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THERAPY IN PRACTICE

Chronic Pancreatitis: Epidemiology, Diagnosis, and Management Updates

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Abstract
Chronic pancreatitis is a clinical entity that results from the progressive inflammation and irreversible fibrosis of the pancreas resulting from the cumulative injury sustained by the pancreas over time. It is an illness with variable presentations that can severely impact quality of life, while its long-term complications such as exocrine pancreatic insufficiency (EPI), diabetes mellitus, and risk of pancreatic cancer can become life threatening. The diagnosis of chronic pancreatitis can be challenging as despite the recent advancements in imaging technology, the radiographic findings do not become prominent until late stages of disease. Thus, the physicians' clinical acumen in obtaining thorough history taking focusing on risk factors, clinical symptoms, in addition to high-quality imaging, often guide to the accurate diagnosis of chronic pancreatitis. Endoscopy also plays a pivotal role in the diagnosis and management of chronic pancreatitis. Endoscopic ultrasound (EUS) is believed to be the most sensitive modality for diagnosing chronic pancreatitis. Despite efforts, however, natural history studies have demonstrated that 61% of individuals with chronic pancreatitis will require at least one endoscopic intervention, while 31% will require a surgical procedure as part of their management strategy. Recent advancements in genomic studies have furthered our understanding of the genetic polymorphisms that are associated with the pathogenesis of chronic pancreatitis. Genetic testing offers the potential to reveal treatable pancreatitis-related disorders, and can inform decision making with regard to radical therapies for persistent or severe disease such as total pancreatectomy with islet autotransplantation (TPIAT). The management of patients suffering from chronic pancreatitis often requires a multi-disciplinary approach, addressing pertinent symptoms as well as the sequelae of chronic inflammation and fibrosis. Abdominal pain is the prevailing symptom and most common complication of chronic pancreatitis, and impairs quality of life. Although heavily dependent on a wide range of analgesia, endoscopic treatment such as endoscopic retrograde cholangiopancreatography (ERCP) and surgical intervention can offer long-lasting relief of symptoms. For EPI, treatment with pancreatic enzyme supplements offers marginal-to-moderate relief. The most feared complication of chronic pancreatitis—the development of pancreatic cancer—has no known prevention measure to date.

1 Introduction

Chronic pancreatitis is a distinct, often difficult to distinguish clinical entity that results from the progressive inflammation and irreversible fibrosis of the pancreas, along with the ensuing clinical syndrome characterized by abdominal pain and sequelae of exocrine and endocrine insufficiency [1, 2]. The syndrome of chronic pancreatitis results from the cumulative injury sustained by the pancreas over time, which is in contrast to the abrupt onset and most often reversible nature of acute pancreatitis that results from an identifiable inciting factor. Chronic pancreatitis is a foreboding illness with variable presentations that can manifest as abdominal pain and can severely impact quality of life, while its long-term complications such as exocrine pancreatic insufficiency (EPI), diabetes mellitus, and risk of pancreatic cancer can become life threatening [3, 4].

Following the initial clinical description of chronic pancreatitis in 1946, there have been numerous iterative changes in its definition and diagnostic criteria [5]. Over the past several years, there has been a paradigm shift to a "bottom-up" mechanistic approach to the definition of chronic pancreatitis that is now widely adopted. The traditional definition of chronic pancreatitis that revolves around the progressive irreversible damage of the pancreas is now giving way to a newer mechanistic definition that also incorporates the underlying fibroinflammatory syndrome in susceptible

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Key Points

Chronic pancreatitis is an illness with variable presentation and long-term complications, which can be life threatening.

Diagnosing chronic pancreatitis can be challenging and involves thorough history taking, high-quality imaging, and endoscopic ultrasound. Genetic testing has potential.

A multidisciplinary approach is required for the management of chronic pancreatitis. Treatment to relieve symptoms includes analgesia, endoscopic treatment, and surgical intervention, and pancreatic enzyme supplementation. There is evidence for a role for antioxidant therapy, and adjuvant therapy such as neuromodulators, anxiolytics, and antidepressants are frequently incorporated into the overall management of patients.

individuals that possess genetic, metabolic, and environmental risk factors who following exposure to parenchymal stress have developed a persistent and pathological response [2, 6]. Along with the evolution of the definition of chronic pancreatitis, there have been technological and therapeutic advancements that have furthered our ability to diagnose and treat this disease. The aim of this review is not only to capture these updates, but to provide a guide to providing current management of chronic pancreatitis. Our literature review was designed to identify original literature frequently cited on the subject of chronic pancreatitis as well as a PubMed search for chronic pancreatitis focused on recent literature published in high-impact journals.

2 Clinical Features

The most common manifestations of chronic pancreatitis are abdominal pain and steatorrhea depending on the degree of gland destruction. The pain associated with chronic pancreatitis can be episodic (< 10 days) interspersed with pain-free intervals, or can be unremitting with occasional exacerbations that require hospitalization [7]. Pain is the most consistent clinical feature of this disease; however, up to 20% of patients with chronic pancreatitis are pain free and present with symptoms related to exocrine or endocrine insufficiency [8]. Steatorrhea results from exocrine dysfunction, and as a result the digestive tract is unable to digest complex foods and fats, resulting in the passage of fatty, bulky stools that are difficult to flush away.

Fat malabsorption typically occurs prior to nutritional protein deficiency, but may be associated with decreased levels of the fat soluble vitamins (A, D, E, and K) and vitamin B_{12} [9–11]. Clinically significant deficiencies even in the presence of steatorrhea typically do not occur until over 90% of pancreas function is lost [10]. However, 10% of patients will show evidence of steatorrhea at the time of diagnosis [8]. At very late stages of disease with extensive fibrosis of the pancreas, individuals can develop type 3c insulin-requiring pancreatogenic diabetes (T3cDM) that can be distinguished from type 1 and type 2 diabetes with an absent pancreatic polypeptide response to mixed nutrient ingestion [12]. These clinical features along with additional complications of chronic pancreatitis will be discussed in greater detail in subsequent sections. Weight loss and malnutrition is frequently encountered as a result of fat malabsorption and anorexia related to the pain syndromes that are associated with chronic pancreatitis.

3 Pathophysiology

Chronic pancreatitis is a progressive and irreversible inflammatory process that results in the destruction of ductal, acinar, and islet cells that are responsible for the gland's exocrine and endocrine functions, respectively [13]. The mechanism of injury varies depending on the underlying cause, and the ultimate result is a product of how the insult interacts with underlying genetic and environmental predispositions. Regardless of etiology, it is evident that pancreatic stellate cell (PSC) activation results in cytokine expression and the production of extracellular matrix proteins, resulting in chronic inflammation, collagen deposition, and fibrosis in the progression to chronic pancreatitis [14, 15].

This observation of PSC involvement supports the sentinel acute pancreatitis event hypothesis that details that pathogenesis follows an initial insult that triggers a series of local pro-inflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], interleukin-1 [IL-1], and IL-6) that lead to matrix metalloproteinase-mediated destruction of normal pancreatic parenchyma and collagen deposition [14]. However, even the most common mechanisms are not completely understood. With respect to alcohol, the prevailing thought is that the ingestion of alcohol leads to elevated toxic metabolites that shift parenchymal cells to a pro-apoptotic state and the ultimate activation of PSC [16]. The genetic polymorphisms that have been identified in the pathogenesis of chronic pancreatitis are related to the function of the acinar cells, ductal cells, or both. For example, mutations in the cationic trypsinogen gene result in acinar cell dysfunction, while those arising from cystic fibrosis trans-membrane conductance regulator cause ductal injury.

Histological confirmation is not required for the diagnosis of chronic pancreatitis, but is defined by the presence of features of chronic inflammation such as perilobular or intralobular acinar atrophy and fibrosis. There is currently

no consensus on a histological grading system, but subclassification schema have been proposed to distinguish features into the following categories based on the relative prevalence of defined characteristics: alcoholic, hereditary, autoimmune, paraduodenal "groove", and obstructive [17]. It is very difficult to identify the cause of chronic pancreatitis on the basis of histology alone, except for in the case of autoimmune pancreatitis (AIP), due to its unique characteristics of periductal lymphoplasmacytic infiltrate, inflamed cellular stroma, obliterative phlebitis, and granulocytic epithelial lesions [18]. Biopsy can also be misleading, as the distribution of chronic pancreatitis may be patchy and is postulated to evolve through a cycle of multiple insults followed by necrosis, leading to the piecemeal progressive fibrosis of the gland [19].

4 Classification, Etiologies, and Risk Factors

Over the past 2 decades, emerging epidemiological data and natural history studies have improved our understanding of the prevalence, contributing pathogenic factors, and complications of chronic pancreatitis [20–22]. Early investigations into chronic pancreatitis suggested that acute and chronic pancreatitis were two distinct entities, but over time this paradigm has shifted towards the understanding that both of these disease processes fall on a continuum, with overlapping clinical features [23]. Current estimates suggest the incidence of chronic pancreatitis ranges from 4.4 to 14 per 100,000 people, with a prevalence of 36.9–52.4 per 100,000 persons, male predominance by a factor of 1.5–4.6, and a median survival of 20 years [24–26]. This wide range is a result of the studies being based on heterogeneous populations with varying methodological quality [27]. A systematic review by Xiao et al., however, including only high-quality studies conducted on general populations, has yielded a global pooled incidence of chronic pancreatitis of ten cases (95% confidence interval 8–12) per 100,000 general population per year [28].

Alcohol use is responsible for the greatest proportion of cases of chronic pancreatitis, but is no longer thought to be the sole inciting factor in its pathogenesis. While alcohol is associated with over half of all cases of chronic pancreatitis, there has been growing appreciation for additional broad etiological influences [2, 29]. Only a relatively low proportion (10%) of patients who sustain an initial episode of acute pancreatitis will go on to develop chronic pancreatitis, while those with recurrent bouts of acute pancreatitis have shown a greater likelihood (36%) [23]. Despite improvements in radiological and endoscopic tools, little longitudinal data exists in patients with early-stage disease as these individuals are likely to be asymptomatic and lack characteristic findings of chronic pancreatitis on routine imaging [29].

Advancements in diagnostic tools and imaging technology such as magnetic resonance cholangiopancreatography (MRCP) and pancreatic fluid analysis will aid future natural history studies in better characterizing the course of chronic pancreatitis by providing greater insight into the health and function of the pancreas [30, 31]. Ongoing investigations such as the Prospective Evaluation of Chronic Pancreatitis for Epidemiologic and Translation Studies (PROCEED), as part of the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer, is a multicenter collaborative effort that has already begun enrolling patients with chronic pancreatitis with the intent to further elucidate chronic pancreatitis disease progression and the role of candidate biomarkers and develop a platform to conduct translational and mechanistic studies [29].

With respect to health care utilization, chronic pancreatitis contributes a significant demand in the form of medical management of pain, PEI and endocrine dysfunction, along with the need for endoscopic and surgical interventions. Natural history studies have demonstrated that 61% of individuals with chronic pancreatitis will require at least one endoscopic intervention, while 31% will require a surgical procedure as part of their management strategy [32, 33]. As a result of the wide spectrum of chronic pancreatitis-related complications, individuals with chronic pancreatitis are increasingly hospitalized, carry a high 30-day readmission rate (26.7%), and in turn are at an increased risk for opiate use disorder (OUD) [34–36]. The annual financial burden of chronic pancreatitis is staggering, as the cost of hospitalizations accounts for £55.8 million, while that incurred treating exocrine and endocrine dysfunction has amassed to $75.1 million (US dollars), with pain management contributing an additional $638 million (US dollars) [37].

To make a definitive diagnosis of chronic pancreatitis, a comprehensive medical history, laboratory evaluations, imaging studies, and endoscopic interventions must be performed in a stepwise fashion [6, 19, 38]. In an effort to improve our understanding of chronic pancreatitis and to accurately identify the risk factors for progression and guide management strategies, newer classification models have been developed. Two such classification models include the TIGAR-O and M-ANNHEIM systems. With the intent to bridge the gap between recent advances in molecular, genomic, and imaging modalities and established classification, the TIGAR-O system was proposed to confer a risk assessment for the development of chronic pancreatitis in individuals who have one or more of the following risk factors: Toxic or metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe AP-associated, or Obstructive factors [39]. The M-ANNHEIM system also incorporates how multiple etiological factors can contribute to chronic pancreatitis pathogenesis; it also includes markers for clinical stage, and severity [5].

When obtaining a clinical history, it is important to inquire about prior episodes of acute pancreatitis, the presence of diabetes and its timing of onset if present, symptoms of maldigestion and weight loss, use of known precipitating factors (alcohol and tobacco), a detailed family history, and disease in organs associated with cystic fibrosis [6]. Alcohol is the most common risk factor for chronic pancreatitis and accounts for 44–65% of all cases [40–44]. Estimated intake of four to five alcoholic beverages per day (80 g/day of alcohol) for a 6-year duration has been suggested to be the threshold for chronic pancreatitis development [38, 45]. Even in the absence of heavy alcohol abuse as described above, ingestion of even lesser amounts has been shown to have disease-modifying activity that predisposes individuals to the development of chronic pancreatitis when exposed to additional insults [46, 47].

Tobacco smoking has been shown to have a uniform and dose-dependent influence on the development of chronic pancreatitis and has been implicated as the inciting factor in up to 25% of chronic pancreatitis cases [48–51]. The pathogenesis of smoking-related chronic pancreatitis results from nicotine deposition in the pancreas, and when compared to non-smokers, it confers a nearly three times greater likelihood of chronic pancreatitis development [52–54]. Smoking cessation should be encouraged, as this has been shown to halt progression and result in a risk reduction in the formation of chronic pancreatitis of 50% [54, 55]. While both alcohol consumption and smoking are known to be causative factors, their combination has a multiplicative effect that carries a greater likelihood for disease progression [48, 56]. Despite the well-described correlation between smoking and the pathogenesis of chronic pancreatitis, it remains an under-recognized risk factor in the development of this disease [57].

Advancements in genomic studies have furthered our understanding of the genetic polymorphisms that are associated with the pathogenesis of chronic pancreatitis. According to data elucidated by the North American Pancreas Study-2, genetic susceptibility is believed to account for 1.6–10.2% of all cases of chronic pancreatitis [58, 59]. Genetic testing should be considered in individuals when the following applies: the etiology of chronic pancreatitis remains unclear despite thorough testing; the patient has early onset of acute pancreatitis (< 25 years); development of chronic pancreatitis occurred at a young age (< 40 years); the patient has a strong family history of acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis; the patient has relatives who carry mutations associated with hereditary pancreatitis (e.g., PRSS1 mutations) [6, 38]. Genetic testing offers the potential to reveal treatable pancreatitis related disorders and can inform decision making with regard to radical therapies for persistent or severe disease such as total pancreatectomy with islet autotransplantation (TPIAT). Even if there is no treatment available for the underlying genetic influence, its identification can provide an end to the time-consuming and costly testing that is performed investigating this complex disease [6]. The identification of a genetic cause can also provide patients with an answer about the origin of their symptoms. Genetic testing is less likely to be clinically meaningful in individuals with advanced disease, except in the setting where the identification of a familial disorder can assist with family planning and aid family members in their own clinical decision making [6].

The genetic polymorphisms implicated in chronic pancreatitis result in either acinar cell or ductal cell dysfunction. The most frequently associated variations leading to acinar dysfunction include cationic trypsinogen (PRSS1, PRSS2), serine protease inhibitor kazal-type 1 (SPINK1), chymotrypsin C (CTRC), and carboxypeptidase A1 (CPA1). Hereditary pancreatitis should be considered when AP or chronic pancreatitis occurs in an autosomal dominant pattern, while familial forms follow a recessive pattern. Mutations in the PRSS1 gene are inherited in an autosomal dominant pattern, while those in SPINK1 can be inherited in a homozygous recessive fashion. Polymorphisms in the cystic fibrosis transmembrane conductance regulator (CFTR) gene are also inherited in a recessive fashion and result in ductal cell dysfunction, which, if identified, can serve as a potential target for pharmacological intervention [60–65]. All of these polymorphisms contribute to dysregulation of trypsinogen, resulting in either increased activation, failure of degradation, or impedance of inhibition, and result in a shift towards the activation of the trypsin pathway [19, 38, 66]. The most dreaded complication is the development of pancreatic ductal adenocarcinoma (PDAC), and the pathogenesis of PDAC and chronic pancreatitis share many of the same underlying epidemiological risk factors. While we have established that there are multiple genetic polypmorphisms that contribute to the pathogenesis of chronic pancreatitis, there is a weak association between these loci and the development of PDAC. Thus, while each of these disease states may result from genetic polymorphisms, Campa et al. have found patients do not share the same genetic susceptibility with respect to high-frequency variants [67].

AIP should also be considered as a potential etiology for the pathogenesis of chronic pancreatitis. AIP results secondary to an abnormal B-cell response and can manifest in an IgG4-mediated lymphoplasmacytic sclerosing pancreatitis (AIP-type 1) form or an IgG4-independent granulocyte epithelial lesion (AIP-type 2) form [68, 69]. The prevalence of AIP as a contributing etiology for chronic pancreatitis has been estimated to be up to 7.5%; it should be strongly considered in the setting of nonalcoholic pancreatitis [70]. The Mannheim-Autoimmune Pancreatitis Activity Score has been found to correlate with disease activity, and should be

used to monitor response to treatment longitudinally, as this subset of patients is prone to complications such as EPI [71].

Metabolic factors can also serve as the precipitating factor in the development of chronic pancreatitis. Hypercalcemia has been documented to lead to chronic pancreatitis and may result from underlying disorders such as hyperparathyroidism. Hypertriglyceridemia is known to cause acute pancreatitis, but has also been shown to result in chronic pancreatitis as well [72]. AIP through multiple recurrent episodes of immune-mediated AP can result in fibrotic changes consistent with chronic pancreatitis. AIP should be suspected when imaging reveals a diffusely enlarged and featureless pancreas, and confirmed by the presence of elevated serum IgG4, other organ involvement, histology, and responsiveness to steroid therapy [73]. Recent classification schemas have also included obstructive processes as a potential factor in the pathogenesis of chronic pancreatitis. The regions of the pancreas proximal to the stenotic duct are prone to acinar cell atrophy and progressive fibrosis [38].

Pancreas divisum is a common pancreatic malformation, but has only been found to be associated with the development of chronic pancreatitis in a small proportion of affected individuals [74]. Pancreas divisum as well as other anatomic variants (e.g., periampullary duodenal wall cysts, choledochoceles, santoriniceles, and annular pancreas) are included as a new category within diagnostic schema such as the TIGAR-O version 2 and must be considered in the evaluation process of idiopathic chronic pancreatitis [75].

5 Diagnosing Chronic Pancreatitis

The first step in establishing a diagnosis of chronic pancreatitis is to perform a detailed history to attempt to elucidate underlying risk factors that the patient possesses [75]. The key historical elements that should be retrieved are the presence of known hypertriglyceridemia, autoimmune conditions, diabetes mellitus, and establishing prior episodes of acute pancreatitis [6, 76]. If prior episodes of acute pancreatitis have occurred, the cause, when they occurred, and whether or not they were complicated by the development of either acute or chronic local complications such as fluid collections or strictures should be determined. Gathering a family history is also informative, and especially so in patients with early-onset disease. When evaluating early-onset disease, it is of paramount importance to determine if hereditary or genetic causes are responsible, as these patients are at higher risk for pancreatic cancer. Social history for alcohol and tobacco use must be performed, as these are the driving factors responsible for the majority of all cases. Routine laboratory testing to reflect the etiologies discussed above should also be performed [6, 75].

Imaging studies are integral to establishing the diagnosis of chronic pancreatitis. Despite advancements in technology, the diagnosis of chronic pancreatitis remains a challenge, as radiographic findings do not become prominent until late stages of disease. The distinguishing features that appear across modalities are the presence of a dilated pancreatic duct, gland atrophy, pancreatic calcifications, presence of fluid collections, and focal areas of pancreatic enlargement [76]. A recent systematic review and meta-analysis on the diagnostic performance of various imaging modalities with head-to-head comparison found that endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and computed tomography (CT) have comparable degrees of sensitivity without significant difference at 81%, 78%, and 75%, respectively. With respect to specificity, there was no significant difference between EUS (90%), endoscopic retrograde cholangiopancreatography (ERCP) (94%), CT (91%), MRI (96%), and abdominal ultrasound (98%) [77]. Despite these findings, the trend has been to move away from invasive procedures such as ERCP as the initial diagnostic modality and to rely on cross-sectional imaging given its relative safety [38]. The ultimate decision of modality, however, should be tailored to the clinical scenario, local expertise, and resources available.

There are unique characteristics that each of these modalities offer in the evaluation of chronic pancreatitis. Abdominal ultrasound, while least sensitive, does offer a cheap and rapid means to evaluate the structure of the pancreas. Ultrasound has limited diagnostic sensitivity until late stages of disease, and as a result has not been included in the step-up approach for diagnosing chronic pancreatitis as outlined in the American Pancreatic Association practice guidelines for chronic pancreatitis [19, 78, 79].

CT imaging is the preferred initial imaging modality in the evaluation of chronic pancreatitis, and is believed to be the optimal method to identify early and small calcifications [38, 80–82]. The most commonly visualized findings of chronic pancreatitis on CT are a dilated pancreatic duct (68%), pancreatic atrophy (54%), and pancreatic calcifications (88%) [83]. Parenchymal atrophy is neither sensitive nor specific for chronic pancreatitis, and in fact 30% of individuals will have regional pancreatic enlargement [83]. An advantage of CT is that it also identifies complications of chronic pancreatitis such as pseudocysts, portosplenic venous thrombosis, arterial pseudoaneurysms, and presence of pancreaticopleural fistula [19]. Importantly, given the increased risk for pancreatic cancer in chronic pancreatitis, CT is able to detect pancreatic neoplasms.

MRI with or without cholangiopancreatography is also an appropriate imaging modality for the diagnosis of chronic pancreatitis. An advantage of MRCP is that it offers the ability to illustrate pancreatic ductal anatomy with great accuracy [84]. Greater clarity of these anatomic features

can be achieved by using intravenous secretin with MRCP to stimulate pancreatic fluid excretion, which in turn will enhance visualization of the ducts, reveal strictures or abnormal dilations, and provide quantification of exocrine function [85–87]. The addition of secretin to MRCP increases the overall sensitivity for detecting chronic pancreatitis from 77% to 89% [85]. Diffusion weighted imaging on MRCP is able to display parenchymal changes of early chronic pancreatitis, thereby allowing earlier diagnosis prior to overt calcification and ductal irregularity [88–90].

Endoscopy also plays a pivotal role in the diagnosis and management of chronic pancreatitis. EUS is believed to be the most sensitive modality for diagnosing chronic pancreatitis [38, 91, 92]. Identification of four or more of the standard diagnostic endosonographic parenchymal (hyperechoic foci, hyperechoic strands, parenchymal lobularity, cysts, and calcifications) or ductal (pancreatic duct dilation, pancreatic duct irregularity, hyperechoic pancreatic duct walls, visible pancreatic side branches, and intraductal calcifications) features is adequate to establish the diagnosis of chronic pancreatitis [91, 93]. A challenge with using EUS in the diagnosis of chronic pancreatitis is the inherent interobserver variability and level of agreement between endosonographers [94].

The endosonographic features that yield the greatest agreement between observers on EUS have been noted to be calcifications, duct dilation, pancreatic lobularity, hyperechoic stranding, and the presence of parenchymal cysts [95, 96]. The diagnostic yield of EUS can be enhanced by performing concurrent exocrine function testing, which when used together, has been shown to yield a sensitivity of 100% [97]. Endoscopic pancreatic function test (ePFT) also provides the benefit of identifying individuals who may have very early forms of chronic pancreatitis with exocrine dysfunction in the absence of morphological changes [97–99]. Given the invasive nature of EUS and that at this time there is limited high-quality evidence to support the use of EUS with or without contrast enhancement or elastography, it cannot be recommended as the first-line diagnostic test [6]. The incorporation of shear wave elastography in addition to EUS is being investigated to provide objective measurements of pancreatic parenchymal fibrosis as a reflection of its elasticity. While pancreatic elastography is not yet incorporated into the diagnostic algorithm in the evaluation of chronic pancreatitis, it has been shown to positively correlate with Rosemont classification stages as well as the classic EUS features [100, 101].

ERCP has become less frequently performed for the purpose of chronic pancreatitis diagnosis as a result of the increasing availability of quality cross-sectional imaging and EUS and the risk of ERCP complications. The role of ERCP has transitioned to be largely therapeutic for the management of ductal complications. Its incorporation into the diagnostic algorithm of chronic pancreatitis should be reserved for patients whose diagnosis is still in question despite previously performed non- and minimally invasive testing [102]. The Cambridge criteria have established accepted criteria for the diagnosis of chronic pancreatitis based on pancreatogram findings of the main duct and its side branches [103]. Based on the ductal anatomy visualized on pancreatogram, this scoring system classifies the findings as being normal, mild, moderate, or severe. The limitations with ERCP as a diagnostic modality is the interobserver variability, lack of visualization of pancreatic parenchyma, and its inability to distinguish age-related changes from those seen in chronic pancreatitis [104, 105].

Assessment of pancreas function (PFT) should be performed in all individuals who are diagnosed with chronic pancreatitis [38]. It is important to perform functional testing in patients newly diagnosed with chronic pancreatitis, as the detection and appropriate management of exocrine failure confers improved patient outcomes and adherence [19, 106, 107]. PFT is executed through indirect and direct testing methods. An indirect PFT (iPFT) utilizes non-invasive tests that do not require hormonal stimulation of the pancreas. A direct PFT (dPFT) on the other hand does require hormonal stimulation and the invasive collection of duodenal fluid in response to cholecystokinin (CCK) or secretin infusion [108]. iPFT utility is limited in the diagnostic process, as this form of testing does not become sensitive until very late in the disease process [38]. A dPFT has greater sensitivity and is able to detect EPI in mild to moderate cases that could potentially lack gross features of chronic pancreatitis on cross-sectional imaging. If the initial PFT at the time of chronic pancreatitis diagnosis is negative, it is important to follow exocrine function annually as this will deteriorate in the majority of patients over time [8, 109].

iPFTs are noninvasive methods to identify and monitor EPI in the later stages of chronic pancreatitis, once steatorrhea is already present and greater than 70–90% of the pancreas has been destroyed. Commonly used iPFTs include serum trypsinogen, fecal elastase (FE), quantitative or qualitative fecal fat, and coefficient of fat absorption (CFA). Serum trypsinogen is suggestive of chronic pancreatitis at levels lower than 20 pg/dL and becomes less likely with greater levels. Using this threshold in patients with known chronic pancreatitis for the determination of exocrine dysfunction had a low sensitivity (28%), but was highly specific (100%) [110]. Stool FE is another iPFT is easy to perform with greater utility in patients with more advanced disease [111]. FE is an enzyme secreted by the pancreas and should be present in stool; therefore, low levels of FE in the stool infer impaired pancreatic exocrine function. When interpreting results, the lower the level, the higher the probability of PEI. FE results < 50 ug/dL are suggestive, and indeterminate

is 50–200 ug/dL. If levels are greater than 500 ug/dL, you can exclude the possibility of EPI with reasonable certainty [112, 113].

Assessing fecal fat offers another means to assess EPI. This can be performed with both quantitative and qualitative approaches. Performing quantitative fecal fat analysis is a cumbersome process that requires the collection of stools for 72 h. A diagnosis of steatorrhea can then be made if there is evidence of more than 7 g of fat in the stool per 24 h over the 72-h test period [114]. Qualitative assessments of fecal fat can also be performed in a much more convenient manner with a similar level of confidence. Spot fecal fat tests, also known as steatocrit, are supportive of steatorrhea if six or greater droplets of fat/HPF are seen, and shares a linear correlation with the 72-h fecal fat test [115]. The CFA is considered to be the gold standard iPFT in assessing steatorrhea and EPI. It is the only test to be accepted by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for use in clinical trials. Establishing the CFA is also a cumbersome task, as this process requires a patient to remain on a 100 g/day fat diet for 5 days. Stool is then collected for the final 3 days for interpretation. The CFA is considered to be pathological if it is less than 93% [10, 116]

A dPFT allows for quantitative assessment of exocrine pancreatic function. While more time consuming and labor intensive, such tests offer an increasingly sensitive approach to evaluating EPI. A dPFT requires the administration of a hormonal stimulus such as secretin or CCK, followed by the aspiration of duodenal fluid for analysis [19, 117]. Placement of a nasoduodenal tube or performance of an endoscopy is required to sample the pancreatic secretions for testing [118]. Compared to iPFTs, dPFTs provide greater sensitivity and are able to detect secretory dysfunction in patients with as little damage as 30% of the pancreas. Non-endoscopic dPFTs can be performed with the placement of nasoduodenal or oroduodenal tubes with lumens to aspirate gastric and duodenal fluid. Once placed, the patient is administered either secretin or CCK; aspiration follows at set time points, and results are analyzed for volume, pH, bicarbonate, and lipase [19, 119]. dPFTs can also be performed with endoscopic assistance (ePFT) to allow collection of duodenal secretions following the administration of a secretin bolus. ePFTs have been shown to improve diagnostic yield of EPI, with a sensitivity of 96%, and have been found to be particularly useful in the setting of inconclusive imaging [108]. The duodenal aspirates obtained by ePFT are primarily analyzed for peak bicarbonate levels and lipase.

When approaching a patient with suspected chronic pancreatitis, the American Pancreatic Association in their most recent clinical guidelines on chronic pancreatitis has proposed a stepwise algorithm that incorporates the aforementioned diagnostic modalities. The decision to proceed with further testing is made if the current evidence remains inconclusive. Following a detailed assessment of clinical signs and symptoms, a history assessment, a physical exam, and a review of laboratory studies, the first step is to perform a CT scan. If the CT findings in combination with the clinical presentation satisfy diagnostic criteria, no further imaging is needed. If unrevealing, an MRI with MRCP secretin enhancement should be performed. Recommendations are then to proceed with EUS quantification of parenchymal and ductal criteria. If the diagnosis remains in question, the subsequent step would be to proceed with a dPFT. The final diagnostic modality would be to proceed with ERCP and to assess the pancreatogram for ductal irregularity consistent with chronic pancreatitis [19].

6 Managing Chronic Pancreatitis

Abdominal pain is the prevailing symptom and most common complication of chronic pancreatitis, and can manifest on a spectrum from mild and intermittent to severe unrelenting pain that impairs quality of life [120]. In natural history studies, pain was experienced at the time of presentation in 75% of individuals and in 97% at follow-up during their clinical course [8, 32, 41]. The pathophysiology of chronic pancreatitis pain is multifactorial and is believed to result from chronic inflammation, local complications of disease, pancreatic hyperstimulation, ischemia and acidosis, and through neuropathic mechanisms [121]. Long-term inflammatory stimuli can result in peripheral sensitization, central sensitization, or both, and lead to neuronal hyperresponsiveness that may lead to a continual state of pain irrespective of an active nociceptive stimulus [122]. The NAPS-2 study led to the categorization of five distinct pain patterns based on severity and pattern according to Wilcox et al. and according to patient responses [123]. Both pain intensity and the frequency of pain attacks correlate with reductions in the quality of life of individuals with chronic pancreatitis [121]. The development of a pain management strategy must be well structured and conducted with a logical approach to minimize the long-term complications and sequelae of chronic pain control. A multidisciplinary approach to understanding the contributing pain pathway, treatment modalities, and patient engagement through behavioral modifications is key to achieving successful treatment. The early incorporation of a pain management specialist is also recommended, as longer delays in specialist consultation lead to poorer health and pain control [121].

Prior to developing a management strategy, the treating providers should assess pancreatic pain, as this will help guide response to treatment. While no subjective scoring system has been rigorously assessed for chronic pancreatitis, both one-dimensional (e.g., visual analog scale)

and multidimensional symptom (e.g., Izbicki score, Brief Pain Inventory) severity scales have been found to reliably express pain intensity [120, 124, 125]. Once symptom intensity is assessed, the initial step is to confirm the precipitating factor of the chronic pancreatitis and to treat the underlying etiology if possible [19, 38, 121]. Non-pharmacological lifestyle interventions would then be appropriate in providing pain relief. Complete cessation of alcohol and tobacco is paramount and should be emphasized to all patients, as their ongoing use will further the progression of disease and perpetuate the cycle of pain [126–128]. With respect to lifestyle modifications, patients should be advised to eat small low-fat meals, as this will help mitigate mild to moderate symptoms. Cognitive and mindfulness-based therapies should also be offered to all patients as part of their pain management, especially those who may need assistance with their contributing substance abuse disorder [129, 130].

The identification of anatomic obstructions or ductal irregularity is integral to the foundation of achieving analgesia in painful chronic pancreatitis. If there is evidence of duct obstruction, the initial management strategies should be geared towards its relief in order to relieve intraductal pressure [131]. Endoscopy therapy is able to achieve therapeutic benefit related to its potential to relieve pancreatic outflow obstructions such as strictures or stones, which can exacerbate pain [121]. Endoscopic (ERCP) therapy aims to restore proper pancreatic duct drainage through a variety of techniques such as sphincterotomy, stricture dilation, stent placement, stone extraction, and extracorporeal shock wave lithotripsy (ESWL) [132]. Significant pain reduction can be achieved when these confirmed ductal irregularities are corrected, stones extracted, and strictures eliminated [133]. ESWL when used as an adjunctive therapy can be utilized to fragment large stones in order to remove them. This technique, however, is not US FDA approved, and its performance requires the collaboration of a urologist at many centers in the USA. Neurolytic interventions such as celiac plexus blocks and splanchnic nerve ablations utilizing bupivicaine with or without triamcinolone are reserved for pain refractory endoscopic and medical therapies. Celiac plexus block can be performed via percutaneous and endoscopic approaches [134]. In a systematic review including six studies, pain alleviation was achieved in only 51.46% of patients [135]. Relief if obtained, sadly, is only short lived, on the spectrum of 3–6 months; therefore, these interventions are being performed less frequently.

Pancreatic enzyme supplementation (PERT) can also be incorporated into the pain management strategy if symptoms persist, utilizing its ability to decrease pancreatic secretion [121, 136]. In an American Gastroenterological Association technical review of randomized controlled trials performed to assess enzyme supplementation in the treatment of pancreatic pain, greater relief was achieved using non–acid-protected preparations than using formulations that were enteric coated and acid protected [137]. Therefore, when PERT is given for analgesic purposes, current recommendations are that it should be given as an uncoated formulation with large amounts of proteases (> 25,000 USP units per tablet) at frequent intervals throughout the day [121]. While many clinicians have adopted the use of PERT for pain management, a recent meta-analysis including all randomized, controlled, parallel or cross-over trials was unable to show definitive evidence of PERT's efficacy in achieving analgesia [138].

There is a growing body of evidence regarding the role of antioxidant therapy in the management of chronic pancreatitis. Oxidative stress has been well established as a catalyst for PSC activation that ultimately contributes to pancreatic fibrosis [139, 140]. The proposed mechanism remains unclear, but it is postulated that oxidative stress creates a pro-inflammatory effect. A 2014 Cochrane review on the role of antioxidants in chronic pancreatitis-related pain that included 12 randomized controlled trials revealed a non-significant trend for improvement in pain [141]. More recent reviews, however, did identify that methionine-containing antioxidant regimens including selenium, ascorbate, beta-carotene, and alpha-tocopherol have a significant benefit on pain reduction [142]. Preparations including the combination of 0.54 g of ascorbic acid, 9000 IU of beta-carotene, 270 IU of alpha-tocopherol, 600 ug of selenium, and 2 g of methionine are believed to be the most promising, based on the available data [143]. An augmented benefit in analgesia has also been demonstrated in narcotic-naïve patients when antioxidants are combined with a neuromodulator such as pregabalin [144]. Overall, the mild improvement seen in pain scores and the heterogeneous results of available clinical studies prevent the widespread recommendation of antioxidant use in chronic pancreatitis. Moving forward, further large, placebo-controlled studies will be required to improve recommendations on antioxidant utilization [145, 146].

To date, there are no guidelines regarding a recommended analgesic, dose, or route of administration; therefore, the management strategy for chronic pancreatitis-related pain is to adhere to guidelines set forth by the World Health Organization's "pain relief ladder" [76, 121, 147]. This approach recommends a stepwise approach of increasing analgesic potency until adequate analgesia is achieved. It starts with non-opioid analgesics and adjuvant therapy for mild pain, with subsequent escalation with the inclusion of a weak opioid for mild to moderate pain, and if pain still persists, the inclusion of a strong opioid for severe pain [147]. Acetaminophen is the preferred non-opioid (simple) analgesic for management of chronic pancreatitis pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., diclofenac, ibuprofen, and naproxen) can be considered as well, but these should be

used with discretion given their potential for gastrointestinal toxicity [148].

Adjuvant therapies such as neuromodulators (e.g., pregabalin), anxiolytics, and anti-depressive medications are also frequently incorporated into the overall management strategy. These agents are attractive as they are non-opiate medications that target the central and visceral hypersensitivity that is believed to contribute to the pathogenesis of pain. In a randomized, double-blind, placebo-controlled trial, the use of pregabalin starting at 75 mg orally (PO), twice a day (BID) and titrated to a maximum dosage of 300 mg PO BID over the course of 1 week provided significant improvement in pain and quality-of-life indices after 3 weeks of treatment [149]. If opiates are required, it is imperative for the prescribing provider to be well informed on the complexity, potential complications, and abuse potential for this class of medications [150]. Patients will require close monitoring at regular intervals throughout opiate treatment to ensure adequate pain relief and the detection of opiate-related side effects and regular assessment in the hope of weaning off these medications [150–152].

Symptoms of EPI result from the insufficient secretion of pancreatic enzymes (acinar function) and/or sodium bicarbonate (ductal function). Steatorrhea does not present until secretion of lipase becomes less than 10% of normal; therefore, the majority of patients remain well compensated until very late in their disease [38]. Typical onset of EPI occurs 10–15 years after initial diagnosis in alcoholic chronic pancreatitis and even later in hereditary or idiopathic forms [8, 106]. Based on iPFT and dPFT results, the degree of insufficiency can be categorized as mild, moderate, or severe on the basis of relative reductions in enzyme production, bicarbonate secretion, and quantity of fecal fat [10, 153]. PERT should be initiated in all patients who have a confirmed diagnosis of chronic pancreatitis along with EPI based on functional testing and the presence of steatorrhea or an associated nutritional deficiency [154]. Use of PERT in a large, meta-analysis has been found to have significant benefits in weight stabilization and quantity of fecal fat; it was also shown to improve gastrointestinal symptoms and quality-of-life indices [107, 155].

PERT preparations come in enteric-coated microspheres or mini-microspheres as well as uncoated formulations. Their therapeutic efficacy is dependent on proper administration and appropriate timing of release. In order to yield the greatest benefit, PERT should be taken with meals and snacks, and if multiple pills are required, they should be interspersed throughout meals. The enteric-coated formulation is pH sensitive, thereby protecting the enzymes from degradation in the stomach via gastric acidity. The coating of the capsule will rapidly release its contents once it reaches a region of bowel with an intraluminal pH of greater than 5.5 [156]. The mini-microspheres provide a higher therapeutic efficacy, which is attributed to their ability to be more effectively incorporated into the food bolus and their rapid emptying into the small bowel [157]. For PERT therapy, doses of 1000 USP units of lipase per kilogram of patient body weight per meal are advised to achieve improvements in nutritional parameters and quality of life [158]. Doses of 25,000–50,000 units of lipase with meals and 50% of the mealtime dose with snacks are typically adequate [159]. While patients are on PERT, routine monitoring should be performed to assess normalization of nutritional parameters and resolution of steatorrhea. If symptoms and deficiencies persist, further non-invasive forms of iPFT should be conducted to assess response to treatment. Based on the results of these studies, enzyme supplements can then be titrated accordingly or addition of anti-secretory therapy can be considered to minimize gastric degradation [38].

Pancreaticogenic diabetes, or diabetes following pancreatic disease, can develop in patients with chronic pancreatitis once extensive damage to the pancreas has occurred, and it has an estimated prevalence of 40% in affected individuals [160]. The onset of insulin deficiency occurs as a result of islet cell destruction from progressive fibrosis. Onset of pancreaticogenic diabetes does not occur until after steatorrhea develops as acinar cell loss occurs prior to endocrine dysfunction. It is important to distinguish diabetes type 3c from type 2, as it is associated with worst glycemic control with greater insulin demands [161, 162]. Initial screening should be performed in all patients and include fasting glucose as well as glycosylated hemoglobin levels, and these tests should be repeated annually for monitoring purposes [12]. If impairment is identified, dedicated testing with a standard 75 glucose tolerance test should be performed along with assessment of the patient's pancreatic polypeptide level in response to mixed nutrient ingestion. An absence of pancreatic polypeptide in this setting is indicative of type 3c diabetes [12]. Medical management of pancreaticogenic diabetes should be designed similarly to that of type 2 diabetes mellitus, relying on metformin as the first-line agent unless severe hyperglycemia is present, warranting the use of insulin therapy [131].

The most worrisome complication of chronic pancreatitis is the increased risk for developing pancreatic adenocarcinoma. Within this population, the greatest risk for development of cancer is in smokers, those with a longer duration of disease, and those with a hereditary etiology [163, 164]. The estimated lifetime risk of developing pancreatic cancer in the setting of chronic pancreatitis is estimated to be approximately 4–5%. There is extraordinarily high risk in patients who develop chronic pancreatitis in the setting of hereditary PRSS1 pancreatitis, to the degree of 40%. At this point, however, there is no consensus recommendation for cancer surveillance, but expert opinion

emphasizes the need for vigilant surveillance with a high clinical suspicion, especially in the setting of unexplained weight loss or new-onset diabetes mellitus [131]. Guidelines do suggest surveillance can be considered in higher risk patients; however, cross-sectional imaging may be unable to identify small lesions in the context of pancreatic parenchymal morphological changes [19, 165, 166].

7 Conclusion

The evaluation and management of chronic pancreatitis can be challenging and requires a pragmatic and well-structured approach. Chronic pancreatitis has been increasing in prevalence and is associated with rising healthcare utilization. A successful assessment process requires multiple diagnostic modalities, and its management requires a multi-disciplinary approach. As our understanding of chronic pancreatitis continues to evolve, our ability to establish the diagnosis earlier on in the clinical course will improve, with the goal of identifying interventions that are capable of not only halting disease progression, but also potentially reversing the effects of its fibroinflammatory path.

Compliance with Ethical Standards

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