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Review Article

Chronic Pancreatitis: Current Concepts

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Abstract

Chronic pancreatitis (CP) is an irreversible inflammatory process of the pancreas resulting in long-term severe abdominal pain and pancreatic exocrine and endocrine insufficiency. There are multiple causes of chronic pancreatitis, with alcohol being the most frequent. Computed tomography with contrast is the radiographic test of choice for diagnosis; frequent findings are calcifications. Treatment is based on changes in lifestyle followed by treatment with analgesics and pancreatic enzyme supplements. Endoscopic treatment is indicated for decompression of the pancreatic duct or treatment of complications of chronic pancreatitis. Several surgical techniques have been described whose main objective is to decompress the main pancreatic duct or to resect the inflammatory process that predominates in the head of the pancreas. Lateral pancreaticojejunostomy is the most commonly performed surgery in patients with chronic pancreatitis.

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Incidence

Chronic Pancreatitis (CP) is an important cause of disabling pain that affects the quality of life of the patients [1]. Globally is the most frequent pancreatic pathology with a mortality of 0.09 deaths (95% CI 0.02-0.47) per 100 000 person-years for chronic pancreatitis [2]. It is estimated an overall incidence of 2 to 200 cases per 100,000 inhabitants per year and prevalence of 13 to 52 per 100,000 population [3]. In some regions there is a higher incidence as in India with an incidence of 114 to 200 per 100,000 inhabitants. The mean age of presentation is at 60 years of age [4,5].

Definition

CP has been defined as a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and permanent loss of function [6]. Progressively the endocrine and exocrine function is lost, generating chronic diarrhea and type 3c diabetes [7].

It is known that there is a genetic predisposition and multiple environmental factors.

The main symptom is pain that occurs in up to 90% of cases. It is also known that there is an increased risk of pancreatic cancer and inflammatory bowel disease [8-10]. CP occurs more frequently in men than in women [11].

Causes of Chronic Pancreatitis

The main cause of CP is alcohol [12]. Pathogenesis can be studied using the MANNHEIM classification (multiple (M) risk factor classification; alcohol consumption (A), nicotine consumption (N), nutritional factors (N), hereditary factors (H), efferent pancreatic duct factors (E), immunological factors (I), and various rare miscellaneous and metabolic (M) factors). This classification helps us to determine the main risk factors for CP and perform an earlier treatment [13,14].

Another frequently used classification is TIGAR-O (Toxic-metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis, Obstructive) which is also based on the risk factors of CP [15].

Pathophysiology

To date there is still controversy about the mechanisms that contribute to the generation of pain in CP, it is known that pancreatic duct hypertension, pancreatic inflammation and peripancreatic infiltration by immune cells are the main mechanisms that could generate pain [16,17]. The most accepted theory was described by Whitcomb et al. The SAPE (Sentinel Acute Pancreatitis Event) hypothesis proposes a sentinel event of acute pancreatitis initiating the inflammatory process [18].

Several factors associated with CP have been described, including alcohol consumption (70% of cases), hereditary factors (the most important genetic factors are the mutations in the cationic trypsinogen PRSS1, the Serine Protease Inhibitor Type Kazal 1 (SPINK1) and carboxypeptidase A1, among others), hyperparathyroidism, hypertriglyceridemia, traumatism, some drugs such as valproate, azathioprine, statins, furosemide, interferon, steroids, cimetidine among others and some anatomic congenital abnormalities (pancreas divisum) [19-21].

Clinical Manifestations and Complications of Chronic Pancreatitis

Abdominal pain is the most frequent manifestation and multiple mechanisms of pain have been described [3]; alteration of the nervous conduction, alteration of the peripheral nociception, pancreatic neuropathy, mechanisms of central pain and alteration of the pancreatic duct pressure [22,23].

The pancreatic and peripancreatic inflammatory process generates multiple complications; endocrine insufficiency manifested with hyperglycemia and diabetes; exocrine pancreatic insufficiency manifested with chronic diarrhea; metabolic bone disease caused by sharing the same risk factors as osteopathy such as alcohol consumption, smoking, probable vitamin D insufficiency due to malabsorption [24] and chronic inflammation that favors the imbalance of bone production; increased risk of pancreatic cancer; presence of pseudocysts, duodenal and biliary obstruction, and splenic vein thrombosis [25].

It would seem that there are some risk factors for developing diabetes in patients with CP such as male sex, alcohol abuse despite knowing the diagnosis and some surgical procedures such as distal pancreatectomy [26].

It is recommended to perform an annual glucose tolerance test to identify any deterioration in glucose levels that may be problematic [27].

Diagnostic Evaluation

Diagnosis can be difficult in the early stages of the disease since patients may present typical clinical manifestations but minimal histological changes and normal findings in imaging studies [28] (Table 1).

Computed Tomography (CT) is considered the first approach study to rule out or confirm CP. Pancreatic calcifications are frequently observed in imaging studies such as CT, mainly in patients in whom the etiology is alcohol (20-40%), and has a sensitivity and specificity of 75% to 90% and 85%, respectively [29,30].

Endoscopic Ultrasound (EUS), Endoscopic Retrograde Cholangiopancreatography (ERCP), Magnetic Resonance Image (MRI) and CT all have comparable high diagnostic accuracy in the initial diagnosis of CP and the choice of imaging can be made based on clinical considerations [31].

Magnetic Resonance Cholangiopancreatography (MRCP) is a useful tool to support the diagnosis of CP; the frequent findings are irregular dilatations of the Main Pancreatic Duct (MPD) and irregular dilatations of pancreatic duct branches of variable intensity with scattered distribution throughout the pancreas and has a sensitivity of 85% and specificity of 100% [30,32].

On the other hand, it has been attempted to correlate the number of EUS pancreatic duct and parenchymal abnormalities, presence of calcification, and smoking or alcohol status, finding a good correlation with the diagnosis of pancreatic insufficiency the more alterations are found and presents a sensitivity and specificity of 97% and 60% respectively [30,33].

ERCP findings are also irregular dilatation of the MPD and irregular dilatation of pancreatic duct branches of variable intensity with scattered distribution throughout the entire pancreas [32].

The role of abdominal ultrasound has not been fully defined; it seems that this noninvasive tool has a good diagnostic result correlated with pancreatic insufficiency [34].

The early diagnosis of CP is difficult because of the lack of clinical and imaging manifestations so that recent miRNA serum markers have been studied to try to diagnose CP earlier and seem to have the potential to be applied clinically for early diagnosis of CP. These serum biomarkers studied are Hsa-miR-221 and hsa-miR-130a [35].

Pancreatic Function Tests

Pancreatic function tests are not diagnostic tests; are used to determine if there is functional complication from CP and are not performed routinely.

Some tests have been described such as the determination of fecal elastase-1 for the early detection of exocrine pancreatic insufficiency mainly in patients who have diarrhea and characteristic chronic abdominal pain [36].

Another diagnostic test of exocrine pancreatic insufficiency is 13C-Mixed Triglyceride Breath Test (TGBT) that assesses fat digestion and absorption and has been suggested as an alternative test to fecal elastase-1, however it is more expensive and shows the same results in diagnosis with a sensitivity of 81%, specificity 94%, Positive Predictive Value (PPV) 86% and Negative Predictive Value (NPV) 92% [37].

Secretin stimulation (SPFT) is a test in which secretin with or without Cholecystokinin (CCK) is administered and a sample of duodenum fluid is taken by endoscopy; this test is considered positive if low bicarbonate is found (peak concentration <75 mEq / L). This is the best test to diagnose exocrine pancreatic insufficiency with a sensitivity of the SPFT in diagnosing CP of 82%, specificity of 86%, PPV of 45% and NPV of 97% [38].

Other tests described to assess pancreatic function are fecal fat estimation, high acid steatocrit on spot stool, and low serum trypsinogen.

Pain Treatment

First-line medical options include the administration of pain medication, adjunctive agents and pancreatic enzymes, and abstinence

Table 1: Diagnostic evaluation.

Computed tomography	The most frequent findings are pancreatic calcifications. Sensitivity: 75%-90%, specificity: 85%
Magnetic resonance cholangiopancreatography	The frequent findings are irregular dilatation of the Main Pancreatic Duct (MPD) and irregular dilatation of pancreatic duct branches. Sensitivity: 85%, specificity: 100%
Endoscopic ultrasound	Sensitivity: 97%, specificity: 60%
Endoscopic Retrograde Cholangiopancreatography (ERCP)	Findings: irregular dilatation of the MPD and irregular dilatation of pancreatic duct branches

from alcohol and tobacco [39]. This conservative treatment is the basis of any adequate management of CP [40] (Table 2).

The first proposed step in the pharmacological treatment of pain is acetaminophen, but even the use of opioids has been suggested such as morphine [41].

The treatment of exocrine pancreatic insufficiency has been performed with Pancreatic Enzyme Replacement Therapy (PERT) and seems to improve nutritional serum parameters, improves pain and quality of life of patients although studies are lacking to determine the optimal regimen of treatment [42].

It has been proposed the use of micronutrients with antioxidants to treat CP but there seems to be no effect of intervention on outcome [43].

Some other therapies have been described as acupuncture with short-term pain control but without sufficient evidence yet to be routinely used [44].

Treatment with pancreatic enzymes

Although some individual studies reported a beneficial effect of pancreatic enzyme over placebo in improving pain control, decreasing the incidence of steatorrhoea and decreasing analgesic consumption, the role of pancreatic enzymes for abdominal pain, weight loss, steatorrhoea, analgesic use and quality of life in patients with CP remains equivocal [45]. As an enzyme replacement treatment, the dose of 90,000 units of lipase per capsule with food is suggested [46].

Indication of invasive treatment with endoscopy or surgery

The main indication for invasive treatment is intractable abdominal pain and treatment of complications already mentioned including suspected malignancy [47] (Table 3).

Endoscopic treatment

Pain can be treated by endoscopic treatment with good long-term results; this therapeutic maneuver has been used over 25 years. Some authors suggest that it should be considered as the initial treatment of choice in patients with dilated duct chronic pancreatitis, and continuous pain [48-51] Long-term pain control ranges from 50% to 77% among multiple series [52-55].

Although some randomized studies have been conducted to compare endoscopic versus surgical treatment where a better long-term pain relief was demonstrated with surgery and half of patients undergoing endoscopic treatment required surgical treatment, endoscopic treatment offers good long-term pain control results without the disadvantage of invasiveness [56,57].

Table 2: Conservative management in chronic pancreatitis.

Treatment of the cause	Alcoholism, smoking
Treatment of chronic pain	Analgesia based on WHO pain scale
Treatment of exocrine pancreatic insufficiency	Treatment with pancreatic enzymes
Treatment of endocrine pancreatic insufficiency	Diet, oral antidiabetic, insulin
Adjuvant therapy	Antioxidants

Multiple endoscopic techniques have been described; the Extracorporeal Shockwave Lithotripsy (ESWL) in combination with interventional endoscopy achieves reduction of pain in 45% to 76% of patients, [58-60] sphincterotomy, stone extraction and stent placement [61].

Other indications for endoscopic treatment are some complications of CP such as pancreatic pseudocysts and biliary obstructions [62].

Endoscopic Retrograde Pancreatography (ERP) is effective as a monotherapy and can be used to remove stones from the MPD [63]. Recently it has been used pancreatoscopy plus Electrohydraulic Lithotripsy (EHL) for pancreatic duct stones extraction using Spyglass [64].

There are some good response predictors to endoscopic treatment such as stones less than 10 mm in size located in the head and body of pancreas, when they are less than 3 stones without evidence of multiple stenosis [65]. On the other hand, some types of CP do not benefit from endoscopic treatment and it has been suggested that they should go on to surgery such as distal obstructions, presence of multiple pancreatic calcifications or the presence of inflammatory mass.

Some complications of stent placement within the pancreatic duct are stent fragmentation, which occurs in about 5% of cases [66]. Another complication that may occur is post-ERCP pancreatitis with similar incidence as in patients who do not have CP [67].

Surgical Techniques

Surgical procedures provide long-term pain relief, a good postoperative quality of life [68]. It has been demonstrated to be more effective than endoscopy in patients with pancreatic duct obstruction [69].

Many surgical treatment options have been described with good long-term results [70] ranging from highly invasive procedures such as total pancreatectomy and pancreatoduodenectomy [71] to more conservative procedures such as lateral pancreaticojejunostomy (Puestow procedure) and duodenum preserving pancreatic head resection such as the Frey, Beger, and Hamburg procedures [72-76]. It appears that pancreatic head resection procedures offer the best results with good safety of surgery [77]. Despite the many surgical techniques described, there is still no consensus on which surgery to perform [78].

Another procedure to treat CP is total pancreatectomy with islet autotransplantation; this procedure seeks to prevent the use of insulin so its main indication is when patients have not yet developed endocrine pancreatic insufficiency. The technique includes the preservation of the gland with culture of pancreatic cells and the infusion of these into the portal vein. It takes 300,000 to 400,000 islets

Table 3: Indications for surgical treatment.

Failure in conservative or endoscopic treatment
Intractable pain
Local symptomatic complications
Suspicion of malignancy

to successfully graft. The amount of islets that are usually obtained depends on the degree of disease present. Unfortunately, 25% to 30% of patients with CP are diabetic and therefore are not considered candidates for this procedure [79]. And like most of the previously mentioned procedures, it is already done by minimally invasive surgery with laparoscopy [80].

Some authors have suggested performing early surgery to prevent endocrine and exocrine failure [81,82] although evidence is lacking to define this behavior [83]. It should be borne in mind that although the pain decreases with surgery due to the reduction of ductal hypertension, the cellular damage continues and that is

why analgesic pain treatment is still required with enzymatic replacement, in addition to the discharge these patients require a nutritional plan and close postoperative monitoring [84,85].

Conclusions

CP is an irreversible inflammatory process of the pancreas. Diagnosis and therapeutic approach is complex because of the many tools we currently have and multiple treatment options. It is expected that the better understanding of the pathophysiology will improve the prognosis of these patients.

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