Chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a chronic inflammatory condition that results in irreversible morphological changes of the pancreas, including fibrosis and loss of both exocrine and endocrine functions. The aetiology of CP is multifaceted, including genetic, environmental, and autoimmune factors. Chronic alcohol consumption, smoking, and genetic mutations are significant contributors, with mechanisms involving oxidative stress, ductal obstruction, and immune-mediated inflammation. The clinical presentation is variable, with abdominal pain, malnutrition due to exocrine insufficiency, and diabetes mellitus being common presentations. Diagnosis of CP involves clinical evaluation, laboratory tests, and imaging studies, such as CT, MRCP, and endoscopic ultrasound, to assess pancreatic damage and complications. Management is complex and includes pain control, nutritional support, pancreatic enzyme replacement and, in severe cases, surgical interventions. Endoscopic treatment, such as stenting, and surgical procedures, like pancreaticojejunostomy, are used for ductal abnormalities and intractable pain. Emerging therapies, including antifibrotic treatments and stem cell therapy, are being explored. Long-term management requires a multidisciplinary approach, addressing not only medical and surgical needs but also psychological support and patient education. Advances in imaging and molecular biology are enhancing the understanding and treatment of CP, promising improved patient outcomes and quality of life.

Keywords Causes; chronic pancreatitis; diagnosis; multidisciplinary treatment

Background

Chronic pancreatitis (CP) is a chronic inflammatory condition of the pancreas that leads to irreversible morphological changes, fibrosis, and the gradual loss of both exocrine and endocrine pancreatic functions. Chronic pancreatitis is part of the disease continuum that follows from acute pancreatitis (AP) and recurrent acute pancreatitis (RAP) accounts for approximately 60% of cases. It poses a significant clinical challenge due to its complex aetiology, variable presentation, and multifaceted treatment approaches. Understanding the pathophysiology, diagnosis, and management of CP are essential to providing effective care and improving patient outcomes.

There is no current consensus on the specific definition that constitutes chronic pancreatitis, although consistent features of the progression to chronic pancreatitis from its precursors are histological (e.g. fibrosis) and morphological changes (e.g. atrophy, calcification). Such findings may be associated with fat-soluble vitamin deficiency leading to malnutrition, endocrine insufficiency manifesting as diabetes mellitus or debilitating abdominal pain. Recognition of CP can be challenging due to the insidious onset of the morphological features and fluctuating nature of its accompanying symptoms which are often inconsistent throughout disease progression. A proposed consensus definition of CP by international experts is: *pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress*.[1] The definition is associated with a progressive framework that organizes risk factors, clinical scenarios, disease biomarkers and individual variables throughout the disease course.

Epidemiology

The estimated incidence of CP ranges from 4 to 14 per 100,000 annually, with a median age at diagnosis of 45 years. Approximately 10% of cases of AP progress to CP and as such its incidence is significantly lower than AP, which can be as high as 56 cases per 100,000 annually. The incidence of CP increases with age peaking at 50–70 years, which is greater than those with RAP, supporting the possibility of a disease continuum between the two conditions.

The prevalence of CP is estimated as 41–154 cases per 100,000 population, varying amongst regions and between ethnic groups, with higher rates observed in African Americans compared to Caucasians. In contrast to Western countries, certain regions in Asia, particularly India, and parts of Africa, report higher prevalence which can be attributed to unique etiological factors such as tropical pancreatitis. Generally, the incidence and prevalence of CP is on the rise, which may be secondary to longer life expectancy in patients with CP, improvements in diagnostic techniques and possibly changes in lifestyle factors, such as increased alcohol consumption and smoking. There is concern that the true prevalence is much higher due to poor recognition. Unlike AP which has a similar gender distribution, CP patients are predominantly male across all age groups. There is higher alcohol and tobacco exposure in men and also a genetic susceptibility to alcohol-induced CP. Common comorbidities in the CP population include diabetes, dyslipidaemia, hypertension, cholelithiasis and fatty liver disease.

Aetiology

Chronic pancreatitis has multiple aetiologies, each contributing to the disease through different mechanisms and with the underlying aetiology having a significant bearing on the likely clinical progression. The aetiologies of CP can be succinctly summarized using the TIGAR-O checklist: T (Toxin-Metabolic), I (Idiopathic), G (Genetic), A (Autoimmune), R (Recurrent acute or severe pancreatitis) and O (Obstructive).[2] The TIGAR-O checklist provides guidance for recording the key risk factors, such as alcohol. An alternative checklist follows the M-ANNHEIM acronym which emphasizes the impact of risk factors for CP (multiple risk factors; alcohol; nicotine; nutritional; hereditary; efferent duct factors; immunological factors; miscellaneous), and incorporates different stages of the disease as well as stages of clinical severity.[3]

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Alcohol

The most common cause of CP is chronic alcohol consumption, which accounts for approximately 34%−80% of cases. The exact mechanisms by which alcohol induces pancreatic damage are not fully understood, but several theories have been proposed. Alcohol is metabolized in the pancreas by the enzyme alcohol dehydrogenase, producing acetaldehyde, a toxic metabolite, and toxic byproducts which cause direct cellular damage. Additionally, alcohol consumption leads to the formation of fatty acid ethyl esters, which disrupt cellular function and induce inflammatory responses. Chronic exposure to these toxic substances results in recurrent episodes of acute inflammation, setting the stage for chronic pancreatitis. Chronic alcohol consumption is believed to cause precipitation and increased viscosity of secretions leading to the formation of protein plugs within the pancreatic ducts. These plugs can lead to pancreatic calculi which obstruct the ducts, causing increased intraductal pressure, ductal dilatation, and eventually fibrosis. Interestingly, epidemiological evidence suggests that alcohol is not sufficient in isolation to cause CP and a number of contributing factors are required as part of a multifaceted etiological mechanism. Positive associations have been demonstrated with nicotine consumption, diet and known genetic mutations and it is proposed that alcohol may sensitize the pancreas to such triggers. Low levels of alcohol (<50 g of ethanol per day) are sufficient in contributing towards disease onset, although higher levels of consumption lower the age of onset and even reduce survival. The M-ANNHEIM classification system groups alcohol consumption into groups of moderate (<20 g), increased (20−80 g) and excessive (>80 g) subgroups. Overall, patients with alcohol-induced acute pancreatitis progress to CP approximately 5 times faster than patients with biliary pancreatitis.

Tobacco

Nicotine consumption is an important risk factor for the development of CP and increases the risk of idiopathic CP in patients who do not consume alcohol. It has also been found to increase the risk of patients with alcoholic CP developing complications, with the risk correlating with the amount of smoking. A smoking history in excess of 15 pack-years results in earlier onset CP and in those smoking in excess of 20 pack-years, up to 76% of patients exhibit pancreatic calcifications and ductal changes. Although, the effect of tobacco was thought to merely enhance the toxic impact of alcohol on the pancreas, recent evidence suggests smoking is both an independent risk factor for CP and accelerates its progression.

Obstructive pancreatitis

Obstructive pancreatitis is another important category, arising from conditions that block or increase the pressure within the pancreatic ducts which leads to upstream dilation and both acinar cell atrophy and fibrosis. During embryonic development, the ventral and dorsal pancreatic ducts normally fuse to create the main pancreatic duct. Pancreas divisum is a common congenital ductal anomaly occurring when this fusion fails to occur in between 5% and 14% of the general population. In view of its high prevalence, the association of pancreas divisum with CP is debated. Annular pancreas, though rare (5−15 cases per 100,000), is another congenital disorder associated with CP, characterized by pancreatic tissue forming a ring around the duodenum. Additionally, obstruction from gallstones in the common bile duct (choledocholithiasis) or dysfunction of the sphincter of Oddi can impede flow, leading to bile retention in the biliary tree and pancreatic secretions in the pancreatic duct. Pancreatic duct obstruction may also occur because of strictures or tumours, such as pancreatic ductal adenocarcinoma, intraductal papillary-mucinous neoplasms and neuroendocrine neoplasms. In smaller pancreatic ducts, ductal papillary hyperplasia often causes lumen narrowing.

Hereditary

Genetic factors play a crucial role in the development of CP, particularly in patients with early-onset CP or in those with idiopathic CP. Mutations in genes such as PRSS1, SPINK1, and CFTR have been implicated in hereditary pancreatitis.[4] The PRSS1 gene encodes cationic trypsinogen, a precursor of the digestive enzyme trypsin. Mutations in PRSS1 lead to increased trypsin activation within the pancreas, causing autodigestion and chronic inflammation. The SPINK1 gene encodes a trypsin inhibitor, and mutations in this gene reduce the effectiveness of the inhibitor, further promoting autodigestion and inflammation. The CFTR gene, associated with cystic fibrosis, is involved in the regulation of chloride and bicarbonate transport in the pancreatic ducts. Mutations in CFTR can lead to ductal obstruction and chronic pancreatitis. Once again, positive associations between toxic metabolites (e.g. ethanol consumption) and key genetic mutations point towards a complex and multifactorial aetiological mechanism.

Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a distinct form characterized by an inflammatory process driven by an autoimmune response. It is often part of the broader spectrum of IgG4-related diseases that can involve other organs, such as the bile ducts, kidneys, and salivary glands. Recognition of its diagnosis is vital as it often responds well to corticosteroid therapy and needs to be differentiated from pancreatic cancer.[5] AIP is classified into two distinct types: Type 1 and Type 2, though the differences in pathogenesis are not yet fully proven. Type 1 AIP, more common in East Asia, typically presents in older patients, with a mean onset age of 62 years. These patients often have elevated plasma levels of IgG4, and around 50% have other affected organs. The distinguishing histological feature of Type 1 AIP is the strong infiltration of IgG4-positive plasma cells and lymphoplasmacytic infiltration. IgG4-positive sclerosing cholangitis is a significant extrapancreatic manifestation, often leading to jaundice. Kamisawa et al. proposed viewing AIP as part of a broader clinicopathological entity of IgG4-associated systemic disease, which includes conditions like retroperitoneal fibrosis, sclerosing sialadenitis, and sclerosing cholangitis. This systemic fibroinflammatory disease may also involve the aorta, breast, and prostate. Type 2 AIP is more common in the United States and Europe, accounting for 45% of cases, and typically affects younger patients, with a mean onset age of 40−48 years. It is frequently associated with Crohn's disease and ulcerative colitis. The hallmark histological feature of Type 2 AIP is granulocytic epithelial lesions, which differentiate it from Type 1 AIP. Unlike

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Type 1, Type 2 AIP generally lacks the extrapancreatic manifestations observed in Type 1 AIP.

Other aetiologies

Tropical pancreatitis, predominantly seen in tropical regions like India and Africa, presents with unique epidemiological and clinical features. The exact cause remains unclear, but it is often associated with malnutrition, dietary toxins, and genetic factors. This variant is typically diagnosed at a younger age and has a higher incidence of diabetes and pancreatic calcifications compared to other types. Tropical pancreatitis often leads to significant morbidity and mortality due to its aggressive course and high rate of complications.

Metabolic factors, including hypercalcaemia and hyperlipidaemia, can also contribute to the development of chronic pancreatitis. These conditions can lead to the precipitation of calcium or fat within the pancreatic ducts, causing obstruction and subsequent inflammation. Hypercalcaemia, for example, can result from hyperparathyroidism and leads to the formation of calcium deposits within the pancreatic ducts. Hyperlipidaemia, particularly severe hypertriglyceridaemia, can cause recurrent episodes of acute pancreatitis that eventually progresses to chronic pancreatitis.

Idiopathic chronic pancreatitis, where no clear cause can be identified, accounts for a significant proportion of cases. Idiopathic cases are often divided into two categories based on the age of onset: early-onset idiopathic chronic pancreatitis and late-onset idiopathic chronic pancreatitis. Early-onset idiopathic chronic pancreatitis tends to present in childhood or adolescence and is frequently associated with genetic mutations. Late-onset idiopathic chronic pancreatitis typically manifests in adulthood without an obvious genetic link.

Pathophysiology

The pathophysiology of chronic pancreatitis involves a complex interplay of genetic, environmental, and immunologic factors leading to persistent inflammation and fibrosis. Although the exact pathophysiological mechanism is debated, it is proposed that the initial insult, whether due to alcohol, genetic mutations, or ductal obstruction, triggers an inflammatory response within the pancreas parenchyma leading to the destruction of acinar, ductal and mesenchymal interstitial cells. Following the initial injury, there is a release of cytokines and growth factors (e.g. interleukin-8, platelet derived growth factor, tumour growth factor b1) from immigrating macrophages and preexisting epithelial and mesenchymal cells. In response to these signals, the damaged cells are phagocytosed causing the further release of cytokines. When this process becomes chronic, pancreatic stellate cells are activated to become myo-fibroblast-like phenotypes, which secrete fibrillar collagens (collagen I and II) and fibronectin. This leads to the deposition of the extracellular matrix leading to pancreatic fibrosis.

As fibrosis progresses, there is a gradual destruction of both the acinar cells for exocrine function, and the islet of Langerhans cells, responsible for endocrine function. Once this process begins any changes are irreversible and functional impairment of endocrine and exocrine function begins to reveal itself as diabetes mellitus or malabsorption, respectively. The ultimate clinical manifestations, however, depend on the type of cellular damage and fibrosis which is dependent on the aetiology. As well as a loss of functional tissue, this process leads to loss of the lobular morphology and loss of the structure of the islets. Structural abnormalities may develop, such as pseudocysts, malformation of the ductal anatomy (e.g. strictures, ectasia), biliary or duodenal obstruction, pancreatic ascites, and vascular involvement, including splenic vein thrombosis and pseudoaneurysms.

Chronic alcohol consumption induces oxidative stress within pancreatic cells, leading to the formation of reactive oxygen species (ROS) and subsequent cell damage. This oxidative stress also promotes the activation of pancreatic stellate cells, which are the primary mediators of fibrosis in chronic pancreatitis. Once activated, these stellate cells secrete collagen and other extracellular matrix components, resulting in the replacement of normal pancreatic tissue with fibrous scar tissue.

Genetic mutations, particularly those affecting trypsinogen and its inhibitors, contribute to the development of chronic pancreatitis by disrupting the balance between proteolytic and antiproteolytic activity within the pancreas.[4] Mutations in the PRSS1 gene, for example, lead to increased activation of trypsinogen to trypsin, an enzyme that can digest pancreatic tissue. Mutations in the SPINK1 gene reduce the effectiveness of the trypsin inhibitor, further promoting autodigestion and inflammation.

In autoimmune pancreatitis, the pathogenesis is driven by an immune-mediated attack on the pancreatic tissue. Elevated levels of IgG4-producing plasma cells infiltrate the pancreas, leading to chronic inflammation and fibrosis. This immune response can also affect other organs, resulting in a systemic disease that requires careful management.

Obstructive pancreatitis arises from conditions that block the pancreatic ducts, leading to increased intraductal pressure and chronic inflammation. Pancreatic duct strictures, tumours, or congenital anomalies like annular pancreas can cause persistent or intermittent obstruction of the pancreatic duct, resulting in damage to the pancreatic tissue. Gallstones can also cause obstructive pancreatitis by blocking the common bile duct and pancreatic duct, leading to backpressure and inflammation.

The complex interplay between the above-mentioned genetic, environmental, and immunologic factors in chronic pancreatitis leads to a cycle of ongoing inflammation, fibrosis, and tissue destruction. This cycle perpetuates the disease and contributes to the progressive loss of pancreatic function over time.

Clinical presentation

The clinical presentation of chronic pancreatitis is highly variable and can range from mild intermittent symptoms to severe, debilitating pain and even major complications. The hallmark symptom is abdominal pain, which is often severe, persistent, and may radiate to the back. The pain is typically exacerbated by eating and is characteristically relieved by sitting forward or bending over. Over time, the pain may become constant and unremitting, and of all symptoms has the most significant impact on quality of life. Up to 90% of patients with CP will suffer at least one episode of hospitalization during their lifetime. A number of theories have been proposed for underlying mechanisms of pain in CP. Many studies have implicated increased

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pancreatic ductal pressure, however others have suggested that it is the result of an inflammatory process.

Exocrine insufficiency or fat-soluble vitamin deficiency occurs in up to 75% of patients with chronic pancreatitis, resulting from the loss of acinar cell function. This manifests as steatorrhea (fatty stools), weight loss, and malnutrition due to impaired digestion and absorption of nutrients. Patients may present with symptoms of fat-soluble vitamin deficiencies, including vitamin A, D, E, and K, leading to complications such as night blindness, osteomalacia, coagulopathy, and immune dysfunction. The risk is greatest in those with alcohol-induced CP and in those with tropical pancreatitis.

Endocrine insufficiency occurs as the disease progresses and the islet cells are destroyed, leading to diabetes mellitus. This type of diabetes, often referred to as type 3c diabetes, can be challenging to manage due to concurrent exocrine insufficiency and malabsorption. Patients may experience fluctuating blood glucose levels and increased risk of hypoglycaemia. In patients with new onset diabetes mellitus, undiagnosed pancreatic ductal adenocarcinoma remains within the differential diagnosis.

In addition to the primary symptoms of pain, malabsorption and diabetes, CP can lead to a range of complications. Pseudocysts, which are collections of pancreatic fluid enclosed by a fibrous capsule, are a common complication and can cause symptoms by compressing adjacent structures. Biliary or duodenal obstruction can result from the inflammatory and fibrotic process encasing these structures. Pancreatic ascites, resulting from leakage of pancreatic fluid into the peritoneal cavity, can present with abdominal distension and discomfort. Vascular complications, such as splenic vein thrombosis and pseudoaneurysms, can lead to gastrointestinal bleeding and require urgent intervention.

The clinical course of chronic pancreatitis can be punctuated by episodes of acute exacerbations, where patients experience a sudden worsening of symptoms. These exacerbations can be triggered by factors such as alcohol consumption, dietary indiscretions, and the development of complications like pseudocysts or strictures. Managing these acute episodes requires prompt medical intervention and may necessitate hospitalization for pain control, nutritional support, and treatment of complications.

Chronic pancreatitis significantly impacts patients' quality of life, leading to chronic pain, malnutrition, diabetes, and frequent hospitalizations. The disease often results in physical and emotional distress, affecting patients' ability to work and perform daily activities. The chronic pain associated with CP can lead to dependence on analgesics, including opioids, which further complicates management. Psychological support and counselling are important aspects of care for patients with chronic pancreatitis to help them cope with the chronic nature of the disease and its impact on their lives.

Diagnostic evaluation

The diagnosis of chronic pancreatitis requires a combination of clinical evaluation, laboratory tests, and imaging studies. A detailed history and physical examination are essential to identify risk factors and assess the severity of symptoms. The clinician should inquire about alcohol consumption, family history of pancreatitis, and symptoms suggestive of exocrine or endocrine insufficiency.

Laboratory tests can provide supportive evidence for the diagnosis of chronic pancreatitis. Serum amylase and lipase levels are often redundant in chronic stages of the disease, as the pancreatic tissue becomes progressively fibrotic and less capable of producing these enzymes. Faecal elastase-1 is a useful marker for exocrine insufficiency, with low levels indicating significant pancreatic dysfunction. Genetic testing may be warranted in cases of suspected hereditary pancreatitis, especially in young patients with a strong family history or those presenting with idiopathic chronic pancreatitis.

Imaging studies play a pivotal role in diagnosing chronic pancreatitis and assessing its complications. Ultrasound is often the initial imaging modality and can detect pancreatic calcifications, ductal changes, and pseudocysts. However, its sensitivity is limited, especially in early stages of the disease or in obese patients. Computed tomography (CT) provides detailed visualization of pancreatic morphology and is more sensitive for detecting calcifications, ductal dilatation, and complications such as pseudocysts and vascular involvement.

Magnetic resonance cholangiopancreatography (MRCP) is a non-invasive imaging technique that allows detailed visualization of the pancreatic ducts and surrounding structures. It is particularly useful for identifying ductal strictures, dilatation, and side branch ectasia. Secretin-enhanced MRCP (s-MRCP) may be more effective in identifying the subtle ductal abnormalities (e.g. dilation or ectasia) that result from the pancreatic fibrosis in CP.[6] s-MRCP stimulates the release of bicarbonate from pancreatic ductal cells which further improves the visualization of the ductal anatomy and gives insight into the exocrine function of the pancreas by quantifying the degree of filling into the duodenum. It may also help visualize the pancreaticobiliary junction to help investigate for reflux into the common bile duct.

Endoscopic ultrasound (EUS) offers high-resolution imaging of the pancreas and allows for fine-needle biopsy (FNB) to obtain tissue samples for histopathological analysis. EUS is also valuable for detecting early parenchymal and ductal changes that may not be visible on other imaging modalities. Where cross-sectional imaging or EUS does not help confirm CP, the ACG guidelines recommend s-MRCP if there is high-suspicion.

Endoscopic retrograde cholangiopancreatography (ERCP) allows for direct visualization of the ductal anatomy, identification of strictures, stones, and leaks. It provides the opportunity for therapeutic interventions such as stent placement and stone extraction. ERCP is invasive and carries a risk of complications, including pancreatitis, infection, and bleeding and is now used for therapeutic intervention rather than as a diagnostic tool alone.

The diagnostic evaluation of chronic pancreatitis should also include assessment of nutritional status and pancreatic function. Nutritional assessment involves measuring body weight, body mass index (BMI), and markers of malnutrition, such as serum albumin and prealbumin levels. Pancreatic function tests, such as the secretin stimulation test, can help evaluate the exocrine function of the pancreas and guide enzyme replacement therapy.

Additional laboratory tests may include serum calcium and triglyceride levels to identify metabolic causes of chronic pancreatitis, such as hypercalcaemia and hyperlipidaemia.

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Autoimmune markers, including serum IgG4 levels, should be measured in cases of suspected autoimmune pancreatitis. Elevated serum IgG4 levels and the presence of IgG4-positive plasma cells in pancreatic tissue can support the diagnosis of autoimmune pancreatitis.

Histopathological examination of pancreatic tissue obtained through EUS-guided FNB can provide definitive evidence of chronic pancreatitis. Histological features of chronic pancreatitis include fibrosis, acinar cell atrophy, ductal changes, and inflammatory cell infiltration. The presence of specific histological patterns, such as lymphoplasmacytic sclerosing pancreatitis in autoimmune pancreatitis, can help differentiate between different aetiologies of chronic pancreatitis.

Patients with CP are reportedly at a higher risk of pancreatic cancer compared to patients without CP. The relationships could be explained by the prevalence of certain risk factors in these patient groups (e.g. alcohol and smoking) and therefore a direct link between CP and pancreatic cancer is yet to be proven. Currently there is no clear evidence which supports the use of screening for pancreatic cancer in patients with chronic pancreatitis.

Management

The treatment of patients with chronic pancreatitis necessitates a customized strategy that takes into account the severity of symptoms, the root cause, and presence of any complications. The emerging management approach is moving away from the traditional clinicopathologic definition of disease, focusing instead on early identification of the underlying mechanistic disorder as the disease progresses. This method promotes comprehensive management of the condition to modify its natural course and mitigate against the development of irreversible damage and loss of function. This perspective is in line with precision medicine for complex disorders, which uses a 'bottom-up' approach to examine the complex interplay between genetic and environmental factors in patients with early signs and symptoms. A comprehensive review of all possible aetiologies should be undertaken which should account for both fixed and modifiable risk factors. Although there is limited evidence supporting its efficacy, strict alcohol cessation and appropriate counselling is strongly advised in patients with alcohol-induced CP.

Pain management

Medical management is the cornerstone of treatment for chronic pancreatitis and incorporates effective analgesia prescribing. Pain management is a critical aspect and often involves a stepwise approach by utilizing the World Health Organization (WHO) pain relief ladder.[7] Starting with non-opioid analgesics such as acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) is often the preferred approach. For pain not responsive to simple analgesics, opioids may be necessary, although their use should be carefully monitored due to the risk of dependence, tolerance, opioid-induced hyperalgesia or narcotic bowel syndrome. Up to 66% of patients with CP use opioids and there is a significant concern over this analgesic practice.

Adjunctive therapies, such as tricyclic antidepressants, gabapentinoids, and nerve blocks, can also be employed to manage pain. Anti-oxidants such as ascorbic acid and selenium have been trialled in randomized-controlled studies with the hypothesis that they will reduce oxidative stress and be anti-inflammatory, but the clinical results are variable. In some cases, coeliac plexus block or neurostimulation techniques such as spinal cord stimulation and transcranial magnetic stimulation may be considered for refractory pain, although they are rarely used in clinical practice.

Nutrition

Nutritional support is essential for patients with exocrine insufficiency. Pancreatic enzyme replacement therapy (PERT) is the mainstay of treatment and involves the administration of pancreatic enzymes with meals to aid in digestion and absorption of nutrients. The dose of enzymes should be adjusted based on the severity of malabsorption and the patient's dietary intake. Dietary modifications, including a low-fat diet and small, frequent meals, can help manage symptoms. Vitamin supplementation, particularly fat-soluble vitamins (A, D, E, and K), is necessary to prevent deficiencies.

Diabetes

Management of diabetes in chronic pancreatitis, referred to as type 3c diabetes, requires a comprehensive approach. Insulin therapy is often necessary due to the loss of beta-cell function, and patients should be closely monitored for hypoglycaemia. Coordination with an endocrinologist can help optimize diabetes management and address the unique challenges posed by concurrent exocrine insufficiency.

Surgical and endoscopic management

Endoscopic interventions play a vital role in the management of chronic pancreatitis, particularly for addressing ductal abnormalities and complications. ERCP can be used to treat ductal strictures by placing stents and treatment of pancreatic stones. Endoscopic pancreatic stenting has also proven safe with high satisfaction rates in patients with refractory pain associated with dilated pancreatic ducts, but re-stenting may be required. Endoscopic ultrasound (EUS)-guided procedures, such as pseudocyst drainage and coeliac plexus block, offer minimally invasive options for managing complications and refractory pain.

Surgical treatment is considered when medical and endoscopic therapies fail to relieve symptoms, most often intractable abdominal pain, when complications arise (e.g. pseudocysts, biliary or duodenal obstruction, and vascular involvement) that cannot be managed endoscopically, or if there is suspicion of malignancy. The choice of surgical procedure is influenced by the location and severity of the disease but should also aim to address symptoms and complications whilst preserving endocrine and exocrine function. Partial pancreatectomy, such as pancreaticoduodenectomy, may be necessary in patients with a large pancreatic head resulting from obstructed ducts and fibrosis where simple decompression of the main pancreatic duct would be inadequate. Localized resection with lateral pancreaticojejunostomy (Frey procedure) has also been proposed with lower complication rates reported and comparable long-term pain relief (48%–91%) compared to major pancreatic resections.[8] When considering endocrine and exocrine function, weight gain has been reported in 64%–79% following a Frey

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procedure. The incidence of re-operation following a Frey procedure ranges from 5% to 30% for various indications including biliary strictures, recurrent abdominal pain and recurrent pancreatitis in the tail of the pancreas. Lateral pancreaticojejunostomy (Puestow procedure) is a drainage procedure, similar to a Frey procedure but without coring of the head of the pancreas, and can be utilized in patients with a dilated pancreatic duct (>7 mm) to decompress the pancreas and improve exocrine function.

Total pancreatectomy is considered a last resort due to the significant morbidity associated with complete removal of the pancreas, resulting in brittle diabetes and lifelong dependency on pancreatic enzyme replacement therapy and insulin. However, results from total pancreatectomy with islet autotransplantation (TPIAT) in selected patients appear promising with high rates of narcotic independence (54%) and insulin-independence (31.8%).[9]

Postoperative management and long-term follow-up are crucial for patients undergoing surgery for chronic pancreatitis. Pain control, nutritional support, and management of diabetes remain the central components of care. Patients should be monitored for postoperative complications, including pancreatic fistula, infection, and recurrent symptoms. Regular follow-up with a multidisciplinary team, including gastroenterologists, endocrinologists, dietitians, and pain specialists, is essential to optimize outcomes and improve quality of life.

Emerging therapies and research

Research in chronic pancreatitis is ongoing, with efforts to better understand the underlying mechanisms of the disease and develop new therapeutic approaches. Advances in molecular biology and genetics have provided insights into the genetic and epigenetic factors contributing to chronic pancreatitis. These discoveries have the potential to identify new targets for therapy and improve the diagnosis and management of the disease.

One area of active research is the development of antifibrotic therapies aimed at preventing or reversing the fibrosis that characterizes chronic pancreatitis. Pancreatic stellate cells are key mediators of fibrosis, and targeting the signalling pathways that activate these cells may help reduce fibrosis and preserve pancreatic function. Preclinical studies have shown promising results with agents that inhibit stellate cell activation, but clinical trials are needed to evaluate their efficacy and safety in patients with chronic pancreatitis.

Stem cell therapy is another emerging area of research with potential applications in chronic pancreatitis, through its potential for regeneration.[10] Stem cells have the ability to differentiate into various cell types and may help regenerate damaged pancreatic tissue. Early studies have explored the use of stem cells to restore pancreatic function, prevent further damage and fibrosis, and reduce inflammation in animal models of chronic pancreatitis. Some centres in South-East Asia and China have begun utilizing stem-cell therapy but the outcomes are unknown and clinical trials are needed to assess the feasibility and safety of stem cell therapy in human patients.

Advances in imaging techniques, such as high-resolution MRI and molecular imaging, are improving the ability to diagnose chronic pancreatitis and monitor disease progression. These imaging modalities can provide detailed information about pancreatic structure and function, helping to identify early changes in the pancreas and guide treatment decisions. Molecular imaging techniques, such as positron emission tomography (PET), can also provide insights into the inflammatory and fibrotic processes associated with CP, potentially guiding the development of targeted therapies.[11]

Patient education and support

Patient education and support are essential components of the management of patients with chronic pancreatitis. Patients need to understand the nature of the disease, its potential complications, and the importance of adherence to treatment plans. Education should cover topics such as the role of pancreatic enzyme replacement therapy, dietary modifications, and the management of diabetes. Patients should also be informed about the risks of alcohol consumption and the need to avoid alcohol to prevent disease progression.

Support groups and counselling can provide valuable resources for patients coping with chronic pancreatitis. Support groups offer a platform for patients to share their experiences, receive emotional support, and learn from others facing similar challenges. Counselling services can help patients manage the psychological impact of their disease, including how to cope with chronic pain, depression, and anxiety.

Healthcare providers should also provide education and support to family members and caregivers, who play a crucial role in the care of patients with CP. Caregivers need to understand the disease and its management to provide effective support and help patients adhere to treatment plans.

Conclusion

Chronic pancreatitis is a complex and challenging disease that requires a comprehensive and multidisciplinary approach to diagnosis and management. The pathophysiology of chronic pancreatitis involves a complex interplay of genetic, environmental, and immunologic factors leading to persistent inflammation and fibrosis. Treatment involves a combination of medical, endoscopic, and surgical approaches tailored to the individual patient's needs and disease severity.

Advancements in imaging techniques and endoscopic therapies have improved the ability to diagnose and manage chronic pancreatitis, reducing the need for surgical intervention in some cases. However, surgery remains an important option for patients with intractable pain, complications, or suspicion of malignancy. Long-term follow-up and a multidisciplinary approach are essential to address the complex needs of patients with chronic pancreatitis, optimize outcomes, and improve their quality of life.

Future research and emerging therapies hold promise for improving the diagnosis and treatment of CP. Advances in molecular biology, genetics, and imaging techniques are enhancing our understanding of the disease and paving the way for the development of new therapeutic approaches. Patient education and support are essential to help patients manage the chronic nature of the disease and its impact on their lives. By adopting a holistic and multidisciplinary approach, healthcare providers can improve outcomes and quality of life for patients with CP. ◆

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Practice points

- The incidence and prevalence of CP is on the rise, which may be secondary to longer life expectancy, improvements in diagnostic techniques and changes in lifestyle factors, such as increased alcohol consumption and smoking
- Alcohol-induced CP progresses up to five times faster than biliary pancreatitis, highlighting alcohol as a major risk factor
- Smoking is both an independent risk factor for chronic pancreatitis and accelerates its progression, especially in those with over 15 pack-years of smoking history
- Chronic pancreatitis significantly increases the risk of developing diabetes, known as type 3c diabetes, due to the destruction of insulin-producing cells
- Total pancreatectomy with islet autotransplantation shows promise in certain CP patients, achieving narcotic independence in over 50% of cases and insulin independence in nearly 32%
- Patients with CP are reportedly at a higher risk of pancreatic cancer compared to patients without CP

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