Chapter 3
Chronic Pancreatitis

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Patient Questions

1. Will I get complete relief from pain?

   Chronic pancreatitis is a disease characterized by progressive inflammation that results in fibrosis of the pancreatic tissue culminating in exocrine and endocrine dysfunction. Pain results from pancreatic ductal obstruction by stones or stricture, and pancreatic neuropathy. Oxidative stress could also drive the intrapancreatic inflammation and thereby contribute to pain.

   Pain can be ameliorated by relieving the pancreatic duct of obstruction by endoscopic therapy. However, since the inflammation in CP is progressive, pain might recur.

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2. How can I prevent painful episodes?
   Abstinence from alcohol and smoking can prevent recurrence of episodes of pain. Intake of antioxidant rich food and avoidance of fatty diet might help.
3. How long do I have to take medications?
   There is no specific duration for therapy; and the treatment regimen needs to be individualized. Single modality therapy is unlikely to provide long term treatment. Antioxidants needs to be initiated early and should be taken at least for 6 months following which it may be titrated or stopped according to the clinical response. If pain relapses after endotherapy or surgery, the pain could be neuropathic predominant and should be treated with pregabalin (β-isobutyl-γ-aminobutyric acid).

Introduction

Chronic pancreatitis (CP) is characterized by recurrent abdominal pain, exocrine insufficiency, and endocrine dysfunction that results from progressive inflammation and fibrosis of the pancreas. CP does not have a definitive treatment and currently available treatments are directed toward management of complications.

Epidemiology and Etiology

The epidemiology and etiology of CP differ across the globe [1]. Its estimated incidence and prevalence in the USA are 4.05/100,000 and 41.76/100,000 population, respectively. Finland has the highest incidence among the European countries (13.4/100,000). While Japan has reported the prevalence of CP of 45/100,000 population, the prevalence of CP has increased from 3.08/100,000 to 13.52/100,000 between 1996 and 2003. CP is endemic in South India with a prevalence of 126/100,000 population as shown in population based studies

in Kerala [2]. The distinctive characteristics of CP in these patients were collectively described as an entity called tropical chronic pancreatitis (TCP). CP is also prevalent in other parts of India and the phenotype currently seen all over the country (including South India) does not always match the one described as TCP, with only 3.8–5.8 % patients satisfying the criteria.

In the west CP is associated primarily with alcohol, though its role as a distinct etiological factor is currently questioned. Even though smoking was earlier considered as a cofactor with alcohol in the pathogenesis of CP, recent population based studies have demonstrated smoking as an independent risk factor [3]. Among the Asia-Pacific countries, alcohol is the etiology in 95 % of CP in Australia, 70 % in the Republic of Korea and 54 % in Japan. In India and China, on the other hand, over 70 % of patients with CP have idiopathic chronic pancreatitis [4]. Oxidative stress and genetic mutations are the predominant factors that have emerged as the risk factors in patients with idiopathic CP in India.

Median survival for alcohol related CP was 20–24 years in an earlier European study but more recently it was found to be 15.5 years from all cause CP. A study form India reported an 83 % probability of surviving for 35 years after the onset of CP [5].

Natural History and Clinical Manifestations

CP is believed to develop after a series acute pancreatic injury at the acinar (trypsinogen activation) or ductal (improper bicarbonate secretion) level. This is the Sentinel Acute Pancreatitis Event (SAPE) hypothesis; and the first or subsequent acute episode may not necessarily be clinically detectable. The clinical course of CP is very variable and can be arbitrarily divided into early (first 5 years), intermediate (5–10 years), and late stages (beyond 10 years), though there can be significant overlap between the three. Recurrent acute pain (with acute pancreatitis) marks the early phase while

development of morphological changes such as pancreatic calculi, ductal strictures, and pseudocysts are predominantly seen in the intermediate phase. Pancreatic exocrine insufficiency (PEI) and diabetes manifest by the late stage, although these begins to develop earlier [6].

Abdominal pain is the dominant clinical manifestation. A small proportion of patients with CP may run a painless course. Even though it appears that with gross parenchymal destruction the pain would decrease or even disappear, this appears unlikely and pain could progress even after pancreatic atrophy. Analgesic requirement in up to 40 % of patients even after total pancreatectomy is a testimony to this [7]. Patients who have early onset CP (onset <35 years of age) appear to have a longer duration of pain. With recent understanding of the mechanisms of pain in CP, it would be important to identify neuropathic pain since this could have therapeutic implications. Even though there are currently no specific clinical tools to confirm neuropathy, the pain DETECT questionnaire (available in the internet) is a semiquantitative tool that could suggest the development of neuropathic pain.

Clinical manifestations of PEI appear after the postprandial output of pancreatic exocrine secretion into the duodenum falls to below 10 % of normal. This can occur either after development of gross pancreatic atrophy or obstructing ductal calculi in the head region. However, since CP is a progressive condition, subclinical PEI sets in much earlier. Steatorrhea is the most conspicuous manifestation of PEI. Other manifestations could be progressive weight loss and deficiency of fat soluble vitamins and micronutrients.

Diabetes secondary to CP is now termed as Type 3c diabetes. Western data show that diabetes in CP usually occurs 10 years after the onset of disease. However, clinical observations and experimental studies suggest that beta-cell dysfunction and diabetes develop much earlier in India, occasionally with diabetes preceding the diagnosis of CP [8].

Diarrhea in patients with CP could result from fat malabsorption, diabetic autonomic neuropathy, small intestinal bacterial overgrowth, and CP associated intestinal dysmotility.

Pathogenesis

Genetics of Chronic Pancreatitis

Foremost among the genetic mutations and polymorphisms recognized in CP are the cationic trypsinogen gene (PRSS1), pancreatic secretory trypsin inhibitor gene (SPINK1) and cystic fibrosis transmembrane conductance regulator gene (CFTR). Studies have demonstrated chymotrypsinogen C (CTRC), cathepsin B (CTSB), calcium-sensing receptor (CaSR), and carboxypeptidase 1 (CPA1) also to be associated with the disease [9]. Recently, genome wide association studies (GWAS) have demonstrated a strong association of the polymorphisms in the claudin 2 and PRSS1-PRSS2 genes with alcoholic recurrent acute and chronic pancreatitis [9–11]. The mechanisms by which genetic polymorphisms could result in CP are varied and involve intraacinar and intraductal mechanisms based on the genetic polymorphism that is operating.

Fibrosis

Progressive fibrosis, which is the pathological hallmark of CP is primarily mediated by the pancreatic stellate cell (PSC) [12]. PSCs are cells that reside in the pancreas surrounding the basolateral surfaces of the pancreatic acini and constitute about 10 % of all resident cells in the pancreas. In the healthy state, PSCs remain in a quiescent state, maintain the pancreatic extracellular matrix, and contribute to physiological exocrine secretion from the pancreas via a cholecystokinin mediated mechanism. After exposure to oxidative stresses (cigarette smoking and alcohol metabolites), and after recurrent acinar injuries, the PSCs transform into an activated phenotype that secrete a wide array of cytokines which are capable of triggering an inflammatory cascade. The cytokine that primarily drives fibrosis is TGF-beta. As a result of the paracrine and

autocrine activation, activated PSCs lay down excess amounts of collagen I in the extracellular matrix thereby resulting in the imbalance between the matrix deposition and degradation towards a pro-fibrogenic state.

Pain

Pain is the most debilitating clinical manifestation of CP. An important pain mechanism that has emerged from recent clinical and experimental studies is oxidative stress and inflammation induced pancreatic nociception and neuroimmune alterations [13]. Experimental evidence supports that PSCs can generate oxidative stress in response to pressure. This observation makes it plausible that pancreatic ductal/interstitial hypertension from obstructing stones and/or strictures could activate PSCs and result in a pro-inflammatory milieu within the pancreas.

Studies have shown that nociceptors (pain receptors) such as the proteinase-activated receptor 2 (PAR-2), the transient receptor potential vanilloid 1 (TRPV-1) receptors and the ligand-gated cation channel transient receptor potential ankyrin 1 (TRPA-1) are expressed in the pancreas specific sensory nerves and dorsal root ganglia. Trypsin and mast cell tryptase (that is known to be secreted in the pancreas in CP) can bind to and activate these receptors. Other receptors that are also shown to be expressed on different neural components include trkA, P75, and GFRα3. These receptors are activated by their ligands, namely nerve growth factor (NGF), brain derived neurotropic factor (BDNF), and artimin, respectively. In addition, several neuroimmune alterations have been described in CP. Predominant among these includes: infiltration of inflammatory cells (especially mast cells and eosinophils); neural edema and perineural disruption; Schwann cell (glial cell in peripheral nerves) proliferation; neural hypertrophy and sprouting and expression of nestin and growth-associated protein (GAP43), which are indicators of neuroplasticity. Several factors namely, glutamine,

calcitonin gene related polypeptide (CGRP), substance P, and fractalkine (a neural cytokine) have been implicated in the causation of the neural infiltration. The persistent inflammation and neuroplastic changes in the pancreatic nerves leading to continuous depolarization of these nerves result in a state of spinal hypersensitivity, a phenomenon known as global sensitization. These result in mechanical allodynia, i.e., generation of pain after a physiological or non-noxious stimulus, and inflammatory hyperalgesia, meaning amplified pain response to normal or minimal pain stimuli. Eventually, these events bring about a change in the entire cortical pain modulating neural network in the brain [14]. These events could explain why patients with long standing CP could develop pain even after total pancreatectomy.

Diabetes

Even though diabetes secondary to CP (Type 3C DM) has long been ascribed to pancreatic parenchymal fibrosis and islet destruction, recent experimental studies have demonstrated that beta cell dysfunction is noticed in patients with CP even in the absence of significant beta cell death (apoptosis). The beta cells do not secrete insulin in response to glucose challenge. This lack of response appears to be mediated by the inflammatory milieu contributed by PSCs and T-helper subsets that infiltrate into the islets [15]. Observations from these studies have important implications in that if the inflammatory milieu can be altered, the functional capacity of the islets could possibly be revived.

Diagnosis

Diagnosis of CP includes evaluation of the morphologic and functional (exocrine and endocrine) alterations. Transabdominal ultrasonography (USG) can show pancreatic atrophy and a dilated pancreatic duct. Contrast enhanced

computed tomography (CECT) scan of the abdomen provides reliable evidence of the pancreatic parenchymal volume, localization of pancreatic stones and calcifications, complications such as pseudocyst, and presence of a cancer. MRI/MRCP is helpful in identifying altered ductal anatomy such as dilatation, strictures, leaks, and communication between the pancreatic duct and pseudocysts. In addition, it has the advantage of avoidance of radiation exposure. The above tests are however, not sensitive enough to detect very early changes of CP, in which case endoscopic ultrasonography (EUS) plays an important role. EUS is an operator dependent procedure which requires expertise and experience. With increasing experience it is becoming apparent though that EUS has the tendency to over diagnose early CP. Endoscopic retrograde cholangiopancreatography (ERCP) is seldom used as a diagnostic tool.

Pancreatic function tests (direct and indirect) can be used to assess secretory function of the pancreas. The direct function tests are used to access pancreatic bicarbonate or exocrine enzyme secretion in response to secretin and cholecystokinin stimulation respectively. Pancreatic secretions are collected through specialized tubes (e.g., Dreiling tube), through a conventional upper GI endoscope or directly from the pancreatic duct after cannulation. Even though the sensitivity and specificity of these tests reach over 80 %, they are invasive, technically challenging, time consuming, expensive, and not available widely. Furthermore, the capability of these tests to diagnose early CP is not clear. The secretin-MRCP test is another direct function test that has the advantage of evaluating the function and structure of the pancreas simultaneously. Indirect pancreatic function tests include 72 h fecal fat estimation, fecal elastase test and the ^{13}C mixed triglyceride test. Of these, the ^{13}C mixed triglyceride test has the best diagnostic capability, but requires a mass spectroscopy technique that may not be universally available. Elastase is a pancreatic exocrine enzyme that is biologically stable throughout the intestinal transit and its level in stool accurately reflects the amount secreted by the pancreas. The sensitivity of this

test to detect mild and severe disease ranges from 0 to 47 % and 73 to 100 %, respectively [16]. The advantage of this test is that the currently available exogenous pancreatic enzyme supplementation does not affect the results since human monoclonal antibody is used for detection, while the supplemented enzymes are from procine source. Presence of diarrhea might however, result in a falsely low fecal elastase concentration.

Evaluation of Type 3c diabetes should begin with testing for fasting blood glucose and HbA1c. Presence of glutamic acid decarboxylase (GAD) antibodies and hyperinsulinemia can distinguish Type 3c diabetes from Type 1 and Type 2 diabetes respectively. In the presence of ambiguity, an absent polypeptide secretory response after insulin induced hypoglycemia or secretin infusion provides a diagnosis of Type 3c diabetes [17]. Plasma C-peptide levels during an oral glucose tolerance or mixed-nutrient meal testing can ascertain functional beta cell reserve.

Treatment

Goals of treatment for CP include pain relief, pancreatic enzyme replacement, nutritional support, and glycemic control. Abstinence from alcohol and smoking is essential and these patients require constant counselling.

Treatment of Pain

Causes of pain in CP includes: the disease process itself; and complications such as pancreatic pseudocyst, duodenal/biliary obstruction, and pancreatic cancer. It is therefore important to assess the disease morphology prior to initiation of treatment. Several options including medical, endoscopic, and surgical are currently available for pain management.

Medical management: In the setting of acute pain, the WHO pain ladder may be followed beginning with a nonsteroidal

anti-inflammatory drug (NSAID). Low potency selective μ-opiate receptor agonist such as tramadol hydrochloride has been shown to be as effective as higher potency narcotics but with a significantly better safety profile. High potency narcotics such as morphine and analogues should be avoided [13].

Currently, there is ample evidence to show a significant reduction of antioxidant defense mechanisms in patients with CP. Therefore, supplementation of antioxidants can be tried for pain management [18]. The primary aim of antioxidant therapy in CP is to supply methyl and thiol moieties for the intra-acinar transulfuration pathway which is essential for protection against oxidative stress. Even though the efficacy of antioxidants in CP has been debatable, two recently published meta-analyses have shown that an antioxidant combination containing organic selenium, ascorbic acid, β-carotene, α-tocopherol, and methionine is effective in improving pain. All the components are required at a higher dose and the most important among them appears to be methionine at a dose of 2–4 g daily [19, 20].

Since there is a neuropathic component to the pain in longstanding CP, neural modulators could have an important role in pain management. Of the several neuromodulators that have been used in clinical practice, only pregabalin has been tested in a randomized controlled setting. An increasing dose from 150 mg to 600 mg per day of pregabalin demonstrated significant reduction in pain in patients with CP when treated for 3 weeks [21]. However, a significantly higher proportion of patients receiving pregabalin experienced adverse events compared with placebo.

A recently completed double blinded placebo controlled RCT demonstrated that a combination of methionine containing antioxidants and pregabalin resulted in a significant reduction of pain in patients with CP who had recurrence of pain after ductal clearance with endotherapy or drainage surgery [22]. Pain recurrence after clearance of ductal obstruction is difficult to treat, and this combination appears to be a viable treatment option for this group of patients.

Pancreatic enzyme supplementation is often used for pain in CP in clinical practice. This is based on the premise that proteins in the food chyme bind to duodenal CCK receptors that results in pancreatic enzyme secretion, which could eventually result in ductal hypertension and pain; and that the protease in the supplemented enzyme cause a negative feedback loop by binding to the CCK receptors. However, a recent systematic review of RCTs showed that pancreatic enzymes did not confer any analgesic benefit. Interestingly, significant pain relief was observed in the individual studies that used non-enteric coated enzyme preparation, thus implying that the binding of non-enteric preparations with CCK receptors is better [23]. However, all the currently available pancreatic enzyme preparations, except Viokase, are enteric coated and are unlikely to be beneficial for pain.

Endoscopic management: Endoscopic management in CP is indicated for obstructing ductal stones, pancreatic and biliary strictures, pseudocyst drainage, and celiac block [24]. Extracorporeal shock wave lithotripsy (ESWL) with or without endoscopic retrograde cholangiopancreatograpgy (ERCP) and stenting is currently the recommended standard of care for the treatment of large obstructive pancreatic ductal stones, especially those located in the head and body region. The primary goal of ESWL is to reduce the stones to fragments below 3 mm size. Best results with ESWL are obtained with the third generation lithotriptors with dual focusing system (fluoroscopy with ultrasonography). Fragmented stones can be removed at ERCP by flushing or using accessories such as baskets and balloons. In a study by Tandan et al. [25] on a cohort of 636 patients, complete pain relief was observed in 68.7 % of patients on intermediate follow-up (2–5 years) and in 60.3 % on long-term follow-up (>5 years) after ESWL. Patients were followed for as long as 96 months. Stone clearance was complete in 77.5 % and 76 % in the intermediate and long-term follow-up groups respectively. Interestingly, 50 % of patients who had recurrence of pain did not have recurrence of stones, implying that a majority of pain recurrences is related to mechanism such

as pancreatic neuropathy. In another retrospective study of 120 patients by Seven et al. [26] complete pain relief was observed in 50 % patients, along with a significant improvement in quality of life scores (VAS) [7.3 (2.7) vs. 3.7 (2.4); $p < 0.001$). The longest follow-up duration in this study was 7 years , and 85 % patients had pain relief pain after the mean follow-up of 4.3 years. In another study, injection of IV secretin (16 mcg) before the procedure resulted in a better stone clearance (63 % vs. 46 %; $p = 0.021$), possibly by release of pancreatic ductal secretion that results in a fluid-stone interface [27]. On multiple logistic regression analysis, secretin use and pre-ESWL pancreatic stenting emerged as independent predictors of complete or near complete stone clearance.

Symptomatic pancreatic ductal strictures, especially the ones located in the head of the pancreas are best treated with a single 10Fr polyethylene stent with planned stent exchanges within 1 year even in the absence of symptoms [28]. Many of the dominant strictures require prior dilatation with bougies, balloons, or a Soehendra stent retriever. Pancreatic stenting was technically successful in 85–98 % cases [29–32] and was associated with immediate pain relief in 65–95 % patients that was sustained in 32–68 % of patients on follow-up of up to 14–58 months [29–34]. Even though there is no consensus on the definition of long-term clinical success, absence of pain at 1 year after stent retrieval may be considered as clinical success [29]. Cessation of further stenting during ERCP can be assessed by demonstrating adequate pancreatico-duodenal flow of contrast medium within 1–2 min after filling the pancreatic duct upstream to the stricture and/or easy passage of a 6 Fr catheter through the stricture. Since pancreatic stents run the risk of clogging and migration, several modifications in the shapes and types of stents (multiple plastic and covered expandable metallic stents) are being studied; unfortunately none has been established as a standard of care. Pancreatic duct strictures that persist despite 12 months of single plastic stenting can be treated with multiple plastic stents placed side-by-side simultaneously [35]. Even though excellent technical (100 %) and functional (97.4 %) success could be

achieved, stent migration may be seen in 10.5 % patients while 15.8 % patient may require reinterventions. Technical success in placing covered self-expanding metal stents (SEMS) can be as high as 100 % with 80 % functional success in relieving pain on short-term follow-up [36]. Stent migration and reintervention may be required in 8.2 % and 9.8 % patients respectively. Currently, use of SEMS is recommended only under clinical trial settings. Multiple strictures and those located upstream towards the tail are difficult to manage endoscopically. These strictures are best treated with surgery in the presence of symptoms. It is important to be vigilant on the possibility of a cancer in the presence of stricture/s in the background of CP. Pancreatic ductal stenting is also indicated in the treatment of pancreatic duct leaks. However, complete ductal disruption might require pancreatic resection.

Symptomatic pancreatic pseudocyst can be treated endoscopically by transpapillary or transmural (cystogastrostomy and cystojejunostomy) drainage. With linear echoendoscope, drainage is now possible even for pseudocysts that do not produce a bulge in the stomach or the duodenum, and also for those located away from the gastrointestinal lumen. Biliary stricture in CP results from pancreatic fibrosis, pancreatic edema and compression by a pseudocyst. It is important to rule out malignancy as a cause. Biliary strictures require treatment if the patients have evidence of cholestatic symptoms and/or cholangitis or if there is elevation of serum alkaline phosphatase by twofold for more for more than a month. These strictures are usually treated with single or multiple plastic biliary stents that are exchanged every 3 months for a total of 1 year. The long-term results of using a single 10 Fr plastic stent are poor (25 % sustained benefit after 46 months follow-up) [37]. Presence of pancreatic calcification is one of the major factors responsible for long-term failure of single plastic stents [38]. In order to circumvent the poor long-term outcome of placement of single plastic stent, multiple plastic stents can be placed side-by-side for 1-year with scheduled exchanges every three months [29]. Scheduled

exchanges are important in order to prevent cholangitis from stent clogging [39]. Successful long-term treatment with placement of multiple simultaneous stents has been shown to be 92 % compared to 24 % with single stent for similar follow-up durations [40]. FCSEMS has also been attempted for biliary strictures, but the current data is not robust enough to incorporate this modality into the routine treatment.

Blocking the celiac plexus is considered as one of the treatment modalities of intractable pain in CP. Celiac plexus block can be achieved with a local anesthetic agent (bupivacaine) with or without steroid (triamcinolone). EUS-guided or percutaneous approaches can be used. However, the overall benefits of celiac plexus block in CP are about 55 % after 4–8 weeks that falls to 10 % by 24 weeks.

Surgical management: Surgical options for pain management in CP include drainage procedures (lateral pancreaticojejunostomy and Frey's procedure), classical (Kausch Whipple) or pylorus preserving (Traverso–Longmire) pancreaticoduodenectomy, distal pancreatectomy, and total pancreatectomy [13]. Pancreaticoduodenectomy is particularly useful in pain with an associated inflammatory mass in the head of the pancreas, especially if a pancreas cancer cannot be excluded in the background of CP. A significant proportion of patients who undergo resection procedures develop exocrine and endocrine insufficiencies. Total pancreatectomy with auto islet-cell transplantation (TPIAT) is being practised in select centers for patients with intractable pain [7, 41]. However, even after removing the entire pancreas, 30–40 % of patients may still experience pain [7]. A lateral pancreaticojejunostomy could be beneficial for painful pancreatic ductal stone located throughout the pancreatic duct.

Treatment of Pancreatic Exocrine Insufficiency (PEI)

The mainstay of treatment for PEI in CP is pancreatic enzyme replacement therapy (PERT) which entails supplementation

of lipase, protease, and amylase. Of these three, lipase supplementation is the most important component. To avoid proteolytic digestion, lipase should be administered in enteric coated form. It is important that the pancreatic enzyme supplements are delivered into the duodenum along with the chyme from the antrum. This can be achieved if the enzyme preparations are loaded into pellets of 2 mm or less in size (microsphere and mini microsphere). Pancreas secretes around 600,000 units of lipase daily and 10 % of this is required for fat digestion [42]. Therefore, the minimum daily requirement of lipase in CP is at least 60,000 units. The approximate dose requirement can be calculated on the basis of fat content of the meal; and an ideal beginning daily dose of 40,000 units of lipase or higher should be sufficient. Starting with a higher dose is important because of bile acid denaturation and high proteolytic activity of proteases on the supplemented lipase. The enzyme doses can be titrated thereafter based on the response and fat content in the diet. Since it is important for the supplemented enzymes to mix well with the food chyme for optimal action, pancreatic enzymes should be taken along with meal. Furthermore, it is advisable to co-prescribe a proton pump inhibitor (PPI) so that the supplemented enzymes get an additional protection from acid degradation besides the enteric coating [43]. The benefit of PERT in patients without clear evidence of exocrine insufficiency is not known. Even though substantial emphasis is given on pain management and PERT in clinical practice, nutritional advice and counselling are frequently overlooked. It is important to realize that any enzyme requires a substrate to exert optimal action. Hence, it is not essential to restrict the patient to an unpalatable fat free diet. Therefore, patients on PERT should take normal amount of dietary fat. In the absence of expected improvement of the nutritional status after PERT, it is important to evaluate for other factors such as noncompliance, high fat content in diet, high duodenal acidity, and small intestinal bacterial overgrowth.

Nutritional Support

A thorough nutritional assessment is essential. Dietary supplements should include antioxidants containing food, multivitamins and diets with high complex carbohydrates. Deep frying of food depletes the naturally occurring antioxidants, and therefore, these kinds of food should be avoided [44]. Medium chain triglycerides (MCT) containing diets have an unpalatable taste and might be a cause for noncompliance to dietary advice and are not routinely recommended. Furthermore, a recent randomized controlled trial has shown that good dietary counselling on homemade food could be as good as commercially available MCT containing diet in improving nutritional status in documented malnourished patients with CP [45]. Food with high dietary fibers could interfere with the action of pancreatic enzymes and should be avoided in patients on pancreatic enzyme replacement therapy [46].

Conclusion and Future Directions

CP is a complex illness and does not have definitive cure so far. Pain is the most common clinical symptom that mandates aggressive treatment. It is essential to assess the disease morphology adequately and rule out an underlying cancer especially in the elderly patient with long standing disease. Presence of obstructive ductal calculi or a major stricture should be managed with endotherapy as the first line. The right preparation of antioxidant formulation at the optimal dose and neuromodulators (e.g., pregabalin) can offer significant pain relief. PERT should include at least 20,000 units or higher of lipase and should be taken along with each meals and the dose titrated according to response. Nutritional assessment and supplementation is mandatory. Finally, continuous counselling, reassurance, and advice to abstain from smoking and consuming alcohol are of paramount importance.

Further research needs to be conducted on the genotype–phenotype associations of the disease and pain mechanisms at the molecular level so that effective personalized prognostication and pain management tools can be developed.

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