, et al. Overlap and cumulative effects of pancreatic duct obstruction, abnormal pain processing and psychological distress on patient-reported outcomes in chronic pancreatitis. *Gut* 2022; **71**: 2518–25.
- 87 Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. *Gut* 2011; **60**: 77–84.
- 88 Machicado JD, Amann ST, Anderson MA, et al. Quality of life in chronic pancreatitis is determined by constant pain, disability/unemployment, current smoking, and associated co-morbidities. *Am J Gastroenterol* 2017; **112**: 633–42.
- 89 Liyen Cartelle A, Shah I, Bocchino R, et al. Long-term follow-up of disabled patients with chronic pancreatitis: evaluation of clinical characteristics, outcomes, and predictors. *J Clin Gastroenterol* 2024; **58**: 98–102.
- 90 Beas R, Riva-Moscoso A, Ribaud I, et al. Prevalence of depression among patients with chronic pancreatitis: a systematic review and meta-analysis. *Clin Res Hepatol Gastroenterol* 2023; **47**: 102115.
- 91 Dunbar EK, Greer PJ, Amann ST, et al. Pain experience in pancreatitis: strong association of genetic risk loci for anxiety and ptsd in patients with severe, constant, and constant-severe pain. *Am J Gastroenterol* 2021; **116**: 2128–36.
- 92 Vujasinovic M, Pozzi Mucelli R, Grigoriadis A, et al. Paraduodenal pancreatitis—problem in the groove. *Scand J Gastroenterol* 2022; **2022**: 1–8.
- 93 Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102–11.
- 94 Vujasinovic M, Dugic A, Nouri A, et al. Vascular complications in patients with chronic pancreatitis. *J Clin Med* 2021; **10**: 3720.
- 95 Kirkegård J, Mortensen FV, Cronin-Fenton D. Chronic pancreatitis and pancreatic cancer risk: a systematic review and meta-analysis. *Am J Gastroenterol* 2017; **112**: 1366–72.
- 96 Greenhalf W, Levy P, Gress T, et al. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the Working Group For The International Consensus Guidelines For Chronic Pancreatitis in collaboration with the International Association of Pancreatologists, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatol* 2020; **20**: 910–18.
- 97 Singh A, Aggarwal M, Garg R, Stevens T, Chahal P. Post-pancreatitis diabetes mellitus: insight on optimal management with nutrition and lifestyle approaches. *Ann Med* 2022; **54**: 1776–86.
- 98 Goodarzi MO, Petrov MS, Andersen DK, Hart PA. Diabetes in chronic pancreatitis: risk factors and natural history. *Curr Opin Gastroenterol* 2021; **37**: 526–31.
- 99 Gandhi S, de la Fuente J, Murad MH, Majumder S. Chronic Pancreatitis is a risk factor for pancreatic cancer, and incidence increases with duration of disease: a systematic review and meta-analysis. *Clin Transl Gastroenterol* 2022; **13**: e00463.
- 100 Shelton CA, Umapathy C, Stello K, Yadav D, Whitcomb DC. Hereditary pancreatitis in the United States: survival and rates of pancreatic cancer. *Am J Gastroenterol* 2018; **113**: 1376.
- 101 Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. *Gut* 2020; **69**: 7–17.
- 102 Albahrani AA, Greaves RF. Fat-soluble vitamins: clinical indications and current challenges for chromatographic measurement. *Clin Biochem Rev* 2016; **37**: 27–47.
- 103 Shea MK, Booth SL. Concepts and controversies in evaluating vitamin K status in population-based studies. *Nutrients* 2016; **8**: 8.
- 104 Dominguez-Munoz JE. Diagnosis and treatment of pancreatic exocrine insufficiency. *Curr Opin Gastroenterol* 2018; **34**: 349–54.
- 105 Shandro BM, Nagarajah R, Poullis A. Challenges in the management of pancreatic exocrine insufficiency. *World J Gastrointest Pharmacol Ther* 2018; **9**: 39–46.
- 106 Lankisch PG, Schmidt I, König H, et al. Faecal elastase 1: not helpful in diagnosing chronic pancreatitis associated with mild to moderate exocrine pancreatic insufficiency. *Gut* 1998; **42**: 551–54.
- 107 Domínguez-Muñoz JE, Hardt PD, Lerch MM, Löhr MJ. Potential for screening for pancreatic exocrine insufficiency using the fecal elastase-1 test. *Dig Dis Sci* 2017; **62**: 1119–30.
- 108 Phillips ME, Hopper AD, Leeds JS, et al. Consensus for the management of pancreatic exocrine insufficiency: UK practical guidelines. *BMJ Open Gastroenterol* 2021; **8**: e000643.
- 109 Rickels MR, Bellin M, Toledo FG, et al. Detection, evaluation and treatment of diabetes mellitus in chronic pancreatitis: recommendations from PancreasFest 2012. *Pancreatol* 2013; **13**: 336–42.
- 110 Monaghan B, Monaghan A, Mockler D, et al. Physical activity for chronic pancreatitis: a systematic review. *HPB* 2022; **24**: 1217–22.
- 111 Eckert KG, Abbasi-Neureither I, Koppel M, Huber G. Structured physical activity interventions as a complementary therapy for patients with inflammatory bowel disease—a scoping review and practical implications. *BMC Gastroenterol* 2019; **19**: 115.
- 112 Layer P, Kashirskaya N, Gubergrits N. Contribution of pancreatic enzyme replacement therapy to survival and quality of life in patients with pancreatic exocrine insufficiency. *World J Gastroenterol* 2019; **25**: 2430–41.

- 113 Barkin JA, Barkin JS. Effect of pancrelipase therapy on exocrine pancreatic insufficiency symptoms and coefficient of fat absorption associated with chronic pancreatitis. *Pancreas* 2021; **50**: 176–82.
- 114 de la Iglesia-García D, Huang W, Szatmari P, et al. Efficacy of pancreatic enzyme replacement therapy in chronic pancreatitis: systematic review and meta-analysis. *Gut* 2017; **66**: 1354–55.
- 115 de Rijk FE, Kempeneers MA, Bruno MJ, et al. Suboptimal care for chronic pancreatitis patients revealed by moderate to low adherence to the United European Gastroenterology evidence-based guidelines (HaPanEU): a Netherlands nationwide analysis. *United European Gastroenterol J* 2020; **8**: 764–74.
- 116 Erchinger F, Tjora E, Nordaas IK, et al. Pancreatic enzyme treatment in chronic pancreatitis: quality of management and adherence to guidelines—a cross-sectional observational study. *United European Gastroenterol J* 2022; **10**: 844–53.
- 117 Barkin JA, Barkin JS. Chronic pancreatitis and bone disease. *J Clin Densitom* 2020; **23**: 237–43.
- 118 Wiese M, Gartner S, Doller J, et al. Nutritional management of chronic pancreatitis: a systematic review and meta-analysis of randomized controlled trials. *J Gastroenterol Hepatol* 2021; **36**: 588–600.
- 119 Andres E, Lorenzo-Villalba N, Terrade JE, Mendez-Bailon M. Fat-soluble vitamins A, D, E, and K: review of the literature and points of interest for the clinician. *J Clin Med* 2024; **13**: 3641.
- 120 Singh S, Midha S, Singh N, Joshi YK, Garg PK. Dietary counseling versus dietary supplements for malnutrition in chronic pancreatitis: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2008; **6**: 353–59.
- 121 Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology clinical practice guideline: developing a diabetes mellitus comprehensive care plan-2022 update. *Endocr Pract* 2022; **28**: 923–1049.
- 122 Davidsen L, Jensen MH, Cook ME, et al. Metformin treatment is associated with reduced risk of hypoglycaemia, major adverse cardiovascular events, and all-cause mortality in patients with post-pancreatitis diabetes mellitus: a nationwide cohort study. *Eur J Endocrinol* 2024; **190**: 44–53.
- 123 Cho J, Scragg R, Pandolfi SJ, Goodarzi MO, Petrov MS. Antidiabetic medications and mortality risk in individuals with pancreatic cancer-related diabetes and postpancreatitis diabetes: a nationwide cohort study. *Diabetes Care* 2019; **42**: 1675–83.
- 124 Goodarzi MO, Petrov MS. Diabetes of the exocrine pancreas: implications for pharmacological management. *Drugs* 2023; **83**: 1077–90.
- 125 Baekdal M, Nielsen SW, Hansen CP, et al. Empagliflozin normalizes fasting hyperglycemia and improves postprandial glucose tolerance in totally pancreatectomized patients: a randomized, double-blind, placebo-controlled crossover study. *Diabetes Care* 2024; **47**: 71–80.
- 126 Giaccari A. Expanding the Use of SGLT2i in diabetes beyond type 2. *Diabetes Care* 2024; **47**: 50–51.
- 127 van Veldhuisen CL, Latenstein AEJ, Blauw H, et al. Bihormonal artificial pancreas with closed-loop glucose control vs current diabetes care after total pancreatectomy: a randomized clinical trial. *JAMA Surg* 2022; **157**: 950–57.
- 128 Duggan SN, Ewald N, Kelleher L, Griffin O, Gibney J, Conlon KC. The nutritional management of type 3c (pancreatogenic) diabetes in chronic pancreatitis. *Eur J Clin Nutr* 2017; **71**: 3–8.
- 129 Nusrat S, Yadav D, Bielefeldt K. Pain and opioid use in chronic pancreatitis. *Pancreas* 2012; **41**: 264–70.
- 130 Farmer AD, Gallagher J, Bruckner-Holt C, Aziz Q. Narcotic bowel syndrome. *Lancet Gastroenterol Hepatol* 2017; **2**: 361–68.
- 131 Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. *Lancet* 2021; **397**: 2082–97.
- 132 Olesen SS, Bouwense SA, Wilder-Smith OH, van Goor H, Drewes AM. Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. *Gastroenterology* 2011; **141**: 536–43.
- 133 Talukdar R, Lakhtakia S, Nageshwar Reddy D, et al. Ameliorating effect of antioxidants and pregabalin combination in pain recurrence after ductal clearance in chronic pancreatitis: results of a randomized, double blind, placebo-controlled trial. *J Gastroenterol Hepatol* 2016; **31**: 1654–62.
- 134 Sureshkumar S, Omang A, Anandhi A, et al. Efficacy of pregabalin and antioxidants combination in reducing pain in chronic pancreatitis: a double blind randomized trial. *Dig Dis Sci* 2021; **66**: 4017–25.
- 135 Siriwardena AK, Mason JM, Sheen AJ, Makin AJ, Shah NS. Antioxidant therapy does not reduce pain in patients with chronic pancreatitis: the ANTICIPATE study. *Gastroenterology* 2012; **143**: 655–63.
- 136 Bhardwaj P, Garg PK, Maulik SK, Saraya A, Tandon RK, Acharya SK. A randomized controlled trial of antioxidant supplementation for pain relief in patients with chronic pancreatitis. *Gastroenterology* 2009; **136**: 149–59.
- 137 Hart PA, Osypchuk Y, Hovbakh I, et al. A randomized controlled phase 2 dose-finding trial to evaluate the efficacy and safety of camostat in the treatment of painful chronic pancreatitis: the TACTIC study. *Gastroenterology* 2023; **166**: 658–666.
- 138 Strand DS, Law RJ, Yang D, Elmunzer BJ. AGA clinical practice update on the endoscopic approach to recurrent acute and chronic pancreatitis: expert review. *Gastroenterology* 2022; **163**: 1107–14.
- 139 Sheth SG, Machicado JD, Chalhoub JM, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in the management of chronic pancreatitis: summary and recommendations. *Gastrointest Endosc* 2024; published online Aug 8. <https://doi.org/10.1016/j.gie.2024.05.016>.
- 140 Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. *JAMA* 2020; **323**: 237–47.
- 141 Cahen DL, Gouma DJ, Laramée P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. *Gastroenterology* 2011; **141**: 1690–95.
- 142 Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) guideline—updated August 2018. *Endoscopy* 2019; **51**: 179–93.
- 143 van der Wiel SE, Stassen PMC, Poley JW, De Jong DM, de Jonge PJF, Bruno MJ. Pancreatocopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones: a prospective consecutive case series. *Gastrointest Endosc* 2022; **95**: 905–14.
- 144 de Rijk FEM, Stassen PMC, van der Wiel SE, et al. Long-term outcomes of pancreatocopy-guided electrohydraulic lithotripsy for the treatment of obstructive pancreatic duct stones. *Endosc Int Open* 2023; **11**: E296–304.
- 145 Talukdar R, Olesen SS, Unnisa M, et al. Extracorporeal shock-wave lithotripsy and endoscopy for the treatment of pain in chronic pancreatitis: a sham-controlled, randomized trial. *Ann Intern Med* 2024; **177**: 749–58.
- 146 Sofi AA, Khan MA, Ahmad S, et al. Comparison of clinical outcomes of multiple plastic stents and covered metal stent in refractory pancreatic ductal strictures in chronic pancreatitis—a systematic review and meta-analysis. *Pancreatol* 2021; **21**: 854–61.
- 147 Kempeneers MA, Issa Y, Ali UA, et al. International consensus guidelines for surgery and the timing of intervention in chronic pancreatitis. *Pancreatol* 2020; **20**: 149–57.
- 148 Bachmann K, Tomkoetter L, Kutup A, et al. Is the Whipple procedure harmful for long-term outcome in treatment of chronic pancreatitis? 15-years follow-up comparing the outcome after pylorus-preserving pancreatoduodenectomy and Frey procedure in chronic pancreatitis. *Ann Surg* 2013; **258**: 815–21.
- 149 Diener MK, Huttner FJ, Kieser M, et al. Partial pancreatoduodenectomy versus duodenum-preserving pancreatic head resection in chronic pancreatitis: the multicentre, randomised, controlled, double-blind ChroPac trial. *Lancet* 2017; **390**: 1027–37.
- 150 Van Veldhuisen CL, Leseman CA, De Rijk FEM, et al. Nationwide outcome of tailored surgery for symptomatic chronic pancreatitis based on pancreatic morphology: validation of the international guidelines. *Ann Surg* 2023; published online Dec 13. <https://doi.org/10.1097/SLA.0000000000006176>.
- 151 Fröberg K, Halimi A, Vujanovic M, et al. Outcome after total pancreatectomy with islet autotransplantation: a European single-center study. *Scand J Surg* 2023; **113**: 80–87.

- 152 Kempeneers MA, Scholten L, Verkade CR, et al. Efficacy of total pancreatectomy with islet autotransplantation on opioid and insulin requirement in painful chronic pancreatitis: a systematic review and meta-analysis. *Surgery* 2019; **166**: 263–70.
- 153 Abu-El-Haija M, Anazawa T, Beilman GJ, et al. The role of total pancreatectomy with islet autotransplantation in the treatment of chronic pancreatitis: a report from the International Consensus Guidelines in chronic pancreatitis. *Pancreatology* 2020; **20**: 762–71.
- 154 Ratnayake CB, Bunn A, Pandanaboyana S, Windsor JA. Spinal cord stimulation for management of pain in chronic pancreatitis: a systematic review of efficacy and complications. *Neuromodulation* 2020; **23**: 19–25.
- 155 Muthulingam JA, Olesen SS, Hansen TM, Brock C, Drewes AM, Frokjaer JB. Cervical transcutaneous vagal neuromodulation in chronic pancreatitis patients with chronic pain: a randomised sham controlled clinical trial. *PLoS One* 2021; **16**: e0247653.
- 156 Gulisano HA, Eriksen E, Bjarkam CR, Drewes AM, Olesen SS. A sham-controlled, randomized trial of spinal cord stimulation for the treatment of pain in chronic pancreatitis. *Eur J Pain* 2024; **9**: 1627–39.
- 157 Lerch MM, Stier A, Wahnschaffe U, Mayerle J. Pancreatic pseudocysts: observation, endoscopic drainage, or resection? *Dtsch Arztebl Int* 2009; **106**: 614–21.
- 158 Kitano M, Gress TM, Garg PK, et al. International consensus guidelines on interventional endoscopy in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. *Pancreatology* 2020; **20**: 1045–55.
- 159 Hawa F, Chalhoub JM, Vilela A, et al. Efficacy and safety of long-term indwelling plastic stents after resolution of pancreatic fluid collections with endoscopic transmural drainage: a systematic review and meta-analysis. *Surg Endosc* 2024; **38**: 2350–58.
- 160 Bouwense SAW, Kempeneers MA, van Santvoort HC, Boermeester MA, van Goor H, Besselink MG. Surgery in chronic pancreatitis: indication, timing and procedures. *Visc Med* 2019; **35**: 110–18.
- 161 Dominguez-Munoz JE, Larino-Noia J, Alvarez-Castro A, et al. Endoscopic ultrasound-based multimodal evaluation of the pancreas in patients with suspected early chronic pancreatitis. *United European Gastroenterol J* 2020; **8**: 790–97.
- 162 Han S, Conwell DL, Li L, et al. The phase 1/2 trial of indomethacin in chronic pancreatitis (The PAIR trial): protocol for a parallel multi-center randomized controlled trial. *Pancreatology* 2023; **23**: 42–47.
- 163 Phillips AE, Afghani E, Akshintala VS, et al. Pancreatic quantitative sensory testing to predict treatment response of endoscopic therapy or surgery for painful chronic pancreatitis with pancreatic duct obstruction: study protocol for an observational clinical trial. *BMJ Open* 2024; **14**: e081505.
- 164 de Rijk FEM, van Veldhuisen CL, Besselink MG, et al. Implementation of an evidence-based management algorithm for patients with chronic pancreatitis (COMBO trial): study protocol for a stepped-wedge cluster-randomized controlled trial. *Trials* 2023; **24**: 18.

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