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Diagnosis and Management of Chronic Pancreatitis
A Review

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IMPORTANCE Chronic pancreatitis (CP) is a chronic inflammatory and fibrotic disease of the pancreas with a prevalence of 42 to 73 per 100 000 adults in the United States.

OBSERVATIONS Both genetic and environmental factors are thought to contribute to the pathogenesis of CP. Environmental factors associated with CP include alcohol abuse (odds ratio [OR], 3.1; 95% CI, 1.87-5.14) for 5 or more drinks per day vs abstainers and light drinkers as well as smoking (OR, 4.59; 95% CI, 2.91-7.25) for more than 35 pack-years in a case-control study involving 971 participants. Between 28% to 80% of patients are classified as having "idiopathic CP." Up to 50% of these individuals have mutations of the trypsin inhibitor gene (*SPINK1*) or the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Approximately 1% of people diagnosed with CP may have hereditary pancreatitis, associated with cationic trypsinogen (*PRSS1*) gene mutations. Approximately 80% of people with CP present with recurrent or chronic upper abdominal pain. Long-term sequelae include diabetes in 38% to 40% and exocrine insufficiency in 30% to 48%. The diagnosis is based on pancreatic calcifications, ductal dilatation, and atrophy visualized by imaging with computed tomography, magnetic resonance imaging, or both. Endoscopic ultrasound can assist in making the diagnosis in patients with a high index of suspicion such as recurrent episodes of acute pancreatitis when imaging is normal or equivocal. The first line of therapy consists of advice to discontinue use of alcohol and smoking and taking analgesic agents (nonsteroidal anti-inflammatory drugs and weak opioids such as tramadol). A trial of pancreatic enzymes and antioxidants (a combination of multivitamins, selenium, and methionine) can control symptoms in up to 50% of patients. Patients with pancreatic ductal obstruction due to stones, stricture, or both may benefit from ductal drainage via endoscopic retrograde cholangiopancreatography (ERCP) or surgical drainage procedures, such as pancreaticojejunostomy with or without pancreatic head resection, which may provide better pain relief among people who do not respond to endoscopic therapy.

CONCLUSIONS AND RELEVANCE Chronic pancreatitis often results in chronic abdominal pain and is most commonly caused by excessive alcohol use, smoking, or genetic mutations. Treatment consists primarily of alcohol and smoking cessation, pain control, replacement of pancreatic insufficiency, or mechanical drainage of obstructed pancreatic ducts for some patients.

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Supplemental content

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Chronic pancreatitis (CP) is a chronic progressive disease with an annual incidence of 5 to 8 and prevalence of 42 to 73 cases per 100 000 adults in the United States.[1-3] Prevalence rates varying from 36 to 125 per 100 000 population have been reported from Japan, China, and India, of which India has the highest prevalence.[4,5]

Chronic pancreatitis is characterized by fibrosis and inflammation of the pancreas in individuals with genetic, environmental, and other risk factors such as hypertriglyceridemia. Chronic pancreatitis is characterized by pancreatic atrophy, fibrosis, ductal strictures and distortion, calcifications, dysplasia, exocrine insufficiency and diabetes, and chronic pain.[6]

This review summarizes current evidence regarding risk factors, pathophysiology, clinical features, diagnostic evaluation, treatment, and prognosis of CP.

Methods

We searched PubMed for relevant English-language articles published from January 1, 2000, to July 1, 2019. Search terms included *chronic pancreatitis* and each of the following: *epidemiology, genetic variants, genetic mutations, genetic polymorphisms, risk factors, acute pancreatitis, recurrent acute pancreatitis, pathophysiology, pain, steatorrhea, weight loss, malabsorption, exocrine insufficiency, diabetes, treatment, management, neuromodulators, pancreatic enzymes, antioxidants, medical management, endoscopy, endoscopic retrograde cholangiopancreatography* [*ERCP*], *extracorporeal shock wave lithotripsy* [ESWL], *endoscopic ultrasound* [EUS]; *surgery*; *pancreatojejunostomy*; *total pancreatectomy*, and *islet autotransplantation*. Case reports and case series were excluded.

Observations

The literature search yielded 28 686 articles, from which 584 randomized clinical trials, 325 meta-analyses, 484 systematic reviews, and 126 guidelines were selected for further review. A total of 637 articles relevant to clinical chronic pancreatitis were included after excluding studies on acute pancreatitis, review articles, animal studies, duplicate articles, and protocols.

Risk Factors

Alcohol abuse is the most common etiology of CP and is diagnosed in 42% to 77% of patients. Idiopathic CP is the second most common type and affects 28% to 80% of people with the condition. In a multicenter study involving 416 patients with CP and 555 participants without it (spouses, family members, or unrelated persons seen at participating institutions), the odds of self-reported alcohol consumption of 5 or more drinks a day were 3.1-fold greater among those with CP than among those without it.[7] In an observational study involving 17 905 participants from the Copenhagen City Heart Study,[8] which had a median follow-up of 20.2 years, the relative risk (RR) of CP increased by 2.7 (95% CI, 1.1-6.6) among those who consumed at least 35 drinks and by 3.3 (95% CI, 1.3-8.3) among those who consumed 48 or more drinks a week compared with those who did not drink (**Table 1**).

Smoking is associated with risk of CP in a dose-dependent fashion. The Copenhagen observational study[9] also found that compared with never smokers, the RR of having CP among those who smoked between 15 and 24 cigarettes a day was 2.0 (95% CI, 1.0-4.1) and was 3.3 (95% CI, 1.5-7.3) among those who smoked 25 or more cigarettes a day (1 cigarette is approximately the equivalent of 1 g). In the US study involving 416 people with CP and 555 without it, the odds of having CP among those smoking 12 to 35 packs-years was 2.15 (95% CI, 1.46-3.17) and among those smoking more than 35 pack-years was 4.59 (95% CI, 2.91-7.25) compared with never smokers (Table 1). Smoking may be associated with other risk factors (such as alcohol consumption) in a synergistic manner.[7] In a recent multicenter US study involving 1159 patients, the 3 most common etiologies identified in 911 white participants with CP were alcohol (42%), idiopathic (28%), and genetic mutations (10%). Among 248 black patients, the most common etiologies were alcohol (77%), idiopathic (12.9%), and genetic (1.6%) causes.[20] In a study involving 2037 patients with CP from China, 19.8% had alcoholic CP and 80.2% had idiopathic CP.[21] In 411 patients with CP from India, 58.9% had idiopathic CP and 38.2% had alcoholic CP.[13]

Variants in several genes are associated with idiopathic CP (Table 1). Among 134 patients from the United States, 88 pathogenic genetic variants were found in the cationic trypsinogen 1 (*PRSS1* [HGNC 9475]), cystic fibrosis transmembrane conductance regulator (*CFTR* [HGNC 1884), serine protease inhibitor Kazal type 1 (*SPINK1* [HGNC 11244), and chymotrypsin C (*CTRC* [HGNC 2523]) genes in 64 patients (47.8%) with idiopathic CP.[22] In a study involving 715 Chinese patients with idiopathic CP, pathogenic genetic variants involving these genes were found in 57.1% of patients compared with only 5.9% of controls (odds ratio [OR], 16.1; $P < .001$).[11] Similarly, mutations in the *SPINK1* and *CFTR* genes were present in 42% of Indian patients with idiopathic CP vs 4% of controls ($P < .001$). Such mutations were present in 39.8% of Chinese patients and 17% of Indian patients with alcoholic CP. Mutations in the *PRSS1* gene were associated with hereditary pancreatitis with an autosomal dominant inheritance but only accounted for approximately 1% of all CP.

Other less common risk factors include hypercalcemia (generally due to a parathyroid adenoma),[23] hypertriglyceridemia, autoimmune disorders (eg, celiac disease, inflammatory bowel disease), and uncommon anatomic abnormalities, such as an annular pancreas. The role of pancreas divisum and sphincter of Oddi dysfunction as causes of idiopathic CP are controversial.

Chronic pancreatitis affects patients of all ages, and the affected age group depends on the etiology. Patients with CP due to alcohol typically present between the ages of 40 and 60 years; two-thirds of patients are men; and black patients have CP more commonly than do white patients. Patients with CP due to genetic mutations typically present between the ages of 10 and 40 years, and both sexes are affected nearly equally. Patients diagnosed with idiopathic CP have a bimodal presentation. A study involving 66 patients with idiopathic CP reported that the median age at presentation for early-onset CP was 19 years; late-onset CP, 56 years.[24]

Pathophysiology

Chronic pancreatitis develops slowly, starting with cellular injury, followed by inflammation and fibrosis. The pathophysiological processes in CP involve the acinar cells, the predominant site of initial injury or stress, leading to an inflammatory cascade.

Cellular Injury

Acinar cells, which constitute the majority of pancreatic volume, synthesize and secrete digestive enzymes into the pancreatic ductal system. Alcohol causes acinar cell injury due to its metabolites, such as acetaldehyde following oxidative metabolism, and fatty acid ethyl esters generated by nonoxidative metabolism.[25] The adverse effects of alcohol on pancreatic ductal and pancreatic stellate cells also contribute to the pathogenesis.[26,27] Smoking contributes to acinar cell injury due to its toxic metabolite nicotine derived nitrosamine ketone.[28] Genetic mutations associated with CP can cause cellular injury either in a trypsin-dependent (ie, trypsin activation involved in pathophysiology) or trypsin-independent (ie, trypsin activation not involved in pathophysiology) manner (Table 1). Mutations or polymorphisms lead to premature or increased activation of trypsinogen due to either gain-of-function variants in the cationic trypsinogen gene (*PRSS1*) or loss-of-function variants in genes such as *SPINK1* and *CTRC* that code for trypsin-inactivating proteins.[13,29,30] Increased intracellular trypsin activation leads to cellular injury through mechanisms such as endoplasmic reticulum stress, oxidative stress, and impaired autophagy.[31-33] Trypsin-independent mutations in *CFTR*, carboxypeptidase A1 (*CPA1* HGNC 2296), and claudin 2 (*CLDN2* [HGNC 2041) genes cause injury due to different mechanisms.[15-17,34] Cystic fibrosis transmembrane conductance regulator dysfunction most likely affects bicarbonate secretion by the pancreatic ductal cells.[27] Individual susceptibility to CP due to excessive alcohol use may depend on these aforementioned genetic variants, those coding for alcohol metabolizing enzymes or other yet unknown genes.[35,36] Low ORs of 1.4 and moderate ORs of 5.3 for most genetic variants suggest that CP is a complex disorder that is due to both genetic and environmental causes (eTable in the Supplement).

Inflammation

Acinar cell injury and death result in inflammation possibly related to release of damage–associated molecular patterns (DAMPs) as

Table 1. Risk Factors for Chronic Pancreatitis

Risk Factor	Frequency of Risk Factor in Chronic Pancreatitis vs Control Patients	(95% CI) Odds Ratio	Relative Risk
Environmental factors[a]			
Alcohol (drinks per d), drinkers vs controls, No. (%)[7]			
Moderate	89 (21.4) vs 132 (23.8)	0.81 (0.56-1.18)	
Heavy	54 (13) vs 74 (13.3)	0.83 (0.54-1.29)	
Very heavy (≥5)	102 (24.5) vs 30 (5.4)	3.10 (1.87-5.14)	
Drinks/wk, No. (%)/Total[8]			
1-6	25 (0.4)/6100 vs 18 (0.4)/3901		1.2 (0.7-2.3)
7-13	17 (0.5)/3543 vs 18 (0.4)/3901		1.2 (0.6-2.4)
14-20	12 (0.6)/1871 vs 18 (0.4)/3901		1.5 (0.7-3.2)
21-34[b]			1.3 (0.6-3.1)
35-48[b]			2.7 (1.1-6.6)
>48[b]			3.3 (1.3-8.3)
Smoking pack-years, smokers vs controls, No. (%)[7]			
<12	70 (16.8) vs 104 (18.7)	1.34 (0.9-2.01)	
12-35	103 (24.8) vs 98 (17.7)	2.15 (1.46-3.17)	
>35	111 (26.7) vs 51 (9.2)	4.59 (2.91-7.25)	
Smoking[9]			
Former	13 (0.4)/3027 vs 11(0.2)/3745		0.9 (0.4-2.0)
1-14 g/d	18 (0.3)/4793 vs 11 (0.2)/3745		1.1 (0.5-2.3)
15-24 g/d	34 (0.7)/4793 vs 11(0.2)/3745		2.0 (1.0-4.1)
≥25 g/d	34 (0.7)/4793 vs 11 (0.2)/3745		3.3 (1.5-7.3)
Genetic variants, No. (%)/total			
Trypsin dependent			
PRSS1			
White[10]	55 (8.3)/660 vs 0 (0)/1758	322.4 (19.8-5230)	
Chinese[11]	55(7.6)/715 vs 25 (2.1)/1196	3.9 (2.4-6.3)	
SPINK1 (N34S)			
White[12]	23 (40.3)/57 vs 3 (1.5)/190	42.2 (11.5-226)	
Indian[13]	48 (42.4)/113 vs 4 (4.0)/100	32.5 (10.9-127.9)	
CTRC			
White[10]	22 (4.0)/546 vs 13 (0.8)/1667 (0.8)	5.3 (2.7-10.7)	
Indian[14]	71 (12.2)/584 vs 22 (3.7)/598	3.6 (2.2-5.9)	
Trypsin-independent			
CFTR			
White[10]	103 (15.3)/660 vs 112 (6.4)/1758	2.7 (2-3.6)	
Indian[13]	3 (2.6)/113 vs 3 (0.3)/900	8.2 (1.1-61.4)	
CPA1			
White[15]	29 (3.1)/944 vs 5(0.1)/3938	24.9 (9.5-82.6)	
Indian [15]	5 (2.2)/230 vs 0/264	2% Risk allele vs 0 in controls	
Japanese[15]	5 (2.0)/247 vs 0/341		
CLDN2 (*MORC4*), allele frequency, % of total[c]			
White[16]	248 (36.7)/676 vs 1176 (26.1)/4507	1.61 ($P = 2.4 \times 10^{-21}$)	
Indian[17]	353 (80)/441 vs 762 (59.6)/1279	2.7 (2.1-3.6)	
CEL (not replicated in nonwhite patients)[18]	42 (3.7)/1122 vs 30 (0.7)/4152	5.2 (3.2-8.5)	
Autoimmune[d]			
Celiac disease[19]	37 (0.2)/ 14 239 vs 13 (0.01)/ 69 381		19.8 (9.2-42.8)

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; *CLDN2*, claudin 2; *CPA1*, carboxypeptidase A1; *PRSS1*, serine protease 1; *SPINK1*, serine peptidase inhibitor Kazal type 1.

[a] Drinking categories are based on the maximum drinking period over a lifetime: abstainers are those who have never imbibed alcohol or had fewer than 20 drinks in a lifetime; light drinkers, 3 or fewer drinks per week; moderate drinkers, from 4 to 7 drinks per week for women and 4 to 14 drinks per week for men; heavy drinkers, from 8 to 34 drinks per week for women and 15 to 34 drinks per week in men; and very heavy drinkers, at least 35 drinks per week for both sexes. The reference group for comparison were abstainers or light drinkers.

[b] The number of women in individual categories of drinking was not stratified for more than 20 drinks per week.

[c] For rs12688220.

[d] Precise odd ratios and relative risks are not available for inflammatory bowel disease, hypertriglyceridemia, hypercalcemia, annular pancreasthese, but multiple studies have shown an associated with chronic pancreatitis.

seen in acute alcoholic pancreatitis.[37] Nuclear factor κB (NF-κB) plays a key role in initiating the inflammatory cascade.[38] Inflammation is promoted primarily by innate immune cells, predominantly macrophages.[39] The role of adaptive immune cells is not clear. Oxidative stress has been shown to be involved in the pathophysiology of CP.[40]

Fibrosis

Pancreatic stellate cells normally exist in a quiescent state and become activated upon stimulation. Activated pancreatic stellate cells are important mediators of chronic inflammation and fibrosis in CP.[41] Transforming growth factor β is the most important cytokine associated with fibrosis.[42] Histopathological characteristics of CP include interlobular and intralobular fibrosis, acinar cell loss, distorted architecture, and dilated ducts.[43]

Development of CP

A widely accepted theory is that an acute event causes significant acinar cell stress or injury, which precipitates a clinically evident episode of acute pancreatitis. Patients with prior acute pancreatitis are susceptible to recurrent episodes due to either chronic toxic insults or genetic susceptibility. Most recurrent pancreatitis episodes present with epigastric pain. Repeated pancreatic parenchymal injury and chronic inflammation result in fibrosis. Fibrosis involving the pancreatic ducts leads to focal duct strictures with dilatation of the duct proximal to the obstruction. Calculi form secondary to stasis of secretions and calcification of protein plugs. Ductal obstruction and repeated injury lead to parenchymal loss and pancreatic atrophy. The necrosis-fibrosis hypothesis of CP pathophysiology consists of progression from acute pancreatitis to recurrent acute pancreatitis to CP.[44,45] In some patients, however, features of advanced disease such as calcifications or marked ductal changes are present at the initial presentation.[46] In patients without antecedent clinically manifest acute pancreatitis, the progression to CP is assumed to be via asymptomatic subclinical parenchymal injury and inflammation. The reasons for the 2 different types of presentations (symptomatic vs asymptomatic) are unknown but could be related to acuity and degree of inflammation or to a patient's pain threshold.[47]

Another hypothesis is the obstructive hypothesis, in which hypersecretion and protein precipitation lead to protein-plug formation in the pancreatic ducts that calcify and lead to obstruction resulting in acinar cell dysfunction and atrophy.[48] The mechanism of protein precipitation is unclear but could involve dysfunction of *CFTR* channels either by alcohol and its metabolites or *CFTR* gene mutations, causing impaired bicarbonate secretion resulting in intraductal acidification.[27,49] The *CFTR* is a selective ion channel involved in chloride and bicarbonate transport that produces bicarbonate-rich alkaline fluid in pancreatic ducts, which helps in solubilization of proteins. The flow of luminal content is thus impaired in *CFTR* dysfunction leading to the formation of intraductal protein plugs.

Sphincter of Oddi dysfunction was previously thought to be a cause of pancreatitis. However, 2 studies, one a prospective cohort of 201 patients[50] and the other a randomized trial of 69 patients,[51] reported acute pancreatitis recurrence rates of 55% over a median follow-up of 37 months and 50% to 77% over a median follow-up of 78 months, respectively, after endoscopic therapy for idiopathic recurrent acute pancreatitis due to suspected sphincter of Oddi dysfunction. The high recurrence rates of acute pancreatitis reported in these studies as well as overall pain relief rates at 1 year of only 28% in a sham controlled trial involving 201 patients undergoing endoscopic therapy for suspected sphincter of Oddi dysfunction[52] have led to declines in the use of invasive therapies for managing this condition.

Table 2. Prevalence of Signs, Symptoms, and Complications of Chronic Pancreatitis

Symptoms	Prevalence in Chronic Pancreatitis, %
No pain[53-55]	6-24
Abdominal pain[53-57]	60-94
Pain pattern types	
A, Usually pain free, but episodes of mild to moderate pain[53,54]	9-13
B, Constant mild to moderate pain[53,54]	8-34
C, Usually free of abdominal pain, but episodes of severe pain[53,54]	19-51
D, Constant mild to moderate pain plus episodes of severe pain[53,54]	45
E, Constant severe pain[53,54]	6
Pain frequency	
Intermittent (types A and C)[58]	32
Constant (types B, D, and E)[58]	53
Pain severity	
Mild-moderate (types A and B)[58]	18
Severe (types C, D, and E)[58]	67
Complications	
Any acute pancreatitis[46,55]	42-50
Recurrent acute pancreatitis[55,57]	31-34
Exocrine insufficiency at diagnosis[24,55]	10-13
Nutritional manifestations	
Low BMI (underweight, <18 kg/m^2)[59]	8
Fat soluble vitamin deficiency	
Vitamin A (<30 μg/dL)[59]	25
Vitamin D (<10 ng/mL)[59,60]	21-38
Vitamin E (<5.7 mg/L)[59]	17
Osteopenia[61]	29-52
Osteoporosis[61]	17-32
Fracture[62-64]	5-21
Endocrine insufficiency at diagnosis[55,65]	10-33

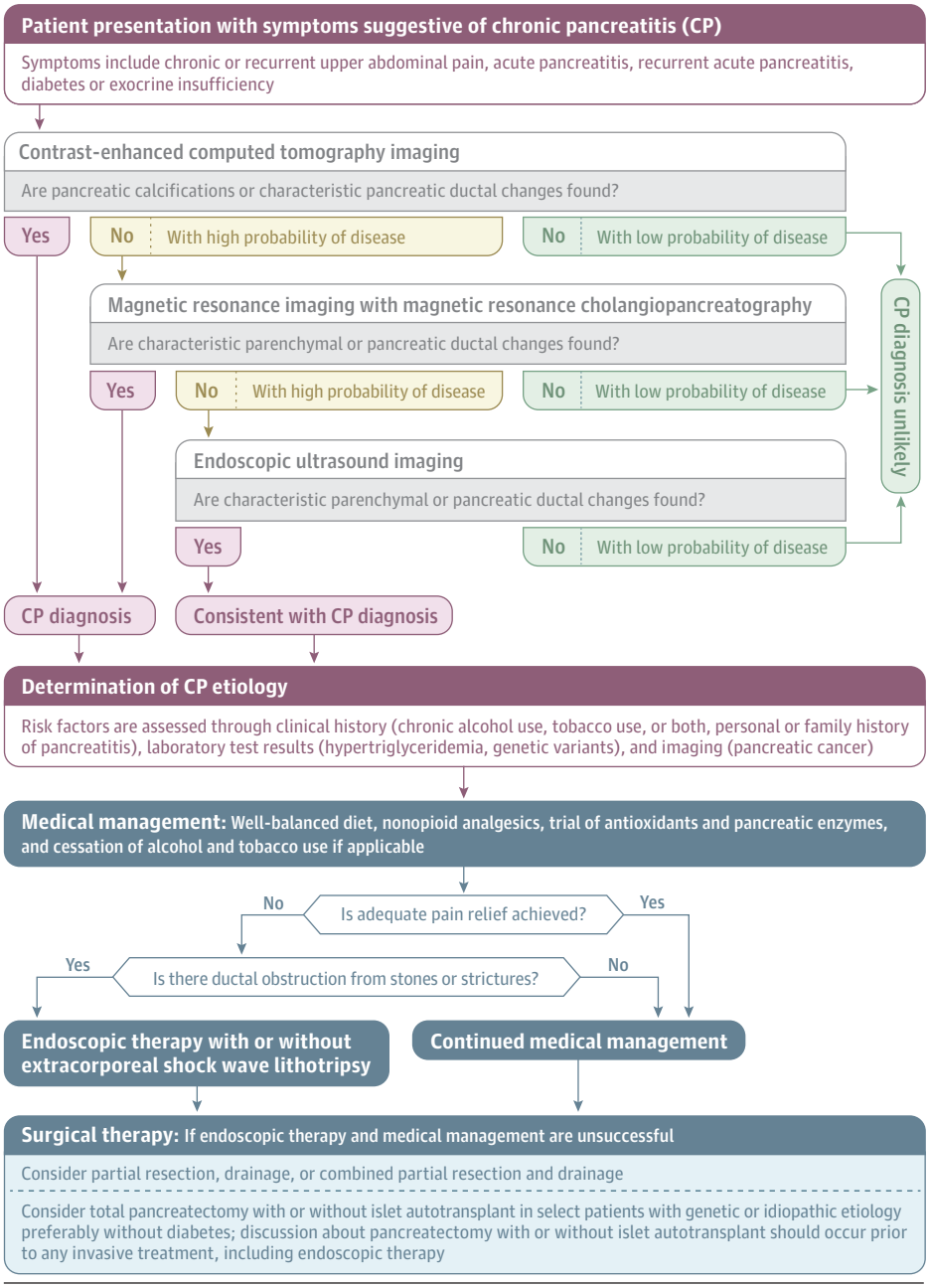
Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

SI conversion factors: To convert vitamin A from μg/dL to μmol/L, multiply by 0.349; vitamin D from ng/mL to nmol/L, multiply by 2.496; and vitamin E from mg/L to μmol/L multiply by 2.32.

Mechanism of Pain in CP

Abdominal pain is clinically the most significant feature of CP, but the etiology is poorly understood. Pancreatic inflammation is associated with the release of inflammatory molecules from damaged cells, activating both mast cells and platelets and resulting in transmission of nociceptive signals to the pain centers of the brain via dorsal root ganglia and dorsal horn of the spinal cord. Patterns of pain vary based on the temporal nature of CP and severity (**Table 2**).[58]

Figure 1. Diagnosis and Treatment Algorithm for Chronic Pancreatitis



This algorithm has not been validated in randomized trials.

Recurrent pancreatic inflammation associated with recurrent pancreatitis results in episodic acute abdominal pain. Patients who develop ductal obstruction due to stones, stricture, or both may have continuous pain and recurrent episodes of pain with both ductal hypertension, ie, increased pressure due to ductal obstruction and inflammation possibly playing a role. Long-term continuous pain may be due to structural complications such as an inflammatory head mass, pseudocyst, or pancreatic cancer.[66] However, many patients with continuous pain do not have structural complications or evidence of inflammation. These patients may have neuropathic pain. Pancreatic nociceptive afferent injury over time can result in peripheral sensitization, central sensitization, or both, characterized by neuronal hyperresponsiveness, which can result in a continual state of pain independent of peripheral nociceptive input.[67] Among patients who experience chronic pain, histological changes in the pancreas including an increase in the density and volume of the intrapancreatic nerves and structural changes in the brain such as alterations in cerebral cortical thickness, suggest that pancreatic and central neural changes occur over long-term follow-up.[68] Sensitization manifests as hyperalgesia and allodynia. Central sensitization is associated with reduced efficacy of invasive endoscopic and surgical treatments directed at the pancreas.[69] Pain resolves among some patients with both long-standing CP and an atrophic pancreas. One study involving 288 patients reported that 57% were pain free at the 5-year follow-up.[70]

Table 3. Sensitivity, Specificity, Advantages, and Disadvantages of Diagnostic Tests for Chronic Pancreatitis

Diagnostic Study	Findings	% (95% CI)[a]		Advantages	Disadvantages	Recommendation
		Sensitivity	Specificity			
CT	Calcifications, marked ductal dilation, atrophy,	75 (66-83)	91 (81-96)	High sensitivity for calcifications High sensitivity for diagnosing CP complications	Suboptimal visualization of pancreatic duct Low sensitivity and specificity for early CP	First-line diagnostic imaging study, best for calcification and marked dilation of the pancreatic duct
MRI with MRCP with or without secretin	Parenchymal changes (atrophy, T1 signal intensity) Ductal changes (main pancreatic duct dilation, stricture or irregularity as well presence of abnormal side branches) Secretin during MRCP stimulates pancreatic secretion, which causes duodenal filling that can be assessed quantitatively for exocrine function	78 (69-85)	96 (90-98)	Secretin-enhanced MRCP has higher sensitivity and specificity than CT for changes of the main pancreatic duct including dilation and strictures as well as changes in the side branches No ionizing radiation	Low sensitivity for small ductal calculi and parenchymal calcifications Lack of widespread availability	If CT shows normal results but suspicion of CP is high, MRI with MRCP should be obtained to evaluate for ductal changes
EUS	Four parenchymal criteria (lobularity, cyst, hyperechoic foci, and hyperechoic strands) Five ductal criteria (dilation, irregularity, calcifications or stones, echogenic duct wall margins, and side branch)	81 (70-89)	90 (82-95)	High sensitivity Less invasive than ERCP Allows for tissue sampling	Low specificity High interobserver variability Not all criteria carry similar importance	If CT and MRI are normal and the suspicion for CP is still high, especially in patients with RAP, EUS should be performed

Abbreviations: CP, chronic pancreatitis; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; RAP, recurrent acute pancreatitis.

[a] Sensitivity and specificity for CT, MRI-MRCP, and EUS were adopted from Issa et al.[76]

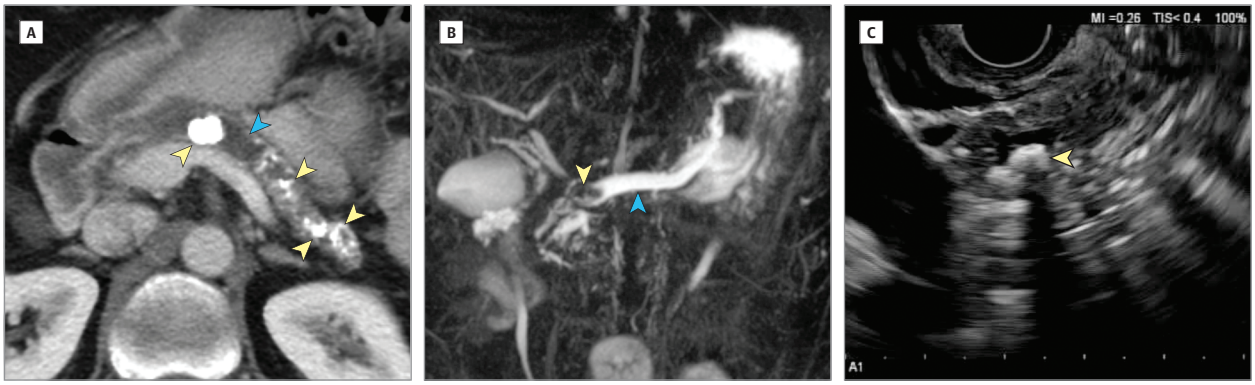
Clinical Presentation

Characteristic symptoms, signs, and complications in patients with CP are shown in Table 2. Abdominal pain is present in more than 80% of patients with CP.[58] Although classically reported as a dull pain localized to the epigastrium with radiation to the back that worsens after meals, the character, pattern, and severity of pain can vary.[71] The presence and characteristics of abdominal pain do not always correlate with the extent of pathological changes of CP.[58,72,73] Patients may experience nausea, vomiting, or both, especially during exacerbations of pain attacks or during episodes of acute pancreatitis. Approximately 70% of adult patients with CP have at least 1 episode of acute pancreatitis and 50% have recurrent acute pancreatitis during the clinical course of CP.[54] Patients with early-onset CP (ie, symptom onset before age 35 years) and those with alcohol etiology are more likely to have abdominal pain and at least 1 episode of acute pancreatitis. The clinical manifestations of exocrine insufficiency are related to maldigestion, which can result in steatorrhea (oily stools), weight loss, and fat-soluble vitamin deficiencies. In a meta-analysis of 10 studies consisting of 513 patients with CP who had undergone dual-energy x-ray absorptiometry, the pooled estimates for osteoporosis were 23.4% (95% CI, 16.6%-32%) and for osteopenia, 39.8% (95% CI, 29.1%-51.6%).[61] During a 10-year period (1998-2008), the period prevalence of low trauma fractures (vertebrae, hip, and wrist) identified by diagnosis codes in patients with a diagnosis of CP was significantly greater than did controls (4.82%, 154 of 3192 vs 1.13%, 16 208 of 1 436 699) and patients with Crohn disease (3%, 182 of 6057). When compared with controls, patients with CP were at 2.7 times greater risk and those with Crohn disease were at 1.7 times greater risk of fractures. The risk of fractures in patients with CP was similar to other gastrointestinal diseases, such as cirrhosis, celiac disease and history of gastrectomy.[63] A recent systematic review of 15 studies involving 8970 patients reported a prevalence of new onset diabetes of 15% within 36 months and 33% after 60 months after a diagnosis of CP.[74]

Assessment and Diagnosis

A contrast-enhanced computed tomographic (CT) scan is an initial diagnostic test and should be performed for all patients with suspicion of CP (**Figure 1**). Amylase and lipase are helpful for diagnosing acute pancreatitis but not CP. Computed tomographic scans have an overall sensitivity of 75% for CP (95% CI, 66%-83%). The presence of either calcifications, marked pancreatic ductal changes, or both of these findings on a CT scan establishes the diagnosis of CP. In patients with a low probability of disease, eg, those with atypical symptoms, normal or minimally elevated pancreatic enzymes during painful episodes and no known risk factors, a normal CT scan result is sufficient to exclude the diagnosis. However, if findings on CT scan are normal or equivocal, patients with a higher pretest probability of disease based on symptoms suggesting pancreatic pain or those with other risk factors, such as exposure to alcohol, smoking, or both; family history; presence of diabetes; or clinical or laboratory evidence of exocrine insufficiency, magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) should be considered for further evaluation. Current MRI-MRCP technology can provide high-quality images of both the pancreatic parenchyma and ductal system. Parenchymal changes

Figure 2. Diagnostic Imaging Modalities Used to Identify Morphologic Features of Chronic Pancreatitis



A, Abdominal computed tomographic image of a dilated pancreatic duct (blue arrowhead) and multiple calcified stones (yellow arrowheads) in the body and tail of the pancreas. B, Magnetic resonance cholangiopancreatographic image showing a large stone in the head of the pancreas (yellow arrowhead) causing obstruction and dilation of the pancreatic duct (blue arrowhead). C, Endoscopic ultrasound image of the head of the pancreas showing a large calcification (yellow arrowhead) with posterior shadowing.

suggesting CP include reduced T1 signal intensity. Ductal changes include main pancreatic duct dilation or irregularity, dilation of the side branches, and the presence of at least 1 stricture. Intravenous secretin administration during MRCP stimulates pancreatic fluid secretion and can improve visualization of the ductal side branches, as shown in a study involving 84 patients with clinically suspected pancreatic disease but whose abdominal ultrasound and CT scan results showed that their ducts appeared to be normal. After administering the secretin, the number of visible ductal side branches increased from 3 (4%) to 53 (63%).[75] Secretin administration can also help evaluate duodenal filling, which is a dynamic marker of pancreatic exocrine function. In a select subset of patients with a high index of suspicion for CP, an endoscopic ultrasound can be considered if findings on MRI-MRCP are normal or equivocal. Endoscopic ultrasound evaluates for 4 parenchymal and 5 ductal criteria that are used for diagnosis (**Table 3**). However, the total number of endoscopic ultrasound criteria required for the diagnosis of CP is not well-established due to high interobserver variability.[77] High false-positive rates from endoscopic ultrasound are found when patients have abdominal pain from dyspepsia,[78-80] are older,[81,82] have a history of smoking or alcohol abuse,[83,84] are obese,[85] or have diabetes.[86] The specificity of endoscopic ultrasound increases if there is a history of acute pancreatitis.[87,88] Although some clinicians directly assess pancreatic function by aspirating duodenal fluid after injection of secretin, the utility of these tests remains unclear outside of research settings.

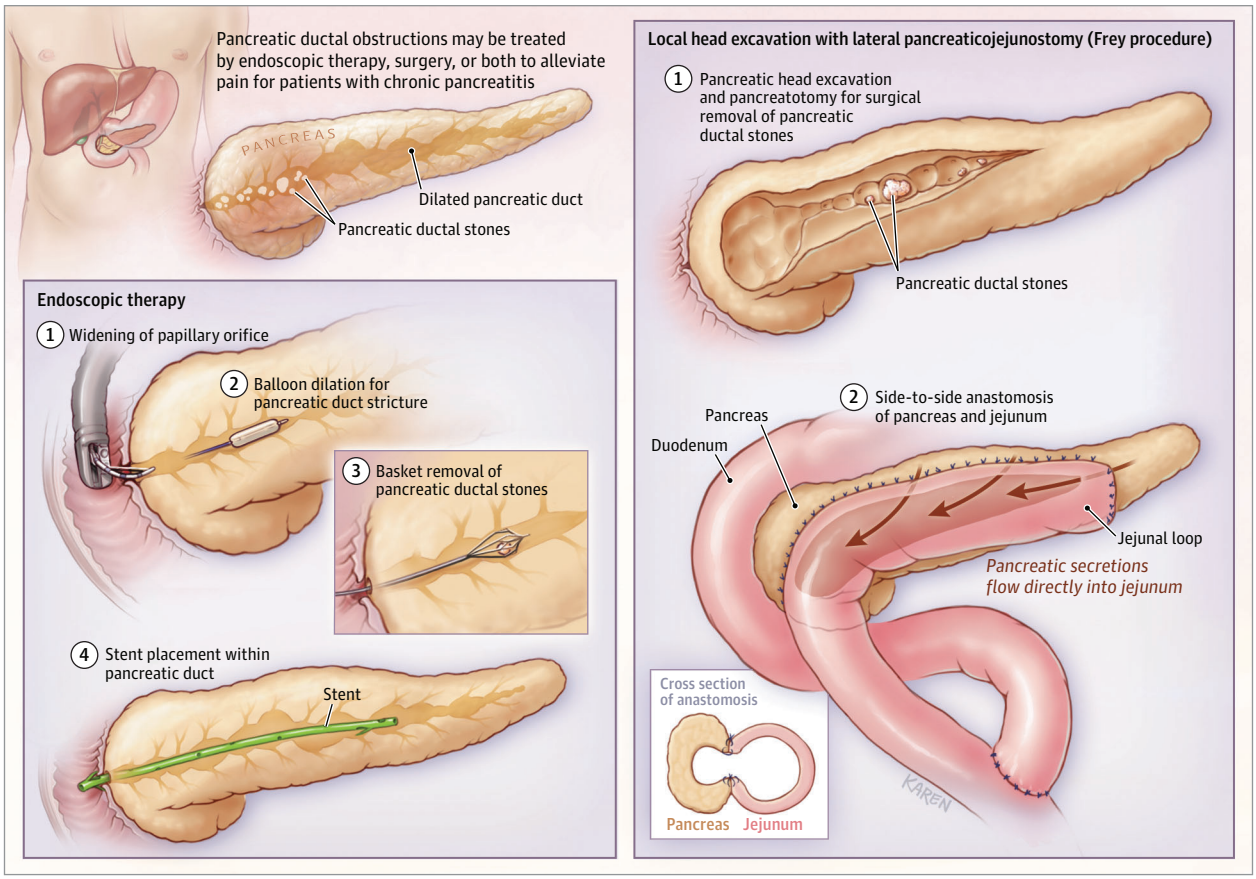
Performance characteristics, advantages and disadvantages of the 3 most commonly used imaging modalities to establish the diagnosis of CP are shown in Table 3 with characteristic CP findings of each shown in **Figure 2**. The sensitivity of each test ranges from 75% to 81%. Sensitivity is modest because the criterion standard used to define CP varies. Although each test performs well in the presence of advanced disease, they are more limited for diagnosing earlier stages of disease. A conceptual understanding of the natural history of disease is also important. Evolution of morphological and functional changes of CP may require years to manifest. For example, manifestation of these changes in patients with idiopathic CP at an early age (ie, <35 years) may be delayed by up to 10 or more years after the onset of symptoms compared with patients with pancreatitis from excessive alcohol in whom morphological and functional changes of CP may be present either at diagnosis or may develop within a much shorter period after symptom onset. In natural history studies, 1 in 5 patients with acute pancreatitis and 1 in 3 with recurrent acute pancreatitis will progress to CP.[89] Therefore, if clinical suspicion of CP is high, patients will need follow-up and repeat imaging because it is likely that morphological and functional changes will evolve with time.

Once the diagnosis of CP is confirmed, its etiology should be established. A thorough clinical history to determine the dose and duration of alcohol and tobacco use as well as personal and family history of pancreatitis, hypertriglyceridemia, pancreatic cancer, cystic fibrosis, and celiac disease is important. In young patients without an obvious cause, genetic testing should be considered.[22,90,91] The delineation of a genetic etiology for CP may reduce repetitive and expensive diagnostic evaluation, assist with determining prognosis (eg, pancreatic cancer risk in *PRSS1* mutation carriers), and guide treatment selection.[92]

Treatment

Treatment of CP begins with medical management (Figure 2). Among 89 patients with newly diagnosed CP in a population-based study with a mean follow-up of 10 years, 76% of patients experienced pain but only 30% required an invasive treatment such as endoscopy, surgery, or both.[55] Thus, medical therapies may be adequate for pain management for many patients with only a subset, typically patients with refractory pain, requiring invasive treatment. When applicable, patients should be counseled to abstain from alcohol and smoking because ongoing exposure is associated with pain relapses.[93] A study[94] involving 205 patients with CP followed up for a median of 15.5 years (range, 10-18 years), found that continued alcohol use and smoking were associated with disease progression. Ongoing smoking was associated with reduced efficacy of both endoscopic[95] and surgical therapeutic intervention.[96] Because there are no guidelines regarding the choice, use, and dose of analgesics, the 1986 World Health Organization analgesic ladder for cancer pain is commonly used by clinicians for treating

Figure 3. Endoscopic and Surgical Procedures for Treatment



CP pain.[97] This guideline recommends acetaminophen and nonsteroidal anti-inflammatory drugs (eg, diclofenac, ibuprofen, and naproxen) as first-line, nonopioid analgesics with escalation to weak opioids (eg, tramadol, codeine) and then strong opioids (eg, morphine, oxycodone, fentanyl) depending on the severity of pain. Although, to our knowledge, there are no data regarding opioid abuse and misuse in patients with painful CP, opioid prescribing and monitoring practices should follow the Centers for Disease Control and Prevention guidelines.[98] Pregabalin has been shown to be effective in a short-term trial, which supports a neuropathic pain mechanism for CP in a subset of patients.[99] Both coated and uncoated pancreatic enzyme supplements in variable doses are often used by clinicians to treat pain in the absence of exocrine insufficiency,[100] but a meta-analysis of 5 trials has shown equivocal efficacy for pain relief.[101] Antioxidant supplementation in combination and in doses of 0.54 g of ascorbic acid, 9000 IU of β-carotene, 270 IU of α-tocopherol, 600 ug of organic selenium, and 2 g of methionine may be beneficial particularly for those patients with nonalcoholic-derived CP but additional trials are needed.[102-104] In a double blind randomized trial, 127 consecutive patients with CP (35 alcoholic, 92 with idiopathic CP) were randomized to receive antioxidants or placebo for 6 months.[101] The primary outcome measure was pain relief. The reduction in the number of painful days per month was significantly higher in the antioxidant group than in the placebo group (7.4 [SD, 6.8] vs 3.2 [4] P <.001; 95% CI, 2.07-6.23). Furthermore, 32% and 13% of patients became pain free in the antioxidant and placebo groups, respectively (P <.01).

Endoscopy and surgical resection, drainage procedures, or both can be used to treat pain when medical therapies are unsuccessful. These procedures alleviate pancreatic ductal obstruction from stones, strictures, or both in an effort to reduce intraductal hypertension and thereby pain (**Figure 3**). The surgical procedures used include partial resection (eg, Whipple, distal pancreatectomy), drainage (eg, Puestow) and combined partial resection and drainage procedures (eg, Frey, Berne, and Beger). Extracorporeal shock wave lithotripsy (ESWL) may be used as an adjunctive therapy to fragment large stones prior to endoscopic removal, but this procedure is not US Food and Drug Administration–approved for pancreatic stones and requires the assistance of a urologist at US centers. Neuroablative techniques such as endoscopic celiac plexus blockade have been evaluated in 3 trials consisting of 151 patients and have reported pain relief rates of 53% to 60% over 4 to 8 weeks of follow-up after the procedure.[105] However, a more recent trial of 40 patients with CP, with stricter inclusion criteria for CP, compared different injected treatments for celiac plexus blockade and reported that only 6 patients (15%) experienced overall pain relief at 1 month, which raises the question of whether this procedure is an appropriate option for patients.[106,107]

Table 4 shows the characteristics, outcomes, and adverse events of high-quality medical and interventional randomized clinical trials

Table 4. Randomized Controlled Trials Evaluating Pain Relief of Medical and Interventional Therapies for Painful Chronic Pancreatitis

Source	No. of Patients	Comparison	Primary Outcome	Duration of Follow-up	Pain Relief	Adverse Events
Bhardwaj et al,[103] 2008	127	Antioxidants (dose: 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, 600 µg organic selenium, and 2 g methionine per d) vs placebo	Reduction in painful d/mo at 6 mo	6 mo	Reduction in mean (SD) number of painful d/mo 7.4 (6.8) vs 3.2 (4) (P < .001) (mainly idiopathic CP)	No significant adverse events noted except headache in 8 and constipation in 4 patients taking antioxidants (n = 71)
Siriwardena et al,[102] 2012	70	Antioxidants (dose: 2 tablets 3/d, contained 38.5 mg selenium yeast, of which 50 µg was l-selenomethionine; 113.4 mg/d α-tocopherol acetate; 126.3 mg ascorbic acid; and 480 mg l-methionine) vs placebo	Change in clinic pain score at 6 mo	6 mo	Nonsignificant reduction in pain score by 2.33 vs 1.97; P = .50, mainly alcoholic CP taking 85 mg of morphine/d)	No significant adverse events noted except 1 patient had diarrhea and 1 developed hepatic encephalopathy in the antioxidant group
Olesen et al,[99] 2011	64	Pregabalin (75 mg 2/d, increased to 300 mg 2/d after 1 wk) vs placebo	Change in pain intensity as measured on a visual analogue scale after 3 wk of treatment	3 wk	36% vs 24% (P = .02)	Four of 34 Patients in the pregabalin group had serious adverse events: pneumonia, worsening abdominal pain, eczema, and shoulder injury in 1 patient each; 35% and 24% of patients taking pregabalin reported feeling drunk and light-headedness
Talukdar et al,[108] 2016	87	Antioxidants + pregabalin vs placebo	Pain relief measured on visual analogue scale and Izbicki pain score	2 mo	48% vs 27% (P = .04)	Mild to moderate self-limiting nausea and vomiting in the treatment group
Dumonceau et al,[109] 2007	55	ESWL vs ERCP + ESWL	Pain relapse	2 y	58% vs 55% (P = .63)	3% Complication (1 patient developed pseudocyst) in the ERCP + ESWL group
Díte et al,[110] 2003	72	ERCP (no ESWL) vs surgery	Complete pain relief	5 y	15% vs 34% (P = .002)	8% Patients in each group had complications
Cahen et al,[111] 2007	39	ERCP + ESWL vs surgery	Complete pain relief	2 y	16% vs 40% (P = .007)	11 Patients (58%) had minor complications in the endoscopy group and 7 (35%) had complications in the surgery group
Cahen et al,[112] 2011	31	ERCP + ESWL vs Surgery	Complete pain relief	6.5 y (follow-up of RCT from 2007)	25% vs 53% (P = .04)	47% Of patients in the endoscopy group required surgery

Abbreviations: ERCP, endoscopic retrograde cholangiopancreatography; ESWL, extracorporeal shock wave lithotripsy; RCT, randomized clinical trial.

for painful CP. Limitations of these studies include relatively short duration of follow-up, small numbers of patients, lack of a validated pain assessment tool for CP, lack of a sham-placebo group and heterogeneity with regards to the use of ESWL. In 2 randomized trials involving patients with CP and ductal obstruction, surgery was associated with greater pain relief than was endoscopy. The first trial[110] randomized 72 patients and found complete pain relief rates of 15% with ERCP (without ESWL) compared with 34% with surgery over 5 years of follow-up. The second trial[111] randomized 39 patients and found complete pain relief rates of 16% with ERCP (with ESWL as needed) compared with 40% with surgery over a 2-year follow-up with continued complete pain relief in 25% vs 53%, respectively, over 6.5 years of follow-up.[112] A Cochrane review of these 2 trials including 111 patients with follow-up data showed that surgery was associated with a higher proportion of patients with pain relief at 2 to 5 years (risk ratio [RR], 1.62; 95% CI, 1.22-2.15) and more than 5 years (RR, 1.56; 95% CI, 1.18-2.05) compared with endoscopy.[113]

A recent clinical trial, comparing the cost effectiveness of endoscopy and surgery, equally randomized 38 CP patients and found a higher mean number of ERCPs performed in the endoscopy group (6.3 vs 0.4) than in the surgery group.[114] Despite the efficacy of surgery and frequent requirement for repeated procedures among people who undergo endoscopy, many patients initially prefer endoscopic therapy because it is less invasive. Surgery may be an appropriate first-line treatment for patients with CP who have large and numerous pancreatic stones or complex strictures, an inflammatory head mass, or disease limited to the pancreatic tail. Endoscopy may be preferred when there are 3 or fewer small (<1 cm) stones located in the head and body of the pancreas.[115] Pain relief was reported in nearly 70% of patients initially treated with multiple medical therapies followed by endoscopy, surgery, or both as needed over 15 years of follow-up.[70] Total pancreatectomy with or without islet autotransplantation is increasingly a therapeutic option in a subset of patients with genetic or idiopathic CP whose pain does not respond to medical or endoscopic therapy with pain relief rates as high as 90% in a single-center series of 80 patients.[116] Longitudinal data from an ongoing prospective multicenter registry study will determine the optimal role of this strategy in the management of CP.[117]

Initial evaluation and monitoring of patients with CP should include an assessment of functional deficiencies. Symptoms of steatorrhea (foul smelling, oily stool), diarrhea and weight loss suggest exocrine sufficiency. Steatorrhea or fat malabsorption is defined

as a coefficient of fat absorption (CFA) of less than 93% (or >7 g of fat per 24 hours from a 72-hour fecal fat collection in a patient who is consuming 100 g of dietary fat each day during stool collection). The 72-hour fecal fat test is the criterion standard for steatorrhea but lacks specificity for pancreatic exocrine insufficiency because it cannot differentiate between different causes of fat malabsorption. Furthermore, the test is difficult to perform properly, contributing to a decline in its use. Although there are several other indirect (eg, fecal elastase or FE-1, serum trypsin) and direct tests (endoscopic secretin) used to diagnose exocrine insufficiency,[118] the accuracy of these tests is highest in the presence of severe exocrine insufficiency when defined as steatorrhea. For example, a study involving 54 patients with CP who underwent both CFA and FE-1 testing, an FE-1 cutoff of 84 µg/g (FE-1 < 100 µg/g is considered severe exocrine insufficiency) was found to have a sensitivity of 87.5% and specificity of 81.6% but a FE-1 cutoff of 200 µg/g was found to have a sensitivity of 93.8% but a low specificity of 63.2%.[118] No established criterion standard exists for mild to moderate exocrine insufficiency. Thus, dietary counseling[119] and pancreatic enzymes should be administered in patients with symptoms consistent with exocrine insufficiency even if diagnostic testing is equivocal. Pancreatic enzymes at doses of 1000 USP units of lipase per kilogram per meal should be administered during meals because they are effective for treating malabsorption as well as improving nutritional parameters and quality of life.[120] Vitamin D levels and bone density studies should be considered to assess for osteopenia and osteoporosis given the risk of low trauma fracture.[121] Biannual fasting glucose and glycated hemoglobin should be obtained to assess for diabetes.[122] During follow-up, if symptoms change or new symptoms develop, imaging with CT or MRI should be obtained to assess for and treat any CP complications.

Prognosis

Median survival in patients with CP has been reported to be 15 to 20 years after diagnosis.[123] In another study involving 411 patients with CP, the probability of survival up to 35 years after the onset of symptoms was 83%.[13] Survival is affected by complications of CP, adverse effects of alcoholism, smoking, and diabetes. One study showed a standardized incidence ratio (SIR) of 26.3 (95% CI, 19.9-34.2) for pancreatic cancer in patients with CP. The cumulative risk of pancreatic cancer was 1.8% at 10 years and 4% at 20 years of follow-up.[124] The risk may be higher for those with genetically determined CP.[125] In patients with hereditary pancreatitis, the risk of pancreatic cancer was significantly greater than age- and sex-matched Surveillance, Epidemiology, and End Results data (SIR, 59; 95% CI, 19-138). The cumulative risk was 7.2% (95% CI, 0%-15.4%) at 70 years and the median overall survival was 79.3 years (interquartile range [IQR], 72.2-85.2 years).[126] Currently, guidelines do not recommend routing screening of patients with CP for pancreatic cancer except in those with *PRSS1* mutation; however, there is no consensus yet on the frequency and mode of screening for these individuals. Computed tomographic scanning should be considered for patients with weight loss associated with CP, jaundice, and new-onset pain after a long pain-free interval to evaluate for pancreatic cancer.

Conclusions

Chronic pancreatitis often results in chronic abdominal pain and is most commonly caused by excessive alcohol use, smoking, or genetic mutations. Treatment consists primarily of alcohol and smoking cessation, pain control, replacement of pancreatic insufficiencies, and mechanical drainage of obstructed pancreatic ducts in some patients.

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