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Chronic Pancreatitis

Matthew J. DiMagno, MD* and Eugene P. DiMagno, MD§

*University of Michigan Medical School, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Ann Arbor, MI 48109, USA

§Mayo Clinic College of Medicine, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Rochester, MN, 55905, USA

Abstract

Purpose of review—We review important new clinical observations in chronic pancreatitis (CP) made in the past year.

Recent findings—Tropical pancreatitis associates with *SPINK1* and/or *CFTR* gene mutations in approximately 50% of patients, similar to the frequency in idiopathic CP. Corticosteroids increase secretin-stimulated pancreatic bicarbonate concentrations in AIP by restoring mislocalized *CFTR* protein to the apical ductal membrane. Most patients with asymptomatic hyperenzymemia have pancreatic lesions of unclear significance or no pancreatic lesions. Common pitfalls in the use of diagnostic tests for EPI confound interpretation of findings in IBS and severe renal insufficiency. Further study is needed to improve the accuracy of endoscopic ultrasonography (EUS) to diagnose CP. Celiac plexus block provides short term pain relief in a subset of patients.

Summary—Results of this year's investigations further elucidated the genetic associations of tropical pancreatitis, a reversible mislocalization of ductal *CFTR* in AIP, the association of asymptomatic pancreatic hyperenzymemia with pancreatic disorders, limitations of diagnostic tests for EPI, diagnosis of CP by EUS and endoscopic pancreatic function testing and treatment of pain.

Keywords

chronic pancreatitis; cystic fibrosis; exocrine pancreatic insufficiency

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory and fibrotic disease of the pancreas with hallmark features of abdominal pain, malabsorption, malnutrition, diabetes mellitus and pancreatic calcifications. Currently, there is no definitive medical treatment for pancreatic inflammation, fibrosis or pain. In this review we focus on genetic associations of tropical pancreatitis, reversible mislocalization of ductal cystic fibrosis transmembrane conductance regulator (*CFTR*) in autoimmune pancreatitis (AIP), asymptomatic pancreatic hyperenzymemia, testing for exocrine pancreatic insufficiency (EPI), diagnosis of CP by endoscopic ultrasound (EUS) and endoscopic pancreatic function (ePFT) testing and neuropathic pain of CP.

Corresponding author: Matthew J. DiMagno, MD, Department of Internal Medicine, Division of Gastroenterology and Hepatology, University of Michigan Medical School, 1150 W Medical Center Drive, Room 6520 MSRB I, Ann Arbor, MI 48109-0682, USA, mdimagno@umich.edu, **Telephone number:** (734) 763-7278, **Fax number:** (734) 763-2535.

Environmental risk factors

We recently reviewed the association of smoking and drinking alcohol with CP, acute pancreatitis and recurrent acute pancreatitis [1]. For updated information we encourage the reader to refer to two new studies [2, 3], a meta-analysis [4] and an editorial [5].

Tropical Pancreatitis

As we previously reviewed [6], gene mutations of the serine protease inhibitor, Kazal type 1 (*SPINK1*) are important in tropical pancreatitis and are detected in 20–55% of patients [7–12]. Recently, Midha et al [13] found that compared to controls *SPINK1* N34S mutation is significantly more common in non-alcoholic CP in India, present in 42% of 242 patients with idiopathic CP (vs. 4% controls). In addition 9 patients with idiopathic CP had *CFTR* mutations and 41 had polymorphisms (50% vs. 10% controls). Overall, more than 50% of patients with idiopathic CP had *SPINK1* and/or *CFTR* mutations, a finding similar to a study of Western populations showing an overall frequency of the *CFTR* and/or *SPINK1* genes in up to 50% of patients with early onset idiopathic CP [14–16]. Typical features of tropical calcific pancreatitis occurred in 5.8% of patients. Hence, based on the phenotypic similarities between idiopathic CP in India and other countries and the strong genetic predisposition in more than 50% of patients, Midha et al [13] suggested that the term ‘tropical calcific pancreatitis’ is a misnomer, which prompted 3 letters to the editor from Indian experts in CP. Ramesh [17] stated “the data...do not support any change in nomenclature of ‘tropical pancreatitis’ and, apart from highlighting the prevalence of genetic mutations which may suggest a genetic etiology, has not significantly changed our understanding or description of the disease”. Similarly Balakrishnan [18] concluded that “To deny retrospectively that there was no entity of TCP is historically incorrect. Rather, we should use this opportunity to study the factors responsible for the changing phenotype of TCP and gain some insights into the factors contributing to the causation of CP.” Paliwal [19] essentially agreed with these responders stating that the criteria for the diagnosis of tropical pancreatitis have changed. Our interpretation of these conflicting opinions is that in India idiopathic CP is commonly associated with *SPINK1* and *CFTR* mutations but the natural history is altered by environmental factors including nutrition, alcohol and smoking. Despite Midha’s insistence that malnutrition is secondary to CP [13], malnutrition particularly, and perhaps other unrecognized environmental factors (cassava has been excluded) may accelerate the development of diabetes and calcifications so that young patients with idiopathic CP previously presented with diabetes and calcific pancreatitis. Support for this hypothesis derives from data showing that etiologic factors such as smoking and ingesting large amounts of alcohol decrease the time to hallmarks of CP (calcification, diabetes and steatorrhea). Likely in present day India, better nutrition delays the onset of diabetes and pancreatic calcification

Autoimmune Pancreatitis (AIP)

We focused this year’s review of AIP on a single, mechanistic study that shows that corticosteroids increase secretin-stimulated pancreatic bicarbonate concentrations in AIP by restoring mislocalized *CFTR* protein to the apical ductal membrane [20]. The reader is otherwise referred to excellent reviews on AIP [21, 22], the Honolulu consensus statement on AIP [23], and primary sources including comparisons between type I and type 2 AIP [24, 25], new targets for serologic testing in AIP [26], diagnostic utility of immunostaining of duodenal papillary biopsy specimens [27] and differentiation of AIP from pancreatic cancer by diffusion-weighted MRI [28].

The limited data indicating that corticosteroid treatment of AIP may improve histopathology and exocrine pancreatic function [29, 30] raises the possibility that steroids may improve

other forms of CP. Ko et al [20] investigated the effect of corticosteroids on AIP by performing pancreatic biopsy and secretin stimulated direct pancreatic function testing on twenty-one patients with AIP, both before, during and at the completion of standardized corticosteroid treatment. The investigators found that corticosteroids reduced pancreatic fibrosis and tissue inflammation, triggered regeneration of acinar tissue and increased secretin evoked pancreatic juice bicarbonate and amylase concentrations, particularly after 12 months. They attributed increases in pancreatic juice amylase concentration to regeneration of acinar tissue and improved bicarbonate secretion to restoration of the mislocalized *CFTR* protein in the ductal cytoplasm to the apical ductal membrane. It remains unclear whether *CFTR* mislocalization and aberrant function (sweat and spirometry tests, nasal potential difference) occur in non-pancreatic organs in patients with AIP. Surprisingly, ductal *CFTR* mislocalization was present in pancreas from 11 patients with other forms of CP.

These data may explain findings of others that patients without *CFTR* gene mutations can have a phenotype indistinguishable from those with *CFTR* gene mutations [31]. Knowles and Durie [32] pointed out previously that other genes or factors may affect *CFTR* trafficking and contribute to a variant CF phenotype. Further studies are warranted to determine whether inflammation or other factors trigger *CFTR* mislocalization, to determine the durability of treatment on reversing pancreatic fibrosis and improving exocrine pancreatic function in AIP, and to confirm whether mislocalization of *CFTR* (and a variant CF phenotype) explains aberrant pancreatic bicarbonate secretion in other forms of CP. Finally, these data raise the possibility that pancreatic fibrosis may be reversible dependent upon etiology, similar to the reversibility of fibrosis reported for several types of liver disease (e.g. autoimmune hepatitis).

Steroid treatment for CP is an old but illusive story. Available data indicates that corticosteroid or anabolic steroid treatment is unlikely to improve exocrine pancreatic secretion and fat malabsorption. In CP corticosteroids increase amylase but not lipase secretion [33]. Therefore the results of this study indicate that corticosteroids may have no effect on lipase secretion in CP and be of little use in treating EPI.

Nevertheless, steroid treatment might have therapeutic potential by decreasing the ratio of trypsin to anti-trypsin activity and thereby reducing the frequency and severity of repeat episodes of acute inflammation in CP. According to a 35-year old report and review by Tuzhilin and Dreiling [34] treatment of CP patients with corticosteroids, anabolic steroids (metandrostendiol) or a high protein diet could normalize low blood levels of 17-hydroxycorticosteroids and reverse the imbalance between high blood trypsin and low blood trypsin inhibitor activities. Several concerns, however, were raised by others who showed that corticosteroids may sensitize CCK receptors to endogenous CCK signaling [35] and may delay tissue recovery following episodes of acute pancreatitis [36]. Hence, although corticosteroids are appropriate for AIP and anabolic steroid treatment has been suggested for CP [37, 38], there are no well-designed human studies to determine whether corticosteroids or anabolic steroids have therapeutic value in forms of CP other than AIP.

Asymptomatic Pancreatic Hyperenzymemia

There is controversy whether asymptomatic pancreatic hyperenzymemia indicates undiagnosed pancreatic disease. Originally, Gullo reported that asymptomatic pancreatic hyperenzymemia was a benign entity with no pancreatic abnormalities [39], sometimes occurring in families [40], but other investigators report a frequent association with surreptitious pancreatic disease. Recently, Donati et al [41] defined asymptomatic hyperenzymemia as less than three-fold increase in lipase and/or amylase for at least 6

months and reported that 71% of affected patients (57/80) have pancreatic abnormalities by MRCP. Moreover, they found that SS-MRCP was superior to conventional MRCP to detect pancreatic abnormalities, mainly by identifying more patients with pancreas divisum (22 vs. 12) and mild CP (12 vs. 2). Their proportion of patients with pancreatic abnormalities is higher than reported earlier by Testoni et al [42] (25%) who also reported superiority of SS-MRCP over MRCP. Thus, SS-MRCP documents pancreatic abnormalities in many if not most patients with asymptomatic hyperenzymemia, but the clinical significance of most of the findings (pancreas divisum and pancreatic cyst <1cm; totaling 55% of the Donati series [41]) is uncertain. In this vein Lankisch [43] opined in an editorial that the findings are “nonspecific and/or of unknown clinical significance, and do not benefit the patient because there are no immediate diagnostic or therapeutic consequences”. Without an evidence based approach for asymptomatic pancreatic hyperenzymemia, perhaps the best course is to measure salivary amylase and macroamylase, and if negative exclude pancreatic disease by performing an imaging test to be repeated in 3–6 months.

Testing for Exocrine Pancreatic Insufficiency (EPI)

Recent studies used fecal elastase and either fecal fat or stool frequency to determine whether EPI associated with severe renal insufficiency [44] and patients who fulfilled the Rome II criteria for diarrhea predominant irritable bowel syndrome (IBS-D) [45]. These studies illustrate how pitfalls in diagnostic tests limit the interpretation and significance of findings.

In patients with severe renal insufficiency Griesche-Phillipe et al [44] reported that fecal elastase was normal in 48 of 50 patients (96%) and that 2 patients with normal fecal elastase had steatorrhea. Finding that most patients had normal fecal elastase in this population is not surprising based on previous investigations of EPI in severe renal insufficiency. For example, 25 years ago, the editor Dr. Owyang, the senior author and others reported that patients on hemodialysis who had a normal body weight had normal lipase, and above normal trypsin outputs [46]. Nevertheless, a small proportion of patients with severe renal insufficiency may have EPI and Griesche-Phillipe et al [44] likely under-estimated this proportion because the fecal elastase test (below) is inaccurate and the fecal fat determinations as performed in this study were not controlled for fat intake and stool collections (see below).

Limitations of fecal elastase measurements

As we recently reviewed [1], investigators continue to use the simple fecal elastase test as a surrogate for EPI and CP despite abundant data indicating it is an inaccurate measure of EPI. Test sensitivity is unacceptably low; for example it is 64% for severe disease and 40% for mild-moderate disease [47]. Test specificity is also poor because low values occur in 25–30% of patients with small bowel conditions [48–52] such that fecal elastase has been promoted as a marker of enteropathy regardless of cause [50]. Diabetes mellitus also causes a low stool elastase [53–56], and in type I diabetes it has an unacceptably low specificity and positive predictive value for EPI based on comparisons to direct pancreatic function tests [56]. Because dilution of stool lowers stool elastase, persons with IBS and large volume diarrhea may have a false positive test [57].

Limitations of fecal fat measurements

The study of Griesche-Phillipe et al [44] illustrates common pitfalls in assessing fat absorption, either to determine its presence or response to treatments in patients with suspected EPI. As in this study, normal fat absorption is usually assumed to be 7 g/fat per 24h based on previous studies of multiple investigators, including Wollaege et al [58], who

also nicely summarized this historic data in two publications [58, 59]. This amount of fat excretion is based upon ingesting 100g fat/day (normal fat absorption = 93% coefficient of fat absorption; CFA). If one assumes fat malabsorption to be >7 g/fat per 24h, ingesting <100 g/24h of fat may yield <7 g/fat per 24h in the presence of fat malabsorption and ingesting >100 g/24h of fat may yield fecal fat >7g/24h when fat absorption is normal. Indeed, in 1947 Wollaeger et al [58] reported that doubling the amount of daily fat in the diet from 101.6 g to 208 g in healthy volunteers will lead to doubling of the fat lost in the stool. Moreover, they reported a linear relationship between fat intake and fecal fat excretion based on analysis of pooled data from six carefully performed older studies published during 1899–1907. Hence, when fat intake is variable CFA should be reported. Lastly, incomplete stool collections may underestimate fat absorption.

In another study Leeds et al [45] used the fecal elastase test to assess EPI and reported that EPI was present in 19 of 314 (6.1%) patients who fulfilled the Rome II criteria for IBS-D. The data is difficult to interpret because fecal elastase is inaccurate to diagnose EPI and definite pancreatic disease was present (by CT) in only 4 of the 19 with a low fecal elastase (21%), or 4 of 314 with IBS-D (~1%). Also, 4 of the 19 had diabetes mellitus (another cause for low fecal elastase), but it is not clear whether the same patients had diabetes and pancreatic disease. The authors supported their findings by reporting that in response to pancreatic enzyme therapy the 19 persons had a significant reduction in stool frequency and abdominal pain. While Wollaeger et al [60] much earlier reported that patients with EPI may develop more frequent and copious bowel movements, patients in the Wollaeger study [60] had multiple reasons to have altered fecal frequency including malabsorption (pancreatic head resections, bacterial overgrowth) and altered motility due to post-surgical anatomy [60]. In our experience in patients with an intact gastrointestinal tract, stool frequency is not significantly increased in severe EPI and does not decrease with treatment [61]. Stool weight, however is increased and decreases with treatment but was not measured in this study. Overall, our interpretation is that the proportion of patients with EPI who met Rome II criteria is ~1% and that using pancreatic enzymes to treat patients who meet Rome II criteria should be based upon measurements of reduction in fecal weight and fecal fat rather than symptomatic responses. Also, a finding not mentioned by the authors is that the Rome criteria for “diagnosis” of IBS is not specific as 76 of 314 patients who met the Rome II criteria had other diseases (specificity = 76% [false positive rate = 24%])

Diagnosis: EUS & Endoscopic Pancreatic Function Testing (ePFT)

The accuracy of endoscopic ultrasonography (EUS) in CP depends upon the criteria employed. There is general agreement that five or more out of nine abnormal features are highly predictive of CP and that fewer features has inconsistent accuracy due to higher sensitivity but lower specificity. As we recently reviewed [1], a consensus group [62] assumed that EUS features of CP have unequal positive predictive value or reliability and devised what is known as the Rosemont classification. This year we focused on studies evaluating EUS alone [63–66] or coupled with pancreatic function testing [65, 66] to diagnose CP.

In a very balanced review of the EUS diagnosis of CP, Gardner and Levy [63] concluded “there has been no meaningful progress in the EUS diagnosis of CP, particularly in patients with early or indeterminate CP. Further study is needed to refine the definitions of EUS features of CP, to determine the relative prognostic value of each feature, to establish an ideal threshold number of criteria, and to consider the composite results in a manner that optimizes their use”. Thus “if we are to err in the use of EUS, we should---(apply)--- more stringent diagnostic criteria to avoid over diagnosis and delivery of unnecessary and potentially risky therapies”. This tactic may fail to diagnose some patients, but we agree

with the authors and advise this approach, particularly since there is no current treatment that reliably alters the natural history and outcome. Gardner and Levy [63] also raised a very interesting point in their review: “we believe that imaging characteristics differ between radial and linear instruments and that imaging characteristics also differ among the various types of echoendoscopes and processors. There is a learning process that one must consider when using new equipment”. However, they do not support this assertion with data. This issue deserves investigation as it may be another reason for nonconformity and variable diagnostic accuracy for the EUS diagnosis of CP.

Two studies published this past year strengthen the opinion that the diagnostic accuracy among endosonographers for CP is not ideal. Lieb et al [64] reported poor interobserver agreement (K 0.39) for diagnosis of CP using standard EUS criteria for CP. Stevens et al [65] reported that the new Rosemont scoring system [62] “did not significantly increase interobserver agreement for EUS diagnosis of CP compared with standard scoring”. The interobserver agreements in this study, however, appear to be better (K=0.54 for standard and 0.65 for Rosemont, respectively).

Previously we extensively reviewed the strengths and weaknesses of pancreatic function tests [1] and won't do so again. Albashir et al [66] in a retrospective study compared EUS findings (4 criteria = CP) and endoscopic secretin stimulated pancreatic function test (secretin ePFT) results (<80mM = abnormal) with histology (2 fibrosis scale = CP) in 25 patients who underwent pancreatic resection (n=9) or surgical biopsy. Compared to histology they report EUS sensitivity of 84% and specificity of 100% and an ePFT sensitivity of 86% and specificity of 67%. By combining results of both tests the sensitivity was 100%. The authors did not comment about 2 aspects of their study. Of the 25 patients 21 had a fibrosis score 2 and apparently all 4 (without an elevated fibrosis score) had an EUS interpreted as having fewer than 4 criteria and 3 of the 4 had a normal ePFT. This statistic indicates that 16% of the patients were submitted to surgery unnecessarily. The authors list the cause of CP as sphincter of Oddi dysfunction (SOD) in 2 patients and pancreas divisum in 1 patient, controversial causes of CP, which raises the question whether these are the patients without fibrosis-the authors do not comment.

In another retrospective analysis, this same group [65] reported a negative correlation between EUS score and peak bicarbonate ($r = -0.38$) in 252 patients evaluated for suspected minimal change CP. The EUS and ePFT results were only moderately concordant (76%). Not surprising the ePFT was 85% sensitive and EUS was 100% sensitive in 38 patients with established calcific CP. Although the results of this study will undoubtedly be used to promulgate combined ePFT and EUS testing in patients with suspected minimal change CP, we urge caution because it is uncertain what the diagnosis is in these patients and using this testing over diagnoses CP (see above). This is particularly so in this study as the authors included 20 patients with pancreas divisum and 26 with SOD, controversial causes of CP.

Neuropathic pain and celiac plexus block or neurolysis

A definition of neuropathic pain is “pain arising as a direct consequence of a lesion or disease affecting the somatosensory system” [67]. We recently reviewed pancreatic neuropathic changes in CP [1]. This year we focus on new data regarding EUS guided celiac plexus block and neurolysis for treatment of chronic pain in CP and pancreatic cancer. Regarding the pathophysiology of neuropathic pain in CP and pancreatic cancer, refer to excellent reviews [68, 69] and primary sources focused on impairment in descending inhibitory pain modulation in human CP [70, 71], the influence of the microenvironment on human neuronal plasticity *in vitro* [72], contribution of astrocytic activation in the thoracic

spinal cord to persistent pain in a rat model of CP [73] and a related study on regulation of central pain mechanisms elicited by esophageal stimuli [74].

Treatment

A subset of patients with CP has unremitting pain that is not explained by anatomic complications and does not respond to conventional therapies. As we recently reviewed [1], therapeutic options include pain management using opioids, endoscopic and surgical treatments (including pancreatectomy) and neuropathic pain treatments (octreotide, nerve blocks, transcutaneous electronic nerve stimulation, acupuncture, and intrathecal pumps for infusion of opioids and anesthetic agents), the latter to block afferent pain nerves accompanying sympathetic nerves to the central nervous system [75]. Other investigational treatments reported in pilot studies include “anti-inflammatory” single, low-dose pancreatic radiotherapy (5–8Gy) [76, 77].

EUS guided celiac plexus block (CPB; Bupivacaine + Triamcinolone) and celiac plexus neurolysis (CPN; Bupivacaine + absolute alcohol) are used to treat painful CP and pancreatic cancer, respectively. Evidence from 3 randomized controlled trials [78–80] and a meta-analysis [81] indicates that CPB provides short-term pain relief in a subset of patients and provides superior short-term pain relief compared to the percutaneous approach [80]. These data were corroborated recently by Kaufman et al [82] who performed a systematic review of 6 studies of EUS guided CPB for painful CP (n=221 patients) and 5 studies of EUS guided CPN for painful pancreatic cancer (n=119 patients) and reported alleviation of pain by CPB in 51% (95% CI, 33–100) and by CPN in 73% (95% CI, 51–100). There were no life-threatening complications. Common complications included transient diarrhea, transient orthostatic hypotension, transient increases in pain and abscess formation. Thus, EUS-guided CPB and CPN appear effective and safe in treating patients with pain due to CP or pancreatic cancer, respectively, but identification of predictors for response to CPB would greatly improve selecting appropriate patients for this therapy in painful CP. Thoracoscopic splanchnicectomy (may provide short-term pain relief similar to CPB [83]) and a trial of this approach vs. CPB to analyze the short and long-term impact of the pattern and severity of pain and health related quality of life in CP would be helpful.

Conclusion

This year the literature contained moderate advances to further elucidate the genetic associations of tropical pancreatitis, a reversible mislocalization of ductal *CFTR* in AIP, the association of asymptomatic pancreatic hyperenzymemia with pancreatic disorders, limitations of diagnostic tests for EPI, diagnosis of CP by EUS and ePFT and the treatment of pain in CP.

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Abbreviations

AIP	Autoimmune pancreatitis
CPB	celiac plexus block
CPN	celiac plexus neurolysis
CCK	cholecystokinin
CP	chronic pancreatitis
CFTR	cystic fibrosis transmembrane conductance regulator
IBS-D	diarrhea predominant irritable bowel syndrome
ePFT	endoscopic pancreatic function test
EUS	endoscopic ultrasonography
EPI	exocrine pancreatic insufficiency
IBS	irritable bowel syndrome
MRCP	magnetic resonance cholangiopancreatography
SS-MRCP	secretin stimulated magnetic resonance cholangiopancreatography
SPINK1	serine protease inhibitor, Kazal type 1
SOD	sphincter of Oddi dysfunction

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Key Points

- Tropical pancreatitis associates with *SPINK1* and/or *CFTR* gene mutations in approximately 50% of patients, similar to the frequency in idiopathic CP.
- Corticosteroids increase secretin-stimulated pancreatic bicarbonate concentrations in AIP by restoring mislocalized *CFTR* protein to the apical ductal membrane.
- Most patients with asymptomatic hyperenzymemia have pancreatic lesions of unclear significance or no pancreatic lesions.
- Further study is needed to improve the accuracy of EUS to diagnose CP.
- Celiac plexus block provides short term pain relief in a subset of patients.