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TOPIC HIGHLIGHT

2016 Pancreatic Cancer: Global view

Management of pain in chronic pancreatitis with emphasis on exogenous pancreatic enzymes

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Abstract

One of the most challenging issues arising in patients with chronic pancreatitis is the management of abdominal pain. Many competing theories exist to explain pancreatic pain including ductal hypertension from strictures and stones, increased interstitial pressure from glandular fibrosis, pancreatic neuritis, and ischemia. This clinical problem is superimposed on a background of reduced enzyme secretion and altered feedback mechanisms. Throughout history, investigators have used these theories to devise methods to combat chronic pancreatic pain including: Lifestyle measures, antioxidants, analgesics, administration of exogenous pancreatic enzymes, endoscopic drainage procedures, and surgical drainage and resection procedures. While the value of each modality has been debated over the years, pancreatic enzyme therapy remains a viable option. Enzyme therapy restores active enzymes to the small bowel and targets the altered feedback mechanism that lead to increased pancreatic ductal and tissue pressures, ischemia, and pain. Here, we review the mechanisms and treatments for chronic pancreatic pain with a specific focus on pancreatic enzyme replacement therapy. We also discuss different approaches to overcoming a lack of clinical response update ideas for studies needed to improve the clinical use of pancreatic enzymes to ameliorate pancreatic pain.

Key words: Pancreatic enzyme replacement therapy; Chronic pancreatitis; Pancreatic insufficiency; Protease; Clinical trials; Trypsin; Fat malabsorption; Pain

Core tip: Pancreatic enzyme replacement therapy

has long been used as a non-invasive treatment for chronic pancreatic pain. Enzyme therapy aims to restore feedback inhibition of pancreatic secretion to lessen pain caused by pancreatic ductal hypertension, increased pancreatic interstitial pressure, and pancreatic ischemia. Although enzyme therapy may play a role the key is individualization of therapy based on disease etiology and severity. Here we review the literature regarding the efficacy of enzyme therapy and the evidence gathered for an entero-pancreatic feedback loop. We also describe alternative strategies for improving pain therapy including using uncoated enzymes with gastric acid suppression.

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INTRODUCTION

Although the pancreas was known to ancient Greeks, its role in health and disease remained obscure until recent times. One of the earliest cases of chronic calcific pancreatitis is described in *History of the Pancreas* by Howard and Hess[1] in which they relate that in 1678 de Graaf reported the case history of a patient seen by a Dr. Gajea. The patient, a nobleman, was "seized by vomiting and diarrhea because of an uncontrolled use of wine and seafood"[1]. At autopsy, seven or eight stones the size of a chick pea were found blocking the pancreatic duct[1]. Later, diabetes was recognized as a complication of chronic pancreatitis[2]. Despite a plethora of autopsy cases, case reports, and reviews[1,3], a clear understanding of the manifestations of chronic pancreatitis had to await medicine's advance to when surgeons could safely enter the abdomen as well as the development of laboratory testing and radiographic imaging.

Pancreatitis can be classified broadly as acute or chronic[4]. In acute pancreatitis, the glands undergo varying degrees of edema, inflammation, and possibly necrosis[4-6]. Although a majority of the glands may be injured, most recover[7]. Chronic pancreatitis is thought to be the end result of a long-term inflammatory process that results in both morphological and structural changes[7]. This has been proposed as a two-step process in which functional and structural impairment to pancreatic secretion eventually leads to activation of zymogens resulting in local destruction of glandular tissue eventuating in fibrosis[7]. This may also result in marked pancreatic structural alterations including formation of pseudocysts and ductal strictures and repeated cycles of increasing damage and inflammation ultimately resulting in both exocrine and endocrine insufficiency[4,6,7]. Ductal dilatation and intraductal calcifications are common in chronic pancreatitis[4-6] and such architectural changes allow one to reliably distinguish between acute and chronic pancreatitis. However, chronic pancreatitis can occur without gross changes and still be diagnosed based on the presence of abnormal structure and function[7].

Histology is the diagnostic gold standard for chronic pancreatitis, but pancreatic biopsy is potentially dangerous and not routinely performed[8]. Instead, there are a myriad of functional tests available such as the cholecystokinin-secretin test[8]. A comparison of the cholecystokinin-secretin test to pancreatic tissue biopsy reported a significant correlation between histology and peak bicarbonate concentration (sensitivity of 67% and specificity of 90%)[9]. In fact, the functional tests are even more sensitive than endoscopic retrograde cholangiopancreatography (ERCP)[9]. Overall, the secretin stimulation test is considered the most sensitive test for diagnosing chronic pancreatitis but is not widely available[7,10]. Imaging studies including radiographs, ultrasound, computed tomography, and magnetic resonance imaging identify abnormal pancreatic structure. ERCP and endoscopic ultrasound are the most widely used to diagnose chronic pancreatitis[8]. A number of classification schemes have been proposed such as the Cambridge and Rosemont Classifications. The Cambridge classification uses findings seen on ERCP, ultrasound, and CT[5], whereas the Rosemont classification diagnoses chronic pancreatitis based on major and minor features present on endoscopic ultrasound[11]. Chronic pancreatitis is also classified for therapeutic studies as large or small duct disease because the two variants differ in natural course and treatment responses[7]. For example, patients with small duct disease tend to have better pain response to pancreatic enzyme supplementation compared to those with large duct disease[7].

ETIOLOGY OF CHRONIC PANCREATITIS

Worldwide, alcohol use is the most common cause of chronic pancreatitis in adults and in most series accounts for approximately 70% of cases (Table 1). A wide variety of other etiologies (cystic fibrosis, hypertriglyceridemia, tumor, pancreatic resection, familial, congenital abnormalities, tropical, autoimmune, genetic) account for approximately 10%, and the remaining 20% are currently considered idiopathic[12]. The focus of this review is on the medical management of patients with chronic pancreatitis presenting with chronic abdominal pain.

PANCREATIC PAIN

Although the proportion of patients with chronic pancreatitis and pain is unclear, many, if not most, patients are originally identified because they seek medical help due to abdominal pain[13]. Other presentations include signs of endocrine or exocrine dysfunction without pain[14]. It has been estimated that overall 5% to 10% of patients with chronic pancreatitis, especially those with late-onset idiopathic disease, do not suffer from abdominal pain[13]. Episodic pain is a defining symptom of chronic

Table 1 Common causes of chronic pancreatitis

Toxic metabolic
Xenobiotics
Alcohol
Cigarette smoking[12]
Genetic mutations
CFTR mutation (Cystic Fibrosis Transmembrane Conductance Regulator) PRSS1 mutation (Protease, Serine 1)
SPINK1 mutation (Serine Peptidase Inhibitor, Kazal type 1)
CTRC (chymotrypsin C)
Chronic Obstruction of main pancreatic duct
Cancer
Post-duct destruction in severe attack
Recurrent acute pancreatitis
Autoimmune
Idiopathic
Early or late onset
Tropical

Table 2 Pattern of pancreatic pain

Episodic mild to moderate pain
Constant mild to moderate pain
Typically pain free between episodes of severe pain
Constant mild pain with episodes of severe pain
Constant pain

pancreatitis and is classically described as constant pain in the epigastric area with radiation to the back[13]. Painful episodes last roughly a week and are often accompanied by fatigue, nausea, vomiting, food avoidance, and weight loss[15]. Pain is typically worsened with food intake and may be ameliorated in part by leaning forward, sitting up, food avoidance, or use of heating pads to the back or abdomen[7,15]. The pain can be severe but varies widely among patients and even in the same individual[13]. This variation complicates interpretation of therapy during pain-free intervals between exacerbations[13]. A thorough history often reveals multiple similar prior episodes, alcohol abuse, and symptoms of weight loss, diarrhea and steatorrhea[7]. While alcohol use is often described as the most common trigger for symptoms (*e.g.*, pain occurring twelve to forty-eight hours after alcohol use)[16], many report no consistent association between alcohol use and pain[13,17-21]. Physical examination is typically negative with the exception that pain in the epigastric region may worsen with palpation.

Disease progression may be associated with a change in the characteristics of pain. Early in the disease, pain tends to be periodic which may then progress to constant debilitating pain[22]. Pain resolves in some patients as the glands are destroyed and the disease "burns out". However, this may require more than 18 years[13,19,20]. While it has been suggested that viable pancreatic tissue may be required for pancreatic pain[15], the natural course of pain in chronic pancreatitis is notoriously difficult to predict. For example, a longitudinal study with 113 patients noted that the pain decreased in 42%, did not change in 32%, and increased in 26% over a 4 year observation period[23]. In contrast, another study reported 85% of patients achieved pain relief at a median of 4.5 years[19]. Patients achieving pain relief were most often those with increased pancreatic calcifications and dysfunction[19].

A large multi-center study evaluated the frequency of different pain patterns among 540 patients with chronic pancreatitis[24]. Their characterization focused on frequency (intermittent *vs* constant) and severity (mild, moderate, or severe); only approximately 20% of patients were unable to self-characterize their pain pattern. Pain patterns (Table 2) were originally scored into one of 5 patterns based on the American Gastrointestinal Association's technical review[25]. The most common pain patterns were constant mild pain with episodic severe pain (56%) and typically pain free with episodic severe pain (31%). Overall, constant pain was more common than intermittent pain (52% *vs* 45%). Patients with intermittent pain tended to be older while those with constant pain were current smokers and had alcohol as the primary etiology of their chronic pancreatitis. As might be expected, those with constant pain and those with severe pain were more likely to be disabled, have poor quality of life, and to utilize health care resources. However, it has been estimated that 30% to 50% of patients with chronic pancreatitis will eventually become pain free[13].

Ammann *et al*[20] study of pain in chronic alcoholic pancreatitis provided data on 207 patients. None were addicted to narcotics or had an inflammatory mass as the potential cause of pain. Two pain patterns were common. In the first pattern, patients experienced short episodes of pain separated by pain-free periods lasting from months to years. Patients with the second pain pattern had persistent daily pain or clusters of severe pain typically occurring 2 or more days per week for at least 2 mo. Among those with intermittent pain and not requiring surgery, 50% had pain relief within 6 years increasing to more than 80% at 10 years. All of those with persistent pain underwent surgery because of the presence of a pseudocyst (most common), presumed high ductal pressure (large duct disease with or without ductal stones and minimal or no exocrine insufficiency), or biliary obstruction. Overall, the response to pain and the proportion developing pancreatic insufficiency in the two groups were similar. In the total series, the most common association with chronic pain was narcotic addiction, and these patients were few in number and were excluded. However, in many series the management of pain in patients with chronic pancreatitis is complicated by narcotic and alcohol dependencies[13].

PATHOGENESIS OF PANCREATIC PAIN

The pathogenesis of chronic pancreatic pain is poorly understood. In the 19th century, thought centered on ductal obstruction and the passage of a stone similar to what occurs with salivary gland or biliary stones,

Table 3 Mechanisms of pain in chronic pancreatitis

Increased intraductal pressure
Ductal obstruction from strictures/stones
Increased intrapancreatic pressure (compartment-like syndrome)
Fibrosis causing lack of distensibility
Neuropathic
Entrapment of nerves
Damage of nerves by enzymes
Increased nerve tissue
Pancreatic ischemia
Worsened during increased enzyme secretion

as well as pressure or other damage to the celiac axis (*e.g.,* neuralgia coeliaca)[3]. Currently, the major theories focus on increased pancreatic pressure (*e.g.,* intraductal pressure, pancreatic interstitial hypertension, or ischemia) and neurogenic causes (Table 3).

DUCTAL HYPERTENSION

Ductal hypertension is often considered "the most important cause of pain"[13] based on the concept that ductal strictures and calculi can cause ductal obstruction which leads to increased ductal pressure, and thus pain, during pancreatic secretion[7,26]. It has been suggested that one role of alcohol in pancreatitis is to promote stone formation in pancreatic secretions[27]. The presence of these stones promotes inflammation leading to scarring and strictures which then elevate intraluminal pressures[27]. Clinical studies have indeed confirmed elevated pancreatic ductal pressures in patients with chronic pancreatitis. For example, normal pancreatic ductal pressure ranges from 7 to 15 mmHg while ductal pressures ranging from 20 to 80 mmHg have been measured in patients with chronic pancreatitis[28-30]. A direct relationship between the reduction in ductal pressure and relief of pancreatic pain has also been reported[31]. For example, there are numerous studies demonstrating pain reduction or relief following decompression of a dilated duct or pseudocyst using drugs, endoscopic stents, by disintegration of pancreatic stones *via* extracorporeal shock waves, surgical drainage procedures, or pancreatic resections[28,32].

While clinical data suggests that pancreatic pain can be reduced by eliminating ductal strictures and obstructions, decreasing pancreatic secretion, or both, significant obstruction is not universally apparent in painful chronic pancreatitis[26] and ductal surgery does not uniformly relieve pain[16]. For example, the prevalence of major duct strictures was reported to be similar (*e.g.,* about 60%) in patients with painful and painless chronic pancreatitis[21]. However, ductal pressures were not measured[21,26].

INTERSTITIAL HYPERTENSION

A related theory focuses on increased pancreatic interstitial hypertension which has been reported to be higher in patients with painful chronic pancreatitis than in painless chronic pancreatitis (*e.g.,* a median of 7 mmHg *vs* 22.5 mmHg)[33]. In those patients with pain, drainage procedures involving the main duct or a communicating pseudocyst often result in both pain relief and a reduction in interstitial pressures to normal levels[33]. An extensive study of the relation of ductal and interstitial pressure in chronic pancreatitis was performed using a cat model[34]. Perfusion of the normal main duct at physiologic flow rates resulted in an increase in ductal pressures but no significant change in interstitial pressure. Perfusion following partial obstruction of the main pancreatic duct at the neck of the pancreas resulted in a further increase in ductal pressure but again without an increase in interstitial pressure. These data suggest that the normal pancreas has sufficient distensibility to dissipate the increase in ductal pressure. Following encasement of the pancreas in latex to decrease its ability to expand, perfusion of the pancreas resulted in significant increases in both ductal and interstitial pressures. Finally, to simulate chronic pancreatitis, the main pancreatic duct was obstructed for 5 wk resulting in histological changes similar to chronic pancreatitis in humans. Perfusion of the duct then resulted in an increase in both ductal and interstitial pressures leading the authors to conclude that the loss of distensibility in chronic pancreatitis likely results in a compartment-like syndrome in which secretion produces increased ductal and interstitial pressures both of which can be partially or completely relieved by pancreatic surgery[26]. They also showed reduced pancreatic blood flow in the cat model[34,35] suggesting possible pancreatic ischemia.

PANCREATIC ISCHEMIA

The ischemia hypothesis is based on the concept that increased interstitial pressures and surrounding fibrosis could increase vascular resistance leading to decreased perfusion of pancreatic tissues[34-38]. As noted above, in the cat chronic pancreatitis model, basal blood flow was reduced by 40% compared to the normal pancreas[34]. In addition, pancreatic secretagogues increased normal blood flow by 27% but decreased blood flow by 14% in animals with chronic pancreatitis. Decompression of the obstructed pancreatic duct resulted in both an increase in basal flow and return to the normal increase following stimulation of secretion consistent with the notion that parenchymal damage and pancreatic pain could be secondary to ischemia (*i.e.,* a compartment-like syndrome).

PANCREATIC NEURITIS

A final, but related, pain theory is based on the concept that altered pancreatic architecture results in inflammation of nerves and altered feedback mechanisms[13,39]. It has been proposed that chronic inflammation of peripancreatic nerves may increase nerve tissue through up-regulation of neuropeptides[28]. The fact that mean diameter of

peripancreatic nerves in chronic pancreatitis patients was significantly greater than controls led to the suggestion that the increased nerve diameter was caused by a fibrotic process that strangulated the nerves[13]. Microscopic analyses have also shown disruptions in perineural structure which could theoretically expose nerves to damaging inflammation, enzymes, and inflammatory cells[28]. Specifically, the number of eosinophils present in pancreatic perineural tissue was shown to correlate with pain and alcoholism scores[40]. The pancreas is highly innervated, and it has been suggested that pain reduction following surgical removal of the head of the pancreas is related to removal of the most highly innervated region[27,41]. The pain relief obtained by removal of inflammatory pancreatic masses is thought to possibly relate to removal of damaged nervous tissue[39]. In the last decade, research has focused on histologic and biochemical features in the involved pancreas, as well as changes in cortical reorganization and electroencephalographic findings and the similarities to patients with neuropathic pain (*e.g.,* reviewed in[39,42-44]). Similar findings have been described in humans and experimental animals with chronic pancreatitis. It is however important to note that the neurogenic theory cannot, by itself, explain pain relief in pancreatic "burn out" or after reduction of intraductal pressures through procedures[13].

TREATMENT OF PAIN IN CHRONIC PANCREATITIS

Pain in patients with chronic pancreatitis is often extremely difficult to manage in that patients frequently receive narcotics and a significant proportion of patients develop dependency on both narcotics and alcohol. Severe constant pain often indicates the presence of a complication such as a pancreatic pseudocyst and should prompt targeted investigations[45,46]. One of the first goals of the clinician is to ensure that the pain is related to chronic pancreatitis and not to some another condition[32]. Patients with chronic pancreatitis may also have malabsorption resulting in flooding of the colon with nutrients leading to meteorism or other symptoms of malabsorption[47-49]. One topic heading in Howard and Hess's *History of the Pancreas* is entitled "Treat the pain, not the disease"[1] (page 291), emphasizing that patients with chronic pancreatitis often have multiple overlapping issues and correct diagnoses and a multidisciplinary approach is essential for successful treatment[13]. Pain remains the most common primary indication for surgical or endoscopic intervention. Treatment failure or only partial success is common[13]. The focus of this paper is on medical treatment of pain in chronic pancreatitis. Nonetheless, medical, endoscopic, and surgical treatments may all be required for a successful outcome.

LIFESTYLE CHANGES

Cessation of alcohol

Although alcohol is involved in a large percentage of cases of painful chronic pancreatitis, it remains unclear why only a small percentage of those who abuse alcohol develop chronic pancreatitis. Chronic pancreatitis is more common among those who also smoke[12]. It is likely that there is a genetic predisposition that associates alcohol or alcohol and smoking with pancreatitis, but no single genetic association has yet been discovered[12]. Because alcohol-induced chronic pancreatitis is a progressive disease leading to structural and functional pancreatic changes, theoretically abstinence from alcohol could result in a reduction or elimination of pain, decrease the degree of pancreatic dysfunction, reduce mortality, and promote a return to normal activity[13]. It has repeatedly been suggested that cessation of alcohol improves the course of the disease[13,50]. For example, in one large study of the natural history of alcoholic chronic pancreatitis, 75% of patients continued to drink and in those patients the death rate and level of physical impairment were three times higher[19]. All agree that one focus should be on promoting cessation of alcohol and tobacco use. However, bouts of pain in alcohol-induced chronic pancreatitis still occur after the cessation of alcohol[18]. The benefits in terms of prevention of flares may in part depend on the stage of the disease in that alcohol, as a secretagogue, may have minimal effect on patients with little or no remaining exocrine function[13].

DIET

Patients and their families often inquire about diet therapy. It has been recommended that meals be low in fat and that large meals be avoided to possibly minimize hyperstimulation of the pancreas[13,27]. However, few of these dietary recommendations are evidence-based. Many patients with chronic pancreatitis will have clinical or subclinical deficiencies in vitamins and micronutrients[51,52]. Testing for retinol-binding protein, prealbumin, magnesium and transferrin has been recommended[8,51,53]. Because smoking is a risk factor for chronic pancreatitis, the formation of stones, and also calcifications, cigarette smoking should be strongly discouraged[15,54].

ANTIOXIDANTS

An intriguing aspect of dietary therapy in chronic pancreatitis is the emerging possible role of antioxidants. For example, Rose *et al*[55] reported deficiencies in selenium, vitamins A, C, and E, and riboflavin compared to healthy controls and patients with recurrent acute pancreatitis. Other studies have reported decreased intake of micronutrients in chronic pancreatitis patients[56]. These findings fueled the hypothesis that a reduction in these micronutrients could enhance oxidative stress and link to

the development of chronic pancreatitis[27,52]. Allopurinol can theoretically decrease toxic free radicals *via* its action on xanthine oxidase[27] leading to trials seeking to alleviate pancreatic pain with allopurinol. However, small studies reported no significant effects[57]. In contrast, a randomized trial of antioxidant supplementation with selenium, ascorbic acid, B-carotene, a-tocopherol, and methionine reported a significant reduction in the number of painful days per month[58]. A meta-analysis of antioxidants in chronic pancreatitis reported a small but significant reduction in visual analog scale pain scores (0.33 out of 10) along with an adverse effect rate of 16% of "mostly mild" symptoms[30]. Finally, a Cochrane review concluded that antioxidant therapy provides slight benefits and also reported adverse events in about 17%[59]. The role of antioxidant therapy in pain in chronic pancreatitis remains unclear and further investigation is warranted[60].

ENDOSCOPIC THERAPY

Endoscopic therapy has continued to play a role in the diagnosis and treatment of chronic pancreatic pain. Recent Cochrane reviews concluded that endoscopic therapy is not as effective as surgical intervention for pain relief, but endoscopy remains a viable option because of its availability and relative safety[59]. The Cochrane reviews were not able to clearly delineate differences between endoscopy and surgery regarding mortality and morbidity and recommended that options be presented to the patient and a joint decision be made[59]. Most endoscopic therapy is utilized for patients with intractable pain or nutritional deficiencies after more conservative therapy has failed[27]. Despite the lack of clear definitions of significant obstruction or methods to reliably identify patients amenable to endoscopic treatment, endoscopy has proven to be useful in relieving duct obstruction secondary to strictures, stones, or ampullary stenosis[27]. An alternative method is the combination of extracorporeal shock-wave lithotripsy followed by endoscopic removal of remaining debris and stones[27]. It has been reported that 80% of stones can be removed with approximately half of the patients reporting long-term pain relief[61]. A comparison of extracorporeal shock wave lithotripsy and extracorporeal shock wave lithotripsy plus endoscopic drainage in painful chronic pancreatitis found no significant difference after 2 years (*i.e.,* 38% of patients with extracorporeal shock wave lithotripsy alone reported pain relapse *vs* 45% of those with combined therapy)[62]. However, both groups experienced a significant reduction in pain episodes per year. Importantly, there was no placebo group and the cost of the combined treatment was three times greater[62].

Another alternative is placement of pancreatic ductal stents. In one study, 94% of 75 patients receiving pancreatic duct stents and dilation of duct strictures initially reported improved symptoms and, after a mean follow-up of three years, 53% remained symptom free[63]. Another study reported symptomatic improvement in 57% of 61 patients over a mean of 19 mo[64]. Anecdotally, pain relief appears to correlate with stone removal resulting in a decrease in main duct diameter[27]. Although stent placement is associated with stent migration, occlusion, aggravation of chronic pancreatitis and further duct changes, the availability and relatively low invasiveness compared to surgery makes endoscopic therapy a first-line consideration for treatment of ductal strictures and obstruction in the management of pancreatic pain[27].

SURGERY

Prior to the advent of endoscopic therapy for pancreatic ductal disease, the primary approach involved surgical interventions. A variety of surgical options were developed and the surgical approach continues to evolve. Nonetheless, no surgical intervention has proved to be one hundred percent effective. The role of surgical therapy is to deal with and prevent complications, as well as attempt to achieve pain control[61]. Indications for surgery include non-resolving ductal or common bile duct stenosis, intractable pain, internal pancreatic fistulas unresponsive to less invasive therapy, vascular erosions, or uncontrollable pancreatic pseudocysts[61]. Traditional surgical options for chronic pancreatitis can be divided into procedures that focus on resection of pancreatic tissue and procedures that focus on drainage of pancreatic ducts[61]. Resection-based procedures such as the Whipple operation, distal and total pancreatectomies, and the pylorus-preserving pancreatoduodenectomy were developed in part to relieve obstruction and because of the belief that chronic pancreatic pain also stemmed from perineural pancreatic inflammation. Drainage-based procedures such as the Frey procedure, Beger procedure, sphincterotomies, and pancreaticojejunostomies were designed to relieve ductal obstructions and ductal hypertension[61]. No gold standard exists, and the surgical procedures used to control pancreatic pain are individualized based on the anatomy, the condition of the patient, and the skill and experience of the surgeon.

In addition to more traditional options, pancreatic autotransplantation and a resurgence in neuroablation are emerging therapies. Endoscopic or even surgical neurolysis of the celiac ganglion remains an option in high-risk surgical patients or in patients who need additional therapy post-operatively[65]. Although less-invasive than traditional surgery, only 10% of neurolysis patients showed a benefit at 24 wk and two-thirds of patients required additional surgery[65]. Pancreatic autotransplantation can supplement resection-based surgery to preserve islet cell function and stave off endocrine insufficiency[65]. For example, the Mirkowitch technique uses a pellet of purified islet cells and segmental transplantation with resected pancreatic tissue that is implanted into the thigh[61].

There are significant limitations to surgical options for treating chronic pancreatic pain in that while pain relief and quality of life can be improved, exocrine and endocrine insufficiency frequently accompany respective options[66,67]. Patients undergoing surgery for chronic

pancreatitis have substantial hospital readmission rates. One recent study found that 31.5% of patients were readmitted in the first 30 d postoperatively and 42.3% were admitted in the first 90 d[68]. These substantial readmission rates are a significant problem especially since reimbursement rates are being more closely tied to outcomes such as rehospitalization. Factors that have been suggested to possibly help maximize surgical outcomes include early surgical intervention, alcohol cessation, retention of duodenal tissue, and concurrent medical therapy[68,69]. One reason given for poor pain control following surgical therapy is that some patients have altered central pain processing[70]. Methods are needed to be able to better select those patients who are destined to have a poor response as post-operative pain remains a significant problem.

The most recent Cochrane review of surgical intervention for obstructive chronic pancreatitis showed that early surgical intervention seemed, but was not definitely shown, to have potential benefits as compared to conservative therapy[59]. More importantly, the review concluded that surgical intervention produced better pain relief scores over a two and five year period (relative effect 1.62, 1.65) with a lower chance of resultant exocrine pancreatic insufficiency compared to endoscopic therapy[59].

PANCREATIC ENZYMES AND THE NEGATIVE FEEDBACK THEORY

The observation that pancreatic enzyme therapy in some patients with chronic pancreatitis results in a reduction in pain has lead to studies that attempt to understand the phenomenon and achieve more reliable results. The theories of ductal and interstitial hypertension and decreased distensibility of the damaged parenchyma note that pancreatic secretion is associated with a further increase in pressure and likely involved in the pathogenesis of pain. Surgical and endoscopic therapies are primarily aimed at altering pancreatic anatomy to facilitate passage of pancreatic juice. Theoretically, replacing endogenous secretion with exogenous pancreatic enzymes will reduce endogenous secretion in response to meals, blunt the increase in ductal and parenchymal pressure, and reduce pain.

NEGATIVE FEEDBACK INHIBITION OF PANCREATIC SECRETION

The normal human pancreas secretes continuously at a low rate. When food enters the duodenum, the hormones cholecystokinin (CCK) and secretin are secreted to deliver pancreatic enzymes (CCK) and bicarbonate (secretin) into the duodenum[32,71,72]. While much is known about the initiation of pancreatic enzyme release, less is known about how the process is stopped. However, there is evidence of negative feedback inhibition related to the presence of proteases in the duodenum. This was first shown in rats by Green and Lyman[73] and subsequently confirmed by a number of other investigators[74-77]. Feedback inhibition is known to occur in the rat, chicken[78] and pig[79]. In rats, one mediator of secretion is CCK[75]. For example, diversion of pancreaticobiliary secretions from the duodenal lumen resulted in a threefold increase in pancreaticobiliary protein secretion[75,80,81]. Pancreatic secretion was also associated with a significant rise of plasma CCK in diverted rats compared to basal levels (16 ± 4 pmol/L from 0.5 ± 0.8 pmol/L respectively)[75]. More specifically, perfusing the duodenum with pancreaticobiliary secretions or trypsin alone (*via* cannulation near the ampullary site) resulted in a decrease in pancreatic protein secretion and plasma CCK to near basal levels and essentially abolished the stimulatory effect of pancreaticobiliary secretion diversion on pancreatic secretion[75,77]. An alternate approach was to add a trypsin inhibitor to the pancreaticobiliary secretions to functionally remove trypsin which resulted in an increase in pancreaticobiliary protein output similar to pancreaticobiliary secretion diversion alone[75]. When the proteinase inhibitor, FOY-305, was given to rats by orogastric tube[76] there was a 15-fold increase in peak serum CCK levels and an increase in pancreatic protein and enzyme secretion[76].

In the rat, the negative feedback mechanism appears to be protease-specific as perfusing the duodenum with amylase does not affect protein output[75,82,83]. The role of CCK was confirmed by showing that the intravenous infusion of the CCK antagonist proglumide before and after pancreaticobiliary secretion diversion reduced protein outputs to near basal levels[75]. Discontinuation of the proglumide infusion removed the inhibition of pancreatic secretion[75]. The feedback mechanism appeared localized to the proximal intestine as ileal perfusion of trypsin did not affect pancreatic output[75]. Subsequent studies have been based on the hypothesis that the presence of trypsin in the duodenum down regulates CCK release resulting in a decrease in pancreatic protein output. The molecular mechanism of the interaction remains unclear. It has been suggested that a protease-sensitive mediator that controls CCK release is present in the duodenal mucosa, or alternatively, is secreted within the pancreatic juice[27,84,85]. Other data suggest that the feedback loop is not confined to the interactions between trypsin and CCK as neural pathways mediated by acetylcholine also appear to play a role[75]. For example, the intravenous infusion of acetylcholine, intraarterial infusion of tetrodotoxin, and intraluminal addition of lidocaine all abolished the rise in CCK and pancreatic output in pancreaticobiliary secretion diverted rats[75,86,87]. The mechanism for the cholinergic pathway remains unclear, but it has been suggested to possibly mediate secretion of the protease-sensitive proteins or be important to their action[75].

NEGATIVE FEEDBACK - EXPERIMENTAL STUDIES IN HUMANS

Owyang *et al*[88] attempted to demonstrate dose-de-

pendent pancreatic enzyme output suppression following intraduodenal infusion of proteases in healthy subjects. Exocrine pancreatic enzyme suppression required a minimum infusion of 0.5 mg/mL of trypsin, with maximal suppression with 1.0 mg/mL. Suppression was not seen with infusions of amylase and lipase. Suppression also correlated with a decline in CCK levels[88]. Interestingly, while a postprandial increase in plasma CCK was not seen in the presence of duodenal infusions of trypsin, a small increase in pancreatic enzyme secretion was observed. The authors hypothesized this was evidence of a separate pancreatic control mechanism, perhaps cholinergic[88]. A subsequent investigation examined the possibility of two distinct feedback mechanisms by stimulating duodenal volume and osmoreceptors by infusing normal saline at increasing rates and increasing osmolality[89]. They noted a dose-related increase in pancreatic output without an effect on plasma CCK levels[89]. Prior studies in rats had also shown a decrease in pancreatic output with anticholinergic agents, but plasma CCK was also affected[75]. The effect on pancreatic output was reversed by intraduodenal atropine but not by intraduodenal proteases[89]. However, the addition of a phenylalanine solution dramatically increased CCK levels and enzyme output. The effect was reduced with the intraduodenal infusion of proteases. The addition of both atropine and proteases completely abolished the pancreatic enzymatic response to intraduodenal phenylalanine[89].

While negative feedback mechanisms in humans have been clearly demonstrated, not all studies have been consistent[90], and many studies used super-physiologic amounts of trypsin[49,91]. The earliest example measured pancreatic secretory output after intraduodenal infusion in a man with carcinoma of the ampulla of Vater which completely blocked biliary and pancreatic secretions from the small intestine[92]. Pancreatic secretory output was measured *via* a percutaneous transhepatic cholangiography catheter. Intraduodenal infusion of the patient's pancreaticobiliary secretions reduced pancreatic secretions and the effect was reversed by a trypsin inhibitor (soy bean trypsin inhibitor which is relatively trypsin-specific)[92]. A similar experiment was done after pancreatoduodenectomy with similar results except that the proximal duodenum had been removed suggesting that the site for stimulation extends beyond the periampullary region[93].

The most detailed study infused an essential amino acid solution into the duodenum and compared pancreatic outputs in patients with differing severity of chronic pancreatitis and healthy controls[94]. The addition of trypsin, 10 mg/mL, resulted in an approximately 32% decrease in pancreatic secretions in patients with reduced pancreatic output and a 74% decrease in those with normal pancreatic secretion. No inhibition was seen in patients with low pancreatic bicarbonate secretion and steatorrhea[94]. Chronic pancreatic enzyme therapy was also associated with a 27% decrease in basal pancreatic secretion and a 46% decrease in amino acid stimulated secretion. A dose-response of trypsin inhibition of exocrine secretion was evaluated in one patient during amino acid infusion. The minimum concentration of trypsin required to inhibit pancreatic exocrine secretion was 0.9 mg/mL and maximum suppression required a trypsin concentration of at least 2.5 mg/mL. Perfusion experiments with amino acids plus trypsin and the relatively trypsin-specific inhibitor, ovomucoid, was still associated with an increase in chymotrypsin secretion. Chymotrypsin (10 mg/mL) also decreased amino acid-stimulated trypsin output whereas protease-free lipase and amylase did not, confirming that only trypsin, chymotrypsin, and pancreaticobiliary secretions suppress pancreatic enzyme secretion in humans. However, the effect was minimal to absent in patients with advanced pancreatic exocrine insufficiency[94]. In addition, patients with advanced insufficiency did not experience pain relief with enzyme supplementation[94].

Studies using pancreaticocystostomies following simultaneous kidney and segmental pancreatic transplantations have also demonstrated feedback inhibition[95,96]. For example, pancreatic exocrine secretions were collected from pancreaticocystostomies after administration of a Lundh test meal orally with or without addition of 6 pancrelipase capsules orally. Total amylase decreased by more than a third, and peak amylase fell 63% with supplemental enzymes. The pancrelipase capsules reduced amylase secretion 16% below basal secretion, and within 1.5 h two of the patients experienced cessation of all graft secretion[96]. Importantly, inhibition of pancreatic exocrine secretion occurred despite denervation of pancreatic tissue consistent with the presence of a hormonally mediated feedback mechanism.

Overall, the results in humans were consistent with the presence of several distinct feedback pathways, one being under hormonal control mediated by proteases (*e.g.,* trypsin/chymotrypsin)[31,97-99], and another by neural control mediated by acetylcholine[89]. However, not all studies have been positive. For example, intrajejunal infusion of normal saline, pancreaticobiliary secretions, and pancreaticobiliary secretions inactivated by heat into normal healthy humans found no significant difference suggesting the absence of a jejunal-pancreatic feedback mechanism[100]. However, this failure can likely be explained by the inhibitory effect being localized to the duodenum, which was not perfused. Studies that infused an active or an inactivated trypsin inhibitor (aprotinin, which is relatively trypsin-specific) into the duodenum of healthy subjects have also reported no significant difference in pancreatic output between the infusates[101,102]. However, as shown previously, in humans both trypsin and chymotrypsin are effective in activating the feedback pathway whereas in rodents the effect appears to be more specific to trypsin. Thus, the use of trypsin-specific inhibitors did not reduce the effect of chymotrypsin present.

USING ENZYMES FOR PAIN - CLINICAL TRIALS AND META ANALYSES

The use of pancreatic enzymes in the therapy of gastrointestinal disease has a long history[103,104]. As noted previously, some, but not all, patients with pancreatic pain respond[49]. The potential mechanisms include feedback inhibition of pancreatic secretion, improvement in digestion that reduces or eliminates symptoms attributable to malabsorption, or altered nutrient-microbiome interactions. As with any medical treatment, for effectiveness one first looks for the results of randomized placebo-controlled studies with well-matched and well-described patient populations and for head-to-head comparisons of different formulations. With pancreatic enzymes, the search leads to more disappointments than enlightenments. Investigators have generally studied what was readily available to them in terms of products and patients. Ideally, a study of pancreatic enzymes for feedback inhibition of enzyme secretion would utilize formulations that reliably produce high intraduodenal concentrations of trypsin and chymotrypsin. For maldigestion, one would choose a preparation that reliably delivered high concentrations of active lipase into the proximal intestine[105]. The choice of formulation has been complicated by the recent removal of traditional products and the substitution of products primarily available as enteric-coated enzymes that fail to reliably release their contents in the duodenum[105].

Despite these problems, it is worthwhile to review the available data which includes several meta-analyses such as one in 1997 by Brown *et al*[106] and another in 2010 by Shafiq *et al*[107]. Brown *et al*[106] included six randomized, placebo-controlled, double blind, prospective studies containing 189 patients with confirmed chronic pancreatitis[94,108-112]. The primary outcome measure was the percentage of patients preferring enzymes to placebo[106]. In only one study was there a greater than 50% preference for enzymes as compared to placebo (*i.e.,* 85%)[108]. Only that result was statistically significant[108] and the authors concluded that the available studies did not support the hypothesis that pancreatic enzyme supplementation was useful to treat abdominal pain associated with chronic pancreatitis[106]. However, it is important to note that the pancreatic enzyme products used differed among studies not only in formulation but also in dosage and timing[106]. The studies also differed in relation of method of diagnosing chronic pancreatitis, length of treatment, and scoring of pain, as well as etiology of pancreatitis, disease severity, and degree of exocrine dysfunction. Two of the studies used non-enteric-coated preparations[94,108] and four used enteric-coated formulations[109-112]. The study using non-enteric-coated enzymes was the only study that demonstrated a significant patient preference of enzymes over placebo[108]. The second meta-analysis set out to address the effect of enzymes on weight loss, steatorrhea, fecal fat, quality of life, and pain in patients with chronic pancreatitis. They also addressed the role of enteric-coated *vs* non-enteric-coated formulations and dosage schedules. They specifically reported on the frequency of abdominal pain, duration of pain episodes, intensity of pain, and analgesic use[107]. Ten studies were included with a total of 361 patients[94,108-116]. The analysis included five of the six studies in Brown *et al*[106] review. Heterogeneity and overall poor data continued to be a hindrance. There were many issues with regard to understanding the effect of pancreatic enzyme supplementation on pain intensity. Although five studies specifically addressed pain, only two studies[111,112] provided mean pain scores and standard deviations. However, the two studies used different pain scores (*i.e.,* 0 to 5 *vs* 0 to 3). Mössner *et al*[111] reported a nonsignificant improvement of pain with enteric-coated enzymes as compared with placebo (1.26 ± 0.8 *vs* 1.08 ± 0.8, respectively). Conversely, Larvin *et al*[112] reported a significant improvement with enteric-coated enzymes *vs* placebo (1.93 ± 1.04 *vs* 2.05 ± 0.8, respectively). The remaining 3 studies either did not report standard deviations or reported pain scores differently such as a mean, median, or sum. This mix of results precluded data pooling. Four studies examined the effect of enzymes on analgesic use but did not report standard deviations. Specifically, Isaakson *et al*[108] reported a small nonsignificant decrease in analgesic consumption (7.8 tablets with enzymes *vs* 8.9 with placebo) whereas Halgreen *et al*[110] reported a nonsignificant decrease in analgesic consumption scores with enzymes as compared to placebo in patients with steatorrhea (49 *vs* 58 respectively) and a nonsignificant increase in patients without steatorrhea (57 *vs* 48). Larvin *et al*[112] also reported a nonsignificant decrease in analgesic consumption, reported as mean daily analgesic use with enzymes as compared to placebo (*e.g.,* 45 mg *vs* 51 mg, respectively). Finally, Malesci *et al*[109] also reported a nonsignificant increase in median analgesic consumption score in enzymes *vs* placebo (12 with range of 0 to 34 *vs* 0 with range of 0 to 44, respectively). The frequency of abdominal pain and duration of pain episodes were not addressed in any of the included studies[107]. The meta-analysis also included one study of enzyme dosing schedules on effectiveness in improving malabsorption but not on reducing pain intensity, pain duration, or use of analgesics[115].

Only one study met the criteria for assessment of quality of life, perhaps an indirect measure of pain control[107]. The double-blind, two week study used the Clinical Global Impression of Disease Symptoms Scale to evaluate quality of life after only two weeks of enzyme supplementation or placebo[113]. The use of enzymes resulted in an improvement in quality of life which approached statistical significance ($P = 0.063$)[113]. The final study in the meta-analysis compared non-enteric-coated with enteric-coated enzymes and focused on changes in steatorrhea[114]. In that study, patients receiving uncoated enzymes plus cimetidine or uncoated

enzymes alone improved steatorrhea better than those receiving enteric-coated enzymes[114].

A recent review of clinical trials using enzymes for painful chronic pancreatitis[117] included three studies not previously discussed in the meta-analyses. One of them, a study by Czako *et al*[118], was a multi-center prospective observational study of pancreatic enzyme supplementation on quality of life and abdominal pain in 70 patients divided into supplemental enzyme naïve patients with a new diagnosis of chronic pancreatitis and patients previously diagnosed and treated with oral enzymes. Patients received enteric-coated microspheres with the dosage based on the severity of exocrine insufficiency[118] along with an H_2 receptor blocker. Thirty-five percent of patients in the new diagnosis group had severe degree pancreatic exocrine insufficiency compared to 64% in the previously diagnosed group. Analgesics were given if requested but the type, dosage, and frequency were not recorded and no control group was included. Outcome was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 modified by adding a disease-specific symptom scale including questions about steatorrhea and abdominal pain[118]. The duration of the study was 4 wk. Overall, they reported a small but significant increase in mean body weight, decreases in defecations per week, and decreases in mean pain scores in both groups (pain score 47.1 to 35.9 in the mild steatorrhea group and 37.8 to 29.4 in the severe steatorrhea group)[118] as well as significant increases in global quality of life[118]. As promising as these results may seem in regards to improving symptoms of pancreatic exocrine insufficiency and relieving abdominal pain, no control group was included and the effect of analgesic use was not reported.

A recent study observed 294 patients with chronic pancreatitis and exocrine pancreatic insufficiency on pancreatic enzyme replacement for a year. The patients were divided into those currently taking enzymes and those with a new diagnosis of exocrine pancreatic insufficiency who were enzyme replacement naive[119]. Patients were given daily doses of an enteric-coated mini-microsphere preparation, Creon, and the presence of recurring pain and changes in quality of life were assessed. At the end of the study, a significant portion of patients reported a decrease in recurrent abdominal pain (66.3% with recurrent abdominal pain before treatment *vs* 34.3% after, $P < 0.001$)[119]. The percent decrease between cohorts was comparable. Similarly, after 12 mo of treatment, the mean total gastrointestinal quality of life index score improved significantly for the entire patient pool, as well as for individual cohorts[119]. Physical function and emotion subcategories also improved significantly[119]. However, despite the impressive results, the lack of a placebo makes it impossible to distinguish between the natural history of the disease and a specific effect of enzyme therapy. Actual dosages were not recorded which made analysis of optimal dosing impossible. The improvement in recurrent abdominal pain in the group previously treated with pancreatin could be related to improved compliance or a more effective treatment regimen. It would have been interesting to include a group randomized to continuing their previous regimen. Only 31% of the patient population had chronic pancreatitis due to alcohol abuse, which may represent a more difficult to treat group.

In conclusion, the heterogeneity in terms of patient characteristics (*e.g.,* presence, absence and severity of exocrine insufficiency, etiology of pancreatitis, reason for presentation, use of narcotics, formulation, dosage, and administration of enzymes in relation to meals, *etc.*) greatly affects the outcome of studies attempting to evaluate pain relief in chronic pancreatitis. Heterogeneity makes meta-analysis a very blunt instrument for evaluation of the effectiveness of therapy or for helping to decide which therapy is ideal for an individual patient. Clearly some patients respond. Current enteric-coated enzyme products are unlikely to be highly effective either in terms of providing sufficient intraduodenal trypsin activity to engage the feedback mechanism or to fully correct steatorrhea. Future studies should either focus on trying to understand why those patients respond or to carefully select parameters thought to be important, such as providing a critical amount of trypsin or chymotrypsin activity into the duodenum. One can reasonably conclude that patients with exocrine pancreatic insufficiency benefit from correction of malabsorption and the ensuing nutritional deficiencies as well as improvement of gastrointestinal symptoms including pain associated with malabsorption. Reviews of the issues with providing adequate delivery of pancreatic enzymes for treatment of malabsorption are recommended for those wanting additional details regarding use of pancreatic enzymes for malabsorption[105].

USE OF PANCREATIC ENZYMES IN CHRONIC PANCREATITIS

Administration of exogenous pancreatic enzymes has long been used as an adjuvant to the treatment of patients with pancreatic pain largely based on the premise that replacement of lost enzymes might rest the pancreas. The current rationale is that feedback inhibition of pancreatic secretion reduces CCK release and prevents pancreatic hyperstimulation and pain[27]. However, achieving this goal requires the ability to provide sufficient active trypsin/chymotrypsin to the proximal intestine. An alternative or complimentary use of enzymes in chronic pancreatitis is to treat overt or occult nutritional deficiencies. For example, low serum magnesium, hemoglobin, albumin, prealbumin, and retinol binding protein levels (a surrogate for fat soluble vitamins) along with a hemoglobin A1C above normal limits are all highly associated with exocrine pancreatic insufficiency[53]. Specifically, vitamin A (3%), D (53%), E (10%), and K (63%) deficiencies are often present in

patients without clinically apparent malabsorption[51,120]. The long term use of enzyme therapy for those with enzyme insufficiency is associated with improvements in stool frequency, fecal fat loss, stool consistency, and both clinician and patient assessment of symptoms[113,121]. However, past and current formulations of pancreatic enzymes are not ideal for achieving feedback inhibition or relief of exocrine pancreatic insufficiency[105,122].

The majority of currently available supplemental pancreatic enzymes are available as enteric-coated microspheres formulated as capsules or tablets. However, none of these preparations will reliably release their contents within the critical zone of the duodenum-proximal small bowel[105]. Uncoated enzymes are also available both from pharmaceutical companies and from health food stores[105,123-125]. Lipase is irreversibly inactivated when the pH falls below 4, whereas proteases are much more pH resistant and are more likely to survive transport through the stomach. However, they can both be destroyed by pepsin. The transplant studies used pancrelipase, specifically enteric-coated Pancrease[96]. Slaff *et al*[94] also clearly demonstrated feedback inhibition in 3 chronic pancreatitis patients without steatorrhea by using 30 d of non-coated Viokase, 8 tablets q.i.d. The high dose, currently available non-enteric enzyme, Viokace, (*i.e.,* with 20880 USP units of lipase) contains 78300 USP units of protease/tablet. If all the protease activity was from trypsin (which it is not) each tablet would contain only approximately 3 mg of trypsin. The dose-response experiments in man suggested at least 1 mg/mL was required for feedback inhibition. It would therefore be very unlikely that this minimum level would be achieved *in vivo* using Viokace even if all the protease activity survived transport through the stomach. Acid-stable proteases are available as over the counter medications, but to our knowledge the ability of the drug to initiate feedback regulation of pancreatic secretions or its resistance to acid-pepsin has not been tested in man. One such inexpensive, over the counter product, "Essential Enzymes 500", has been used successfully in irritable bowel syndrome. It contains 12 mg of acid stable proteases/capsule[124]. Studies are still needed using acid stable proteases for their ability to initiate feedback inhibition of pancreatic secretion.

GENERAL RECOMMENDATIONS FOR ENZYME USE AND TREATING CHRONIC PANCREATIC PAIN

Unfortunately, there are very little long-term data exploring the efficacy of treating chronic pancreatic pain with enzyme supplementation. One recent study included daily treatment with enteric-coated pancreatin for one year and noted a significantly positive impact on pain, quality of life, and emotional and physical well-being in both chronically treated and treatment naïve patients[119]. No placebo group was included which is important considering the high placebo effect reported in prior studies[32,109-111]. Another recent study compared pancreatin alone, pancreatin plus a proton pump inhibitor, or pancreatin plus a proton pump inhibitor and the NSAID aceclofenac[126]. All three regimens produced significant improvements in pain compared to no pretreatment, but the lack of a placebo questions whether the effect was due to the enzymes.

Evaluation of a new patient with suspected chronic pancreatitis requires careful consideration of multiple factors and includes a search for potentially correctable conditions (Table 3). One must also be aware of the possibility of an occult malignancy. It is important to attempt to identify and treat any nutritional deficiencies present and to strongly discourage alcohol use and smoking. This review focuses on pancreatic pain, a condition where treatment typically requires a variety of expertise often including experts in pain management. Severe pain will likely require narcotics which may eventuate in narcotic addiction. One should try to use non-narcotic drugs whenever possible (*e.g.,* nonsteroidal anti-inflammatory drugs, acetaminophen, and tramadol) and avoid opiates with a higher predilection to abuse such as *Dilaudid* (hydromorphone) and oxycodone.

Until recently the mainstay of chronic pancreatitis pain management has been opioid-based. However, as the risks of long-term opioid therapy have crystalized, clinicians are increasingly looking for alternatives. Prescription opioid overdoses have quadrupled in the last 15 years, and deaths from drug overdose are now more common than automobile collision fatalities[127]. In an effort to educate healthcare providers and curb these growing statistics, the United States Center for Disease Control issued a statement in March 2016 with guidelines regarding the prescription of opioids[127], which includes recommendations about the preferred use of non-opioid pharmacologic and non-pharmacologic therapy. They also recommend consistent reevaluation of risks and benefits of opioid therapy, using the lowest effective dosage, the avoidance of extended-release tablets and a warning against the use of opioids with benzodiazepine therapy. Clinicians providing care to chronic pancreatitis patients with high levels of pain may find these guidelines helpful in their efforts to help with pain control.

Opioid therapy can be quite effective for the short-term management of acute pain, but the long-term benefits of opioid therapy are murky as the majority of studies are of short duration[127]. Long-term comparative studies are rare and often show those who receive opioid therapy to have poorer function, are less likely to return to work, and are less likely to have good pain control[128,129]. Opioid therapy also affects smooth muscle tone leading to gastrointestinal motility disturbances and abdominal pain[130-134]. While morphine is effective in reducing pain in chronic pancreatitis, a double-blinded comparison with tramadol reported that patients with chronic pancreatitis preferred tramadol to morphine for anesthesia[130]. In addition, tramadol does not increase smooth muscle tone in the sphincter of Oddi[130].

The first choice for chronic pain should likely be non-steroidal anti-inflammatory drugs (NSAIDs) and/

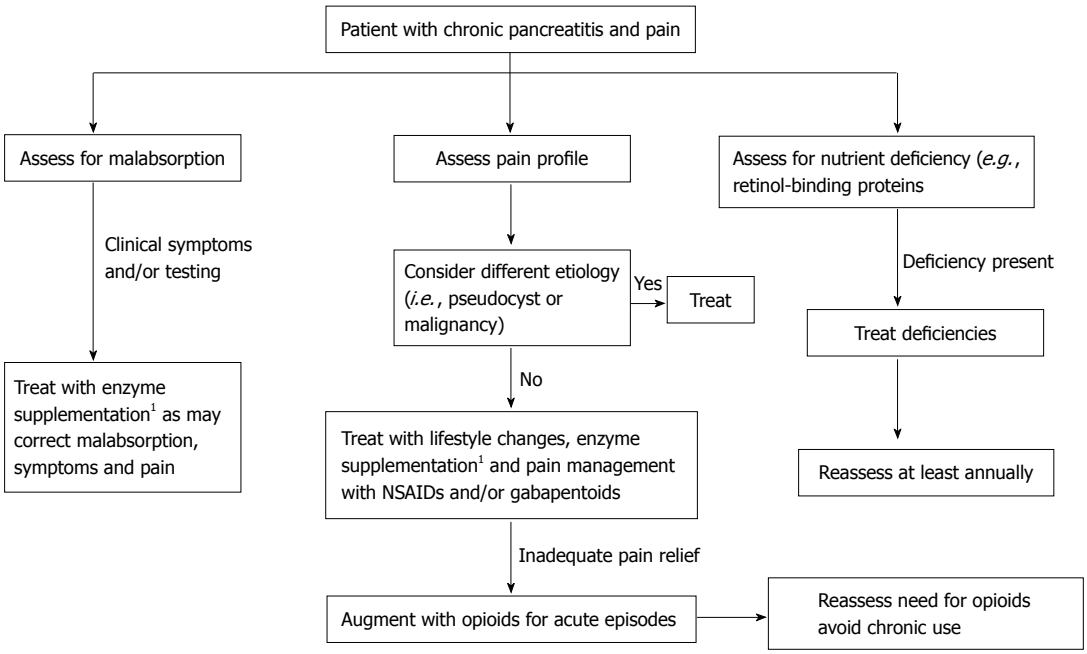

Figure 1 Flow chart demonstrating recommendations for using pancreatic enzyme replacement therapy in a patient with abdominal pain and chronic pancreatitis. [1]Start with non-enteric coated products such as Viokace along with a PPI. The figure suggests approaching the patient with a three-pronged method. First, one should assess the patient's pain profile and investigate whether the pain is from chronic pancreatitis alone or from other etiologies, *i.e.*, a developing pseudocyst or malignancy. Next, pain control should be attempted first with conservative measures such as lifestyle changes, enzyme supplementation, NSAIDs, and/or gabapentoids before moving to treat with opioids. If opioids are deemed appropriate for pain control, the decision should be consistently reassessed as to avoid dependency and addiction. Second, one should assess the patient for malabsorption, and if present, the patient should be treated with exogenous enzymes as that may improve absorption and pain symptoms. Lastly, the physician should assess the patient's nutritional status and correct deficiencies, if present. A non-enteric-coated enzyme such as Viokace along with a proton pump inhibitor is recommend for first-line enzymatic treatment. Alternatively, can use combination of non-enteric-coated and enteric-coated formulations. NSAIDs: Nonsteroidal antiinflammatory drugs; PPI: Proton pump inhibitors.

or gabapentoids to treat neuropathic pain. Generally, NSAIDs are used for analgesia and full anti-inflammatory doses are neither required nor indicated. Primarily analgesic NSAIDs include low dose naproxen, ibuprofen, nabumetome and etodolac[135]. Higher doses typically do not increase analgesia but increase risk of side effects. Co-therapy with a proton pump inhibitor should be considered. Gabapentoids such as pregabalin are often used as adjuvant therapy due to possible similarities between chronic pancreatic pain and neuropathic pain[136]. A study of pregabalin enrolled patients who were concurrently undergoing opioid therapy and reported success suggesting a role for pregabalin in chronic pancreatitis pain[136]. However, none of these approaches are without accompanying side effects and long-term studies are needed.

The natural history of pain in any particular patient is impossible to predict[23]. In general, those with constant pain have a worse prognosis than those with intermittent pain[24]. While pancreatic enzyme therapy is a mainstay in the therapy of exocrine pancreatic insufficiency, it can also be used in an attempt to produce feedback inhibition of enzyme secretion although this is likely only useful for those who retain exocrine function.

Prior studies have suggested that feedback inhibition was only effective in those without steatorrhea[94]. Indeed, longer term studies in pancreatic pain have confirmed that those with pain and pancreatic insufficiency generally are the most difficult to treat[17,94]. However, a reduction in malabsorption can also lead to reduced symptoms[47-49]. We recommend that all patients with chronic pancreatitis should be screened for nutritional deficiencies which includes measuring serum magnesium, hemoglobin, albumin, prealbumin, retinol binding protein levels, hemoglobin A1C, and body mass index. For those with low retinal binding protein, one should consider that fat-soluble vitamin deficiencies are likely present. For initial therapy for patients with pancreatic pain, we recommend that the focus be on correcting nutritional deficiencies and malabsorption. Treatment of fat malabsorption requires at least 20000-30000 USP units of lipase/meal[105]. One might start with the non-enteric-coated 10000 lipase unit Viokace formulation (*i.e.*, one tablet at the beginning of the meal or just before the meal, and 2 or 3 more tablets spread throughout the meal plus one per snack). The use of a proton pump inhibitor is recommended, possibly as a double dose such as 40 mg of esomeprazole twice a day, to reduce destruction of lipase during transit through the stomach. Potassium competing acid blockers should simplify therapy when they become available in that they provide reliable pH control. Alternatively, one could use a combination of non-enteric-coated and enteric-coated formulations[105]. Improved nutritional status should be assessed at least once a year and include measuring serum magnesium, hemoglobin, albumin, prealbumin, retinol binding protein levels (a surrogate for fat soluble

vitamins), and body mass index (Figure 1).

However, enzyme therapy is not without its pitfalls as properly mimicking the normal physiology of nutrient digestion and absorption is difficult[47,105]. Enteric-coated enzymes must mix properly in the stomach, not separate from the meal, and dissolve and remain active in the duodenum as to allow proper metabolism, digestion, and absorption for the completion of the feedback loop and resting of the pancreas. With current formulations, delivery of sufficient protease to the duodenum is impossible with enteric-coated products and difficult with non-enteric-coated ones.

CONCLUSION

Whether pancreatic enzyme administration for chronic pancreatic pain is effective remains a debated subject. Although reviews on the topic suggest there is little evidence for benefit, the conclusions are based on a potpourri of studies which vary dramatically in design and execution. Enzyme preparations also differ greatly in size, composition, and action but are generally treated as equal despite a lack of information and formal studies. A majority of experiments have used only enteric-coated preparations which have been shown to separate from meals and dissolve distal to the duodenum. Until formal studies including head to head comparisons are performed and characteristics such as mixing and dispersion properties are known, we are left without the crucial information needed. Uncoated enzymes, while largely being replaced by more modern preparations, have shown promise in treating pain and need to be explored further. Use of acid resistant proteases are needed as well as better strategies to overcome the gastric and intestinal pH barriers to maximize proper enzyme delivery to the duodenum for both uncoated and enteric-coated preparations. Future studies evaluating the use of enzymes with concurrent antacid and/or anti-secretory therapies, especially with potassium competing acid blockers, are needed. Furthermore, clinical trials will ideally include long-term treatment arms and large treatment groups to allow for more reliable data gathering. Patients should also be subcategorized based on etiology and severity in order to specifically study response to treatment. Most importantly, the complexity of data gathered here should serve to help individualize enzyme replacement therapy. For example, clinical trials could be done to confirm suggestions that patients with idiopathic chronic pancreatitis and mild to moderate exocrine insufficiency respond better to enzyme therapy than those of alcoholic origin and severe exocrine impairments. Pain scores must be standardized and validated. Exogenous enzyme therapy may decrease secretion, is noninvasive, has relatively no adverse effects, and improves malabsorption in those with exocrine insufficiency. There is little to be lost and potentially much to be gained by trying enzyme therapy, but more studies are needed before they can be used in evidence-based medicine.

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