HHS Public Access

Author manuscript

Curr Opin Gastroenterol. Author manuscript; available in PMC 2018 April 03.

Published in final edited form as:

Curr Opin Gastroenterol. 2017 September ; 33(5): 330–338. doi:10.1097/MOG.0000000000000390.

Total pancreatectomy for recurrent acute and chronic pancreatitis: a critical review of patient selection criteria

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Abstract

Purpose of review—Critical review of the indications for total pancreatectomy and highlight limitations in current diagnostic criteria for chronic pancreatitis.

Recent findings—The diagnosis of noncalcific chronic pancreatitis remains controversial because of an overreliance on nonspecific imaging and laboratories findings. Endoscopic ultrasound, s-magnetic resonance cholangiopancreatography, and/or endoscopic pancreatic function testing are often used to diagnose noncalcific chronic pancreatitis despite the fact that there is no gold standard for this condition. Abdominal pain is not specific for chronic pancreatitis and is more likely to be encountered in patients with functional gastrointestinal disorders based on the high incidence of these conditions. The duration of pain and opioid analgesic use results in central sensitization that adversely affects pain outcomes after total pancreatectomy. An alcoholic cause is associated with poorer pain outcomes after total pancreatectomy.

Summary—The lack of a gold standard for noncalcific chronic pancreatitis limits the diagnostic accuracy of imaging and laboratory tests. The pain of chronic pancreatitis is nonspecific and is affected by duration, preoperative opioid use, and cause. These factors will need to be considered in the development of future selection criteria for this morbid surgery.

Keywords

acute recurrent pancreatitis; chronic abdominal pain; chronic pancreatitis; total pancreatectomy

INTRODUCTION

Chronic pancreatitis is a progressive, inflammatory disorder characterized by irreversible morphological changes and a gradual loss of exocrine and endocrine function [1–3]. In contrast, recurrent acute pancreatitis (RAP) can present without symptoms in between episodes but ongoing episodes over time eventually lead to morphologic changes and

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Conflicts of interest

V.K.S.: Consultant to Novo Nordisk, Akcea, Ariel Precision Medicine, and Abbvie. Advisory board participant for Nordmark. These financial interests do not pertain directly to this work. All the other authors have no disclosures.

functional deficits of chronic pancreatitis. Both disorders are believed to be part of a disease continuum. The difficulty encountered by most practitioners is that the diagnosis of chronic pancreatitis is based on advanced morphologic changes (e.g. calcifications) and functional deficits but there are no accurate tests for early stages of the disease. Chronic abdominal pain (CAP) is the most common and morbid symptom of chronic pancreatitis but is not specific for chronic pancreatitis.

Total pancreatectomy can reduce pain, improve quality of life (QOL), and eliminate the risk of developing pancreatic cancer in chronic pancreatitis [1]. Because of the potential morbidity and mortality associated with total pancreatectomy, patient selection is crucial to achieve optimal outcomes. The present article will review current selection criteria for total pancreatectomy and discuss recent data that should be incorporated into future criteria. Islet autotransplantation is also often pursued in eligible patients at the time of total pancreatectomy but is beyond the scope of this review.

SELECTION CRITERIA FOR TOTAL PANCREATECTOMY

Of the dozen or so centers that perform total pancreatectomy in the United States, there are only two centers that have published their selection criteria [4,5]. The primary limitation of these criteria include an overemphasis on imaging and functional assessments for diagnosing noncalcific chronic pancreatitis (NCCP), in particular, the use of endoscopic ultrasound, secretin-enhanced magnetic resonance cholangiopancreatography (MRCP), and endoscopic pancreatic function testing. The second limitation surrounds the oversimplification of abdominal pain associated with chronic pancreatitis. What many label as ‘pancreatic-type abdominal pain’ is not visceral pancreatic pain because of central sensitization that occurs over time and is greatly impacted by opioid use.

EPIDEMIOLOGY OF CHRONIC PANCREATITIS

The incidence of chronic pancreatitis is estimated to be between 2 and 200/100 000 individuals per year worldwide [6–10]. This variability in incidence likely reflects the limitations of the diagnostic criteria currently used for chronic pancreatitis. Furthermore, many patients with the diagnosis of chronic pancreatitis have other causes for their CAP. Patients with functional dyspepsia and irritable bowel syndrome (IBS) experience symptoms that overlap with other chronic gastroduodenal disorders and are often misdiagnosed as chronic pancreatitis [11]. The pooled prevalence of undiagnosed dyspepsia was reported to be 21% [95% confidence interval (CI), 18–24] across 100 population-based studies [12]. The leading gastrointestinal reason for an emergency visit in 2012 was a functional or motility disorder, diagnosed in 11.2% of all gastrointestinal patients [13]. A recent long-term study (1980–2012) of emergency room visits in Finland showed non-specific abdominal pain was the most common diagnosis [14]. A recent survey study of 1924 patients with a history of gastrointestinal symptoms showed 43% were not formally diagnosed with IBS despite meeting the diagnostic criteria for this condition [15].

DIAGNOSIS OF CHRONIC PANCREATITIS

Recent guidelines by American Pancreatic Association [1] and United European Gastroenterology [16] focus primarily on radiologic and endoscopic studies for diagnosing chronic pancreatitis. A summary of the limitations of current diagnostic studies are presented in Table 1.

There is no gold standard for the diagnosis of chronic pancreatitis. Although prior studies utilized histologic fibrosis as the gold standard for chronic pancreatitis, fibrosis can also be seen in advanced age [28–31], alcohol use [32,33], diabetes mellitus [34▪], smoking [35], chronic kidney disease [36], and obesity [1] in the absence of any clinical or radiographic features of chronic pancreatitis. Furthermore, pancreatic morphology has not been shown to correlate with the severity of pain, even with advanced changes of chronic pancreatitis (e.g. calcifications) [37,38▪,39]. Current endoscopic and surgical interventions are largely directed towards patients with a dilated pancreatic duct on the presumption that increased intraductal pressure leads to abdominal pain. However, there is poor correlation between the treatment of pancreatic obstruction caused by stones and/or strictures and pain relief [40▪, 41,42].

ENDOSCOPIC AND IMAGING STUDIES

The Cambridge classification is used diagnoses and grade the severity of chronic pancreatitis based on pancreatic ductal changes seen during endoscopic retrograde cholangiopancreatography (ERCP) [43,44]. However, this classification has low sensitivity and specificity for the diagnosis of chronic pancreatitis. In addition, the interpretation of pancreatography is operator dependent and cannot assess parenchymal changes. Computed tomography (CT) and MRCP play an important role in the early detection of pancreatic calcifications and dilation of the pancreatic duct [3]. Although the diagnosis of calcific chronic pancreatitis on abdominal imaging is relatively straightforward, there is no gold standard for the diagnosis of NCCP (Table 1). EUS provides high-resolution imaging of the entire gland, providing a detailed parenchymal and ductal assessment, and is considered to be more sensitive than CT [45]. Multiple studies have attempted to correlate EUS findings with histopathology in chronic pancreatitis patients (Table 1) [46,47]. However, these studies have been limited by small sample size, the fact biopsies may not be representative of changes present in nonsampled areas of the pancreas [48–50], many patients underwent resection for pancreatic cancer (Table 1) and patients who were included had variable pretest probabilities for chronic pancreatitis (Table 1).

ASSESSMENT OF PANCREATIC EXOCRINE FUNCTION

Pancreatic exocrine insufficiency (PEI) occurs when there is insufficient production and/or secretion of pancreatic digestive enzymes. Although chronic pancreatitis is the most frequent cause of PEI, there are other pancreatic diseases in which PEI occurs because of the loss of pancreas parenchyma including pancreatic necrosis, pancreatic cancer, partial surgical resection of the pancreas, cystic fibrosis, and obstruction of the pancreatic duct [51–53]. However, the pancreas has a large functional reserve, and malabsorption leading to

steatorrhea is not expected until lipase output is reduced to less than 10% of normal [54]. Multiple tests are available for the detection of PEI, including fecal elastase-1 (FE-1), C^{13} mixed-triglyceride breath test (MTG-BT), and the pancreatic function test (PFT) [55].

FE-1 is a simple indirect test for the evaluation of PEI (Table 1) [56]. However, it only has sensitivity between 54 and 75% (Table 1) [56–58]. Furthermore, there is no consensus regarding the threshold for diagnosing PEI using FE-1, and values ranging from 15 to 200 μg/g have been suggested in the literature (Table 1) [31,55,59]. A recent prospective study comparing FE-1, MTG-BT, and a 72-h fecal fat test found that a cut-off value of 84 μg/g was associated with a sensitivity and specificity of 87.5 and 66.7% for PEI, respectively (Table 1). Several studies have shown that direct PFT has the highest sensitivity for detecting PEI (Table 1) [59,60]. A retrospective study of secretin-stimulated endoscopic PFT found a sensitivity of 86% and a specificity of 67% for histologic fibrosis (Table 1). However, there are also limitations to ePFT. The procedure is cumbersome, as pancreatic juice needs to be collected 1 h after secretin administration for assessment of the peak bicarbonate concentration [61]. Sedation [62,63], fluid contamination (Table 1), CFTR mutations (Table 1), and smoking [64,65] can affect the pancreatic fluid volume and bicarbonate concentrations. Moreover, there is no reference range for a normal bicarbonate concentration across a large population of patients [66].

CAUSE AND RISK FACTORS

Alcohol and smoking

Chronic alcohol consumption is implicated as the primary etiologic factor in 44–53% of patients with chronic pancreatitis in the United States [7,67]. A recent meta-analysis found a strong correlation between drinking more than 40 g/day and the development of pancreatitis [68]. However, only 3% of heavy drinkers develop chronic pancreatitis [69]. There is a problem of overdiagnosis of chronic pancreatitis in individuals who drink moderately and have abdominal pain because the threshold of drinking that increases chronic pancreatitis risk is not widely known. Recent studies have shown that men are more likely to have alcoholic pancreatitis than women (58.2 vs. 30.3%; OR = 3.2; 95% CI, 2.2–4.7) [70▪]. This is could be because of higher prevalence of heavy alcohol consumption among male patients with alcoholic pancreatitis as a previous study by Lowenfels *et al.* [71] showed that, at equal levels of alcohol consumption, the rates of alcoholic pancreatitis are similar for males and females. Several studies evaluating endoscopic and surgical interventions for alcoholic chronic pancreatitis have showed better pain outcomes in nonalcoholic patients with chronic pancreatitis [72–75]. Another study of alcoholic patients ($n = 30$) found reduced QOL and no improvement in pain after TPIAT compared to patients with nonalcoholic chronic pancreatitis ($n = 70$) [76].

Smoking is a strong and independent risk factor for chronic pancreatitis [67,77–80] and the combination of alcohol and smoking leads to the highest cumulative risk for developing chronic pancreatitis [42,81▪,82]. Furthermore, prior studies of smokers with chronic pancreatitis have shown that they also have poor pain outcomes after surgical and endoscopic intervention [83,84]. Smoking is associated with the progression from acute pancreatitis to chronic pancreatitis [82], development and progression of calcifications

[8,85–87], and an increased risk of pancreatic cancer. Previous studies have shown that the risk for pancreatic cancer decreases a decade after smoking cessation, when compared to current smokers [88].

Pancreas divisum

Pancreas divisum is the most common congenital anomaly in humans, present in 5–10% of the global population [89,90]. Retrospective studies have shown that pancreas divisum does not modify the natural history of disease among alcoholic and nonalcoholic patients with chronic pancreatitis [91,92]. Furthermore, recent studies suggest that gene mutations such as CFTR and SPINK-1 are the underlying cause for pancreatitis in individuals with pancreas divisum [93,94]. A recent study of patients with chronic pancreatitis who underwent TP-IAT showed that pancreas divisum was independently associated with persistent abdominal pain in the first year after surgery (OR = 2.5; 95% CI, 1.1–5.6) [95]. It is not clear whether total pancreatectomy was pursued in these patients because they had clear evidence of RAP or chronic pancreatitis versus CAP.

Recurrent acute pancreatitis

RAP is defined as at least 2 episodes of acute pancreatitis [4,96,97]. The diagnostic value of serum lipase and amylase in acute pancreatitis is unclear. Approximately 10% of patients may be incorrectly diagnosed with acute pancreatitis because of non-specific elevations in pancreatic enzymes [98]. A recent Cochrane review assessed the diagnostic accuracy of index pancreatic enzyme levels in patients who presented to the emergency department with abdominal pain. This study found that a significant number of patients diagnosed with acute pancreatitis had enzymes less than three times the upper limit of normal. This could be partially related to delayed presentation for medical evaluation because of short half-life of serum amylase and lipase [99]. Among 100 patients with lipase and amylase levels less than three times the upper limit of normal, only 68 and 74 patients had acute pancreatitis, respectively [98]. There are many other causes of elevated lipase that could be misdiagnosed as acute pancreatitis [100]. Therefore, the diagnosis of RAP should not be based solely on the presence of abdominal pain and pancreatic enzyme elevations. Abdominal imaging within 72 h of symptom onset showing acute pancreatitis on at least two occasions should be required to make diagnosis of RAP. Because abdominal imaging is commonly pursued in patients with acute pancreatitis, this requirement for a diagnosis of RAP is important for their subsequent management particularly because the majority of patients with chronic pancreatitis have a preceding history of RAP [82].

HEREDITARY/GENETIC PANCREATITIS

Hereditary/genetic pancreatitis (HGP) is the likely etiology for a large number of patients with idiopathic pancreatitis. Prior studies reported gene mutation prevalence in 12–43% of idiopathic chronic pancreatitis and 30–60% in idiopathic RAP [101–107]. One of the limitations of these studies was the evaluation of subsets of the mutations associated with pancreatitis. As additional mutations become available for commercial testing, it is quite likely that a greater proportion of patients will have a pathogenic variant found on testing.

The first symptoms of HGP, usually acute pancreatitis, often begin during childhood. Progression of disease with morphologic changes begins at a median age of 22–25 years [108,109]. The risk of developing pancreatic cancer among patients with PRSS1 mutations is as high as 53.5% (95% CI, 7–76%) by the age of 75 [110], which is 50–70 times greater than the general population [111,112]. This risk will be higher among chronic smokers [108,109]. Patients with HGP who are smokers have a cumulative risk of pancreatic cancer that is more than 50% at age 70, which is two-fold higher than patients with HGP who do not smoke. In addition, pancreatic cancer develops 20 years earlier than general population [71,112,113]. The risk of pancreatic cancer associated with other genetic mutations is not as well established as with PRSS1 mutations [108,111]. There is recent data on pancreatic cancer in chronic pancreatitis because of SPINK1 mutations [114,115▪]. Since the progression of chronic pancreatitis, as measured by the development of calcifications, is more rapid in patients with SPINK1 versus PRSS1 mutations, [116] the risk of pancreatic cancer may be greater as well, because it has been shown that number of calcification(s) is significantly associated with fibrosis in chronic pancreatitis [40▪].

Patients with HGP are excellent candidates for total pancreatectomy as they can benefit from pain relief, and prevention of acute recurrent pancreatitis and pancreatic cancer. A 10-year follow-up study by Chinnakotla *et al.* [108] demonstrated a significant improvement in pain, better metabolic outcomes and less opioid analgesic use in the HGP group (n =80) when compared to the non-HGP group (n =404). It should also be noted that partial pancreatectomy and/or drainage procedures resulted in subsequent completion pancreatectomy among 42 (66%) patients with idiopathic chronic pancreatitis in one series [116]. Therefore, total pancreatectomy may be the preferred approach in idiopathic chronic pancreatitis to avoid redo surgery.

DURATION OF THE DISEASE

The timing for an elective surgery such as total pancreatectomy is controversial. Prior studies showed that advanced chronic pancreatitis increases the risk of central sensitization [117▪,118], poor pain relief [119▪], malignancy, and mortality in chronic pancreatitis [82,120–122]. A recent meta analysis of 406 patient from three studies showed that surgery preformed early in the course of chronic pancreatitis was associated with higher rates of complete pain relief after surgery (RR = 1.67; 95% CI, 1.09–2.56; P = 0.02) [123]. Another retrospective study of 66 patients with a median chronic pancreatitis duration of 28 months (interquartile range, 12–67) showed that the optimal time for surgery was within 26.5 months from diagnosis and was associated with less pain and opioid dependence over 3 years of follow-up [119▪]. Three or more endoscopically inserted stents has also been shown to be an independent risk factor for persistent abdominal pain 1 year following total pancreatectomy [95]. This is likely because of the collinearity between the number of stents inserted and the duration of disease. Overall, the data from these studies suggest that surgical intervention should be considered earlier during the disease course.

CENTRAL SENSITIZATION IN CHRONIC PANCREATITIS

CAP is experienced by almost 90% [123] of patients with chronic pancreatitis and half of them report having constant pain, which has a significant impact on QOL [124,125▪,126]. Neuropathic changes best correlate with pain in chronic pancreatitis [127]. Nociceptive afferents selectively respond to nerve damage and local inflammation and the sensitization of these afferents can result in changes in central pain processing, which is a common in patients with chronic pancreatitis [128–130]. Over time, ongoing nociceptive afferent barrage of the central nervous system results in loss of the descending inhibitory control and activation of the descending facilitator mechanism [131]. This can lead patients with chronic pancreatitis to experience pain in the absence of painful stimuli (allodynia) or experience increased pain with only mildly painful stimuli (hyperalgesia), even after total pancreatectomy. A recent study compared pain outcomes in patients with chronic pancreatitisafter surgical decompression or resection and showed that poorer outcomes were associated with increased central sensitization based on neurosensory testing [132].

OPIOID ANALGESICS

Chronic opioid use can result in effective analgesia in some patients with chronic pancreatitis but long-term use associated with considerable adverse effects, such as abuse, dependence, overdose, and opioid induced hyperalgesia, which can be difficult to diagnose and treat [133]. Furthermore, several studies have shown that preoperative opioid use increases the risk of failing to achieving complete long-term pain relief after an endoscopic or surgical intervention [134–137]. A recent prospective study by Negi *et al.* suggested that surgery should be performed before initiating opioids for pain relief. Their results were confirmed in a long-term follow up study of 266 patients, which found that a duration of pain more than 3 years (OR = 1.81; 95% CI, 1.02–3.37) and preoperative daily opioid use (OR = 2.14; 95% CI, 1.23–3.96) were independently associated with persistent severe pain after pancreatic surgery [134]. Opioids are not effective in chronic pancreatitis patients with central sensitization [138]; rather, pharmacologic treatments for chronic pancreatitis should directly target the central nervous system. A recent meta-analysis evaluating 1793 patients across 17 randomized control trials showed that the use of gabapentin prior to surgery resulted in less opioid use and dependence in the postoperative period [139▪].

The duration of opioid use should be considered when determining the optimal timing of surgery [4]. Therapeutic education and behavioral support before and after surgery are essential components in the management of chronic pancreatitis.

CONCLUSION

We summarize our criteria for total pancreatectomy in Table 2. Our criteria incorporate many aspects of the data presented in this review.

Acknowledgments

None.

Financial support and sponsorship

None.

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- ■ of special interest
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KEY POINTS

- There is no ‘gold standard’ for the diagnosis of noncalcific chronic pancreatitis.
- Chronic ‘pancreatic-type’ pain is nonspecific for chronic pancreatitis as many functional gastrointestinal disorders can present with similar pain.
- Patients with chronic pancreatitis with alcohol and smoking causes are less likely to benefit from total pancreatectomy than patients with HGP.
- Total pancreatectomy should also be avoided in patients with pancreas divisum and chronic abdominal pain who do not have unequivocal evidence of RAP or chronic pancreatitis.
- Duration of pain more than 2–3 years and opioid use are associated with poor pain outcome after intervention for chronic pancreatitis.
- Use of gabapentin prior to surgery may result in less opioid use in the postoperative period.

Table 1

Advantages and disadvantages of standard tests commonly used to diagnose chronic pancreatitis

Standard Test	Advantages	Limitations
Imaging Tests [3,17,18▪,19,20]		
CT	Highly sensitive for the detection of calcification and assessment of pancreatic duct dilation	Imaging does not diagnose noncalcific chronic pancreatitis
MRCP	Evaluate bile and pancreatic ducts	Low sensitivity in noncalcific CP
	T1-weighted images can show chronic inflammation and fibrosis in early stages of CP	Difficult to assess subtle changes in main pancreatic duct and side branches
EUS	More reliable for parenchymal and ductal assessment	Operator dependent
	More sensitive than CT	Changes could be result of aging, smoking, alcohol use and obesity
Functional Tests [21–27]		
Stimulating tests (Secretin, CCK Stimulation Tests)	PPV (45%)and NPV (97%) suggests ability of test to exclude CP in those with CAP	Invasive
		Costly
		Sedation, fluid contamination, CFTR mutation and smoking affect pancreatic fluid volume and bicarbonate concentrations
FE-1	Simple, rapid	Not as sensitive as stimulation tests using secreatagogues
	Inexpensive	Requires patient compliance with procurement and handling of specimen
	Can be performed in outpatient setting	
MTG-BT		Test takes 6 h to perform
	Noninvasive	Not commercially available in all countries

CAP, chronic abdominal pain; CCK, cholecystokinin; CT, computed tomography; EPI, exocrine pancreatic insufficiency; FE-1, fecal elastase-1; MRCP, magnetic resonance cholangiopancreatography; MTG-BT, mixed-triglyceride breath test; NPV, negative predictive value; PPV positive predictive value.

Table 2

Johns Hopkins criteria for total pancreatectomy

Indications for total pancreatectomy
I. Documented CP
i. Chronic abdominal pain with one of the following:
ii. Calcification (s)
iii. Moderate to severe ductal changes on Cambridge criteria
iv. Histology confirmed CP on prior surgery
v. RAP
II. RAP with impaired QOL
Two or more episodes of acute pancreatitis with confirmed imaging and no evidence of a treatable etiology
III. Documented hereditary/genetic pancreatitis with either I and/or II
Contraindications for total pancreatectomy
I. Alcoholic/smoking etiology
II. Active substance addiction/abuse
III. Duration of pain >3 years
IV. Opioid use longer >3 years unless patient can successfully wean off and initiate centrally acting drugs (e.g. gabapentinoids) prior to surgery
V. Poorly controlled psychiatric comorbidity
VI. Medical noncompliance

CP, chronic pancreatitis; HGP, hereditary genetic pancreatitis; QOL, quality of life; RAP, recurrent acute pancreatitis.