Chronic Pancreatitis: A Review


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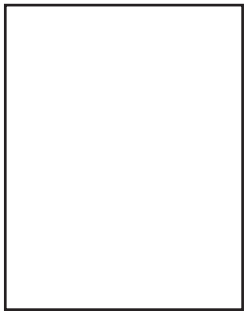
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Chronic pancreatitis (CP) is a progressive, irreversible disease that manifests as morphological changes of the pancreatic parenchyma, such as fibrosis and calcifications, and functional abnormalities including exocrine and endocrine insufficiency. However, the most common presentation of CP is abdominal pain, which has a severe impact on the quality of life of patients and is costly to the healthcare system. CP can be caused by toxic substances such as alcohol or tobacco, genetic mutations, and/or recurrent attacks of acute pancreatitis. The incidence of CP is rising and there is no curative treatment outside of total pancreatectomy. The condition can be difficult to diagnose and treat due to the varying presentations in a patient's history of acute pancreatitis, pain levels, or degree of exocrine or endocrine insufficiency. This review article focuses on the clinic presentation, etiology, diagnosis, and management of CP.

INTRODUCTION

Chronic pancreatitis (CP) is a syndrome that results from acute and chronic inflammation and injury of the pancreas leading to fibrosis, atrophy, and ultimately functional abnormalities of the pancreas including exocrine and endocrine insufficiency.[1] Exocrine pancreatic insufficiency (EPI) results in steatorrhea, fat-soluble vitamin deficiency (Vitamins A, D, E and K) and its sequelae, such as malnutrition, weight loss, osteoporosis and osteopenia. Endocrine insufficiency of the pancreas manifests as type 3c diabetes mellitus (DM).[2] The most common symptom of CP is abdominal pain that is usually constant, severe, and epigastric with radiation to the back, but patterns of pain can vary.[3] The majority of CP cases are due to alcohol or tobacco use, genetic polymorphisms, or recurrent attacks of acute pancreatitis, and the incidence of the disease is on the rise.[2,4]

CLINICAL PRESENTATION

The course of CP can be divided into three phases. The early phase occurs in the first five years of the disease, and is dominated by acute pancreatitis, pain, hospitalizations and surgical treatments. The middle phase occurs from five to ten years, and is when morphological changes

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of the pancreas manifest such as strictures of the main biliary duct, pseudocysts and calcifications. The late phase occurs onwards of ten years and is approximately when DM and EPI occur. The course and presentation vary widely among patients, and phases may overlap.[5]

Abdominal pain is the most common symptom of CP and can be found in up to 80% of patients.[3] Pain is usually described as severe, constant, and located in the epigastric region with radiation to the back, but patterns of pain can differ.[3] Pain from CP severely impacts patient quality of life, and over 90% of patients have been hospitalized at least once for pain associated with CP.[4] Psychological comorbidities due to pain, such as anxiety and depression, are common in these patients.[6] Pain also carries a major financial weight on the health care system, costing over $600 million dollars annually.[4,7] The reasons for chronic abdominal pain in CP are multifaceted and poorly understood. The cause of pain can be due to inflammation of the pancreas, or pancreatic duct obstruction by stones, and/or strictures. However, changes in the peripheral and central nervous system such as peripheral sensitization and pancreatic neuropathy may also lead to a maladaptive state of neuropathic pain. Acute flares of pain such as in recurrent pancreatitis may increase sensitization of the nervous system, leading to a self-perpetuating cycle of pain.[2,8,9]

Another cause of abdominal pain in patients with CP could be pancreatic pseudocysts, which occur in 20% to 40% of patients with CP.[10] Pseudocysts more commonly cause abdominal pain, early satiety, nausea/vomiting, jaundice, and weight loss, but can lead to more serious problems such as rupture, infection, bleeding, and obstruction.[10,11]

EPI refers to inadequate pancreatic secretion or deficient activity of pancreatic digestive enzymes most importantly pancreatic lipase, which has a major role in fat digestion.[12,13] EPI can be due to insufficient production of pancreatic enzymes, anatomic abnormalities obstructing the excretion of enzymes via the pancreatic duct, or desynchronization of enzyme delivery to food in the intestine.[14] This results in the reduced absorption of essential fatty acids, fat-soluble vitamins A, D, E and K, calcium, magnesium, zinc, thiamine and folic acid leading to malnutrition, weight loss, steatorrhea, bloating and cramping.[15,16] The prevalence of EPI ranges from 40% to 75% and is greatest in those with CP due to alcohol and/or tobacco use.[2] Levels of Vitamin D have a significant role in bone homeostasis, with lower levels being a risk factor for osteopenia and osteoporosis.[17] The prevalence rate for osteoporosis and osteopenia in CP patients is 23% and 40% respectively.[18] Although, patients with CP may also have other risk factors for osteopenia or osteoporosis, such as low body mass index or smoking use.[18]

Endocrine insufficiency of the pancreas manifests as type 3c DM, a type of DM that results from pancreatic disease.[2,19] The risk of new-onset DM after CP is 30%, and the risk of insulin-dependent DM is 15%.[20] Risk factors for the development of type 3c DM in CP include smoking, duration of disease, history of pancreatic surgery, and the presence of calcifications on imaging of the pancreas.[19] Patients with CP are at increased risk of large swings in blood glucose due to nutrient malabsorption, impaired glucagon secretion, and chronic pain leading to poor oral intake.[19,21]

Another complication of CP is pancreatic cancer. Over a 20 year period, it has been found that pancreatic cancer develops in about 5% or less of patients with CP, however, the risk is increased in those with genetic polymorphisms.[22-24] The risk of malignancy in CP appears to even decrease over time, however this may be due to pancreatic cancer being misclassified as CP in the first few years of symptoms due to overlapping clinical symptoms or radiological evidence.[25]

ETIOLOGY

Alcohol use is the most common etiology of CP being found in 42% to 77% of patients, and the odds of CP increase 3.1 times in patients who consumed at least five alcoholic beverages per day.[26, 27] Idiopathic CP is the second most common cause, which affects 28% to 80% of patients.[26] In some cases, genetic variants have been observed.[26] However, multiple studies confirm that about 60% of CP cases evolved from an acute pancreatitis or recurrent acute pancreatitis (RAP).[2]

The TIGAR-O system, an acronym for Toxic/Metabolic, Idiopathic, Genetic, Autoimmune,

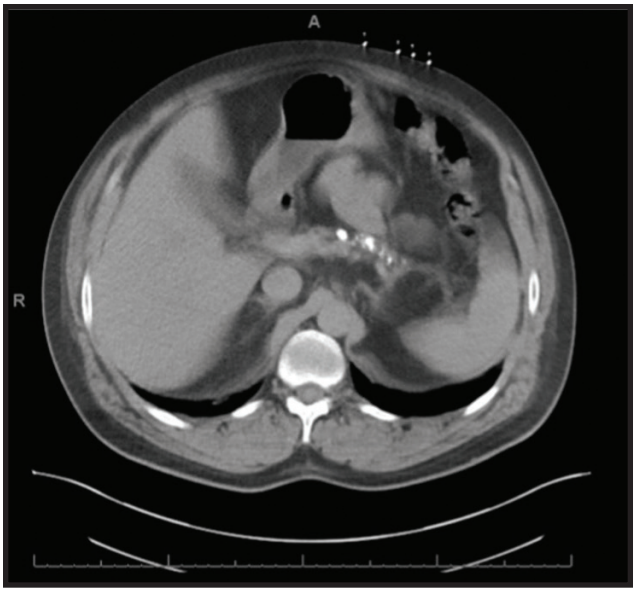

Figure 1. Presence of Pancreatic Calcifications on CT

Recurrent acute or severe pancreatitis, and Obstructive risk factors, is used to categorize factors that confer risk or contribute to the etiology of CP.[2,28] Please see Table 1.[28,29]

DIAGNOSIS

The diagnosis of CP remains a clinical challenge, especially in the early stages, as the classic signs and symptoms of CP such as morphological changes of the pancreas or functional insufficiencies, are more often seen in its advanced stages and can require years to manifest.[26] Nonetheless, CP must be suspected when patients have a history of chronic abdominal pain, relapsing acute pancreatitis, symptoms of EPI (steatorrhea, or weight loss), or history of alcohol abuse.[29]

Computed tomography (CT) or Magnetic Resonance Cholangiopancreatography (MRCP) are first-line in the diagnosis.[2] When using CT, three-phase protocols are used including an unenhanced phase, a pancreatic parenchymal phase and portal venous phase scan.[30] The presence of pancreatic atrophy, calcifications, or marked pancreatic ductal changes on CT establishes the diagnosis of CP.[26] Pancreatic calcifications on CT can be seen in Figure 1. On MRCP, reduced T1 signal intensity can be seen, and is a sign of fibrotic replacement of the parenchyma, as well as ductal changes including main pancreatic duct dilation or irregularity, dilation of the side branches, and the presence of at least one stricture.[26,30]

If the diagnosis is still in question after cross-sectional imaging, endoscopic ultrasonography (EUS) can be used, but sparingly due to the procedure's invasiveness and lack of specificity due to similar changes in the pancreas seen in older individuals, those with a history of alcohol abuse or smoking, and diabetics.[2,26] Conventional criteria (Minimal Standard Terminology) for diagnosing CP based on EUS include: Parenchymal abnormalities such as hyperechoic foci, hyperechoic strands, lobular contour or cysts, and ductal abnormalities such as main duct dilation, duct irregularity, hyperechoic margins, visible side branches or stones.[31,32] However, the presence of five or more of the above criteria is frequently used to establish the diagnosis of CP.[32] Of note, non-endoscopic ultrasound, often used in the assessment of patients with abdominal pain, is insensitive and can only detect advanced disease.[33]

Secretin-enhanced magnetic resonance cholangiopancreatography (s-MRCP) is costly, however is used in patients with a high clinical suspicion of CP without a confirmed diagnosis after the above imaging techniques.[2] Secretin stimulates pancreatic fluid secretion, improves visualization of the ductal side branches, and evaluates duodenal filling.[26]

If all tests are inconclusive, endoscopic retrograde cholangiopancreatography (ERCP) may be considered to diagnosis CP, but has the possibility of high risk complications such as pancreatitis, hemorrhage, or infection, and it is not recommended for diagnosis unless all other imaging has been inconclusive.[34]

Laboratory tests for EPI can be used complementarily to imaging, however the sensitivity is low because large derangements in lab values occur only with significant loss (usually over ninety percent) of pancreatic function.[2] For the primary care physician, some laboratory tests are more beneficial than others. For example, tests including fecal elastase-1 are widely available, non-invasive, and require only a small stool sample.[16] Very low levels of fecal elastase-1 are associated with CP, however the test is less suitable for excluding mild to moderate EPI and more invasive tests such as a secretin or cholecystokinin (CCK)

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stimulation tests are needed. It should be mentioned that results of the fecal elastase-1 test may be obscured due to do excessive dilution in those with large volume diarrhea.[16,35] Tests such as CCK or secretin stimulation tests are not widely available and require an invasive procedure to collect pancreatic fluid as it enters the duodenum.[16] Of note, lipase is often measured in acute pancreatitis, however is not useful in CP.[26]

To assess for endocrine insufficiency and the diagnosis of Type 3c DM**,** biannual fasting glucose and glycated hemoglobin should be obtained.[26] The major criteria for the diagnosis of Type 3c DM are EPI, absence of antibodies associated with type 1 DM, and pathological pancreatic imaging. Minor criteria include absent pancreatic polypeptide secretion, impaired incretin secretion, no excessive insulin resistance, impaired β cell function, and low serum levels of fat-soluble vitamins.[36]

Finally, genetic testing is recommended in younger patients or those with a family history of pancreatitis or a pancreatitis-associated disorder, and patients with an unclear etiology.[2]

MANAGEMENT

Management of CP involves a multi-disciplinary approach between the patient, primary care physician, gastroenterologist, radiologist, anesthesiologist, nutritionist and many other healthcare professionals.

Alcohol cessation and tobacco smoking cessation are cornerstones of treatment, and continued alcohol and smoking use is associated with further disease progression.[2,26,37] Thus, effective intervention is necessary with emphasis on patient education.

Pancreatic enzyme replacement therapy (PERT) for EPI includes adding 30–40,000 IU of lipase starting with every meal and 15–20,000 IU with snacks.[12,13,38] 30,000 IU with each meal should alleviate steatorrhea.[12-14] Since steatorrhea only develops in advanced disease, this dose reflects only about 10% of healthy pancreatic secretion of lipase. Patients should take half of the total dose with the first bite of the meal and the other half during or at the end of the meal.[12] There has been some demonstrated benefit to the addition of a proton pump inhibitor or H2 antagonist to prevent degradation of supplemented lipase.[16] PERT should not be used to control pain, but rather improve symptoms of EPI such as discomfort, abdominal cramping, or flatulence. It is appropriate to advise small, frequent meals without restriction of fat, however a low-fiber diet is recommended as dietary fiber can prevent the action of pancreatic enzymes.[2,16,26] Periodic evaluation of fat-soluble vitamin deficiencies and osteoporosis is warranted, and supplementation of vitamins when indicated is recommended.[2,16,18,35]

Metformin is first line therapy for Type 3c DM and is continued if insulin treatment is added for better glycemic control. If insulin is necessary, general insulin dosing for type 2 DM should be used. It is important to know that insulin and insulin secretagogue treatment may increase the risk of pancreatic malignancy, whereas metformin therapy may reduce it.[20]

The management of abdominal pain obeys a stepwise approach based on severity. First line agents such as acetaminophen and nonsteroidal anti-inflammatory drugs are used primarily, escalating to nonopioid analgesics, then to weak opioids, and lastly strong opioids depending on the severity of pain.[26] It is important to control chronic pain and monitor opioid use as both can decrease appetite and oral intake, furthering malnutrition and weight loss.[16] The celiac plexus blockade is a combination of local anesthetic and steroid that can be executed through endoscopy, interventional radiology, or surgery. A single blockade can alleviate pain for 3–6 months and reduce the need for oral analgesia.[2] Given the oxidative nature of substances such as alcohol, antioxidants have been used to alleviate pain in combination with other modes of pain treatment. These include a combination of at least selenium, ascorbic acid, β-carotene, and methionine.[2] Pregabalin can diminish transmission of pain through nerves, and in combination with antioxidants, reduces the need for non-opioid analgesics and the number of hospital admissions in CP.[39]

Table 1. TIGAR-O System

Toxic-Metabolic	Alcohol Tobacco Chronic renal failure Hypercalcemia Hyperlipidemia Medications - angiotensin-converting enzyme inhibitors, statins, didanosine, azathioprine, steroids, lamivudine, hydrochlorothiazide, valproic acid, oral contraceptives, and interferon Toxins
Idiopathic	Early and late onset Tropical pancreatitis
Genetic	Autosomal dominant – certain cationic trypsinogen mutations Autosomal recessive – CFTR, SPINK1, certain cationic trypsinogen mutations
Autoimmune	Syndromic autoimmune CP - Inflammatory Bowel Disease, Sjogren syndrome, Primary biliary cirrhosis Isolated autoimmune chronic pancreatitis
Recurrent and severe acute pancreatitis	Post-irradiation Post-necrotic Recurrent acute pancreatitis Vascular diseases/ischemia
Obstructive	Duct obstruction (pancreatic or ampullary tumors) Post-traumatic duct fibrosis Pancreas divisum

There is little evidence suggesting benefit of screening examination for pancreatic malignancy in all patients with CP, except in forms of CP due to hereditary pancreatitis.[26] When necessary, screening is performed using EUS or MRCP, with some studies finding EUS to be superior.[40] Screening for malignancy is not often performed because of its invasive and costly nature, difficulty due to the structural changes of CP, and the inability to alter treatment significantly or improve survival even if malignancy is found at an early stage.[2,22,26] When indicated, screening for pancreatic malignancy in CP can be performed starting at age 40, but there is no consensus on timing of interval screening.[29] However, a triphasic CT can be considered in patients with CP who present with jaundice, weight-loss and/or increase in pain frequency.[2,26,29,41]

The M-ANNHEIM Surgery Score measures disease activity through a grading scale of one to four points using evaluation of patient's pain, imaging findings, complications, need for surgical intervention, and status of exocrine and endocrine insufficiency. The score defines severity as minor, increased, advanced, marked or exacerbated, and a score at or above 9 establishes the risk for pancreatic surgery.[42]

For patients with obstructive symptoms due to stones, strictures or pseudocysts, drainage can be achieved through ERCP with sphincterotomy, stricture dilation, and/or duct stenting.[34] Studies have shown that endoscopic therapy for treatment of pseudocysts has similar efficacy to surgical drainage and was associated with improved quality of life and decreased healthcare utilization.[11] The most common indications for surgery include intractable pain after multiple treatment failures

including endoscopic intervention, or suspicion of neoplasm.[2,43] The Frey surgical procedure involves coring out the head of the pancreas and a longitudinal pancreaticojejunostomy, and resulted in more improvement of pain and quality of life when compared to other surgeries.[44,45] In those with refractory pain, total pancreatectomy with islet autotransplantation can be discussed.[3]

CONCLUSION

The diagnosis and treatment of CP involves an organized, multi-disciplinary approach. CP is a complex condition with varying manifestations that can be severely distressing to patients resulting in lower levels of quality of life and even disability. Current management involves alcohol and tobacco cessation, multimodal control of pain, replacement therapy for EPI, assessing the sequelae of malnutrition, and screening for endocrine dysfunction such as type 3c DM. ■

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