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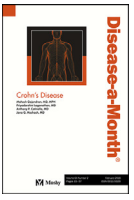

Current advances in the management of chronic pancreatitis

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ABSTRACT

Chronic pancreatitis is characterized by irreversible destruction of pancreatic parenchyma and its ductal system resulting from longstanding inflammation, leading to fibrosis and scarring due to genetic, environmental, and other risk factors. The diagnosis of chronic pancreatitis is made based on a combination of clinical features and characteristic findings on computed tomography or magnetic resonance imaging. Abdominal pain is the most common symptom of chronic pancreatitis. The main aim of treatment is to relieve symptoms, prevent disease progression, and manage complications related to chronic pancreatitis. Patients who do not respond to medical treatment or not a candidate for surgical treatment are usually managed with endoscopic therapies. Endoscopic therapies help with symptoms such as abdominal pain and jaundice by decompression of pancreatic and biliary ducts. This review summarizes the risk factors, pathophysiology, diagnostic evaluation, endoscopic treatment of chronic pancreatitis, and complications. We have also reviewed recent advances in endoscopic retrograde cholangiopancreatog-

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raphy and endoscopic ultrasound-guided therapies for pancreatic duct obstruction due to stones, strictures, pancreatic divisum, and biliary strictures.

Introduction

Chronic pancreatitis is an inflammatory condition of the pancreas associated with significant morbidity due to undulant pain and pancreatic insufficiency. The annual incidence of chronic pancreatitis is estimated to be 5 to 12 per 100,000 persons and prevalence of 50 per 100,000 persons globally.[1–3] It is 1.5 to 3 times more predominant in men than women.[4] The average age of diagnosis of chronic pancreatitis is 35–45 years, and the median survival period is 20 years.[5,6]

Historically chronic pancreatitis was defined as recurrent irreversible inflammatory changes leading to destruction and fibrosis of pancreatic parenchymal and ductal structures.[7,8] However, diagnostic and translational advances have led to a better understanding of the condition. The definition has evolved to reflect the underlying pathophysiology, its causes, and associated pancreatic dysfunction. Chronic pancreatitis is defined as pathologic fibro-inflammatory syndrome of the pancreas in a person with genetic, environmental, or other risk factors who develop persistent pathologic responses to parenchymal injury/stress. This mechanistic definition introduced in 2016 also defined features of advanced chronic pancreatitis, which include pancreatic atrophy, fibrosis, pancreatic duct distortion and strictures, calcifications, pain syndromes, dysplasia, pancreatic exocrine and endocrine dysfunction.[7]

Several observational studies have shown an association between chronic pancreatitis and pancreatic cancer.[9–12] However, these studies were confounded by other risk factors for pancreatic cancer, such as tobacco smoking, alcohol, and diabetes. In a cohort study of 1656 chronic pancreatitis patients, pancreatic cancer was detected in 1.3% of patients.[13] A recent meta-analysis of 13 studies reported that patients with chronic pancreatitis have an eight-fold increase in the risk of pancreatic cancer at the end of five years follow up effect estimate of 7.90 (95% CI 4.26–14.66). However, the risk of pancreatic cancer decreases as the time interval from chronic pancreatitis diagnosis increases. The overall effect estimate of pancreatic cancer decreased to 3.53 (95% CI 1.69–7.38) at follow up period of a minimum of 9 years.[14]

Pathophysiology

Chronic pancreatitis is a progressive and irreversible process, which leads to fibrotic destruction of pancreatic parenchyma leading to exocrine and endocrine insufficiencies.[7,15] The mechanism of injury differs depending on the underlying etiology, and ultimate insult to tissue depends upon how this injury interacts with underlying environmental and genetic predispositions.[6]

Pancreatic stellate cells are key cells involved in the pancreatic tissue injury in these patients.[16] In response to oxidative stress, cytokines growth factors, and toxins, pancreatic stellate cells activated to myofibroblast-like phenotype in which cells synthesize and produce an excessive amount of extracellular matrix proteins, resulting in chronic inflammation, collagen deposition, and fibrosis progressing to chronic pancreatitis.[17–19]

There are five proposed mechanisms for the pathophysiology of chronic pancreatitis. First, a "two-hit" model in which the first hit is an episode of acute pancreatitis, and the second hit is the inflammation response to the first hit leading to activation of inflammatory and profibrotic cells, including pancreatic stellate cells. This leads to collagen deposition and fibrosis through activated immune cells, leading to chronic pancreatitis.[1,20–23] Second, a necrosis-fibrosis sequence hypothesis suggests that chronic pancreatitis develops due to repeated episodes of acute pancreatitis resulting in activation of inflammatory and pancreatic stellate cells; thus fibrosis.[24,25]

Third, oxidative stress due to free radicals in acinar cells results in membrane lipid oxidation and expression of transcription factors. This can lead to acinar cell necrosis, intra-vesicular protease activation, and fibrosis.[26,27] Fourth, a direct metabolic-toxic effect proposed a direct effect of environmental factors and their metabolites on acinar cell leading to pancreatic inflammation.[28] Fifth, a ductal dysfunction leading to the formation of protein plugs and upstream ductal obstruction.[24,29]

The etiology of abdominal pain involves several mechanisms and still not completely understood. Repeated episodes of inflammation and pancreatic injury lead to a release of inflammatory molecules from the injured cell, which in turn results in transmission of nociceptive signals to the brain via dorsal root ganglia and dorsal horn of the spinal cord.[30,31] In patients who have obstructed pancreatic ducts due to stone or stricture, patients may have recurrent episodes or continuous pain due to ductal hypertension. Patients can also have long-term pain due to pancreatic and extra-pancreatic complications like pseudocysts, pancreatic cancer, duodenal and bile duct obstruction.[31,32]

In patients with advanced chronic pancreatitis, pancreatic parenchyma is replaced with fibrosis. It can exert extrinsic pressure on the common bile duct due to the close anatomic location of CBD with the pancreatic head. Moreover, in advanced cases, due to recurrent inflammatory episodes, patients can develop periductal fibrotic strictures. These patients with biliary duct obstruction can present as asymptomatic to abdominal pain and jaundice with abnormal liver function tests.[33–35]

Diagnosis

Chronic pancreatitis diagnosis is made based on a combination of patient history, clinical presentation, risk factors, diagnostic tests such as imaging, endoscopic, and pancreatic function tests. Early chronic pancreatitis is difficult to diagnose with the absence of radiographic changes or changes in pancreatic functions.[5,36] Patients usually present with nausea, vomiting, mid-epigastric abdominal pain radiating to the back, and unexplained weight loss.[36–38] Approximately 10–20% of patients with chronic pancreatitis do not have any pain.[39] As the disease progresses and 90% of pancreatic functions are lost, the patient develops exocrine dysfunction with symptoms like steatorrhea, fat malabsorption, and fat-soluble vitamin deficiencies (A, D, E, K, B12).[37,39,40] Chronic pancreatitis can also lead to endocrine dysfunction and, thus, diabetes.[39–41] Fig. 1 shows various diagnostic tests for chronic pancreatitis.

Risk factors

Alcohol is the most common risk factor for chronic pancreatitis, accounting for 70% of cases in adults.[5] Another independent risk factor is smoking.[42] The TIGAR-O system and M-ANNHEIM are the two major classification methods established to categorize risk factors for chronic pancreatitis. The acronym TIGAR-0 stands for T (Toxic-Metabolic), I (Idiopathic), G (Genetic), A (Autoimmune), R (Recurrent acute or severe pancreatitis), and O (Obstructive). The acronym M-ANNHEIM stands for M (Multiple risk factors)-A (Alcohol), N (Nicotine), N (Nutritional factors), H (Hereditary factors), E (Efferent duct factors), I (Immunological factors), M(Miscellaneous and rare metabolic factors).[5,8] Once there is a suspicion for chronic pancreatitis based on clinical presentation and risk factors, further diagnostic tests, including imaging, endoscopic, and pancreatic function tests, should be done.

Diagnostic techniques for chronic pancreatitis:

Accurate diagnosis of chronic pancreatitis is important, especially in the setting of non-specific abdominal pain where there are several differential diagnoses causing abdominal pain.

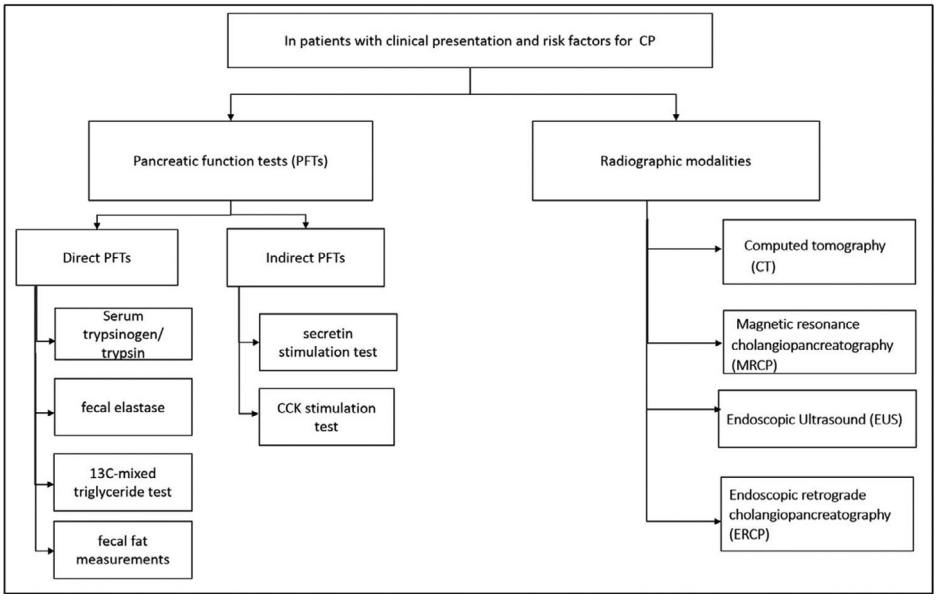


Figure 1. Diagnostic test for chronic pancreatitis

The diagnostic tests can be in the form of imaging tests, diagnostic endoscopy evaluation, and blood and fecal tests.

Imaging studies

Computed tomography (CT). American college of gastroenterology (ACG) clinical guidelines recommend either CT or Magnetic resonance imaging (MRI) as the first line of test for diagnosis of chronic pancreatitis.[8] CT scan is easily available, noninvasive, and relatively cheaper compared to other modalities with a sensitivity and specificity of 74–90% and 80–89%, respectively. Three common findings on CT in chronic pancreatitis are pancreatic ductal dilation (68%), parenchymal atrophy (54%), and pancreatic calcification (50%) (Figs. 2 and 3).[43] CT can also detect acute pancreatitis changes, complications of chronic pancreatitis like pseudocysts, ductal dilation, pseudoaneurysms, biliary, duodenal obstruction, and parenchymal atrophy.[44,45] During early chronic pancreatitis, CT findings may be normal.[38] When CT is inconclusive, alternative diagnostic studies should be considered to establish the diagnosis.[21]

Magnetic resonance imaging (MRI)/ magnetic resonance cholangiopancreatography (MRCP). MRI is superior to CT for the evaluation of pancreatic parenchymal and ductal changes.[5,36,38] Pancreatic parenchymal changes seen on MRI include pancreatic atrophy, depressed T1 signal, the irregular contour of the head or body of the pancreas, and delayed contrast enhancement of the parenchyma.[21] Moreover, MRI is more sensitive than CT for the diagnosis of early chronic pancreatitis without the risk of radiation.[36,38] Current guidelines from the ACG recommend secretin stimulated MRCP (s-MRCP) in patients with high suspicion for chronic pancreatitis and inconclusive CT, MRI, or EUS.[8] s-MRCP allows better visualization of the main pancreatic duct and the side branches than MRCP alone.[8] It can also help visualize the pancreatic duct flow rate and quantify the degree of filling into the duodenum, which in turn correlates to the severity of disease.[8,38] s-MRCP has a sensitivity and specificity of 77% and 83% for early chronic pancreatitis, respectively.[21,46] However, s-MRCP is an expensive test; therefore, it should be considered only when the diagnosis is not made with other cross-sectional imaging.

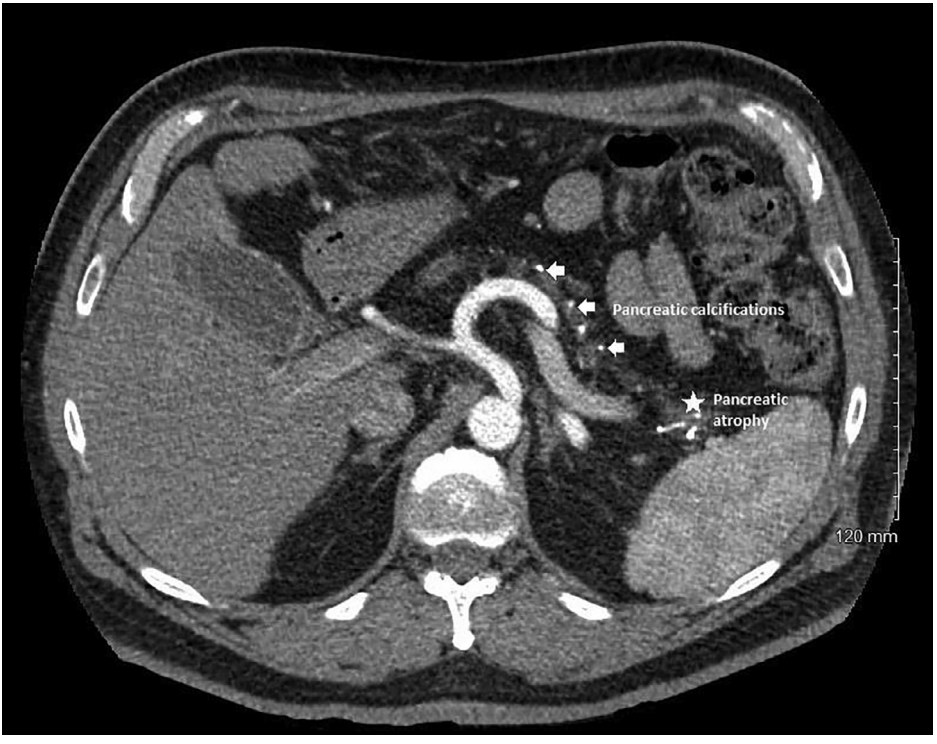


Figure 2. CT abdomen showing pancreatic calcification and pancreatic atrophy

Endoscopic ultrasound (EUS). EUS is superior to CT and MRI imaging for the evaluation of pancreatic parenchymal and ductal changes. EUS can help in the diagnosis of chronic pancreatitis in the early stages.[21,47,48] EUS can also detect complications of chronic pancreatitis, such as strictures, stones, malignancy, and differentiate chronic pancreatitis from other pancreatic lesions.[48,49] The international working group for diagnosis of chronic pancreatitis proposed nine EUS criteria (four parenchymal and five ductal) for the diagnosis of chronic pancreatitis. Four parenchymal criteria included hyperechoic foci, hyperechoic strands, lobular contour, and cysts (Fig. 4). The five ductal features include main duct dilatation, duct irregularity, hyperechoic margins, visible side branches, and stones inside the duct (Fig. 5(a) and (b)).[36,38] EUS findings seen in chronic pancreatitis are nonspecific and can also be observed in normal pancreatic tissue, which increases with age.[50] In addition, EUS is an operator-dependent procedure that leads to significant inter-observer bias**.**

A study comparing EUS interpretation by 11 different endosonographers showed good agreement on only two [duct dilatation ($\kappa = 0.6$) and lobularity ($\kappa = 0.51$)] of 9 features and poor agreement on the other seven.[51] Because of significant interobserver disagreements on EUS findings, Rosemont criteria-a consensus opinion of 32 internationally recognized endosongraphers on the interpretation for chronic pancreatitis was established. The Rosemont criteria are divided into major and minor criteria. Major criteria include major A (hyperechoic foci with shadowing and main pancreatic duct calculi) and major B (lobularity with honeycombing). The minor criteria include pancreatic cysts, dilated ducts ($\geq$3.5 mm), irregular pancreatic duct contour, dilated side branches ($\geq$1 mm), hyperechoic duct wall, strands, non-shadowing hyperechoic foci, and lobularity with noncontiguous lobules (Fig. 6a and Fig. 6b).[47]

EUS elastography is another new technique that can be used for the diagnosis of chronic pancreatitis as it can provide information about the degree of fibrosis by evaluating tissue

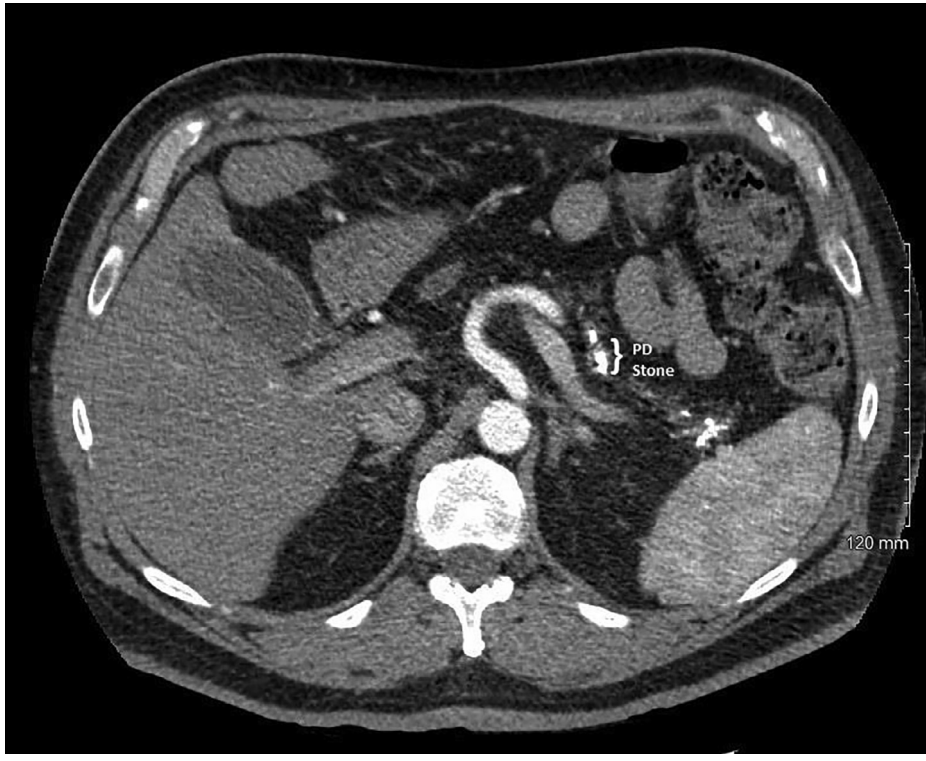


Figure 3. CT abdomen showing pancreatic stone

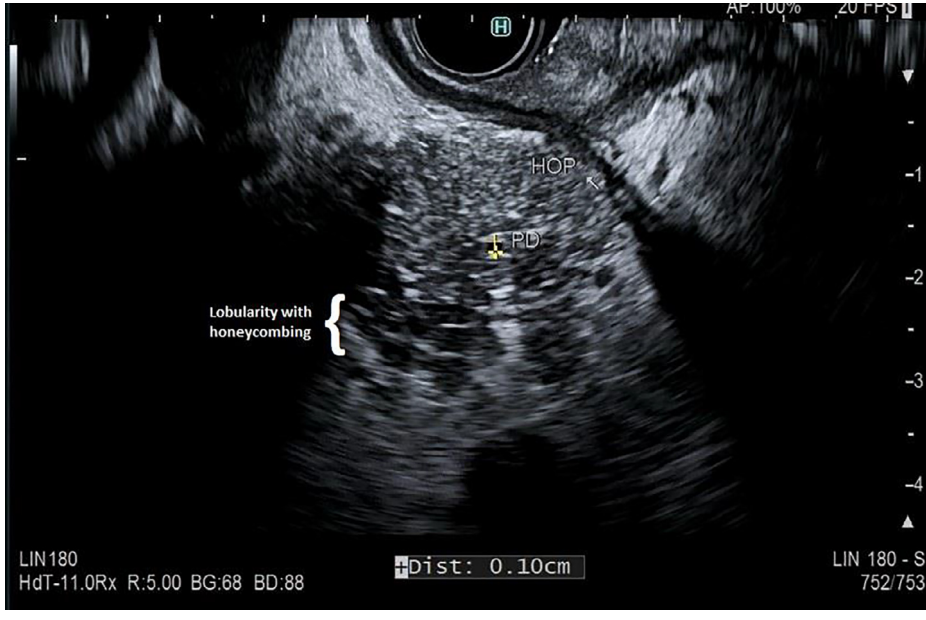
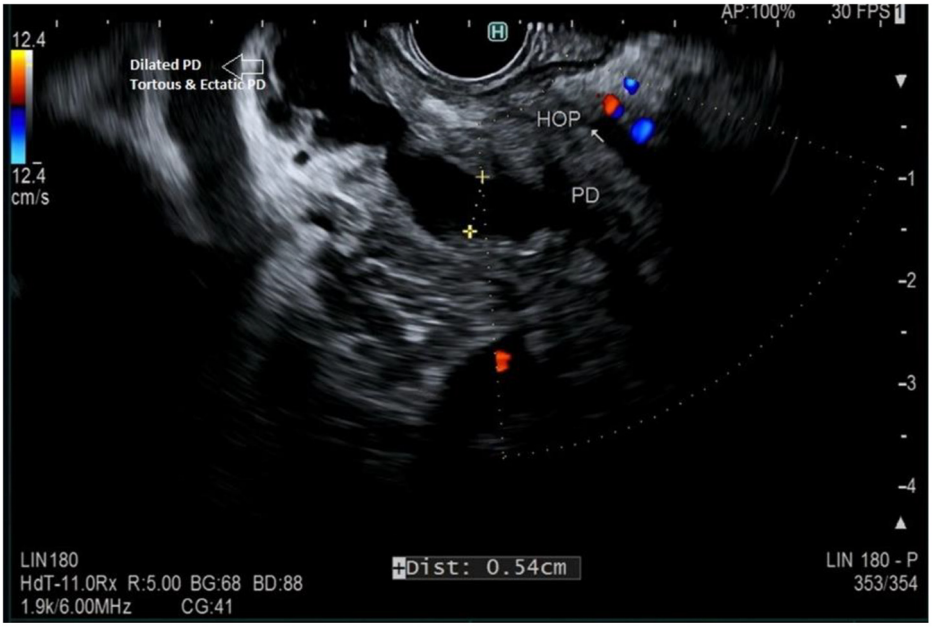


Figure 4. Endoscopic Ultrasound showing lobularity with honeycombing of the pancreas

a



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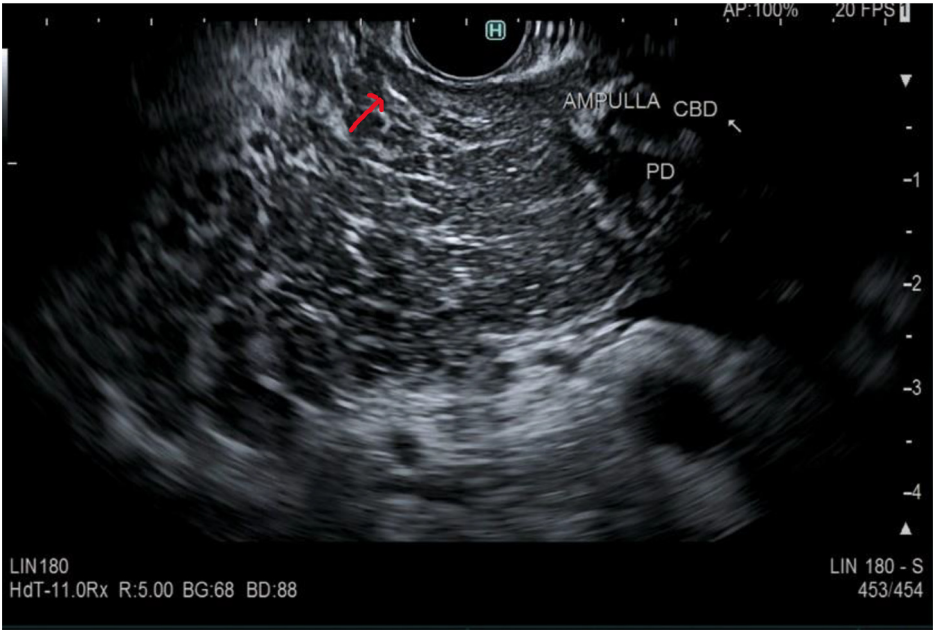

Figure 5a. Endoscopic Ultrasound (EUS) showing dilated pancreatic duct
Figure 5b Endoscopic Ultrasound (EUS) showing hyperechoic strands

a

Features		Parenchymal	Ductal
Major	Major A	Hyperechoic foci with shadowing	Stones in the main pancreatic duct
	Major B	Honeycombing lobulation	
Minor		Lobulation without honeycombing	Irregular main pancreatic duct
		Stranding	Dilated side branches
		Hyperechoic foci without shadowing	Dilated main pancreatic duct
		Cysts	Hyperechoic main pancreatic duct margin

b

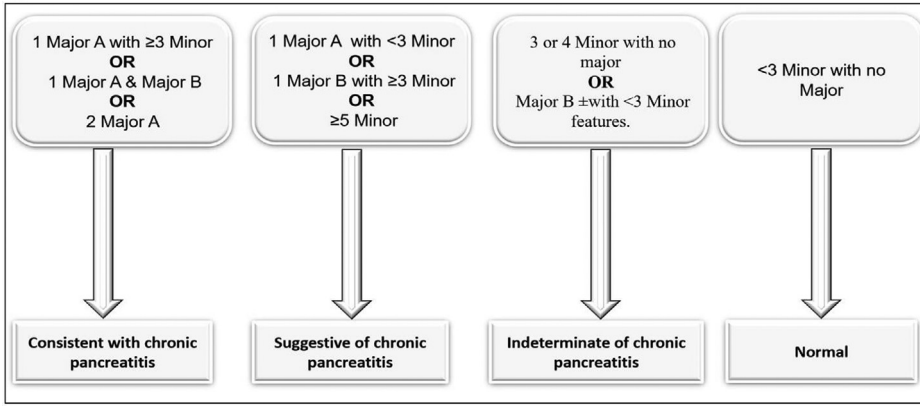

Figure 6a. Figure 6a and figure 6b Endoscopic ultrasound diagnosis of chronic pancreatitis based on Rosemont Criteria

strain/stiffness. In a prospective study, a direct linear correlation was found between EUS criteria based on the Rosemont classification and strain ratio ($r = 0.813$; $P < 0.0001$) for the diagnosis of chronic pancreatitis (91.1% accuracy at a strain cutoff point of 2.25).[52] Further clinical trials are needed to assess the use of EUS elastography for the diagnosis of chronic pancreatitis.

Endoscopic retrograde cholangiopancreatography (ERCP). ERCP allows visualization of the pancreatic ductal system but not pancreatic parenchyma. It is an invasive and expensive procedure. With the availability of CT, MRI with MRCP, and EUS, ERCP is reserved for cases where the diagnosis is inconclusive after other imaging and pancreatic function tests.[53] Cambridge criteria are being used to diagnose chronic pancreatitis with ERCP by standardizing the interpretation of ERCP findings (Fig. 7). Pancreatic ductal changes on ERCP are classified as normal or equivocal to mild, moderate, or severe based on changes in the main pancreatic duct and side branches (Fig. 8). Abnormalities in the main pancreatic duct are noted in the moderate and severe categories, whereas no abnormal changes are noted in normal, equivocal, and mild categories. In the case of side branches, no abnormalities are noted in the normal category, whereas for the equivocal and mild category, <3 and ≥ 3 side branch abnormalities are noted, respectively. Moderate and severe categories have >3 side branches involved and, in addition, changes like a large cavity, obstruction, filling defects, severe dilatation, or irregularity are seen.[54]

ERCP is also an operative-dependent procedure so susceptible to inter-observer bias as it is an invasive procedure and can lead to complications such as bleeding, infection, and post-procedure pancreatitis. Therefore, ERCP should be reserved for therapeutic intervention for chronic pancreatitis.[53]

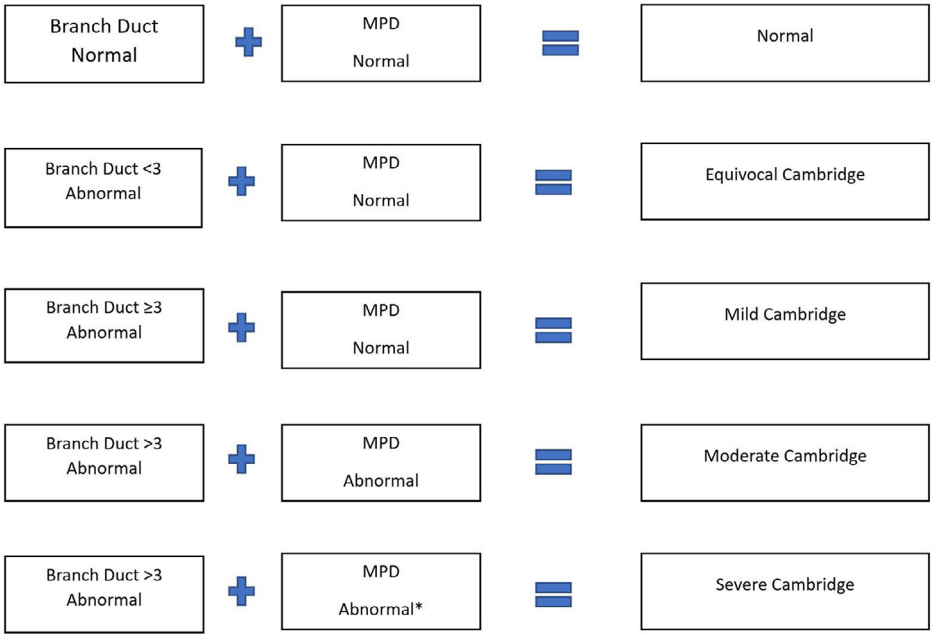

Figure 7. Endoscopic retrograde cholangiopancreatography diagnosis of chronic pancreatitis based on Cambridge classification.

A meta-analysis of 43 studies with 3460 patients showed comparable high diagnostic accuracy for diagnosis of chronic pancreatitis by CT, MRCP, EUS, and ERCP. The sensitivity for CT, MRCP pancreatitis, EUS, and ERCP to diagnose chronic pancreatitis was 75%, 78%, 81%, and 82%, respectively. Similarly, specificity for CT, MRCP, EUS, and ERCP to diagnose chronic pancreatitis was 91%, 96%, 90%, and 94%, respectively. So, imaging for chronic pancreatitis workup should be selected on cost-effectiveness, availability, and invasiveness of modality in a stepwise manner.[55]

Blood tests

In chronic pancreatitis, healthy pancreatic tissue is replaced by fibrotic tissue leading to the destruction of exocrine and endocrine tissue. This can lead to a normal to low level of serum pancreatic enzymes in advanced stages of Chronic pancreatitis.[36,48] A prospective study of 121 patients with chronic pancreatitis and 94 healthy patients in the control group showed that amylase level below 17.3 U/l has 94% of specificity and 59% of sensitivity for the diagnosis of chronic pancreatitis**,** and these results were more prominent in the case of advanced disease.[56] In 5 to 10% of cases of biliary obstruction due to chronic pancreatitis, serum bilirubin and alkaline phosphatase can be elevated.[5,36]

Pancreatic function tests

Pancreatic function tests can be used to diagnose exocrine pancreatic insufficiency but not to diagnose chronic pancreatitis, as most of the patients with chronic pancreatitis do not have exocrine pancreatic insufficiency during early disease. Pancreatic function tests can be used along with other diagnostic tests to establish the diagnosis.[8] Most patients develop exocrine pancreatic insufficiency symptoms once they lose more than 90% of pancreatic function in advanced stages. There are two types of pancreatic function tests, indirect (noninvasive) or direct (invasive).[38]

Indirect pancreatic function tests. Indirect pancreatic function tests are cheap and noninvasive tests. Commonly used indirect pancreatic function tests are serum trypsinogen/trypsin, fecal

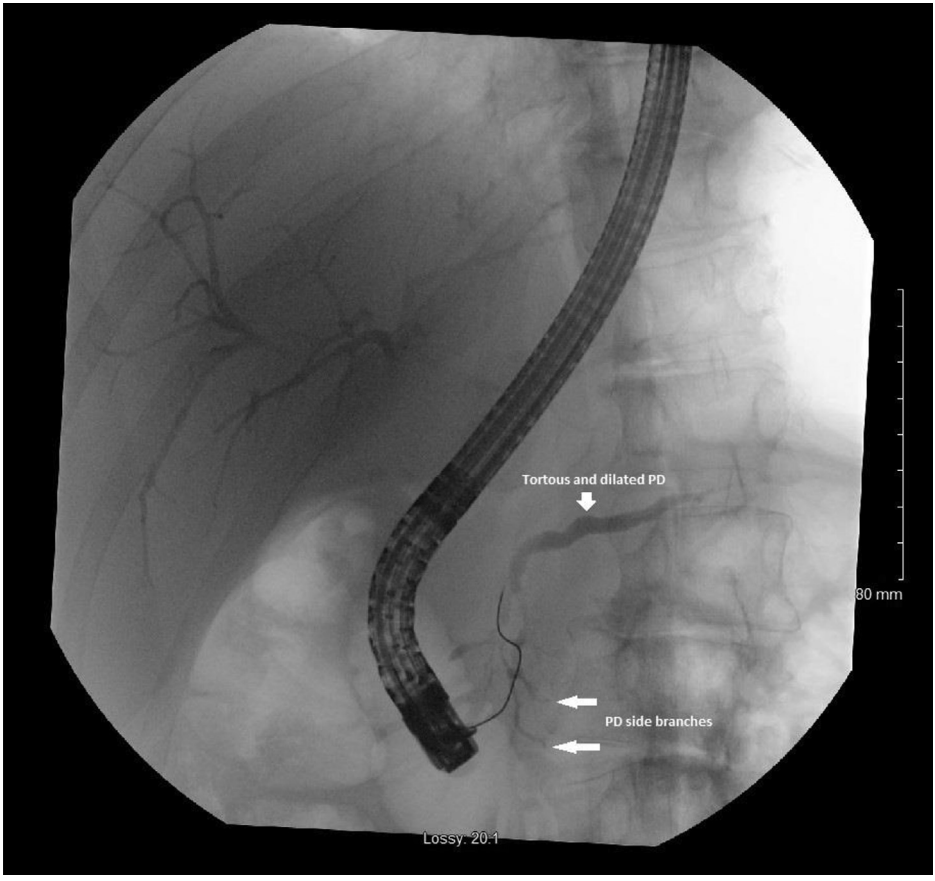

Figure 8. ERCP showing dilated and tortuous main pancreatic duct and side branches of pancreatic duct.

elastase, 13C-mixed triglyceride test, and fecal fat measurements.[8] Although a 72 h fecal fat collection test is considered as the gold standard test for quantification of steatorrhea; it is not specific for chronic pancreatitis since steatorrhea can be seen in other diseases like Celiac disease, Crohn's disease, and bacterial overgrowth. Elastase-1 is an enzyme produced by the pancreas. In patients with severe pancreatic insufficiency, fecal elastase levels are less than 100 mcg/gm of stool, and levels between 100 and 200 mcg/gm of the stool are considered indeterminate.[57] Serum trypsin assay is a blood test for exocrine pancreatic insufficiency. Serum trypsin level $<$20 ng/ml is specific for chronic pancreatitis but sensitive for only advanced disease. Serum trypsin level can be elevated in non-pancreatic conditions like acute alcoholic hepatitis, carcinomatosis, chronic renal failure, and peptic ulcer perforation; therefore, testing for serum trypsin level is usually not recommended.[8,57,58]

Direct pancreatic function tests. Direct pancreatic function tests are invasive tests and involve testing pancreatic function by measuring secretions from the pancreas after stimulation. These tests include the secretin stimulation test, which involves stimulation of duct cell and measuring bicarbonate level, cholecystokinin stimulation test involves stimulation of acinar cells and measuring trypsin and/or lipase level.[8] In a retrospective study of 116 patients who underwent secretin Pancreatic function tests for suspected chronic pancreatitis with normal imaging, the sensitivity, specificity, positive predictive value, and negative predictive value of secretin Pan-

creatic function tests were 82, 86 , 45, and 97% for the diagnosis of chronic pancreatitis. These results show that indirect tests can be used to diagnose suspected cases of early chronic pancreatitis based on symptoms but normal imaging findings.[59]

Therapeutic approaches and prognosis for treatment of chronic pancreatitis

Treatment for chronic pancreatitis involves the management of abdominal pain, exocrine and endocrine pancreatic insufficiency, disease-related complications, and improving quality of life. Effective treatment includes a combination of medical and endoscopic therapies. Surgical interventions are usually reserved for patients who do not respond to conservative measures.[5,60]

Medical management

Alcohol and smoking cessation are strongly recommended in patients with chronic pancreatitis.[8] In patients with abdominal pain without any main duct obstruction or with low severity of pain, medical therapy should be tried first.[60] Dietary changes by eating low fat, small but frequent, can alleviate pain.[5] Analgesics are the mainstay for treatment for abdominal pain.[5,36,60] Pain should be managed in a stepwise approach as recommended by the world health organization, starting with non-steroidal anti-inflammatory drugs or acetaminophen before introducing opioids.[61] Tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors have also been shown to reduce the pain in these patients.[5,36] Antioxidants, including vitamins A, C, and E, selenium, and methionine, have been proposed to help with pain by decreasing oxidative stress, thus reducing the damage of pancreatic and acinar cells.[8,36,60] A Cochrane review of randomized controlled trials (RCT) showed that there might be a slight improvement in pain with antioxidants in patients with chronic pancreatitis.[62] Systematic reviews have shown improvement in fat malabsorption with pancreatic enzyme supplements for pancreatic exocrine insufficiency.[63] However, results were equivocal for abdominal pain and quality of life.[64]

Around 30–60% of patients who have uncontrolled pain with medical therapy require invasive procedures like endoscopic interventions or surgery.[65] The most common cause of intractable pain in chronic pancreatitis is obstruction of the main pancreatic duct (by stones or strictures), biliary obstruction, and pseudocyst.[5,36]

Endotherapy

Debilitating repeated abdominal pain can be the main symptom for which patients seek treatment, and endoscopic treatment can be effective. Abdominal pain can be due to increased ductal pressure in the bile duct and or pancreatic duct. Chronic pancreatic fibrosis can lead to distal bile duct stricture leading to jaundice and pain.

Distal bile duct strictures treatment

The incidence of common bile duct stricture in patients with chronic pancreatitis varies between 3 and 46%.[66–71] It is found to be incidental in 17% of patients. Symptomatic patients can present with abdominal pain, jaundice, and cholangitis.[72,73] On laboratory testing, elevated alkaline phosphate is commonly seen in these patients.[67] Multislice CT scan, MRI, and MRCP imaging techniques shown to provide adequate imaging of pancreaticobiliary system.[74,75] Management of bile duct stricture depends on the patient's presentation and morphological changes in the pancreas. Biliary decompression is recommended when patients have persistent jaundice for more than one month, and it can be done either endoscopically or surgically.[34] Endoscopic treatment of bile duct stricture involves placement of either plastic or metal stent.

Plastic stents. Traditionally endoscopic treatment of bile duct strictures involved placement of plastic stent across the stricture.[76] Plastic stents require frequent stent exchanges due to increased incidence of stent obstruction. Patients require every 3-month scheduled exchange or whenever there is obstruction.[77,78]

In a retrospective study, 20 patients with post-operative benign bile duct stricture and 13 patients with bile duct stricture due to chronic pancreatitis underwent endoscopic treatment with plastic stent placement. Patients with bile duct stricture due to chronic pancreatitis were followed for a mean period of 85.3 months. Endoscopic therapy was successful in 7.7% of patients with bile duct stricture due to chronic pancreatitis and whereas 92.3% of these patients had stent-related clogging.[79] In another retrospective study, 58 chronic pancreatitis patients with common bile duct stricture underwent biliary stenting with plastic stents and were followed up for a median period of 45 months. Endoscopic treatment was successful in 38% (22/58) of cases. Out of these 22 patients, three died due to unrelated causes, and 18 patients did not have restenosis on a median follow-up of 85 months. In this study, concomitant acute pancreatitis was found to be a successful predictor for a successful outcome. Sub analysis showed complete resolution of stenosis in 92% of patients with concomitant acute pancreatitis, whereas it was only 24% in the group without concomitant pancreatitis.[80] This study showed the overall poor success rate of plastic stents in these patients with biliary strictures except for concomitant acute pancreatitis.

Metal stents. Metal stents require fewer endoscopic treatment sessions and usually have fewer stent occlusion than plastic stents.[77,81] A study of 20 chronic pancreatitis patients with signs of persistent biliary obstruction underwent endoscopic self-expandable metal mesh stents placements for common bile duct strictures. These patients were followed up for a mean of 33 months. Out of 20, 18 patients (90%) had relief from obstruction and patent stent. Only two patients (10%) developed epithelial hyperplasia within stents resulting in recurrent biliary obstruction at 3 and 6 months. One patient had obstruction resolution with the plastic stent, and the other needed surgical intervention.[82] In another prospective single-center study, 17 chronic pancreatitis patients with biliary stricture underwent fully covered self-expandable metal stents placements. Out of 17, 7 patients had unflared-self expandable stents (UE-SEMS), and ten patients had flared end-self expandable stents (FE-SEMS) placed. At six months of scheduled stent removal, stricture resolution was observed in 70.6% (12/17) patients and 47% of these patients had no stricture recurrence at 24 months follow up.[83]

Metal vs. plastic stents. A prospective randomized multicenter trial compared multiple plastic stents vs. covered self-expandable stent (cSEMS) for biliary stricture treatment in 60 chronic pancreatitis patients. Initially, all patients had a plastic stent placed, and at three months, it was either changed to single cSEMS or three plastic stents. Then at six months, either another three plastic stents were added, or cSEMS position was checked, and then at 9 months, all stents were removed. Patients were followed for a median of 40 months period. The two-year stricture-free success rate in plastic stent and cSEMS group was 90% (95%: 72–97%) and 92% (95%: 70–98%), $p{=}p = 0.405$ respectively.[84] A systematic review of 25 studies with 946 patients evaluated cSEMS and multiple plastic stents to treat chronic pancreatitis-related biliary strictures. The technical success rate for cSEMS and plastic stents was 100% and 98% ($p{=}p = 0.8$). The clinical success rate for strictures related to chronic pancreatitis at 12 months after stent removal was 77% (95% CI 61–94%) vs. 33% (95% CI 4–63%), $p{=}p = 0.06$ in cSEMS and plastic stents, respectively. There was no difference in early complications in both groups, but there were fewer late complications (pain infection, stent migration, stent occlusion) in the cSEMS (3%; 95%: 0%-–13%) than plastic stent group (67%; 95% CI:17–99%), $P{=}P = 0.02$. This systematic review showed a better clinical success rate with cSEMS than plastic stents for patients with biliary strictures related to chronic pancreatitis.[85]

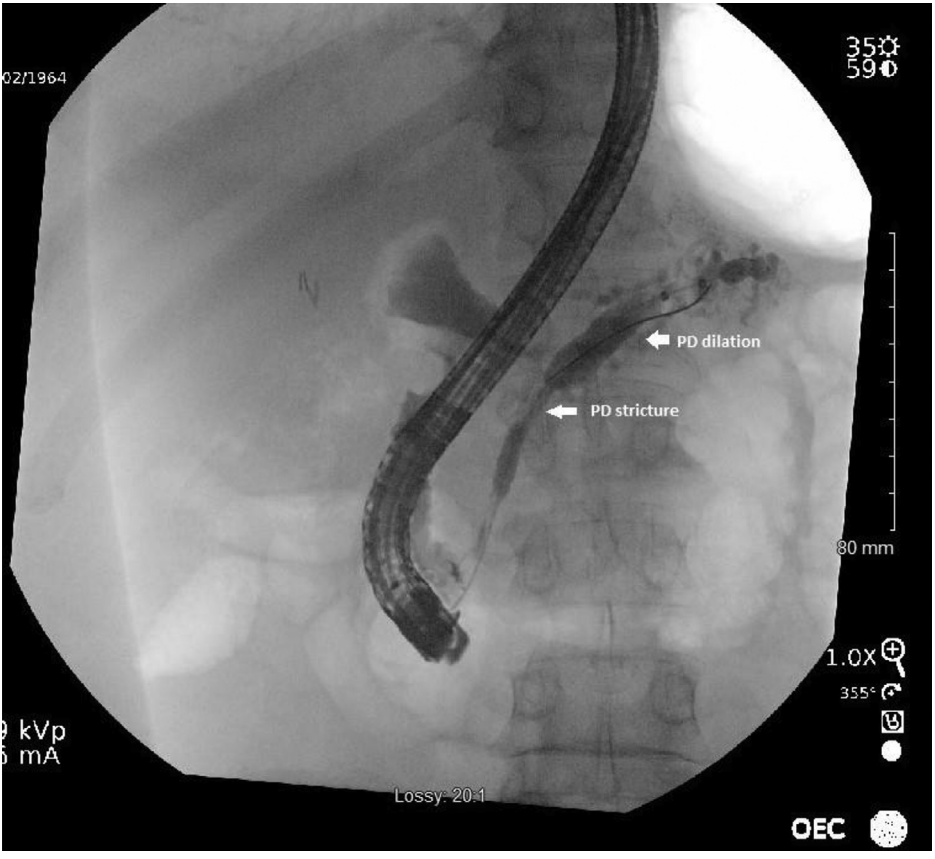

Figure 9. ERCP image showing pancreatic duct stricture

Pancreatic duct dilatation treatment

Pancreatic duct dilatation can be associated with chronic severe abdominal pain, and endoscopic therapy is the first-line treatment.[49] The most common causes of duct dilatation are obstruction due to stones or stricture, or both. Duct obstruction can be relieved with endoscopic procedures like ERCP with sphincterotomy, stone removal, dilation of stricture, and stent placement. Other endoscopic interventions include EUS guided procedures like duct decompression with stent when not successful by ERCP.[8] Various endoscopic procedures in the case of pancreatic stone or stricture are discussed below.

Pancreatic duct stricture treatment. Most pancreatic strictures occur due to inflammation, fibrosis, and previous stone and are benign in nature (Fig. 9).[49] In a multicenter study of 1211 patients treated with endoscopic therapy for ductal obstruction, 79% of patients (47% strictures alone and 32% strictures plus stones) had stricture as a cause of ductal obstruction.[86] In another study, nearly 12 % of the study population ($n = 355$) with isolated pancreatic duct strictures had malignancy.[87] Therefore, all new pancreatic duct strictures should be evaluated for malignancy by EUS or CT/MRI first before dilation or stent placement. The technical success of treating main pancreatic duct strictures is described as complete runoff of contrast material and ability to pass inflated extraction balloons through stricture.[88,89] Multiple factors like location of stricture, the number and length of the strictures, and the presence of upstream dilatation affect the suc-

Table 1
shows various studies with ERCP and plastic stents as intervention.

Author, year, and reference	Number of patients (n)	Duration of stenting (months ±SD) IQR	Pain relief-Immediate and long term (%)	Complications	Long follow-up interval (months)
Ponchon 1995[98]	23	6	74 % and 52 %	N/A	12
Binmoeller 1995[99]	93	15.7	NA and 65%	6%	59
Smits 1995[100]	51	6	82% and 55%	5%	34 (6 to 128)
Vitale 2004[101]	89	6	N/A and 83%	N/A	43
Gabbrelli 2005[102]	22	N/A	100% and 55%	N/A	66 (range 12–162)
Bartolli 2005[103]	24	6 (3–21)	100% and 64%	7%	9.7 (range 2–48)
Eleftheriadis 2005[104]	100	6	70% and 62%	N/A	27 (range-12–26)
Topazian 2005[105]	15	6	87% and 73%	N/A	36
Farnbacher 2006[106]	98	0.5	N/A and 67%	N/A	46 ±27 (4–111)
Costamagna 2006[107]	19	6–12	N/A and 84%	0%	38
Ishihara 2006[108]	20	12	95% and N/A	0%	N/A
Weber 2007[109]	19	5.6	89% and 83%	N/A	12
Cahen 2007[110]	19	7	N/A and 32%	58%	24
Boursier 2008[111]	13	4.5± 3 (0.5–13.5)	85% and 92%	10%	11±7 (range 1.5–24)
Ito 2018[95]	59	9 (1–19.6)	90.2% and N/A	3.6%	26 -36
Tringali 2019[97]	48	6–12	N/A and 74.4%	0%	114 (3 -186)

N/A: Not available; IQR: Interquartile range, SD: Standard deviation

cess of endoscopic treatments.[90] The management of pancreatic stricture involves ERCP-guided sphincterotomy, balloon dilatation, and stent placement through stricture.[91]

The techniques of endoscopic procedure:

After the major/minor papilla is cannulated using the ERCP side-viewing scope, a guidewire is passed through the stricture, and sphincterotomy is performed. Stricture is then dilated with a graduated dilation catheter or balloon dilators, and one or more pancreatic duct stents are then advanced over the guidewire. The pancreatic duct stents can be metallic or plastic stents. The type of stent used would depend on the size of the pancreatic duct downstream of the stricture.[90] Strictures due to chronic pancreatitis are tight and resilient; therefore, dilation without stenting is not effective in these strictures.[92]

Plastic stents. More than 80% of the main pancreatic duct strictures are single. There are multiple plastic stent designs like straight, S-shaped, and winged stents and stents with or without side holes.[93] Current European Society of Gastrointestinal Endoscopy (ESGE) guidelines recommend placement of a single 10-F plastic stent for one uninterrupted year in patients with painful dominant main pancreatic duct strictures if symptoms improve after initial successful ductal drainage. If a patient has persistent symptomatic main pancreatic duct stricture after one year of single plastic stent placement, surgery, or multiple side-by-side plastic stents should be considered after multidisciplinary consultation.[93] Stents should be typically exchanged every two to three months due to the risk of stent occlusion or should be exchanged as needed based on patient symptoms and/or additional images.[91,93,94] **Table 1** shows various studies with ERCP and plastic stents as interventions.

In a retrospective study involving 59 patients with the main pancreatic duct strictures due to chronic pancreatitis, 69.5% of patients had successful placement of 10 F S-shaped pancreatic stent. The median duration of stent placement was 276 days (range 30–589 days). Among those who had stent placement, 90.2% of the patients reported pain relief. The stent-related complications were observed in 3.6% of the patients, and recurrent main pancreatic duct strictures were observed in 41.5% of the patients after the follow-up of 27 months. During the follow-up period, three patients developed pancreatic cancer. Multivariate analysis showed that the remaining stones after stent removal were found to be an independent risk factor for the development of main pancreatic duct restenosis (odd ratio 11.4; 95% Cl 1.22–107.4; $p=p == 0.03$).[95]

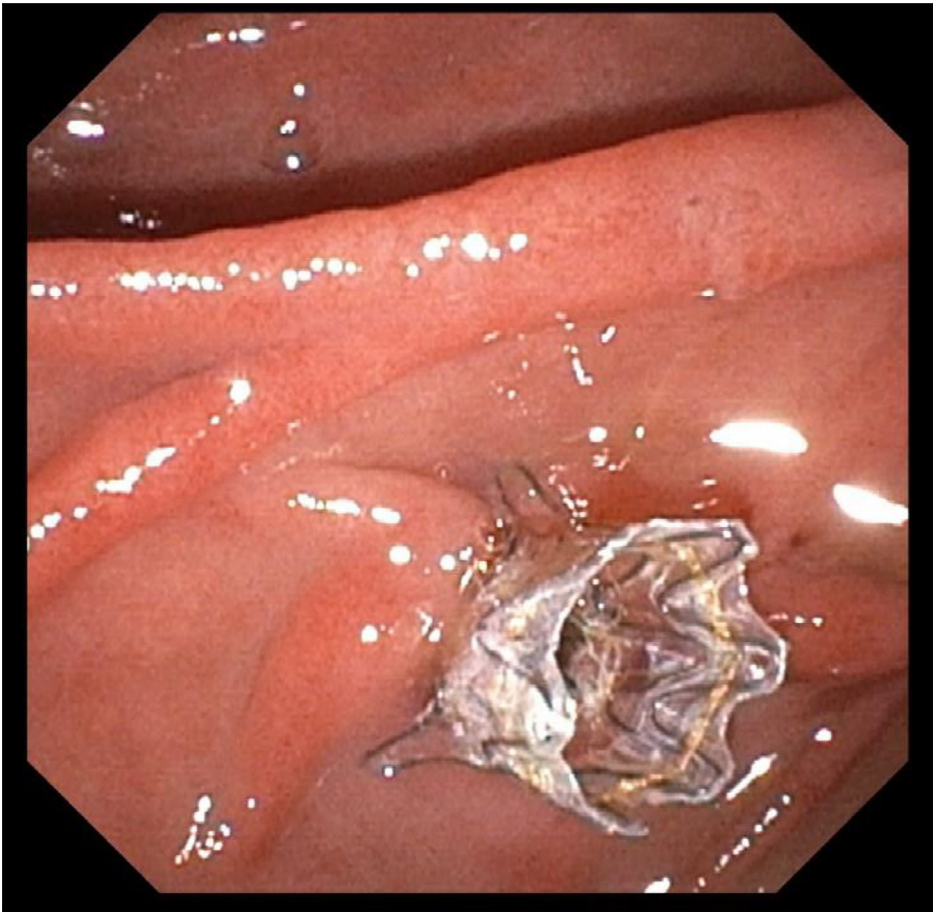

Figure 10. showing fully covered self-expandable stent in the pancreatic duct.

A meta-analysis of 16 studies ($n = 1498$ patients) evaluated the effectiveness of endotherapy for the treatment of pain associated with chronic pancreatitis. The pooled estimate of immediate pain relief and long-term pain relief (mean follow-up of 47.4 months) was found to be 88% and 67%, respectively. The complication rate was 7.85%, including acute pancreatitis, stent occlusion, and stent migration.[96]

Pancreatic duct stricture refractory to a single stent may require multiple side-by-side stents. In a retrospective study of 48 patients with pancreatic duct stricture related to chronic pancreatitis refractory to the single plastic stent, multiple side-by-side plastic stents were placed. The median number of stents placed was three, and all stents were removed after a mean follow-up of 6.8 months (6–18 months). Approximately 89.6% of the patients had stricture resolution, with 83.3% (40/48 patients) had resolution after initial stents removal and an additional 6.25% (3 patients) after the second treatment. During the mean follow-up period of 9.5 years, 74% of patients found to be asymptomatic, and 25% developed recurrent pancreatitis or other pancreatic type pain during the mean time of 26.4 months.[97]

Metal stents. Due to the number of procedures needed, as well as the cost involved with using plastic stents, the use of metal stents was proposed.[90,91] Previous studies suggest that fully covered-self expanding metal stents (FC-SEMS) (Fig. 10) are better than uncovered and partially covered SEMS.[90,93,112] **Table 2** shows various studies with ERCP and metallic stents as interven-

Table 2
shows various studies with ERCP and metal stents as intervention.

Author,year, and references	Number of patients (n)	Duration of stenting (months)	Resolution of stricture (%)	Complications	Long-term follow-up interval (months)
Okushima 2005[115]	3	< 1 month (2–7 days)	100%	0%	22
Park 2008[116]	13	2	100%	69%	5 (2–10)
Sauer 2008[117]	6	3 (2.9–3.3)	66.7%	0%	4.25 (1–8)
Moon 2010[118]	32	3	100%	25%	5 (3–7)
Giacino 2012[119]	10	5.7 (1–9)	100%	20%	19.8 (13–34)
Matsubara 2016[120]	10	2.7 (0.5–6.8)	80%	60%	35 (19–57)
Ogura 2016[121]	13	5.8 (5.1–6.2)	84.3%	23%	8.6 (6.6–18)
Yamada 2018[122]	22	4.7 (1.6–6.3)	86.3%	4%	13.9 (8.7–16.1)
Tringali 2018[113]	15	7.1 (5.8–10.3)	93%	93%	38.9 (5.3–55.3)
Korpela 2019[123]	17	5.6 (0.5–26.8)	71%	12% immediate and 76% late	29 (8.3– 80.1)
Lee 2019[124]	25	3.6 (3–4.2)	100%	4%	34 (25–56)

tions. The metal stent is mainly used for distal pancreatic duct stricture (near ampulla), and the pancreatic duct needs to have an upstream dilation of at least 5 mm for placement of a metal stent. The longest metal stent currently available is 10 cm long, and therefore these can be used for pancreatic duct stricture length of <10 cm distally (near ampulla). An upstream dilation of at least 5 mm beyond the stricture is required as the smallest diameter of the stent available in the USA is 8 mm, although, in Europe, 6 mm metal stents are available. Stretching of the small-diameter stricture can lead to pain from the stent itself and can also lead to stricture from the stent in the future. The main advantage of the metal stent is that they are usually larger in diameter and therefore can maintain patency for a long time. This will reduce the need for repeated endoscopic procedures and thereby decreasing the procedure-related complications.

In a retrospective study of 18 patients who underwent FC-SEMS stent placement for benign refractory pancreatic ductal stricture due to chronic pancreatitis, a 100% technical success and more than 50% reduction in the pain score was achieved in 83.3% of the patients. No stent migration was reported.[88] In another prospective study, FC-SEMS stents were placed in 15 patients with chronic pancreatitis and symptomatic main pancreatic duct stricture after ≥ 3 months of single plastic stents. Stricture resolution was observed in 60% of the patients, and 89% were asymptomatic with a follow-up of 38.9 months. One patient developed cholangitis 24 h after stent placement, and stent migration was reported in 7 (47%) patients.[113]

In a meta-analysis of 10 studies, 163 patients with main pancreatic duct strictures due to chronic pancreatitis were managed with FC-SEMS. After a mean follow-up of 19.3 months (range 1–80 months), 78.5% of patients reported persistent pain relief. The weighted pooled rate of main pancreatic duct stricture resolution was 93% (95% Cl: 84–99%). A subgroup analysis showed no significant difference between those who had a stent for ≤3 months compared to those who had the stent in place for >3 months 93% (95% Cl:76–100) vs. 93% (95% Cl: 80–100) $p=p == 0.91$. The pooled stricture recurrent rate after FC-SEMS treatment was 5%; 95% Cl: 0–12%. There was no statistically significant difference in stricture recurrence between a follow up of <12 months (5%;95% Cl:0–21%) and more than 12 months (5%; 95% Cl:0–16%) $p=p == 0.93$. The overall adverse events rate was 34.9%, with stent migration in 14.1%, stent induced de novo stricture in 7.4%, and cholestasis in 1.2%.[114]

Metal stents vs. plastic stents. A meta-analysis of 5 studies compared FC-SEMS and multiple plastic stents for the treatment of refractory pancreatic strictures due to chronic pancreatitis. The technical success rate and the functional success rate of FC-SEMS and plastic stents were 100% vs. 100% and 100% vs. 94.7%, respectively. The stent migration rate was 8.2% in FC-SEMS and 10.5% in multiple plastic stents. Pain relief was 85.2 and 84.2% in FC-SEMS and multiple plastic stent placement groups, respectively. No significant difference between FC-SEMS and multiple plastic stents for the treatment of refractory pancreatic strictures in chronic pancreatitis.[125]

Larger clinical trials are needed to evaluate FC-SEMS stents and plastic stents in patients with pancreatic strictures.

Biodegradable stents. In a pilot study, biodegradable non-covered self-expandable stents were used for the treatment of pancreatic duct strictures due to chronic pancreatitis. Biodegradable stents were designed to disintegrate in three to six months and had a similar delivery mechanism as uncovered SEMS. Stents were placed successfully in all patients. The stricture resolution was achieved in 58% of the patients and clinical success of 52%, requiring no further endoscopic intervention for pain at one year. The noted complications were stent occlusions (2), stent disintegration in one, one cholecystitis, and one with abdominal pain requiring readmission. Although these results are encouraging, larger randomized controlled trials are needed to assess their efficacy.[89]

Stricturoplasty with laser treatment. Laser dissection is a salvage therapy for refractory pancreaticobiliary strictures. After achieving deep cannulation of the pancreatic duct with a duodenoscope, a 200- to 272 m laser fiber is passed into the desired duct in patients with normal anatomy. In patients with intraductal stricture, cholangio-pancreatoscope can be used for direct visualization and passage of laser fiber. Stricture dissection is performed with gentle strokes of the laser fiber from a distal to proximal approach until the lumen patency improves to allow the advancement of cholangio-pancreatoscope.

A retrospective study of 11 patients with refractory benign stricture who had prior dilatation and stenting underwent ERCP-guided laser dissection/ablation using holmium or thelium. The immediate technical success rate was 84.1%, with one failure in a post-Whipple patient with an anastomotic stricture. Short-term technical success (>90% resolution of the treated stenosis on subsequent ERCP pancreatitis) was 88.2% with failure in 2 patients, one in chronic pancreatitis patients where stricture did not improve after two sessions and the other in a post-Whipple patient with anastomotic strictures. No stricture recurrence was reported during a mean follow-up of 12.1 ($\pm$11.1) months. Laser dissection can be alternate to stent placement for pancreatic stricture in chronic pancreatitis patients, but further larger clinical trials are needed to establish its role in the treatment of refractory pancreatic strictures due to chronic pancreatitis.[126]

Pancreatic duct stone treatment. Pancreatic stones are found in up to 50% of the patients with pancreatic strictures due to chronic pancreatitis (Figs. 11 and 12).[86] Pancreatic stones can be either evenly calcified radiopaque or radiolucent protein plugs, which may calcify during later stages of the disease.[90,93] A multicenter Italian survey showed pancreatic calcification in 62% of the patients with chronic pancreatitis.[127] The prevalence of calcified stones increases as time increases from the onset of disease, 50% at five years, and 100% at 14 years after the onset of the disease.[128] One of the potential mechanisms for exacerbation of chronic abdominal pain or acute pancreatitis in chronic pancreatitis patients is thought to be due to ductal hypertension as a result of pancreatic duct obstruction.[90]

ERCP and stone removal. ESGE guidelines-2018 recommend ERCP guided stone removal using pancreatic sphincterotomy and balloon or a retrieval basket for main pancreatic duct stones for radiolucent or <5 mm size stone.[93]

In a retrospective study of 580 patients with chronic pancreatitis who underwent pancreatic endotherapy, 80 patients underwent endoscopic pancreatic sphincterotomy and then extraction of stone using either a retrieval balloon or Dormia baskets. The study population had large radiolucent stones (n = 31/80), unyielding radiopaque stones post extracorporeal shock wave lithotripsy (ESWL) (n = 20/80), or pancreatic duct stricture combined with stones (n = 29/80). The technical success of the procedure was 98.75% (79/80. In patients with main pancreatic duct stones, complete ductal clearance required one session in 25 patients and two sessions in 26 patients. Adverse events were noted in 3 patients with abdominal pain, requiring admission for two patients and minor bleeding in one patient. During the initial three-month follow-up, no residual stones were found, and at the mean follow-up of eight months (range 6–12 months), all patients were asymptomatic.[129] This study found endoscopic pancreatic sphincterotomy is a safe procedure for radiolucent stones and in patients with combined stones and strictures.

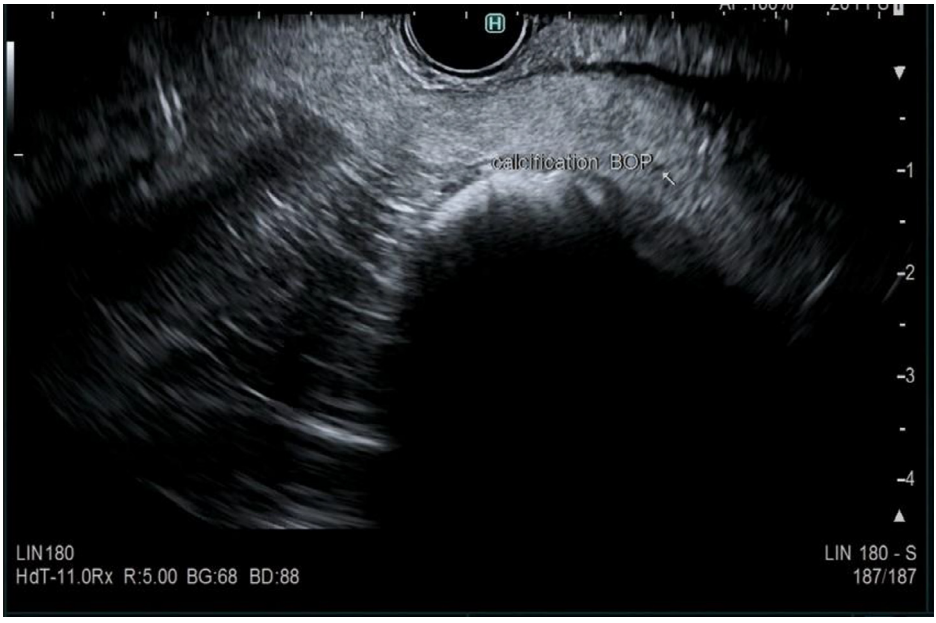

Figure 11. Endoscopic ultrasound showing calcification in the body of pancreas

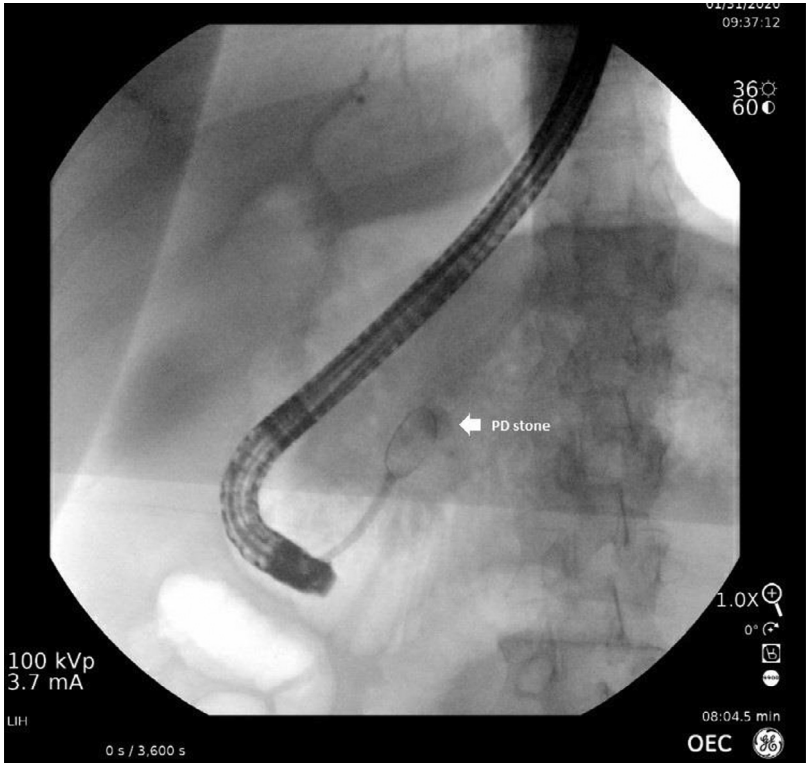

Figure 12. ERCP showing pancreatic duct stone

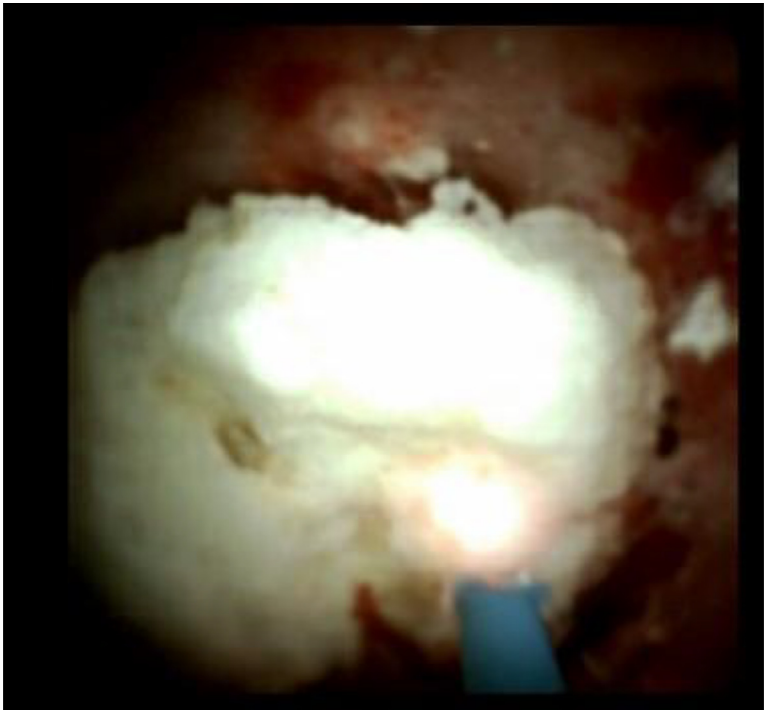

Figure 13. ERCP showing laser lithotripsy for pancreatic duct stone

In another study, 32 Chronic pancreatitis patients with pancreatic ductal stones underwent endoscopic removal of stones. Complete and partial pancreatic stone removal was achieved in 59.4% and 12.5% of patients. Overall, 67.7% of patients reported clinical improvement after an endoscopic procedure. During a follow-up ERCP performed at a mean time of 6.8 months (1.5 to 36 months) in 14 patients, 11 (91.7%) had no recurrence of stones, and 3 (25%) showed regression of pictographic changes of chronic pancreatitis. This study defined the following factors for successful stone removal with the endoscopic procedure: (1) the presence of $\leq$3 stones. (2) stones in the head and/or body of the pancreas rather than diffusely, (3) absence of stricture distal to the stone (4) stone diameter less than and equal to 10 mm (5) absence of impacted stones.[130]

Large (>5 mm), radiopaque, upstream, and impacted stones usually require extracorporeal shock wave lithotripsy (ESWL) or electrohydraulic lithotripsy (EHL) procedure for stone removal.[90,94]

ERCP and stone destruction by spyglass and laser therapy, electrohydraulic lithotripsy (EHL). Mechanical lithotripsy or intraductal lithotripsy with Laser Lithotripsy (LL) or Electrohydraulic lithotripsy (EHL) can be used to clear large radiolucent pancreatic stones that cannot be targeted by ESWL (Figs. 13,14).[90,131] The new digital spyglass system can be used as a pancreatoscope and has made these procedures more efficient.[131]

In a single-center 10-year cohort study of 46 chronic pancreatitis patients with pancreatic ductal stones underwent per oral pancreatoscopy (POP) with EHL or LL for stone fragmentation and removal during ERCP pancreatitis. POP was performed using either endoscope-based with 10 F cholangioscope (POP-Endo) or catheter-based (POP-Cath) technology. Technical success and complete clearance in POP-endo vs POP-cath was 87% vs 100% (p =0.29) and 68% v 73% (p =0.519), respectively. Overall clinical success was 74%, and patients were followed for a

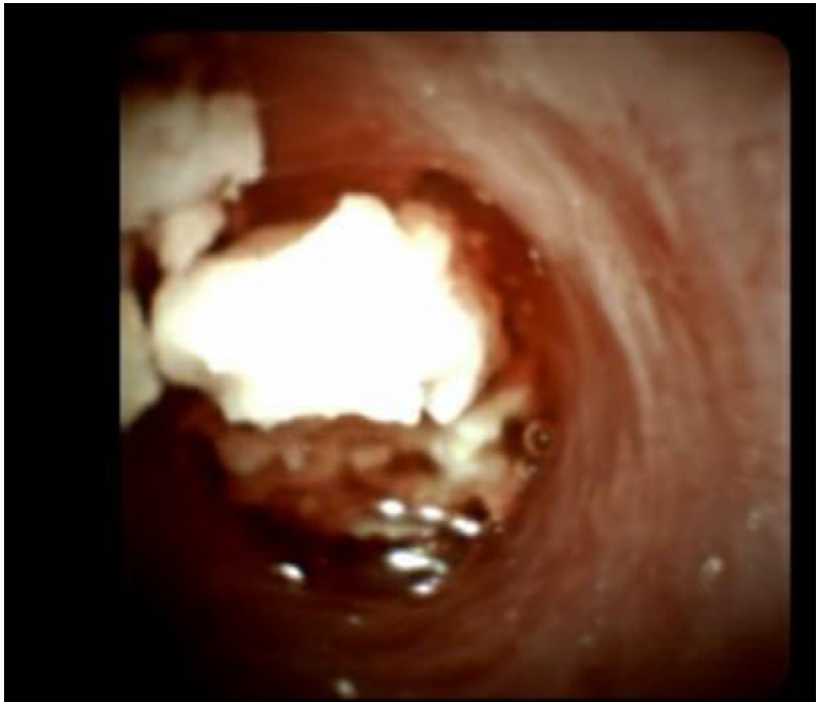

Figure 14. ERCP showing stone in the pancreatic duct

median of 18 months (range 1–60 months). Complications with pancreatoscopy were found to be 10%.[132]

A retrospective, multicenter study was conducted at 17 tertiary care centers internationally to assess the safety and efficacy of pancreatoscopy using either EHL or LL for treatment of pancreatic duct stones in chronic pancreatitis (n =109). Complete ductal clearance was achieved in 89.9% of the patients, and it was achieved in one session in 73.5% of the cases. Clinical success was achieved in 88.4% of the patients. Adverse events like pancreatitis, pancreatic duct perforation, bleeding, fever, and abdominal pain without pancreatitis were reported in 10.1% of patients (median follow-up 210 days). Incomplete stone clearance and recurrent stones were seen in (9/89)10% of the cases after a median follow-up of 105 days. On subgroup analysis, technical success and adverse events for LL vs EHL group found to be 100 % vs. 94.1 %, P = 0.243 and 8.5 % vs 12 %, P = 0.54, respectively. Although this is a retrospective study, results showed that pancreaticoscopy using EHL or LL is safe and efficacious for the management of pancreatic duct stones in chronic pancreatitis patients.[133]

This technique requires an expert to perform the procedure and should be considered in patients with large obstructive pancreatic duct stones when ESWL fails.[90,131]

ERCP and extracorporeal shock wave lithotripsy (ESWL). The European society practice guidelines recommend ESWL for clearance of radiopaque >5 mm located in the head/body of the pancreas.[93] The goal of ESWL is to fragmentation of calculi into <3 mm size pieces, which either pass spontaneously or are removed with ERCP-guided pancreatic sphincterotomy (Fig. 15 (a) and (b)).[91,134] **Table 3** shows various studies with ERCP and ESWL as interventions.

A prospective study of 214 patients with pancreatic stones due to chronic pancreatitis underwent a total of 473 ESWL, followed by ERCP. In this study, complete stone clearance from the pancreatic duct and successful endoscopic decompression were accomplished in 72.4% and 90.8% of patients. During the follow-up periods of 18.5 ± 3.3 months, 71.3 and 24.0% of patients

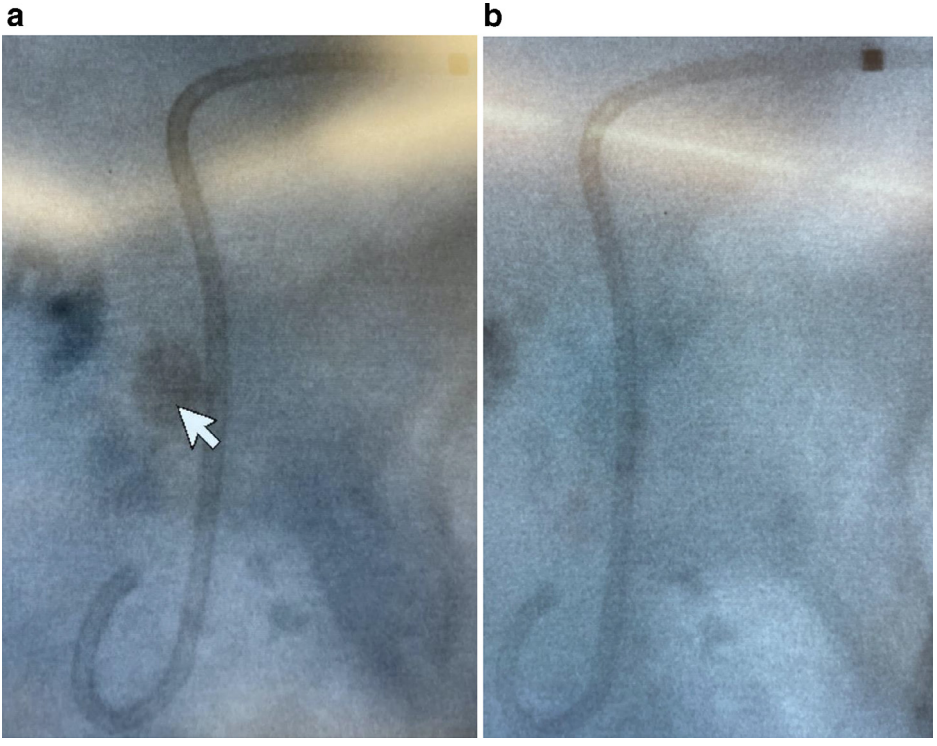

Figure 15a. Stone in Pancreatic duct pre-treatment with ESWL
Figure 15b Post-treatment with ESWL after stone destruction

had complete and partial pain relief. Out of 473 procedures, the complication was noted after 20 (4.23%) procedures.[135]

Similarly, a randomized controlled trial was conducted to compare ESWL alone (n =26) and ESWL (n =29) with endoscopy for stone removal in 55 patients with chronic painful pancreatitis and main pancreatic duct stone. Two years after the treatment, 38% of patients in the ESWL alone group presented with relapse compared to 10% in ESWL combined with the endoscopy group (OR 0.77; 95% CI 0.23 to 2.57). The main pancreatic duct diameter decreased significantly in both groups (mean decrease of 1.7 mm; 95% CI 0.9 to 2.6; $p < 0.001$), but there was no statistically significant difference in the two groups ($p = 0.391$). Although there was no procedure-related mortality in either of the groups, procedure-related complications were observed in 0% and 3%, p =1 in ESWL alone, and ESWL combined with the endoscopy group, respectively. However, the cost of the treatment per patient three times higher in the ESWL combined with the endoscopy group compared to ESWL alone ($p = 0.001$). This is the first randomized trial, and it showed that ESWL is a safe and effective procedure in these selected patients.[136]

Pooled estimates from a meta-analysis of 22 studies with 3868 patients who underwent ESWL for chronic symptomatic pancreatitis with pancreatic duct stones showed complete ductal clearance in 69.8 %. The pooled proportion of completely pain-free during the follow-up period was 64.2 %. Pancreatitis was the most common complication post procedurally, seen in 4 %. ESWL technique should be used as the first line in a patient with radiopaque stones of >5 mm in size and can be an alternative to endoscopic therapy in other cases[137]

Table 3
shows various studies with ERCP and ESWL as intervention.

Author, year, and reference	Number of patients (n)	Complete ductal clearance, n (%)	Pain relief, n (%)	Complications	Long term mean follow-up interval (months)
Wang 2018[138]	1017 (50 in the pancreatic surgery history group, 967 in the control group).	37 (77.1%)	36 (75%)	14% in pancreatic surgery vs 13.2% in control, p=0.877	30 (12 -53)
Hu 2016[135]	214	155 (72.4%)	71.3 %	4.23%	18.5 ± 3.3
Korpela 2016[139]	83	69 (83.1%)	57 (93%)	n/a	53 (24–124)
Li 2016[140]	849 (59 in the pancreatic pseudocyst (PPC) group and 790 in the control group)	39/58 (67.24%) in PPC and 657/790 (83.17%) in control, p=0.106	35 (63.6%)	7/59 (11.86%) in PPC and 98/790 (12.41%) in control, p=0.940	21.9 (12–45.1) in PPC group
Lapp 2016[141]	37	29 (80%)	35%	n/a	12
Vaysse 2016[142]	146	75/132 (56.8%)	76%	6 (4%)	23 (6–90)
Ohyama 2015[143]	128	66/128 (51.6%)	115/128 (89.8%)	4/128 (3.1%)	42.4 ± 35.8
Tandon 2013[144]	636	489/636 (76.9%)	414/636 (65.09%)	N/A	96
Merrill 2011[145]	30	12/30 (40%)	n/a	5/30 (16.67%)	2
Tandenuma 2005[146]	117	65/117 (56%)	114/117 (97%)	5 (4.7%)	77.5±30.9
Inui 2005[147]	555	403/555 (72.6%)	91 %	35 (6.3%)	43
Farnbacher 2002[148]	125	39/114 (34.2%)			
Kozarek 2002[149]	40	100%	n/a	8/40 (20%)	28 months (3–64 months)
Karasawa 2002[150]	24	13/24 (54.2%)	Only 20 out of 24 presents with pain, and it was relieved in 19/20 (95%)	15/24 (63%)	12 months
Brand 2000[151]	48	21/48 (43.8%)	17/38 (45%)	N/A	7 months

EUS guided therapy for chronic pancreatitis

EUS guided pancreatic duct intervention can be an option in patients where pancreatic ducts cannot be accessed by ERCP, in patients with surgically altered anatomy and tight stricture and stones, which are not amenable to ERCP-guided techniques.[94,152,153] There are two different techniques to accomplish EUS guided pancreatic drainage; 1. EUS guided retrograde (rendezvous) and 2. EUS guided antegrade (direct) drainage).

EUS guided retrograde (rendezvous) technique. In this technique, a curvilinear array echoendoscope is used first to puncture into the pancreatic duct in order to gain access. After obtaining access into the pancreatic duct, an echoendoscope is exchanged with either a side-viewing duodenoscope or forward-viewing endoscopy, depending on anatomy. And then, a retrograde stent can be placed from the gut lumen via papilla or anastomosis into the pancreatic duct.[152, 153]

EUS guided antegrade technique. In this technique, only a curvilinear array echoendoscope is used for pancreatic duct access and stent placement. In this technique, the pancreatic duct is accessed under EUS guided puncture and creating a tract with the antegrade placement of stent from the bowel into the pancreatic duct, either terminating across the obstruction/papilla/anastomosis or not. This approach can be subdivided into transluminal, transanastomotic, and trans-papillary depending on stents deployed across the site of ductal obstruction, or anastomosis or papilla. The transluminal approach is reserved for cases when transanastomotic and trans-papillary is not possible as there are high chances of stent migration with a transluminal approach.[152,153] Since a EUS-guided rendezvous technique is not feasible when

the papilla or anastomosis cannot be accessed or passed with a wire; the antegrade approach is applied in such cases.

A multicenter prospective study of 80 patients who underwent EUS guided pancreatic drainage for pancreatic strictures after failed ERCP was conducted at four academic centers in 3 countries. Technical success was accomplished in 71/80 (89%) patients, and the method of stent deployment was not a predictor of technical success (p=0.23). Stents were deployed in an anterograde manner in 51/71 (72%) and retrograde manner in 20/71 (28%) cases. Overall clinical success was accomplished in 65/80 (81%) cases and 92% (65/71) technical success. Clinical success was higher in the retrograde stent placement (95%) group compared to the anterograde stent placement (76%) group. Overall adverse events were seen in 16/80 (20%) cases. Out of these immediate adverse events (<24 h after the procedure) such as post-procedure pain, bleeding at the puncture site, post-ERCP pancreatitis, main pancreatic duct leak, pancreatic fluid collections, and perforations were seen in 16/80 (20%) cases and delayed adverse events (>24 h after the procedure) such as mild postprocedural pain, perforation requiring surgical repair, pancreatitis, main pancreatic duct leak and abscess needing antibiotics were seen in 9/80 (11%) cases, and these were the same patients who had immediate adverse events.[154]

In a single-center retrospective study, 45 patients who underwent EUS guided main pancreatic duct therapeutic intervention after failed ERCP (n =37) or due to surgically altered anatomy (n =29) with a median follow-up of 23 months after initial EUS-guided intervention. Out of 45, two patients underwent EUS guided stent removal, and 43 patients underwent EUS guided main pancreatic duct stent placement. Complete technical success with stent placement was 74%, and stents were deployed by the retrograde and antegrade technique in 14 and 18 patients, respectively. In postoperative patients with altered anatomy, the anterograde technique (84%) was more commonly used than retrograde (35%), with a p-value of 0.06. The moderate to serious adverse events rate was 6%. Complete symptom resolution was seen in 24 patients (82.8%) during stent in place. After a median of 4 months (range 1–47 months), stents were removed in 23 patients, and then these patients were followed for a median of 32 months, and symptoms recurred in 4 months.[155]

Literature suggests that EUS guided pancreatic duct intervention is a safe and minimally invasive option in patients with pancreatic strictures who failed ERCP-guided therapy. However, the technique has a substantial risk of complications. In a systematic review of studies on EUS-guided pancreatic duct drainage, the complication rate was found to be 18.9%, and it included abdominal pain (7.7%), pancreatitis (3.1%), bleeding (1.8%), perforation(0.9%), peripancreatic abscess(0.9%) and shaving of guidewire coating (0.9%).[156] These procedures should be performed by experts in the field with the help of a multidisciplinary team. Further randomized controlled trials are needed in this field.

EUS guided celiac plexus block. Abdominal pain in patients with chronic pancreatitis can be very debilitating. Pain is multifactorial in these patients, and one of the pain mechanisms is peripancreatic and celiac neuronal inflammation. Steroids can decrease this neuronal inflammation, and pain perception can be decreased either with anesthetics or neurolysis with alcohol.[90]

Celiac plexus block is a temporizing treatment involving the injection of a mixture of local anesthetics and corticosteroids into the celiac plexus (Fig. 16). Celiac plexus block is preferred for benign conditions like chronic pancreatitis.[48,134] In contrast, celiac plexus neurolysis involves injecting alcohol or phenol, which has a more permanent effect. It is reserved for patients with pancreatic cancer as alcohol can induce fibrosis and thus make pancreatic surgery difficult.[90,157] Pain relief benefits from celiac plexus block are temporary, as shown in a prospective study of 90 chronic pancreatitis patients with abdominal pain. Overall, pain improvement is seen in 55% of patients, but only 26% of patients have persistent benefits beyond 12 weeks and only 10% at 24 weeks. Patients <45 years of age and with previous surgery were unlikely to respond to chronic celiac plexus block.[158]

There are different methods for celiac plexus block, like EUS, guided, surgical, and interventional radiology.[8] A randomized trial compared pain control in chronic pancreatitis patients who underwent celiac plexus block either by percutaneous technique with fluoroscopic guidance or

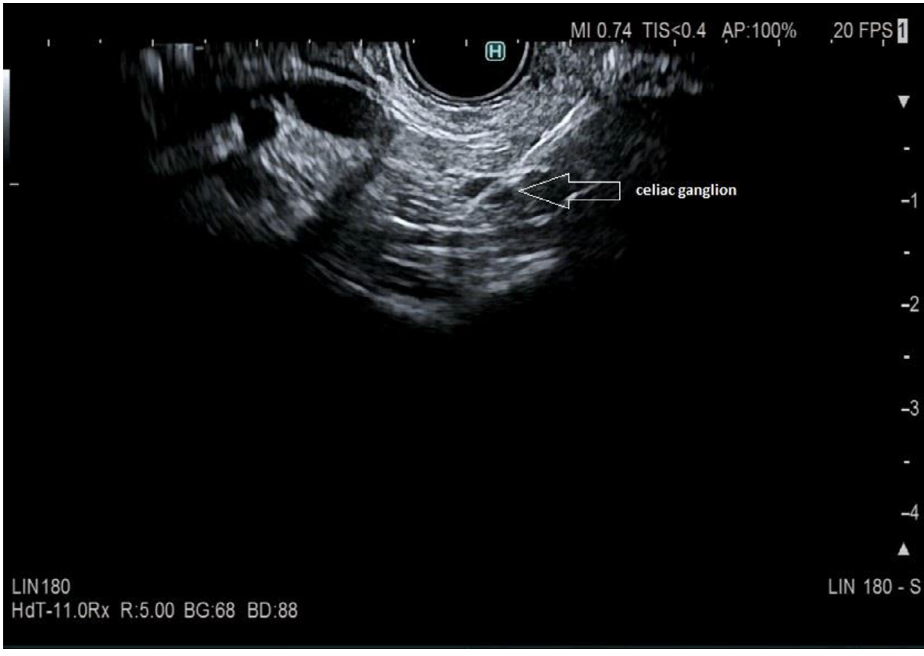

Figure 16. Endoscopic Ultrasound showing celiac ganglion (arrow pointing)

EUS guided technique. It showed that pain score improved in 70% of patients who underwent celiac plexus block with the EUS technique compared to only 30% in the percutaneous technique with fluoroscopic guidance group with a p-value of 0.044.[159]

A prospective randomized study of 51 patients comparing injection into 1 or 2 site injections during EUS guided celiac plexus block showed pain relief for a mean of 51.3 days in 28 patients (55%). Pain relief was reported in 56.5% cases with one injection compared to 53.6% in 2 injection groups with a *p*-value of 0.8. There was no statistically significant difference in the onset or duration of pain relief in both groups.[160] Similarly, a systematic review and metanalysis of six studies with 221 patients who underwent EUS guided celiac plexus block showed improved pain in 51.46 % of patients. The most common adverse events include transient diarrhea, transient orthostatic hypotension, transient pain relief, and abscess.[161]

Although EUS guided celiac plexus block is shown to provide pain relief in patients with chronic pancreatitis, it should be reserved for selected patients due to their temporary relief and side effects. It addition, it can be considered as temporary measures in chronic pancreatitis patients with pain refractory to medications.

Pancreatic divisum therapy by ERCP

Definition and incidence

Pancreatic divisum is the congenital abnormality from the failure of fusion of the dorsal and ventral pancreatic duct during the second month of gestation (Fig. 17).[90,162] Normally, the main duct (Wirsung duct or ventral duct) drains the pancreas head through the major papilla, and the Santorini duct drains the body and tail through the minor papilla. In pancreatic divisum, most pancreatic exocrine juices are drained into the duodenum by the Santorini duct (dorsal duct) through minor papilla.[163] Pancreatic divisum is one of the common anatomic variations

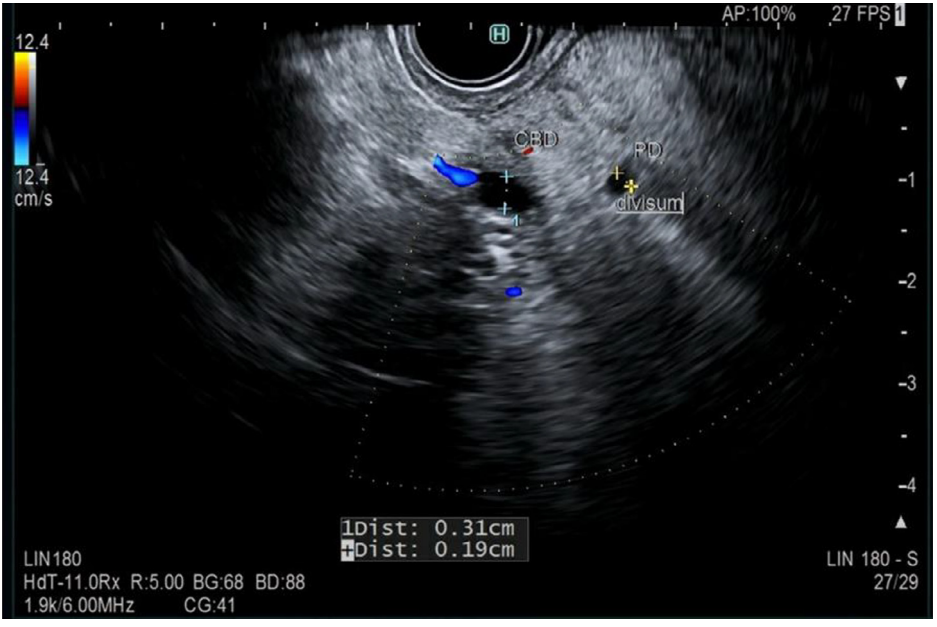

Figure 17. Endoscopic ultrasound showing pancreatic divisum

of the pancreatic ductal system, with an incidence of 4.5 to 9.6%.[164,165] The vast majority of patients with pancreatic divisum are asymptomatic, and about 5% of patients present with recurrent acute pancreatitis, chronic pancreatitis, and chronic abdominal pain.[163]

Bertin et al. conducted a study that showed that pancreatic divisum itself is not a cause of pancreatitis as the frequency of pancreatic divisum in patients with idiopathic chronic pancreatitis was comparable to that of the control group. It showed a higher incidence of pancreatitis in patients with pancreatic divisum and genetic mutations like PRSS1-, SPINK1-, and CFTR mutations, showing that it may be acting as co-factors in patients with genetic mutations.[166] In a study of 5357 patients, 304 (5.7%) were found to have pancreatic divisum and 406 (6.4%) chronic pancreatitis. Out of 304 patients with pancreatic divisum patients, 26 (8.5%) had Chronic pancreatitis.[167] .

Management

Most patients with pancreatic divisum are diagnosed incidentally on imaging or EUS (Fig. 17) and do not require further workup and treatment. In symptomatic patients, the type of treatment modality depends on the intensity and duration of symptoms and complications. Management involves relieving obstruction at the minor papilla, which can be done by the endoscopic or surgical method.[162] In patients with symptomatic pancreatic divisum, ERCP, including papillotomy of the minor papilla with or without a stent, is the first line of intervention.[163]

A systematic review and metanalysis of 34 articles showed an endoscopic detection rate of 2.9% for pancreatic divisum. The study showed similar pooled overall response rates (complete or partial pain relief) to endotherapy (69. 4%) and surgery (74.9%, $p = 0.106$) for pancreatic divisum. It also showed that pancreatic divisum patients with acute recurrent pancreatitis (81/2%) had a better response to surgery or endotherapy than patients with chronic pancreatitis (68.8%, $p < 0.05$).[168]

There is limited data on endoscopic therapy in patients with chronic pancreatitis and pancreatic divisum. A study of 48 patients with chronic pancreatitis and pancreatic divisum treated with endoscopic therapy showed a successful outcome (deep cannulation of the dorsal duct by ERCP) in 47/48 (95.7%) cases. Abdominal pain was presenting symptoms in all patients, which was for 36.6 ± 40.5 months. Out of 48 patients, 19 had chronic calcific chronic pancreatitis, and the rest had non-calcific chronic pancreatitis. Ductal calculi were noted in 3/48 and stricture in 2/48 patients. Patients with ductal calculi underwent ESWL, whereas ductal strictures were dilated with bougie dilators or balloon dilators, followed by the insertion of a stent. All 47 patients had ERCP with stent (5 or 7 Fr) successfully placed in the dorsal duct. During a follow-up period of 2–174 months, with a median of 67 months, 38.7% of cases required restenting for recurrence of pain, and none of these patients required surgery.[169] Boerma et al. followed 16 patients with chronic pancreatitis and pancreatic divisum for a median of 51 months (range 6–120 months) after ERCP guided stent placement into the main dorsal duct to bypass either narrow papilla or dominant stricture. All these patients had abdominal pain for a median of 2.5 years before the diagnosis of pancreatic divisum. One patient developed post ERCP pancreatitis. The median number of stents per person was one, and stents were extracted after a mean time of 13 weeks. Out of 16, 5 (31%) patients remained pain (median of 45 months), six patients were temporarily pain-free (median of 14 months), and the remaining five patients had no effect of the stent and underwent surgery.[170] These studies showed that pancreatic endotherapy in patients with pancreatic divisum and chronic pancreatitis is safe, effective, and less invasive than surgery, so it should be tried first before surgery if feasible based on clinical presentation.

One study showed that patient requiring 1–2 ERCPs for dorsal duct dilation were less likely to have back pain on initial presentation (4 vs. 24%, $p = 0.02$) and/or have dilated bile duct on imaging (8 vs. 30%, $p = 0.04$) than those requiring three or more ERCPs which in turn was associated with the need for surgical intervention for chronic pancreatitis. Patients requiring three or more ERCPs were more likely to require surgical intervention for chronic pancreatitis and pancreatic divisum than one requiring only 1–2 ERCPs (44 vs. 24%, $p = 0.047$).[171] So, these factors should be considered while selecting patients for endoscopic vs. surgical intervention for chronic pancreatitis in patients with pancreatic divisum.

Further large randomized controlled studies investigating endoscopic intervention in Chronic pancreatitis patients with underlying pancreatic divisum are needed.

Surgical treatment

About half of patients with chronic pancreatitis will require surgical treatment for chronic abdominal pain, which does not respond to other less invasive measures.[172] Various surgical procedures used in managing Chronic pancreatitis include drainage, resection & combined partial resection, and drainage procedures.[31,172]

Surgical drainage procedures are preferred in patients with obstructed and dilated main pancreatic ducts and avoid extensive resection. The Peustow procedure/Lateral pancreaticojejunostomy is a drainage procedure where the dilated part of the pancreatic duct is opened up longitudinally, and then the Roux-en-Y jejunal limb is placed laterally to opened pancreatic duct create a side to side anastomosis.[48] Studies have shown postoperative morbidity of 6% to 19% and mortality of 0 to 4% with this procedure.[173–176]

Surgical resection procedures are preferred in chronic pancreatitis without pancreatic duct dilation (<3 mm size), cases where drainage procedures have failed, obstructed common bile duct, and inflammatory pancreatic head mass.[48,177–180] There are three different resection procedures: (a) total pancreatectomy with islet auto-transplantation (TP-IAT); (b) pancreaticoduodenectomy (Whipple procedure) and pylorus-preserving pancreaticoduodenectomy, and (c) distal pancreatectomy. ACG recommends that TP-IAT should be reserved for selective patients with refractory pain who have failed all other measures. Patients should have a multidisciplinary evaluation before this procedure.[8] Pancreaticoduodenectomy (Whipple procedure) and pylorus-preserving pancreaticoduodenectomy are indicated in Chronic pancreatitis present with inflamed pancreatic

head, small duct disease, and when pancreatic malignancy cannot be ruled out.[181] Postoperative pain relief ranges from 80 to 90%, but it has significant morbidity.[181–183] During distal pancreatectomy, 95% of pancreatic tissue is removed, commonly considered for patients with significant obstruction or stricture in the pancreatic duct, which is located in the body and tail area of the pancreas. Postoperative long-term pain relief ranges from 55 to 81%, with high morbidity in the range of 15 to 35%.[184–188]

There are three combined resections and drainage procedures, including Frey, Beger, and Berne technique. Frey procedure is indicated in patients with dilated pancreatic ducts in the setting of the thickened pancreatic head. In contrast, the Beger procedure is indicated for patients with chronic pancreatitis and portal hypertension or biliary stenosis secondary to inflammation of the pancreatic head. And Berne procedure is indicated for patients with inflammatory head mass, and it is a combination of Beger and Frey procedure.[172] A meta-analysis of 23 studies comparing the Frey procedure, pancreatoduodenectomy, and Beger procedure showed that the Frey procedure had shorter operation time and morbidity than the pancreatoduodenectomy and Beger procedure.[189] A randomized clinical trial comparing Berne and Beger technique showed similar quality of life after both procedures, but hospital stay and operator time were shorter with the Berne technique.[190]

Comparing endoscopic versus surgical treatment

Cochrane review of two RCTs comparing endoscopic and surgical interventions in patients with painful obstructive chronic pancreatitis showed that patients in the surgical group had higher pain relief both at 2–5 years follow-up (risk ratio 1.62; 95%CI 1.22–2.15; p =0.0008) and long term ($\geq$ 5 years) follow-up (RR 1.56; 95%CI 1.18- 2.05; p = 0.002) when compared to patients with endoscopic treatment. There was no difference in postoperative complications, mortality, and morbidity in the surgical and endoscopic groups.[191]

A retrospective of 2000 Chronic pancreatitis patients from the Healthcare Cost and Utilization Project (HCUP) Florida State Inpatient Database (SID) showed that complications, hospital stay, and cost of care were higher for patients who underwent surgical procedures compared to non-surgical intervention.[192]

Endoscopy intervention is preferred when a patient has three or more small stones (<1 cm) or has single stones and stones located in the head of the pancreas.[31,91,93] ESGE also suggests that surgery or multiple side-by-side plastic stents should be considered for a patient with the symptomatic main pancreatic stricture that persists one year after initial plastic stenting, and this should be pursued after discussion with a multidisciplinary team.[93] In addition, in patients with complex stricture or numerous large stones or inflammatory mass in the pancreatic head area or disease confined to the tail of the pancreas or more complex disease, surgery may be the first line of option after discussing with a multidisciplinary team.[31]

Conclusion

Chronic pancreatitis is a progressive, debilitating disease with chronic abdominal pain. The cause of pain is usually multifactorial but commonly due to obstruction of pancreatic duct secondary stricture or stones and due to complications like pseudocyst and cancer. Alcohol abuse and smoking are modifiable risk factors, and patients should be encouraged to make lifestyle modifications (alcohol and smoking cessation) before any other intervention. Other interventions include pain control, replacement with the pancreatic enzyme in case of exocrine pancreatic insufficiency, diabetes treatment in case of endocrine insufficiencies, and invasive interventions, surgical and endoscopic interventions. Endoscopic intervention includes ERCP guided interventions like pancreatic sphincterotomy, stent placement, stricture dilation, stone removal, lithotripsy, and EUS guided interventions like EUS guided pancreatic duct intervention and celiac

nerve block. The decision about medical, endoscopic, or surgical intervention should be made after a multidisciplinary consultation.

Declaration of Competing Interest

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