Review Article**Chronic Pancreatitis - An Update****Gobishangar S¹**¹*Department of Surgery, Faculty of Medicine, Jaffna***Abstract**

Chronic pancreatitis (CP) is a progressive inflammatory process that causes irreversible damage to the pancreas due to fibrosis and scarring. The incidence of CP varies among regions. Alcohol consumption and smoking are the main aetiological factors of CP. In addition, autoimmune diseases, hereditary and genetic factors, and tropical CP also contribute to this condition. Though no single mechanism has been shown to initiate CP pathogenesis, this disease ultimately results in fibrosis, scarring, and insufficiency in the pancreas. Chronic upper abdominal pain, steatorrhea, malnutrition, and diabetes mellitus are the main clinical features of CP. Detecting this disease at an early stage is difficult unless it is explicitly checked for due to strong suspicions. Nevertheless, pancreatic function tests, imaging, and endoscopy are used to diagnose CP. Pain management, exocrine supplementation, diabetic management, and endoscopic or surgical drainage and resection procedures are essential for managing CP. Early surgical intervention can improve the remaining pancreatic reserve, delay pancreatic failure, and improve the quality of life of patients with this disease.

Keywords

Chronic pancreatitis, Recurrent acute pancreatitis

Introduction

Chronic pancreatitis (CP) is an established and progressive inflammation of the pancreas that causes irreversible damage with scarring, eventually leading to exocrine pancreatic failure and malnutrition. CP then progresses to endocrine failure, leading to diabetes mellitus. [1] The traditional classification of acute, recurrent, and CP has been replaced by the concept of single disease entities. [2] The incidence of CP is poorly studied and varies across different parts of the world. CP

commonly affects men more than women [4]. Recent data have shown an increasing worldwide trend over the last few decades. [2] A study conducted in France revealed that the incidence of CP is 7.8 per 100,000. [5] Similarly, research in the United States showed that the incidence of CP is 5 per 100,000. [6] A Mayo Clinic study showed that the incidence of chronic pancreatitis increased from 2.94/100,000 during 1977–1986 to 4.35/100,000 during 1997–2006. [7]

Review**Aetiological factors**

The main aetiological factors for CP are alcohol intake and smoking. [8] Other risk factors include genetic factors, autoimmune pancreatitis, and anatomic variations. [9] Approximately 44%–77% of CP cases are related to alcohol consumption and smoking, with the incidence of CP being three times higher in smokers than in the general population. [10] [11] Both of these risk factors increase the progression of acute pancreatitis to CP, which is very rare in patients with recurrent pancreatitis due to non-alcohol aetiological factors. [12] In addition, multiple genetic mutations play a vital role in the pathogenesis of CP. Specifically, a known CP-related pathogenic mutation is in protease serine 1 (PRSS1), which causes hereditary pancreatitis (HP) and contributes to approximately 1% of CP cases. [13] HP differs from other forms of CP in that it rapidly damages the pancreas, leading to complete pancreatic shutdown and significantly increasing the risk of pancreatic adenocarcinoma. [9] Coeliac diseases, inflammatory bowel disease, and systemic lupus erythematosus are diseases shown to be involved in autoimmune pancreatitis development. [14] [15] [16] Tropical chronic pancreatitis is a juvenile form of CP seen in developing countries in tropical regions. [17] The majority of CP cases are idiopathic (28%–80%), and nearly 50% of them have a mutation in the trypsin inhibitor gene

Corresponding author: Gobishangar S., email: gobishangar@gmail.com, <https://orcid.org/0000-0001-6826-6874>

Submitted April 2021, Accepted June 2021

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution and reproduction in any medium provided the original author and source are credited

serine peptidase inhibitor Kazal type 1 (SPINK1) or the cystic fibrosis transmembrane conductance regulator gene (CFTR). [13]

Pathogenesis

Although there is no clear evidence for the pathogenesis of CP, it consists of multiple acute pancreatitis episodes in the early stage and progresses into pancreatic fibrosis, insufficiency, calcification, and diabetes mellitus in the later stages. [18] In addition, some studies emphasise that pancreatic failure due to CP may be delayed or cease when the patient is abstinent from alcohol or undergoing a surgical drainage procedure. [19]

There are several mechanisms described as CP pathophysiology; however, none of them predominantly cause CP. Important mechanisms are (1) the direct effect of toxic metabolites on acinar cells, (2) acute pancreatitis causing activation of pancreatic stellate cells with subsequent fibrosis (two-hit model), (3) formation of protein plugs causing ductal dysfunction leading to obstruction, (4) free radicals promoting fusion of lysosomes causing oxidative stress to acinar cells, and (5) repeated episodes of acute pancreatitis causing a necrosis-fibrosis sequence. [20]

Clinical features

Chronic pain is the main symptom in patients with CP. [1] Nearly 80% of patients with CP develop recurrent upper abdominal pain, and half of all patients with CP have persistent, severe pain that affects their daily activities. Constant pain indicates a low quality of life in patients with CP. [13] [21] In addition, approximately 40% of people with CP develop endocrine failure, and approximately 30%–48% of patients develop exocrine pancreatic failure. [13] Exocrine pancreatic failure usually develops after a 90% loss of pancreatic function and results in steatorrhea, weight loss, malnutrition, metabolic bone disease, and vitamin and mineral deficiencies. [9]

Clinically, CP can have the following four stages: (1) a preclinical stage with no symptoms; (2) recurrent acute episodes of pancreatitis with no specific signs of CP; (3) recurrent episodes with intermittent or constant pain in between and signs of CP, such as duct dilatation and pancreatic calcification on imaging tests; and (4) a final stage where acute flares have mostly ceased, and there is

an absence or decreased frequency of pain, which is possibly associated with exocrine and endocrine insufficiency. [22]

Complications

Approximately 1.8% of patients with CP develop pancreatic cancer after 10 years of diagnosis, with this number increasing to 4% in 20 years. [23] In addition, pancreatic parenchymal fibrosis in CP may cause duodenal and common bile duct obstructions. Some individuals may also develop pseudocysts of the pancreas.

Diagnosis

The gold standard for diagnosing CP is histological evidence from a biopsy, which is rarely available. [22] Therefore, the diagnosis of CP depends mainly on clinical findings, imaging, pancreatic function tests, and endoscopic findings. However, it is challenging to diagnose CP early due to a lack of sensitive tests. [24] Recurrent upper abdominal pain history provides a high index of suspicion for further investigation. [13] Therefore, CP diagnosis is primarily based on investigations to assess the functional and structural status of the pancreas. [25]

Pancreatic Function Tests

Pancreatic function tests are usually performed to diagnose CP. These tests identify exocrine and endocrine dysfunction of the pancreas. [26] Faecal elastase level ($<200 \mu\text{g/g}$ stool, although $<100 \mu\text{g/g}$ stool is more specific) is used to assess the exocrine function of the pancreas. However, the specificity and sensitivity of this test is low. Practical tests of serum amylase and lipase can also be performed. When the levels of each are lower than average, an accurate CP diagnosis is nearly 100%, except for in patients who have undergone partial or total pancreatectomy. [27] A serum trypsin level of $<20 \text{ ng / mL}$ may also serve as a useful marker of CP, with a sensitivity ranging from 33%–65%. [9] The secretin stimulation test has been shown to be the most reliable test due to its high specificity and sensitivity. However, as it is an invasive procedure that is not freely available, its use is minimal for the diagnosis of CP. [25] In addition, most pancreatic function tests are not sensitive enough to detect mild and moderate cases of CP. In severe cases, imaging investigations detect CP very well; therefore, the usefulness of this test is questionable. [22]

Radiological Investigation

Imaging is a critical investigation for the diagnosis of CP. [24] Different imaging techniques are used to diagnose CP, such as transabdominal ultrasound, endoscopic ultrasound (EUS), computerised tomography (CT), and magnetic resonance imaging (MRI). If certain abnormalities are displayed, CP can also be diagnosed based on imaging, such as pancreatic parenchymal fibrosis and calcification and pancreatic duct obstruction, dilatation, distortion, and stricturing. Other findings suggestive of CP include narrowing of the duodenum, thrombosis of the superior mesenteric, portal, and splenic veins, and pseudocysts around the pancreas. [28] If the above two investigations are equivocal, EUS is usually the next testing method chosen. [28] [13] This is because it can detect mild parenchymal and ductal changes before they are detectable by CT. Moreover, its sensitivity and specificity are approximately 80%. [29] In addition, EUS elastography may improve the detection of early pancreatitis by measuring the parenchymal fibrosis ratio. [27]

Transabdominal ultrasound can detect multiple echogenic foci in the pancreas, representing numerous pancreatic calcifications in advanced CP. Unfortunately, only 40% of patients with CP have ultrasounds that show these findings; therefore, the sensitivity of a transabdominal ultrasound scan is low. [30] CT imaging for detecting advanced CP has a sensitivity of 74%–90% and specificity of 80%–90%. [31] In contrast, magnetic resonance cholangiopancreatography (MRCP) combined with intravenous secretin can detect early CP with high sensitivity (77%) and specificity (83%). [32] Previously, endoscopic retrograde cholangiopancreatography was used to detect CP until the introduction of MRCP and EUS. However, it is now reserved for patients with other imaging techniques that are equivocal. [33]

Endoscopic Pancreatic Function Test

Endoscopic pancreatic function tests include intravenous secretin administration, where duodenal secretions are stimulated and the aspirates are collected 15, 30, 45, and 60 minutes afterwards. A bicarbonate concentration of 80 mmol/L or more in any of the aspirates is considered normal. Although this test is the gold standard for assessing exocrine pancreatic function, it is time-consuming and not freely available in most centres. [34]

Genetic Testing

Genetic testing indicates CP or recurrent acute pancreatitis in a patient if one or more of the following criteria is met: (1) Uncertain aetiology; (2) early age at onset of idiopathic chronic pancreatitis (<25 years); (3) unexplained pancreatitis during childhood; (4) family history of idiopathic chronic pancreatitis, recurrent acute pancreatitis, or childhood pancreatitis involving first- or second-degree relatives; and (5) family members of an individual with an identified pathogenic gene mutation associated with HP. Genetic tests include testing for mutations in PRSS1, SPINK1, carboxypeptidase A1 (CPA1), chymotrypsin C (CTRC), and calcium-sensing receptor (CASR). [27]

Treatment

Treatment options for CP include medical, radiological, endoscopic, and surgical methods. [28] General management includes advice on abstinence from alcohol consumption and smoking. [13] though pain is the main component of CP management. [20]

Pain Management

Pain management should address the mechanisms and severity of pain. Some pain mechanisms include pancreatic duct obstruction, parenchymal inflammation, malabsorption, and neurogenesis. [35] Inflammation, inflammatory cells, and cytokines (inflammatory cell secretions) are the primary causes of abdominal pain in CP. [35] Primary analgesic therapy includes non-steroidal anti-inflammatory drugs and tramadol-like mild opioids. [13] In addition, pancreatic enzyme supplementation and antioxidants control the pain in up to 50% of patients. [13]

When analgesic drugs and other medications fail to alleviate pain, endoscopic ultrasound-ceeliac plexus block (EUS-CPB) is usually helpful. However, it controls pain in slightly over 50% of patients and is relatively safe, moderately effective, and repeatable. [36]

Most of these treatment modalities do not address the cause of pain. Therefore, a significant number of patients need endoscopic or surgical management for pain relief, such as pain caused by pancreatic duct obstruction due to intraductal stone, stricture, or peripancreatic fibrosis, which causes intraductal hypertension leading to pain. [37]

Extracorporeal shock wave lithotripsy is the first-line treatment for pancreatic duct stones. Other management techniques include pancreatoscopy-guided lithotripsy, endoscopic retrograde cholangiopancreatography with stone extraction, and stenting. [38] If these pain management techniques fail, the final option would be the surgical method. [27]

Surgical Management

Pancreatojejunostomy with or without partial resection of the pancreas is a surgical option. Many studies have revealed that early surgical intervention improves quality of life and preserves pancreatic function (exocrine/endocrine). In addition, it is better for the patient to undergo surgery within three years of symptoms. [20]

Patients with pancreatic head inflammatory masses may experience pain, gastric outflow obstruction, and biliary obstruction. These patients typically benefit from pancreaticoduodenectomy with reconstruction, duodenum-preserving pancreatic head resection, or partial resection of the pancreatic head with pancreaticojejunostomy (Frey's operation). Patients with a dilated pancreatic duct (> 6 mm) without an inflammatory mass may benefit from drainage procedures, such as side-to-side pancreaticojejunostomy (Puestow procedure). Long-term studies have shown that this procedure relieves pain in 60%–98% of patients with minimal mortality. Some patients may develop small pancreatic ducts (<3 mm) due to parenchymal inflammation and fibrosis, and surgical intervention may relieve the symptoms and improve pancreatic function. Total pancreatectomy with or without autologous islet cell transplantation may benefit some patients with endocrine insufficiency. [20]

Management of Exocrine Insufficiency

Pancreatic exocrine insufficiency is a central problem in patients with CP. Identifying nutritional impairment requires anthropometric parameters, biochemical nutritional markers, and imaging. Fat malabsorption and steatorrhea occur when the lipase level reaches less than 10% of the average level. Oral supplementation of lipase enzyme (usually 50000 U/ meal) is available and reduces the fat absorption problem. [22] Pancreatic enzyme supplementation has proven beneficial in improving symptoms, quality of life, and nutritional status. [27]

Management of Endocrine Insufficiency

Exocrine pancreatic insufficiency causes type 3c diabetes mellitus (DM) due to the complete loss of islet cells. Patients with this condition have a high chance of developing hypoglycemia, and in addition to diabetic medication, they require pancreatic enzyme replacement treatment (PERT). [9]

Management of Pancreatic Pseudocyst

Patients with pancreatic pseudocysts are managed by endoscopic cyst-gastrostomy or image-guided percutaneous drainage. Surgical drainage is also needed in some patients, such as those with infected or necrotic peripancreatic collections. [27]

Conclusion

Although a method that definitively diagnoses early-stage CP has not been established, identifying this clinical-stage is critical during CP progression. We believe the findings presented in the current literature review will aid in the understanding and diagnosis of early-stage CP. In addition, early intervention has been shown to improve patient quality of life and slow or prevent further pancreatic damage. Therefore, in the future, CP patients can receive the appropriate, timely treatment to alleviate symptoms and enhance their quality of life overall.

References

1. Mayerle J, Hoffmeister A, Werner J, Witt H, Lerch MM, Mössner J: Chronic pancreatitis—definition, aetiology, investigation and treatment. *Deutsches Ärzteblatt International*. 2013, 110:387-93.
2. Weiss FU, Laemmerhirt F, Lerch MM: Aetiology and risk factors of acute and chronic pancreatitis. *Visceral Medicine*. 2019, 35:73-81.
3. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R.: Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. *Best Practice & Research Clinical Gastroenterology*. 2010, 24:349-58.
4. Jupp J, Fine D, Johnson CD: The epidemiology and socioeconomic impact of chronic pancreatitis. *Best pract Res Clin Gastroenterol*. 2010, 24:219-31.

5. Lévy P, Domínguez-Muñoz E, Imrie C, Löhr M, Maisonneuve P: Epidemiology of chronic pancreatitis: burden of the disease and consequences. *United European Gastroenterol Journal*. 2014, 2:345-54.10.1177/2050640614548208.
6. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST: Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *American Journal of Gastroenterology*. 2011, 106:2209.
7. Yadav D, Timmons L, Benson JT, Dierkhising RA, Chari ST: Incidence, prevalence, and survival of chronic pancreatitis: a population-based study. *American Journal of Gastroenterology*. 2011, 106:2192-199.10.1038/ajg.2011.328.
8. Kleeff, J, Whitcomb, DC, Shimosegawa, T, et al.: Chronic pancreatitis. *Nat Rev Dis Primers*. 2017, 3:17060.
9. Pham A, Forsmark C: Chronic pancreatitis: review and update of aetiology, risk factors, and management [version 1; peer review: 2 approved] *F1000Research*. 2018, 7:17.
10. Wilcox CM, Sandhu BS, Singh V, et al.: Racial differences in the clinical profile, causes, and outcome of chronic pancreatitis. *American Journal of Gastroenterology*. 2016, 111: 1488-496.
11. Andriulli A, Botteri E, Almasio PL, Vantini I, Uomo G, Maisonneuve P: Smoking as a cofactor for causation of chronic pancreatitis: A meta-analysis. *Pancreas*. 2010, 39:1205–210
12. Lankisch PG, Breuer N, Bruns A, Weber-Dany B, Lowenfels AB, Maisonneuve P: Natural history of acute pancreatitis - A long-term population-based study. *The American Journal of Gastroenterology*. 2009, 104:2797-805.
13. Singh VK, Yadav D, Garg PK: Diagnosis and management of chronic pancreatitis: A Review. *JAMA*. 2019, 322:2422-434.
14. Ludvigsson JF, Montgomery SM, Ekblom A: Risk of pancreatitis in 14,000 individuals with celiac disease. *Clinical Gastroenterology and Hepatology*. 2007, 5:1347-353.
15. Pitchumoni CS, Chari, Suresh: Ulcerative colitis and autoimmune pancreatitis. *Journal of Clinical Gastroenterology*. 2013, 47:469.
16. Thiruvengadam M, Harry RA, James F, Priya AJ: Chronic pancreatitis, a comprehensive review and update. Part I: epidemiology, aetiology, risk factors, genetics, pathophysiology, and clinical features. *Disease-a-month*. 2014, 60:530-50.
17. Barman KK, Premalatha G, Mohan V: Tropical chronic pancreatitis. *Postgraduate Medical Journal*. 2003, 79:606-15.
18. Clemens DL, Schneider KJ, Arkfeld CK, Grode JR, Wells MA, Singh S: Alcoholic pancreatitis: New insights into the pathogenesis and treatment. *World Journal of Gastrointestinal Pathophysiology*. 2016, 7:48-58.
19. Ammann RW, Heitz PU, Klöppel G: Course of alcoholic chronic pancreatitis: A prospective clinicomorphological long-term study. *Gastroenterology*. 1996, 111:224-31.
20. Frola C, Somasundaram M, Hariharan D. et al.: The role of surgery in chronic pancreatitis. *European Surgery*. 2019, 51:114-20.
21. 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.
22. Heiko W, Minoti VA, Volker K, Jeremy SW: Chronic pancreatitis: challenges and advances in pathogenesis, genetics, diagnosis, and therapy. Review in basic and clinical gastroenterology. 2007, 132:1557-73.
23. Dutta AK, Chacko A: Head mass in chronic pancreatitis: Inflammatory or malignant. *World Journal of Gastrointestinal Endoscopy*. 2015, 7:258-64.
24. Daniel W, Elham A, Stephen P: Chronic pancreatitis: Current status and challenges for prevention and treatment. *Diagnotic diseases and sciences*. 2017, 62:1701-12.
25. Gupta V, Toskes PP: Diagnosis and management of chronic pancreatitis. *Postgraduate Medical Journal*. 2005, 81:491-97.

26. Chowdhury RS, Forsmark CE: Pancreatic function testing. *Alimentary Pharmacology & Therapeutics*. 2003, 17:733-50.
27. Kwon CI, Cho JH, Choi SH, Ko KH, Tirkes T, Gromski MA, Lehman GA: Recent advances in the diagnosis and management of chronic pancreatitis. *Korean Journal of Internal Medicine*. 2019, 34:242-60.
28. Jorg K, David CW, Tooru S, et al.: Chronic pancreatitis. *Nature Reviews. Disease Primers*. 2017, 7:17060.
29. André KHC, Robert HH, Brenda JH, David BA, David NL, Joseph R: Diagnostic performance of EUS for chronic pancreatitis: a comparison with histopathology. *Gastrointestinal Endoscopy*. 2007, 65:808-14.
30. Alpern MB, Sandler MA, Kellman GM, Madrazo BL: Chronic pancreatitis: ultrasonic features. *Radiology*. 1985, 155:215-9.
31. Luetmer PH, Stephens DH, Ward EM: Chronic pancreatitis: reassessment with current CT. *Radiology*. 1989, 171:353-57.
32. Temel T, Evan LF, Stuart S, Chen L, Jordan S, Fatih A, Kumaresan S: Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. *Abdominal Radiology (New York)*. 2017, 42:544-51.
33. Adler DG, Lichtenstein D, Baron TH, et al.: The role of endoscopy in patients with chronic pancreatitis. *Gastrointestinal Endoscopy*. 2006, 63:933-37.
34. Tyler S, Mansour AP: Update on endoscopic pancreatic function testing. *World Journal of Gastroenterology*. 2011, 17:3957-61.
35. Anderson MA, Akshintala V, Albers KM, et al.: Mechanism, assessment and management of pain in chronic pancreatitis: Recommendations of a multidisciplinary study group. *Pancreatology*. 2016, 16:83-94.
36. Pietro F, Giancarlo C: Is there a role for celiac plexus block for chronic pancreatitis. *Endoscopy International Open*. 2015, 3:E60-E2.
37. Karanjia ND, Reber HA: The cause and management of the pain of chronic pancreatitis. *Gastroenterology Clinics of North America*. 1990, 19:895-04.
38. Sharzei K: Management of pancreatic duct stones. *Current Gastroenterology reports*. 2019, 21:63.