A Clinical Approach to Treating Pain in Chronic Pancreatitis

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ABSTRACT
• Objective: To discuss the clinical approach to treating pain in chronic pancreatitis (CP).
• Methods: Review of the literature.
• Results: CP is an inflammatory condition characterized by irreversible and progressive destruction of the pancreatic parenchyma and pancreatic ducts, which leads to debilitating symptoms of severe abdominal pain. The etiology of pain in pancreatitis is multifactorial. Currently, as none of the therapies can counteract the inflammatory process of CP, management has included analgesics for pain management and enzyme replacement for exocrine insufficiency, with endoscopic and surgical techniques reserved for treating the complications of CP, such as ductal anatomic abnormalities. Diagnostic techniques are now underway to improve early detection of CP for both optimizing treatments and for prevention of complications, which include malabsorption, ductal obstruction, and pancreatic cancer. Noninvasive methods for pain management such as nonenteric-coated pancreatic enzymes, prokinetics in cases of concomitant gastric dysmotility due to CP, pregabalin, antioxidants, nerve blocks, and endoscopic interventions have yielded better results than were found in the past decade.
• Conclusion: As the pathophysiology of CP is fully delineated, the resultant pancreatic exocrine and endocrine insufficiencies associated with the disease can be better treated.

Chronic pancreatitis (CP) is an inflammatory disorder that leads to permanent parenchymal damage and replacement with fibrous tissue. Its most characteristic symptom is abdominal pain, usually starting as acute, intermittent attacks and then progressing to constant, debilitating pain [1]. Abdominal pain is common in CP, seen in 85% of patients, and ranges from mild to unbearable. Pain may lead to unemployment due to disability, excess use of narcotics, multiple medical and surgical interventions, and frequent hospitalizations [2]. Although alcohol has been considered the number one cause of CP, with previous studies generally attributing it as the cause in 51% to 70% of CP patients in the United States, more recent data have shown a decrease in CP due to alcohol consumption, suggesting a higher prevalence of other mechanisms [3].

Idiopathic causes are the second most common cause of CP, followed by pancreatic intraductal obstruction, which can have multiple etiologies, including cystic fibrosis, stones, trauma, tumors, or anatomic variants like pancreatic divisum. Hyperlipidemia has also been shown to cause CP. Another important cause of CP is hereditary pancreatitis which although uncommon may account for the cases of CP previously labeled as idiopathic CP [4].

Type 1 autoimmune pancreatitis, which affects multiple organ systems, is characterized by sistemically high levels of serum IgG4 antibodies [5]. In contrast, type 2 autoimmune pancreatitis is confined to the pancreas and does not increase IgG4 levels in serum. It is important to distinguish autoimmune pancreatitis as a cause of CP because of its potential response to steroids [6].

PATHOPHYSIOLOGY
Multiple theories have been developed to explain the pathophysiology of CP, all of which to some degree include excessive inflammation. Other theories have focused on the importance of free radical stress in the development of CP. Nutritional deficiencies of antioxidants also contribute to this problem [7]. Mutational abnormalities in specific genes can lead to susceptibility for development of CP [8].

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Another potential cause of abdominal pain in the face of CP includes gastroparesis. Alcohol’s effects on gut motility have also been well delineated, with delay in gastric emptying seen with acute ingestion of alcohol [9].

Multiple factors have been discussed as initiators of pain in CP. These include but are not limited to active inflammation, neurogenic inflammation, central nerve sensitization, ductal hypertension, and tissue ischemia. In addition, complications of CP, including pseudocysts, cancer, and inflammatory masses, are all potential causes of pain [10].

PRESENTATION

Depending on the etiology of CP, the age of presentation varies. Alcoholic CP usually develops in the fourth to fifth decade of life, while idiopathic CP usually develops anywhere between the second and sixth decade of life [11]. The pain produced usually begins in the epigastrium but radiates to the back and also to the left infrascapular region, occurring either in acute flares or remaining constant. This pain can become severe enough to cause nausea, vomiting, and substantial weight loss through decreased caloric intake. In advanced cases of CP, exocrine function is diminished, which leads to malabsorption and steatorrhea. If damage progresses, endocrine dysfunction will also occur, leading to diabetes.

Clinicians must rule out pancreatic cancer in patients suspected of having CP, as pancreatic cancer can also present as epigastric pain with weight loss. Moreover, patients with CP are at an increased risk for pancreatic cancer, making ruling out this condition essential [12]. Complications of CP, such as pseudocysts or duct obstruction, should also be ruled out.

DIAGNOSIS

Laboratory findings may not be useful in testing for CP early in the course of the disease. However, in patients with advanced disease and steatorrhea or new-onset diabetes who have a history of recurrent pancreatitis, laboratory testing for fecal elastase and serum trypsin are usually sufficient to make the diagnosis. Both of these would be low in the setting of CP. Serum IgG4 levels can be useful if type 1 autoimmune pancreatitis is suspected. Other helpful laboratory findings might include hypercalcemia or liver function abnormalities in patients with alcoholic hepatitis or even cirrhosis. Amylase and lipase are usually not elevated in CP and therefore are not useful for the diagnosis.

To date, the gold standard for diagnosing CP is by direct hormonal stimulation testing such as the secretin stimulation test (SST), which uses secretin to stimulate the pancreas to release bicarbonate. However, the SST procedure is too complex to be used in most physicians’ offices and is currently performed only in a few medical centers in the country [13,14]. Alternatives to the traditional secretin stimulation testing described above have been proposed, such as endoscopic secretin stimulation testing; however, these tests are only predictors of CP in late stages of pancreatic dysfunction [15].

Radiographic studies can also be very helpful for diagnosing CP; however, the limitations to these tests are the exposure to radiation and insensitivity to mild disease. A recent report calls for guidelines to reduce the rising radiation dose exposure by limiting CT scans [16]. CT can provide evidence of pseudocysts, pancreatic atrophy, or dilated ducts. An abdominal plain film will show pancreatic calculi in about one-third of patients with CP [17]. In addition, magnetic resonance cholangiopancreatography (MRCP) has become a popular modality for diagnosing CP but is somewhat restricted as it lacks useful views of the side-branch from the pancreatic duct. Secretin administration has been used to help stimulate the pancreatic ducts before MRCP, improving the viewing of pancreatic ducts [18].

Endoscopic retrograde cholangiopancreatography (ERCP) has become less favorable for diagnostic use in CP due to its associated risk of pancreatitis. In contrast, endoscopic ultrasound (EUS) has become a better modality for diagnosing CP, although more studies still need to assess its usefulness [19].

TREATMENT

The focus of treatment in CP is to control pain, handle acute exacerbations, monitor for complications, and treat metabolic conditions like diabetes and or steatorrhea. The importance of alcohol and smoking cessation should be addressed immediately. In general, the approach to treating CP should be multidimensional thereby including specialized psychology, nutrition, and pain management when appropriate.

Analgesia

Analgesics are readily used in patients during acute attacks but should be used routinely if the patient has constant pain. Currently, standard pain management begins with nonsteroidal anti-inflammatory agents (NSAIDs). If this approach is unsuccessful in addressing pain, tramadol may be used instead. The use of narcotic agents
for constant abdominal pain should be discouraged, not only because of the addiction possibility but also because the chronic use of narcotics may lead to serious side effects, such as drug overdose, constipation or obstipation, loss of mental acuity, and general instability of the patient as well as severe gastroparesis. In a subset of patients with severe CP, opioids can be used cautiously to treat the abdominal pain. However, for most patients with CP, alternative medical treatment with pregabalin and other drugs targeting neuropathic pain have been proven to effectively manage the debilitating pain without the risk of GI dysmotility that can be caused by opioid use in this vulnerable patient population.

Important findings show not only evidence for central sensitization due to chronic pain of pancreatitis, with changes in the central nervous system, but also support using gabapentoid medications such as pregabalin for treatment of pain in CP. In addition to the study of Olesen et al [20], 3 other placebo-controlled, randomized trials support the value of pregabalin in treating the pain of CP. In each of these studies, 300 mg given 3 times daily was statistically significant as compared with placebo. The striking benefit is the absence of addiction to pregabalin [21,22].

Nutrition
Dietary changes are recommended in CP. They focus mainly on decreasing fat intake, which theoretically takes pressure off the pancreas and which decreases secretion of cholecystokinin (CCK) associated with delayed gastric emptying [23]. Common vitamin deficiencies such as vitamins A, D, E, K, and B12 should be corrected.

Pancreatic Enzyme Supplementation
In CP, serine proteases are not produced adequately, leading to continued stimulation of pancreatic enzymes by CCK. Using pancreatic enzyme supplements that contain pancrelipase (mixtures of amylase, porcine lipase, and proteases), such as Creon, Zenpep, Ultresa, Viokace, and Pancreaze, seems to benefit most patients with small-duct disease [24]. In contrast, in patients with large-duct disease, which includes alcohol-related pancreatitis, enzyme supplementation is effective only for pain control in about 25% of patients [25]. Moreover, only nonenteric-coated tablets have been shown to foster pain management in patients with both small- and large-duct disease [25,26]. To increase delivery of enzymes into the target site of the duodenum, patients should take pancreatic enzymes paired with a proton-pump inhibitor [24]. For patients with small-duct disease, if no improvement occurs after 1 month of pancreatic enzyme replacement, the physician should order a gastric emptying study to rule out gastroparesis, which may prevent enzymes from reaching their target destination [27]. Supplementation with pancreatic enzymes has also been shown to improve steatorrhea. Enteric-coated formulations (Creon, Zenpep, Ultresa, and Pancreaze) are preferred in these cases, as fat absorption will occur throughout the small intestine. Pancreatic enzyme supplementation may not eliminate pain and steatorrhea for several reasons, including compliance, low dose of enzymes, acidic intestinal pH, and intestinal bacterial overgrowth [28].

Antioxidants
Although oxidative stress occurs in the acinar cells of the pancreas, the situation with antioxidants as therapy in CP remains confusing. Contrary to a previous study by Bhardwaj et al (2009) that evaluated 127 patients with good results, a recent randomized placebo-controlled trial failed to show any beneficial effect on pain or quality of life [29]. Thus, the present evidence is not strong enough to support antioxidants for treating the pain of chronic pancreatitis.

Octreotide
Octreotide is a synthetic analog of somatostatin, which can reduce circulating levels of CCK and thus reduce pancreatic secretion. However, its use in CP patients has to date yielded only mixed results. Generally, patients should be started on the short-acting form (200 mcg 3 times a day subcutaneously) and switched to a long-acting form (approximately 60 mg intramuscularly once monthly) only if the short-term outcome is efficacious in reducing pain. Despite its efficacy in reducing pancreatic secretions, octreotide dosed at levels sufficient to reduce secretions may also inhibit gastric motility [30], which can exacerbate the pain in CP.

Cholecystokinin Antagonists
Two reports have shown promising results using 2 different CCK antagonists. Proglumide, a nonselective CCK receptor antagonist targeting both gut and brain receptors, has been shown to improve pain in CP patients [31]. Proglumide also has delta opioid receptor properties, which may be responsible for such an effect. Also, in a multicenter, randomized, dose-response controlled
trial, loxiglumide, a selective CCK receptor antagonist, relieved pain in CP up to 59% in the group receiving 600 mg of loxiglumide compared with only 36% in the placebo group [32].

**Treatment of Gastrointestinal Dysmotility in Chronic Pancreatitis**

The symptoms of gastroparesis are very similar to those of CP: chronic postprandial abdominal pain, nausea, vomiting, early satiety and severe weight loss if untreated. Although gastroparesis may affect 4% of the population, the true prevalence of gastroparesis is unknown in patients with CP [33]. The coexistence of small-duct CP and motility disturbances should be considered in patients with CP presenting with abdominal pain not responding to therapy. Treatment with NSAIDS, pregabalin, and prokinetics should be considered.

**Endoscopic Treatments**

Advanced endoscopic treatments for CP are generally reserved for patients who fail medical management and conservative measures. Typical procedures include EUS-guided celiac nerve plexus block, dilation of pancreatic duct strictures, stone extractions, pancreatic duct sphincterotomy, and lithotripsy. Selecting which therapy is appropriate is often challenging, as no direct causal relationship exists between the presence of duct dilation, pancreatic duct stones, pancreatic duct strictures, and abdominal pain [34].

Celiac plexus block was a commonly used procedure but has received strong criticism as to whether it should be done in patients other than a very select few due to frequent failure (inability to decrease pain and severe side effects such as impotence and paralysis).

While celiac nerve block and neurolysis seems to produce better results in patients with pancreatic cancer than in those with CP [35], this approach might not be as useful for CP, as most patients will outlive the block’s efficacy.

Endoscopy can also be useful for drainage of the main pancreatic duct to relieve pressure. This procedure does not necessarily correlate with pain relief. Better pain relief results have been demonstrated in patients who undergo endoscopy for stricture or stone after the first attack of pain in CP [36,37]. Using endoscopy for main pancreatic duct drainage effectively reduced pain in about 51% of patients with strictures, stones, or both at 4.9 years of follow-up [38]. For stones, in particular, the traditional approach was to use extracorporeal shock wave lithotripsy (ESWL) to break up stones initially and then follow up with endoscopic duct drainage. However, a trial in patients with calcifications in the main pancreatic duct had similar pain relief measured at 2 years, irrespective of whether they received ESWL alone or ESWL followed by endoscopy [39]. Nevertheless, stone removal by endoscopy is usually preferred if the stones are not too large (< 1 cm) or too numerous, are located in the main duct and close to the head of the pancreas, are not tightly impacted, and are close to the working tip of the endoscope [34]. For strictures, dilation with plastic stenting can be performed, providing pain relief in 70% to 94% of patients in the short-term and 52% to 82% in the long term [40].

Other uses for endoscopy in CP include pseudocyst drainage, which is less invasive than surgery and provides a long-term success rate, and stenting, which is also indicated, as biliary strictures can arise from CP, making stenting a preferred option in the presence of jaundice, common bile duct stones, biliary cirrhosis, consistently asymptomatic alkaline phosphatase, or obstruction caused by pseudocysts [40].

**Surgery**

When medical and endoscopic therapy has failed, or when surgery is a more reasonable option than endoscopy, surgical therapies should be considered. Common procedures that are performed surgically include thoracoscopic bilateral splanchicectomy, decompression and stenting procedures, resection procedures, and autologous islet stem cell transplantation. Results of the thoracoscopic bilateral splanchicectomy procedure have shown positive results. Multiple prospective studies have shown patients experience improvement in pain over the course of a few years [41–43].

The lateral pancreaticojejunostomy procedure involves incision of the pancreatic duct with subsequent alleviation of any strictures or stones. The procedure is usually performed when a ductal dilatation of > 5 mm exists, making the duct easy to identify. This procedure provides short-term pain relief in 80% of patients and long-term pain relief in 50% [24].

Other surgical procedures involving resection have been employed in CP. These procedures include pancreaticoduodenectomy (Whipple procedure), distal pancreatectomy, and duodenum-preserving head resection with a lateral pancreaticojejunostomy. The Whipple
procedure is a major operation but can provide effective relief of pain. In contrast, distal pancreatectomy ignores the head of the pancreas, where fibrosis and inflammation can often progress and may often worsen pain. To redress the shortcomings of distal pancreatectomy, surgeons can perform a duodenum-preserving head resection with lateral pancreaticojejunostomy. This procedure has provided excellent results, with 77% of patients in one study completely pain free at 3.6 years [44]. Moreover, modifications to these procedures have been made to improve drainage of ducts in the pancreatic head and to make the procedure more suitable for patients with minimal pancreatic duct dilatation. With these adjustments, the number of patients reporting moderate to severe pain before the procedure dropped from 58% in patients receiving the standard duodenum-preserving head resection with lateral pancreaticojejunostomy to 38% receiving the improved procedure at 41 months postop [45].

In severe cases, total pancreatectomy can be performed; however, this results in the loss of both endocrine and exocrine function of the pancreas. As a result, islet stem cell transplantation has been investigated as a complement to total pancreatectomy. Transplantation initially showed promise, with patients achieving normoglycemia for up to 7 years [46]. Nevertheless, other studies have not shown transplantation to be as successful in achieving insulin independence [47].

CONCLUSION

Chronic pancreatitis is an inflammatory process of progressive destruction of pancreatic tissue with end-organ damage, resulting in both pancreatic exocrine and endocrine insufficiency. Although significant advances have been made in the management of pain in CP, still most of the pharmacologic treatments are suboptimal, with surgical and endoscopic treatments targeting mostly the ductal anatomic abnormalities.

For patients with small-duct CP, treatment is often successful with nonenteric-coated enzymes and a PPI. When utilized with caution, opioids may be helpful to treat chronic pain in a subset of patients. Preferably, pregabalin, NSAIDS, and prokinetics should be used in patients with pain due to secondary gastroparesis and large-duct disease. Finally, in patients who fail usual measures, octreotide, given either subcutaneously 3 times daily or once a month intramuscularly can help in alleviating the pain associated with CP.

REFERENCES


