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Chronic pancreatitis

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Abstract

Purpose of review—We review selected important clinical observations reported in 2012.

Recent findings—Celiac disease is a risk factor for pancreatitis. Patients with recurrent acute pancreatitis likely have chronic pancreatitis, do not benefit from pancreatic sphincterotomy, and may not benefit from biliary sphincterotomy. Analysis of endoscopic ultrasonography (EUS) images with an artificial neural network (ANN) program may improve chronic pancreatitis diagnosis compared with clinical interpretation of images. In a multicenter, randomized controlled trial of chronic pancreatitis patients, 90 000 USP U of pancreatin with meals decreased fat malabsorption compared with placebo. Detection of visceral pain in chronic pancreatitis predicts pain relief from various treatments, but nonvisceral pain due to altered central pain processing may respond to agents such as pregabalin. Predictors of surgical pain relief include onset of symptoms less than 3 years and preoperatively no opioid use and less than five endoscopic procedures. Total pancreatectomy for presumed painful chronic pancreatitis remains controversial.

Summary—Celiacs are at risk for pancreatitis. The diagnosis of chronic pancreatitis may be enhanced by ANN analysis of EUS imaging. Treatment of fat malabsorption requires 90 000 USP U of lipase with meals. Relief of pain from organ directed treatment of chronic pancreatitis may depend upon timing of interventions and whether pain is visceral or nonvisceral.

Keywords

chronic pancreatitis; exocrine pancreatic insufficiency; pain

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Conflicts of interest

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INTRODUCTION

Currently, there is no definite medical treatment for pancreatic inflammation, fibrosis or pain of chronic pancreatitis. In this review, we focus on the association between celiac disease and pancreatitis, impact of biliary and pancreatic sphincterotomy on recurrent acute pancreatitis (RAP), differentiation between pancreatic cancer and chronic pancreatitis, dosing of pancreatic enzyme replacement therapy (PERT) to treat exocrine pancreatic insufficiency (EPI), detecting visceral pain as a predictor for pain relief to various treatments, predictors of pain relief from surgery and effectiveness of antioxidants and total pancreatectomy to treat painful chronic pancreatitis.

CELIAC DISEASE AND PANCREATITIS

Sadr-Azodi *et al.* [1■] agree that there is an increased risk of developing pancreatitis in patients with celiac disease [2,3]. The authors report an overall three-fold increased risk of developing any pancreatitis compared with the general population, a hazards ratio (HR) of 1.9 in acute pancreatitis and an HR of 3.3 in chronic pancreatitis. In a previous analysis of the same Swedish Patient Register [2], the HR for any pancreatitis was similar, but the HR for chronic pancreatitis was much higher (19.8). Recognizing that celiac disease is a risk factor for pancreatitis is clinically important, but the magnitude of the risk is uncertain likely because of the inaccuracies of the diagnoses of acute and chronic pancreatitis.

The diagnosis of acute pancreatitis was based on International Classification of Diseases-Clinical Modification (ICD-CM) codes (editions 7–10) in the Swedish Patient Register, which is 83% accurate for definite acute pancreatitis based on a previous validation study [4]. Thus, acute pancreatitis was misdiagnosed in ~ 20% of patients. It seems likely that the method of diagnosing acute pancreatitis and characteristics of the celiac population may have contributed to an even higher misdiagnosis rate. Diagnosis was based on a ‘combination of elevated serum amylase or lipase and clinical symptoms, including abdominal pain’, which would under-diagnose acute pancreatitis in patients with lower serum amylase values but imaging evidence of acute pancreatitis and would overdiagnose acute pancreatitis due to hyperamylasemia without acute pancreatitis, which the authors note may occur in a variety of conditions [1■], including celiac disease [5,6]. More importantly, there is no apparent validation for the methods to diagnose chronic pancreatitis, which was based on either ICD-CM codes in the registry and/or documentation of PERT prescriptions from the Swedish Prescribed Drug Register. In our experience, significant overdiagnosis of chronic pancreatitis may occur when ICD-9-CM code (577.1) is used for the diagnosis of chronic pancreatitis rather than one or more clinical scoring systems employing clinical criteria, tissue diagnosis, calcifications, abnormal imaging and objective findings of EPI and diabetes mellitus. For example, in 1343 patients with an ICD-9-CM code (577.1) for chronic pancreatitis, only 49% fulfilled criteria for chronic pancreatitis in any of three scoring systems [7] (Japanese Pancreas Society [8], Zurich Workshop [9] and the Mayo Score [10]). Thus, diagnosis of chronic pancreatitis based solely on ICD-9-CM (577.1) may result in overdiagnosis of chronic pancreatitis [7] and erroneous conclusions. Using prescriptions for PERT to diagnose chronic pancreatitis is also problematic; PERT might erroneously be

prescribed for a variety of patients with conditions such as irritable bowel syndrome and malabsorption due to celiac disease or causes other than chronic pancreatitis.

Sadr-Azodi *et al.* [1■] overlooked earlier observations when they report that, '…the effect of celiac disease on pancreatic function is poorly understood'. The association of EPI and chronic pancreatitis with celiac disease has been known for over 50 years. And 30 years ago, DiMagno *et al*. [11] determined the underlying pathophysiology of these associations. They demonstrated subnormal outputs of enzymes and failure of increasing bile outputs (lack of gallbladder contraction), following infusion of intraluminal essential amino acids or eating but normal outputs occurred after exogenous cholecystokinin (CCK), leading to the hypothesis that CCK secretion is lacking in celiac disease. Postprandially, these abnormalities resulted in maldigestion of fat because of the asynchronization between transit of the meal and delayed and reduced secretion of pancreatic enzymes and bile into the small intestine that occurred during the first 30 min after eating. After the initial 30 min, postprandial dilution of intraluminal content secondary to abnormalities of fluid and electrolyte absorption/secretion also contributed to impaired fat digestion. Fat maldigestion was worse after a second meal. In a second study [12], they showed that in 31 celiac patients, CCK stimulated enzyme outputs were decreased in 42% and 3 (10%) had severe EPI contributing to malabsorption.

IDIOPATHIC CHRONIC PANCREATITIS AND SPHINCTER OF ODDI DYSFUNCTION

Cote *et al.* [13■■] in a prospective randomized trial evaluated the effects of biliary endoscopic sphincterotomy (BES) or dual (biliary and pancreatic) endoscopic sphincterotomy (DES) in patients with RAP. Patients in this study likely had idiopathic chronic pancreatitis, as 17% developed chronic pancreatitis during follow-up, a likely underestimate because tests to determine the presence of chronic pancreatitis were not performed regularly. The abstract conclusions are: 'Among patients with pancreatic SOD [sphincter of Oddi dysfunction], DES and BES have similar effects in preventing recurrence of acute pancreatitis. Pancreatic SOD is an independent prognostic factor, identifying patients at higher risk for RAP.' These conclusions are based on finding that the odds of RAP were greater in patients with SOD (48.5% who received BES and 47.2% who received DES), than in patients with a normal sphincter of Oddi manometry (27% had BES and 11% had a sham procedure). Unfortunately, the conclusions are problematic because there is no control group of SOD who had a sham procedure. An alternative conclusion might be that endoscopic procedures associate with increased recurrence of acute pancreatitis. Another problem is that genetic testing is not reported or not done (the study began in 1997, perhaps before genetic testing was done at the institutions, but certainly these were available in later years).

Thus, we conclude that patients enrolled in this study had idiopathic chronic pancreatitis, which will be confirmed by long-term follow-up. Further, genetic testing could identify one or more gene mutations associated with idiopathic chronic pancreatitis. More importantly, results of this study indicate that in these patients pancreatic sphincterotomy should not be

done and BES is questionable and requires future well designed, placebo-controlled/sham-controlled clinical trials to justify its use.

DIFFERENTIATION BETWEEN PANCREATIC CANCER AND CHRONIC PANCREATITIS

Differentiation between pancreatic cancer and chronic pancreatitis with imaging tests is improving but remains imperfect. To improve interpretation of endoscopic ultrasonography (EUS) images, we first reported and demonstrated that an artificial neural network (ANN) analysis of EUS images differentiated between pancreatic malignancy and chronic pancreatitis with similar accuracy compared with blinded videotape analysis and real time analysis (80, 83 and 85%, respectively) [14]. Since then advances in EUS technology such as EUS elastography have occurred and this past year Saftoiu *et al.* [15■■] evaluated an ANN of EUS elastography in the diagnosis of focal pancreatic masses in a prospective, blinded study of 258 patients (211 with pancreatic cancer and 47 with chronic pancreatitis) from 13 centers in Europe. They reported an overall accuracy of 84% and a significantly higher area under the receiver operating characteristic (ROC) curve compared with mean hue histogram analysis (0.94 vs. 0.85). Thus, this study provides more evidence that ANN analysis of EUS images may improve diagnosis.

MANAGEMENT OF EXOCRINE PANCREATIC INSUFFICIENCY

Inadequate dosing of PERT is prevalent among patients with chronic pancreatitis and EPI. For example, Sikkens *et al.* [16■] conducted an anonymous survey of 176 Dutch patients with chronic pancreatitis and found that the median enzyme intake was six capsules per day (25 000 Units lipase per capsule), 25% of patients took three or fewer capsules, and 70% of patients reported steatorrhea-related symptoms, despite treatment. The survey method had many shortcomings (no data on how or when the capsules were taken, no quantification of supposed steatorrhea, etc). Nevertheless, the presence of significant symptoms is not surprising, as the patients were taking doses of pancreatin that would not correct steatorrhea. On the basis of gastrointestinal intubation and fat balance studies performed in persons with severe chronic pancreatitis and EPI [17–21] the minimal dose of lipase which may correct steatorrhea is 90 000 USP U with meals (~3–4 capsules per meal), 10% of the normal prandial lipase output of 900 000 USP U.

The benefit of 90 000 USP U of pancreatin [two capsules of CREON (Abbott Laboratories, Abbott Park, Illinois) 40 000 containing 45 000 USP U lipase with meals and one capsule with snacks] compared with placebo was assessed in a multicenter, randomized controlled trial (RCT) in 62 patients with chronic pancreatitis and a coefficient of fat absorption (CFA) less than 80% [22■]. Pancreatin increased the CFA from 66.5 to 86.1% (mean change of CFA vs. placebo, 18.5 vs. 4.1%; $P = 0.001$) and the coefficient of nitrogen absorption (CNA) from 78.8 to 83.8% (mean change of CNA vs. placebo 4.7 vs. 0.8%; $P = 0.005$) and decreased stool frequency and weight. Of note ~35% of patients were on a proton pump inhibitor. Similar to a histamine H2-receptor antagonist [19,20], proton pump inhibitors likely alleviate fat malabsorption if 90 000 USP U [30 000 international units (IU)] of pancreatin are ingested with meals containing 25 g of fat by producing postprandial

intraduodenal lipase concentrations of 75 USP U/ml (25 IU/ml), the concentration that corrects steatorrhea.

MANAGEMENT OF PAIN

The medical, endoscopic and surgical management of painful chronic pancreatitis remain contentious. Some questions are which patients will achieve pain relief and what is the proper timing for initiating various treatments? Inroads, however, are slowly being made.

The Cleveland Clinic group [23■] performed a retrospective but interesting study using a differential nerve block (DNB) to distinguish visceral from nonvisceral (somatosensory, central and psychogenic) pain in patients who had severe chronic pancreatitis based on imaging studies. They found that the distribution of visceral vs. nonvisceral pain among the three classes of chronic pancreatitis based on EUS findings (normal, mild and severe) was not significant (47 to 67%). The conclusion is somewhat confusing because it is unclear how the diagnosis of chronic pancreatitis was made in patients with a normal EUS and how the severity (mild and severe) of chronic pancreatitis was determined.

A more interesting finding was that only patients with visceral pain had pain relief in response to a variety of visceral neural (e.g. celiac plexus block) or pancreatic surgical treatments. DNB to differentiate types of pain, however, needs to be validated prospectively in a much larger study with chronic pancreatitis patients of different causes and treatments. In contrast, it is becoming increasingly apparent that patients with nonvisceral (central) pain with changes in central pain processing may respond to agents such as pregabalin [24], which may modestly reduce peripheral hyperalgesia (a marker of central sensitization to pain). If larger and longer clinical trials indicate that pregabalin durably reduces pain and increases the quality of life in chronic pancreatitis patients with central pain, we may be able to stratify patients by categories of types of pain and choose appropriate treatments on this basis.

ANTIOXIDANTS

Whether antioxidants, a treatment based upon the oxidative stress hypothesis, reduce pain in chronic pancreatitis remains controversial. Siriwardena *et al.* [25■■] found in a RCT in the United Kingdom that an antioxidant cocktail increased blood levels of antioxidants but did not reduce pain or improve quality of life of patients having chronic pancreatitis mainly associated with alcohol. These data contrast with conclusions of a previous RCT, also published in *Gastroenterology*, from India of a young population of mostly patients with idiopathic pancreatitis [26] that ‘antioxidant supplementation was effective in relieving pain in patients with chronic pancreatitis’. These contrasting data, therefore, do not lend support for treating chronic pancreatitis with antioxidants, an opinion expounded by Forsmark and Liddle in an editorial [27■]. In view of the relatively new information regarding visceral vs. nonvisceral pain another difference among studies might be the different distribution of these types of pain among studies. Possibly, only patients with chronic pancreatitis and visceral pain respond to antioxidants.

SURGERY

The Dutch Pancreatitis Study Group [28■] evaluated pain relief, quality of life and other outcomes in a long-term cohort of 266 patients who underwent a variety of surgical procedures for constant pain. By multivariate analysis, they found that greater pain relief occurred if surgery was less than 3 years after onset of symptoms, there was no preoperative opioid use and if less than five endoscopic procedures were performed before surgery. By using these variables the probability of achieving pain relief varied between 23 and 75% when patients have none to all three favorable variables. Decreased postoperative physical and or mental quality of life associated with preoperative opioid use, pancreatic head resection and relaparotomy.

It is unclear, however, what is the optimal timing of surgery, and if early surgery would be superior to a step-up approach beginning with a medical program and surgery done only after failure of such a program. The Dutch Pancreatitis Study Group is currently carrying out a RCT comparing early surgery as soon as patients develop the need for opioid analgesics vs. a control arm consisting of a step-up approach of opioid analgesics, if needed, followed by a limited period of endoscopic interventions and finally surgery if previous steps are insufficient to relieve pain. Such randomized control studies may provide answers to these questions.

TYPES OF SURGERY

Yin *et al.* [29■] performed a meta-analysis comparing conventional pancreaticoduodenectomy and duodenal preserving pancreaticoduodenectomy procedures and reported that compared with conventional pancreaticoduodenectomy, the Beger procedure achieves complete pain relief in most patients, but not better postoperative morbidity. In contrast, the Frey procedure significantly reduces postoperative morbidity, but complete pain relief does not occur in most patients.

TOTAL PANCREATECTOMY

We have concerns with recommendations voiced again this year for total pancreatectomy treatment of chronic pancreatitis [30–32]. Some patients undergoing total pancreatectomy in these studies may not have chronic pancreatitis because many patients have questionable causes for pancreatitis such as pancreas divisum and SOD, have clinical histories that are not convincing for chronic pancreatitis, are predominantly women (when there is an equal distribution among sexes or a predominance of men in most causes), and pancreatic tissue diagnostic proof of chronic pancreatitis is apparently lacking. To submit these usually young patients, even children, to total pancreatectomy and lifelong exocrine and endocrine insufficiency may not be justified, particularly if the diagnosis of total pancreatectomy is not ironclad and when outcomes are less than ideal.

One series of 409 patients who underwent total pancreatectomy included 53 children [32]. Although the authors list criteria supporting the diagnosis of chronic pancreatitis before total pancreatectomy is done, it is unclear how many have definite tissue proof of chronic pancreatitis by histology, which would settle this issue. The authors claim total

pancreatectomy reduces pain and prevents diabetes, but it is impossible to determine the effect of total pancreatectomy on clinical outcomes because data are presented on subsets of the 409 patients ranging from 268 for islet function to 207 for narcotic use and pain (Figures 3 and 4 of the article). Even these selected data reveal that preoperatively 92% are nondiabetic patients but postoperatively more than two-thirds use insulin and 41% continue narcotics at 2 years. No data are presented regarding EPI but certainly all have malabsorption postoperatively requiring PERT, which likely hampers glycemic control of diabetes. Likely, a significant proportion of these patients have central pain (perhaps originally resulting from painful chronic pancreatitis or from nonpancreatic causes) instead of visceral pain. In these patients it is unreasonable to perform total pancreatectomy, producing diabetes, malabsorption without relieving pain. Another potential concern is possible decreased long-term survival; overall 10-year survival is 81% and of children (ages 5–18 years old) it is 79%. To be certain of the benefit of total pancreatectomy on survival as well as outcomes for diabetes and pain requires a comparison with a population of chronic pancreatitis without total pancreatectomy and the general population.

CONCLUSION

This year's literature contained moderate advances to further elucidate the influence of celiac disease on pancreatitis, the potential of ANN computer programs to aid diagnosis of chronic pancreatitis by EUS, detection of visceral pain as a predictor of pain relief from various treatments and prediction of pain relief from pancreatic surgery.

Acknowledgments

None.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 573–574).

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KEY POINTS

- Celiacs are at increased risk for pancreatitis.
- Detection of visceral pain using a DNB predicts pain relief in response to various treatments.
- Agents such as pregabalin modestly reduce peripheral hyperalgesia in nonvisceral (central) pain.
- Three variables independently predict pain relief following pancreatic surgery: onset of symptoms is less than 3 years, no opioid use preoperatively and less than five endoscopic procedures.
- Total pancreatectomy for presumed painful chronic pancreatitis remains controversial.