Conservative treatment of chronic pancreatitis

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Chronic pancreatitis has been difficult to treat because the origin, pathophysiologic mechanisms and causes of unrelenting pain are so poorly understood. Furthermore, the pharmacologic agents often employed in other diseases with pain appear to be ineffective in many cases. The conservative management of chronic pancreatitis aims at (1) limiting progression and complications of the disease; (2) replacing lost exocrine and endocrine function; and (3) pain control. Thus, life style changes such as cessation of alcohol consumption and tobacco smoking, trials of pancreatic enzymes, treatment of duct obstruction and pseudocysts, and surgical therapies are currently employed. The good news is that the understanding of the underlying pathophysiological mechanisms is now advancing rapidly, and hopefully patient-specific and highly effective therapies will become available in the near future.
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Introduction

Chronic pancreatitis is characterized by progressive and irreversible loss of pancreatic structure and function. The majority of cases in the Western world are attributed to alcohol abuse, but other factors such as genetic mutations, duct obstruction from strictures or tumours, hypertriglyceridaemia and hypercalcaemic states have also been implicated. Current evidence suggests that a combination of predisposing factors, including environmental, toxic and genetic, are likely involved in most cases rather than one single factor. Repeated episodes of necroinflammation initiated by autodigestion, one or more episodes of severe pancreatitis, oxidative stress, and/or toxic–metabolic factors lead to activation and continued stimulation of pancreatic stellate cells. These cells cause the fibrosis characteristic of chronic pancreatitis. Histologically, chronic pancreatitis is characterized by acinar cell atrophy, obstruction of pancreatic ductules by protein plugs and calcifications, and finally fibrosis, [1–7].

A major component of the conservative (and surgical) treatment of chronic pancreatitis centers on management of complications. The reason is that we are just now discovering the aetiological mechanisms causing pancreatitis itself. The major complications of chronic pancreatitis include abdominal pain, maldigestion, diabetes, pseudocyst, splenic vein thrombosis with gastric varicies and bleeding risk, bile duct obstruction, duodenal obstruction, and pancreatic cancer [8–12]. The management of these complications requires a synchronized interplay of conservative medical, endoscopic and surgical approaches. This multifaceted approach requires individualization in nearly every case. A complication of chronic pancreatitis managed medically in one patient may be best handled surgically in another because of confounding factors. Hence the importance of the team approach.

The conservative management of chronic pancreatitis aims at (1) limiting progression and complications of the disease; (2) replacing lost exocrine and endocrine function; and (3) pain control. In the following section we will discuss the medical management of pain, maldigestion and diabetes secondary to chronic pancreatitis, with a major emphasis on pain.

Pain

Elucidation of the cause of pain and its management remains one the most challenging aspects in the management of patients with chronic pancreatitis. The aetiology of pain in chronic pancreatitis varies from patient to patient, while some have multiple sources of pain. It should be recognized, however, that chronic inflammation and the resulting release of various growth factors may lead to irreversible and pathologic changes in the neuroanatomy of the pancreas and it's central connection resulting in exaggerated and irreversible pain patterns. In other patients improvement in pain can be achieved. The first step therefore is to identify and treat causes of pain that are amenable to therapy. Examples include pseudocysts, biliary and duodenal obstruction, and coincident peptic ulceration. The origin of pain in a majority of patients is multifactorial initiated by a combination of mechanisms including recurrent tissue inflammation and necrosis, pancreatic ductal hypertension [13], increased interstitial fluid pressure [14,15], and pancreatic ischaemia

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[16–18]. Furthermore, histopathological examination of pancreatic tissue from patients with chronic pancreatitis reveals proliferation of unmyelinated nerve fibres, infiltrates of mononuclear cells around nerve sheaths, and upregulation of pain mediators such as substance P and calcitonin gene related peptide [19]. These later features reflect the complex neuroadaptation to pancreatic inflammation as noted above.

The literature contains a paucity of well-designed, prospective, randomized, and placebo controlled, double-blind trials utilizing adequate measures for the evaluation of pain and quality of life criteria in chronic pancreatitis. The primary reason lies in the difficulty in collecting a homogeneous population for study. This has led to data from other disease processes being used as a surrogate in guiding pain management in chronic pancreatitis, which is often not ideal. Most centres have developed a practice style based on their experience and the literature that is available. Our own group has come to the conclusion that an organized team approach in the management of these patients is critical for success.

In the initial evaluation of a patient with chronic pancreatitis it is important to document the duration and character of pain. It is not sufficient to estimate the severity of pain subjectively; rather objective measures like the visual analogue scale should be a part of the history and physical examination, and are useful upon follow-up as well. Narcotic use and the presence/potential for addiction should be evaluated. A measure with accepted validity and reliability like the SF-36 should be used to document quality of life, and social and family support structure should be documented.

Concomitant complications of chronic pancreatitis should be evaluated and treated while other possible sources of abdominal pain are excluded. Evidence for coexistent depression, alcohol use and drug abuse should be sought. A clear plan as to the aims of therapy and realistic expectations thereof, and parameters for narcotics analgesia should be mutually agreed upon early in the doctor–patient relationship. The success of this approach depends on the team involvement of the primary care physician, a gastroenterologist, a pancreatic surgeon, a psychiatrist or psychologist and social services. Frequently, pain specialists need to be involved.

Avoidance of alcohol and tobacco are the first step in limiting the progression in pancreatic structural and functional loss. Frequent small meals with a low fat content may help to limit pancreatic stimulation while maintaining caloric intake. However, the role of a high fat diet in exacerbating pain has not been fully defined. Analgesics remain the cornerstone of therapy. Many experts recommend that non-narcotic analgesic agents be used. However, most patients will require narcotic analgesics at some time. Frequently, it is impossible to determine the difference between pain, drug seeking behaviour and impending addiction. This is especially an issue if the aetiology for chronic pancreatitis is alcohol. One safeguard is to identify one physician who coordinates and provides all prescriptions, thereby limiting overprescription and limiting the potential for abuse or addiction. Input from a pain specialist is frequently valuable in managing difficult cases. Like many pancreatic centres, we frequently use tri-cyclic antidepressants and serotonin reuptake inhibitors for their visceral pain perception altering properties. Again, much of the critical literature on their benefit, specifically in chronic pancreatitis, is lacking.

Antisecretory therapy, most commonly in the form of acid suppressive therapy with either H_2-receptor antagonists or proton pump inhibitors, has become a mainstay in the management of chronic pancreatitis. The aim of this therapy is to reduce acid-induced secretin release from the duodenum and consequent pancreatic stimulation. Acid suppression may have added benefit for reducing pain arising from other acid related disorders, and by improving the survival of non-enteric coated pancreatic enzyme supplements. Theoretically, the pancreatic pain is diminished by reducing pancreatic ductal and/or parenchymal pressure from pancreatic stimulation. An alternative approach to decrease pancreatic secretion is to administer somatostatin or octreotide. However, the role of octreotide in managing pain of pancreatic origin remains controversial [20].

Another topic of controversy amongst pancreatologists remains the use of pancreatic enzyme supplementation for pain control. The rationale for enzyme use lies in the observed negative feedback mechanism regulating pancreatic stimulation. The enzymes are given to digest cholecystokinin (CCK) releasing peptide and therefore inhibit CCK release [21,22]. This negative feedback mechanism is hypothesized to be disrupted in chronic pancreatitis, secondary to diminished pancreatic enzyme secretion, thereby leading to intraduodenal accumulation of CCK releasing factors, marked CCK release, and pancreatic stimulation by CCK. There have been six randomized, controlled trials on the use of pancreatic enzyme replacement therapy in painful chronic pancreatitis [23–28]. Two trials utilized pancreatic enzymes in tablet form and reported benefit [23,24]. The patients more likely to benefit were females with idiopathic pancreatitis and less advanced disease. Four trials used enteric-coated enzymes in advanced disease, and showed no benefit [25,28]. It has been suggested that enteric-coated preparations may be less effective because of sub-optimal quantities of

protease delivery to the duodenum. However, the study design of the trials using enteric-coated enzyme preparations may have been flawed by including patients with steatorrhoea, having too short an evaluation period, and inadequate numbers. In patients with steatorrhoea, the functional pancreatic mass is minimal, enzymes would have minimal pancreatic secretion to suppress, and the pain would likely be from a different mechanism. Due to the often frustrating nature of pain management in chronic pancreatitis, most centres consider a trial of enzyme therapy worthwhile, usually in tablet form, especially in idiopathic and early disease.

An area of recent interest is the use of antioxidants in chronic pancreatitis related pain. There have been two trials addressing such. The first was a randomized, double-blind, cross over trial looking at the role of allopurinol in reducing pain and improving daily life activities. No benefit was seen over placebo [29]. Another randomized, double-blind, cross over trial involving 20 patients found decreased attacks of pain in patients receiving a cocktail of vitamin E, vitamin C, methionine, selenium, and β-carotene, compared to those receiving placebo [30]. This study, however, has been criticized for inadequate blinding and an inhomogeneous patient population.

Exocrine insufficiency

The normal pancreas secretes digestive enzymes in excess of the amount that is required for normal nutrient absorption. A reduction in digestive enzyme output to less than 10% of normal is required before malabsorption occurs [31]. The 'tubed' secretin–pancreozymin test is considered the 'gold standard' in evaluating exocrine pancreatic function, allowing a direct evaluation of enzymatic and electrolyte secretory capacity of the pancreas. It is, however, invasive and unpleasant for the patient and no uniform standards have been accepted. Human faecal elastase-1 (EL-1) is a non-invasive, moderately sensitive, and specific pancreatic function test. Recent literature suggests that EL-1 is the most accurate non-invasive test in the evaluation of pancreatic function both in adults [32–36] and children [37–39]. Although it has been available in Europe for some time, it has just recently become available in the United States of America. A number of studies have documented properties of this test that make its use in the clinical arena very attractive, including (1) EL-1 is not completely destroyed in the intestine; thus its concentration in stools reflects pancreatic secretion [40,41]; (2) enzyme therapy does not interfere with its measurement by ELISA since it is specific for human elastase; and (3) the correlation with the direct measure of pancreatic function is good. Advocates of its use have faced some criticism for its reported inability to distinguish between pancreatic insufficiency and intestinal malabsorption [42,43]. In a recent study faecal EL-1 determination was less sensitive, but more specific than faecal chymotrypsin in identifying pancreatic maldigestion from intestinal malabsorption in patients with cystic fibrosis [44].

In alcohol induced chronic pancreatitis, fat malabsorption occurs earlier than protein and carbohydrate malabsorption, as the loss of proteolytic enzymes and amylase lags behind lipase secretion [45]. The cardinal sign of fat malabsorption is steatorrhoea, defined as 7–15 g/day of fat in the stool (mild steatorrhoea) to $>$ 15 g/day (severe steatorrhoea) on a diet containing 100 g of fat. Patients with maldigestion of fat often report loose, greasy, foul-smelling stools that are difficult to flush away, bloating, abdominal cramps, and excessive flatus. The passage of 'oil' in the faeces (representing a faecal fat excretion of 30–40 g per day) is considered pathognomonic of chronic pancreatitis [46]. Clinically apparent steatorrhoea is seen in approximately 30% of patients with chronic pancreatitis [47]. Mild to moderate steatorrhoea, however, is often not obvious clinically and should be documented biochemically [46]. The van de Kamer [48] technique is considered the gold standard for the diagnosis of steatorrhoea. This test involves a 72 h stool collection in the setting of a standardized dietary fat intake and preparation of faecal homogenates, followed by extraction, hydrolysis and titration of faecal fat. A fat content of 7 g/24 h in a patient consuming 100 g fat per day is considered abnormal. This test, of course, is not specific for steatorrhoea secondary to pancreatic insufficiency alone, and therefore a two-stage test with and without pancreatic enzymes has been advocated by some. A newer technique involving near-infrared reflectance analysis [49] is reported to have comparable accuracy. Most experts, however, agree that a simple qualitative microscopic examination for fat globules in the stool (e.g. the Sudan III method [50]) will suffice in most cases. Whichever test is used, the important point to remember is that steatorrhoea should be documented biochemically and is invaluable when following response to pancreatic enzyme replacement therapy.

The absorption of the fat soluble vitamins (A, D, E and K) is better in pancreatic insufficiency than in mucosal malabsorptive disorders such as coeliac disease [51]. About 40% of patients with pancreatic exocrine insufficiency malabsorb vitamin B12 but clinical deficiency of fat soluble vitamins or vitamin B12 in chronic pancreatitis is uncommon [52].

Before embarking on pancreatic enzyme replacement therapy (ERT) for pancreatic failure it is necessary that the physician is cognizant of a number of factors that affect the efficacy of ERT. These can be broadly divided into issues related to delivering sufficient quantity of digestive enzyme to the duodenum and use of antacid therapy.

Sufficient enzyme must be delivered to the duodenum to digest a meal. For adequate digestion of protein, fat and carbohydrate at least 5–10% of the normal maximal digestive enzyme output needs to be delivered to the duodenum. The minimum amount of enzymes required to achieve this goal are 30 000 IU of lipase and 10 000 IU of trypsin during a 4 h postprandial period [31,45]. Most commercially available enzyme preparations contain from 4000 to 17 000 IU of lipase per tablet or capsule. Preparations with high lipase activity have raised concerns, given their reported association with colonic strictures (fibrosing colonopathy), especially in children with cystic fibrosis [53–55]. However, the 'epidemic' of fibrosing colonopathy has nearly vanished, and fear of this disorder should not interfere with efforts to achieve adequate treatment.

Antacid therapy is also important in treating pancreatic insufficiency. Pancreatic enzymes are susceptible to degradation by gastric acid. It is estimated that 35% of trypsin and 17% of lipase in non-enteric coated supplements ingested with a meal arrives in the duodenum if gastric acid is not suppressed [31]. In chronic pancreatitis there is insufficient bicarbonate secretion in pancreatic juice [56–58], leading to abnormally low duodenal pH in the late postprandial period. This problem is compounded in cystic fibrosis where the duodenal epithelial cell bicarbonate secretion is also impaired. This bicarbonate deficiency can lead to a scenario where the patient continues to have steatorrhoea and azotorrhoea despite seemingly adequate concentrations of ERT. To counteract this adverse effect of hyperacidity on the activity of ingested pancreatic enzymes, antacids [59], H_2-blockers [59,60], and proton pump inhibitors [61–63] are frequently used. Enteric coated preparations [64,65] (the polymer coating is resistant to dissolution at pH < 5) or using lipases that are resistant to acid denaturation [56,66–69] are additional measures that can be used. At this time the search for the ideal acid resistant and bile acid resistant lipase has not met with clinical success, although a bacterial lipase has been extracted which shows promise [69–71]. Some antacids may interfere with digestive enzyme supplementation. Therefore, the use of proton pump inhibitors, which also suppress meal stimulated acid secretion, are growing in utilization.

Enteric coating of pancreatin tablets or capsules effectively prevents acidic denaturation of lipase activity. Clinical studies, however, have not shown these preparations to be superior to unprotected preparations. The reason being that particles that exceed 1–2 mm in diameter are retained in the stomach during the digestive period and are delivered into the duodenum only during phase III of recurring interdigestive motility several hours after meal ingestion [72,73]. To overcome this problem, preparations that contain enzyme encapsulated in acid resistant enteric-coated microspheres (micropellets or microtablets) have been developed. These microspheres mix with gastric chyme without releasing their enzyme content and are then emptied into the duodenum together with the meal where enzymatic activity is released due to an increase in pH to about 6. The superior efficacy of enteric-coated mini-microsphere preparations compared with conventional pancreatin extracts has been demonstrated [73–75]. Studies suggest that $> 60\%$ of the lipase contained in microspheres survives passage through the stomach [76], and dose–response studies indicate that with these preparations, administration of 20 000 to 30 000 units of lipase per meal markedly reduces steatorrhoea [74]. Finally, there are increasing anecdotal reports of failure of ERT even when mini-microspheres are used. This can be sometimes traced to substitution of a name brand product with a generic product of questionable biological equivalency without the physicians knowledge. Returning to a name band product should solve this problem.

Several other observations about the digestive process in patients with chronic pancreatitis should be noted. For example, it has been demonstrated that the survival of lipolytic activity is increased in the presence of fat and protein during duodenal–ileal transit in humans [77,78]. Thus, a high-fat diet with ERT may improve fat absorption in pancreatic insufficiency. However, low-fat diets are used to reduce pancreatic stimulation and pain. Adequate studies are needed to determine the appropriate recommendations for fat intake.

Motility may also be altered in chronic pancreatitis. There is evidence that the site of maximal digestion and absorption in chronic pancreatitis is shifted from the duodenum to the more distal small bowel [79]. This leads to increased amounts of nutrients being delivered to the distal ileum, which results in disturbed regulation of motor and secretory function of upper gastrointestinal tract [80–84]. Finally, small intestinal transit is decreased by up to 50% in patients with pancreatic insufficiency compared with healthy subjects [78]. Hence, the available time for digestion and absorption is altered. The observation that both digestion and gastrointestinal transit is improved by enzyme replacement suggests that malabsorption is both a consequence and a cause of abnormal motor function [78]. Taken together, much remains to be learned about the pathophysiology of digestion in chronic pancreatitis.

Endocrine insufficiency

Managing endocrine failure associated with chronic pancreatitis is particularly challenging. Diabetes is reported to occur in 30–50% of patients with chronic pancreatitis [7,9,85]. Although glucose intolerance is

not uncommon in patients with chronic pancreatitis, overt diabetes mellitus usually occurs late (i.e. more than 20 years after onset of the disease). Most of these patients develop insulin dependence. A number of factors are involved in the development of this complication. Firstly, there is loss of islet cell function, possibly related to ischaemia. The ischaemia may develop from disruption in the normal vasculature due to inflammation and fibrosis in the surrounding exocrine tissue [86]. Secondly, there is decreased secretion of hormones such as glucose dependent insulinotropic peptide (due to malabsorption, particularly of glucose [87,88]), and impaired release of glucagon [89–91]. Lastly, due to the attendant malabsorption and frequently associated alcohol abuse in chronic pancreatitis, there is irregular caloric intake and therefore a high risk of hypoglycaemia [46]. For these reasons patients are frequently under-treated to avoid hypoglycaemia, occasionally avoiding insulin altogether. This is despite the risks of retinopathy, [92] neuropathy, [93] and nephropathy secondary to 'pancreatic' diabetes being as high as those seen in primary diabetes, [94] hence the term 'brittle diabetes'. Again, a multidisciplinary team that, in this case includes an endocrinologist, is important for optimal care.

The future of medical management of chronic pancreatitis may be much different than the present. Efforts to classify, organize, stage and intervene early in the course of chronic pancreatitis are being considered [9]. Indeed, the true advances will come with the ability to delay or prevent the natural course of this disease rather than to only manage the many complications.

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