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Chronic and Idiopathic Pancreatitis—A Personalized Treatment Approach

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ABSTRACT

Chronic pancreatitis is a fibroinflammatory disease of the pancreas with heterogeneous clinical features and a significant socioeconomic burden. Assessing its aetiology and early diagnosis of associated complications remain challenging. Personalized therapy necessitates precise knowledge of the genetic, biological, and clinical differences within a patient population. In this context, the identification of the underlying aetiology represents an essential cornerstone. This review elucidates current standards for identifying underlying aetiologies and the diagnostic work-up for idiopathic cases. It provides an overview of general therapeutic approaches and highlights individual treatment options. Additionally, the follow-up management of pancreatitis-associated complications, namely exocrine pancreatic insufficiency, post-pancreatitis diabetes mellitus, pain management, pancreatic fluid collections, and pancreatic cancer risk, is summarized.

1 | Introduction

Chronic pancreatitis (CP) is characterized by recurrent inflammatory episodes leading to the replacement of parenchyma with fibrous connective tissue. As a consequence, post-pancreatitis diabetes mellitus (PPDM) and pancreatic exocrine insufficiency (PEI) occur with disease progression [1]. CP significantly impacts quality of life and increases mortality by 3.6-fold. Almost half of all CP patients become unable to work or unemployed [1, 2]. There is a growing body of evidence that CP is a heterogenous disease with various aetiologies and a pleiotropic range of disease-related complications [3]. A personalized treatment approach relies on precise diagnostic assessment of the underlying aetiology and CP-associated complications, such as PEI, diabetes, pain, pancreatic fluid collection and the risk of pancreatic cancer. This review intends to elucidate a diagnostic work-up for distinct aetiologies, outline specific therapeutic approaches, and propose a clinical surveillance strategy for managing CP related complications.

2 | Aetiology

Identifying aetiologies with potential treatment options is crucial to prevent fibroinflammatory progression and CP-associated complications. The TIGAR-O classification was developed to provide clinicians with a comprehensive checklist for assessing the aetiology of CP. It categorizes CP into six distinct groups: Toxic/metabolic, Idiopathic, Genetic, Autoimmune, Recurrent and severe acute pancreatitis, and ductal Obstructions [4]. This classification system was originally introduced in 2001 and updated in 2019, including recent scientific findings [4]. It is important to emphasize that in most patients, more than one risk factor contributes to the development of CP. Therefore, CP must

Abbreviations: AIP, Autoimmune pancreatitis; AP, Acute pancreatitis; CFTR-RD, CFTR-related disorders; COPPS, Chronic Pancreatitis Prognosis Score; CP, Chronic pancreatitis; DEP, Diabetes of exocrine pancreas; DM, Diabetes mellitus; ESWL, Extracorporeal shock-wave lithotripsy; EUS, Endoscopic ultrasound; FE-1, Faecal elastase 1; HTG, Hypertriglyceridemia; ICDC, International consensus diagnostic criteria; ICP, Idiopathic CP; LAMS, Lumen-apposing metal stents; PDAC, Pancreatic adenocarcinoma; PEI, Pancreatic exocrine insufficiency; PERT, Pancreatic enzyme replacement therapy; PFC, Pancreatic fluid collection; PPDM, Post-pancreatitis diabetes mellitus; RAP, Recurrent acute pancreatitis; SVT, Splanchnic vein thrombosis; US, Ultrasound.

be considered as a multifactorial disease. The following sections will elucidate the key aspects of each group.

2.1 | Toxic/Metabolic

Although the incidence of non-alcohol-related CP is increasing, alcohol misuse remains the leading cause of CP [5]. The association between the amount of alcohol consumed and the risk of developing CP is logarithmic. Consumption of 80 g of alcohol daily for 6–12 years is typically required to develop CP. When combined with other risk factors, lower alcohol intake might pose a similar level of risk. Intriguingly, larger cohort studies revealed that increased alcohol consumption leads to CP in only 3% of cases [6]. Thus, alcohol misuse alone might not be sufficient to cause CP, and additional risk factors, such as the diet, the genetic background, obstruction by sludge or microlithiasis in the common bile duct, and smoking are necessary [7]. Smoking, in particular, is an independent risk factor with a dose-depending effect and is associated with a higher risk of developing PEI and diabetes mellitus (DM). Other causes of CP include hypercalcaemia and hypertriglyceridemia (HTG). While HTG is a well-characterized risk factor for AP and recurrent AP, its significance in CP remains a topic of debate. However, data from the NASP-2 Continuation and Validation Study led to an increased recognition of the importance of HTG in the second version of the TIGAR-O classification [8]. A cohort study based on the UK Biobank reinforces the association between CP and HTG [9]. Elevated triglyceride levels above 11.3 mmol/L (1000 mg/dl) are required to induce a first pancreatitis episode, while levels above 5.65 mmol/L (500 mg/dl) seem to be sufficient to induce further episodes [10].

2.2 | Genetic

In recent years the landscape of depicted mutations in CP patients became more and more complex with mutations in Cationic Trypsinogen (*PRSS1*), Serine Protease Inhibitor Kazal-Type 1 (*SPINK1*), Carboxypeptidase A-1 (*CPA1*), Chymotrypsin C (*CTRC*), Carboxyl Ester Lipase (*CEL*), Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*), Pancreatic Lipase (*PNLIP*), and Transient Receptor Potential Vanilloid subfamily member 6 (*TRPV6*). Additionally, associations with common variants for example in Claudin 2 (*CLDN2*) were reported. Some genetic alterations such as p.R122H in *PRSS1* do not need additional risk factors to induce CP (hereditary CP). Otherwise, genetic alterations such as the p.N34S *SPINK1* variant in the heterozygous state seem to need further factors (genetic or environmental) to pass the threshold for CP development. In line, current guidelines recommend genetic testing in patients younger than 20 years and/or those with a family history of two or more first- or second-degree relatives with CP [11]. Genetic testing for other genes is not recommended outside studies [11]. In adults with idiopathic CP and no further clinical signs of cystic fibrosis, only a chloride iontophoresis should be performed to rule out cystic fibrosis [11].

2.3 | Autoimmune Pancreatitis

In idiopathic cases, autoimmune pancreatitis (AIP) may be the underlying aetiology. European studies have identified up to 9% AIP patients in their non-alcoholic CP cohorts [12]. For the diagnostic work-up, international consensus guidelines should be followed (e.g., International consensus diagnostic criteria (ICDC) for AIP) [13]. According to the ICDC, Type I AIP is classified as an IgG4-related disease, while AIP Type 2 is associated with inflammatory bowel disease. Both AIP types can be histologically distinguished.

2.4 | Recurrent and Severe Acute Pancreatitis

The incidence of CP ranges from 5 to 10 per 100,000 inhabitants in European countries, which is lower compared to the incidence of acute pancreatitis (AP) (30-40/100,000) [14]. However, every 10th patient with a first AP episode and 36% of those with recurrent AP progress to CP. Smoking and alcohol consumption are the main drivers of this progression [15].

2.5 | Obstruction

Chronic obstruction of the main pancreatic duct by benign cystic lesions, mucous, ampullary stenosis, or tumours can lead to parenchymal atrophy distal of the obstruction. The role of anatomical variants, such as pancreas divisum, in the development of this condition is still debated. Current opinions consider it as one contributing factor in a multifactorial process. Pancreatic duct dilation is often detected via transabdominal ultrasound. However, further evaluation of potential obstructing factors should be conducted by endoscopic ultrasound or MRI [11].

2.6 | Idiopathic

If no aetiology can be identified after a comprehensive work-up (Figure 1), CP is designated idiopathic. In small cohorts, a more favourable clinical course of idiopathic CP compared with other aetiologies was reported. Particularly, the development of pancreatic fluid collections (PFC), PEI, thrombosis, and biliary obstruction, as well as the need for complex pain management, were significantly lower in the idiopathic CP group [3].

3 | Treatment Approaches

Currently, there are no established treatments targeting pancreatic fibrosis itself. However, addressing the aetiologies outlined in the TIGAR-O classification can potentially prevent disease progression and CP-associated complications (Figure 2). Aetiologies that currently can be addressed therapeutically are: Toxic/metabolic, CFTR-RD, AIP and ductal obstruction. However, in each of these aetiology pitfalls may impair treatment success.

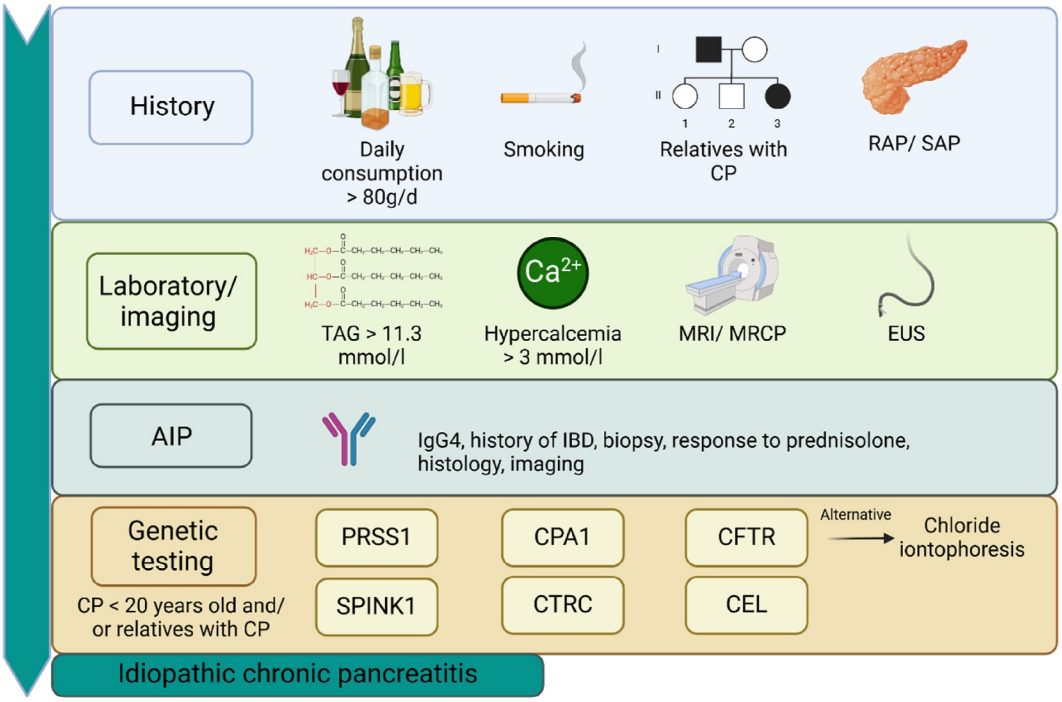

FIGURE 1 | Diagnostic workflow to assess the aetiology of chronic pancreatitis To identify the underlying aetiology, a sequential approach is suggested including history, laboratory and imaging modalities. If the cause of chronic pancreatitis remains unclear, autoimmune pancreatitis and genetic variants should be tested. Idiopathic chronic pancreatitis can be diagnosed if the workflow does not reveal a known risk factor. AIP = Autoimmune pancreatitis; CP = chronic pancreatitis; EUS = Endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography; RAP = Recurrent acute pancreatitis; SAP = Severe acute pancreatitis; TAG = Triacylglycerides.

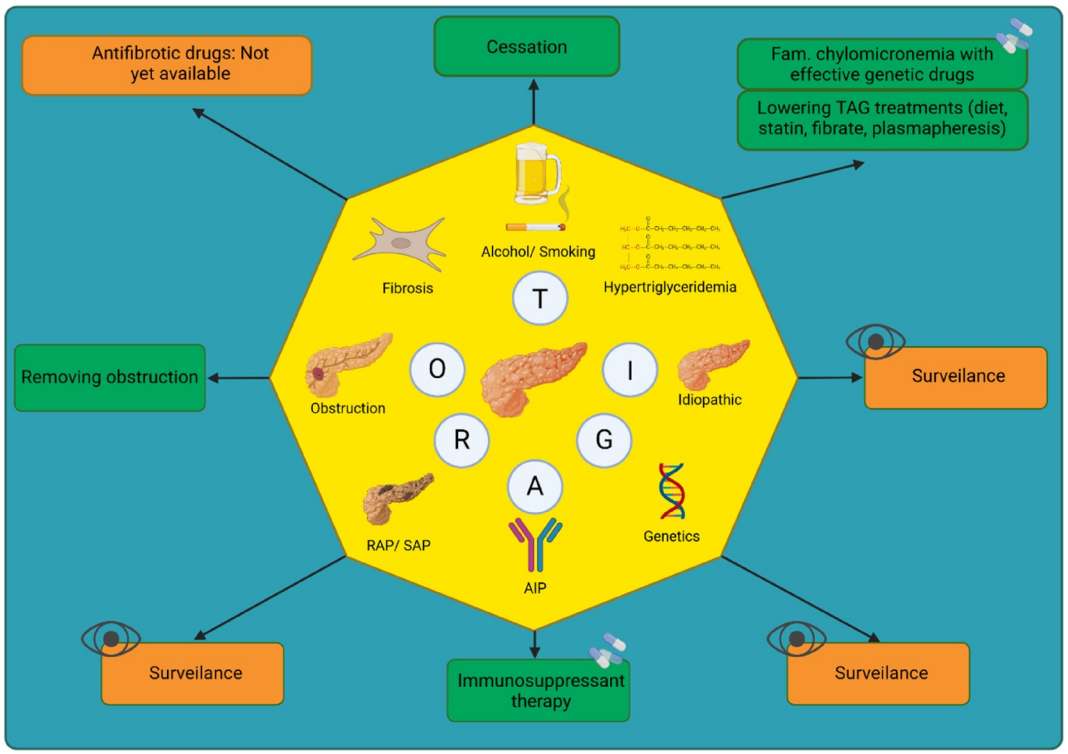

FIGURE 2 | Therapeutic options for different aetiologies of chronic pancreatitis Aetiologies are categorized following the TIGAR-O classification. Treatment options are available for toxic/metabolic, autoimmune pancreatitis and obstructions. AIP = Autoimmune pancreatitis; RAP = Recurrent acute pancreatitis; SAP = Severe acute pancreatitis; TAG = Triacylglycerides.

3.1 | Toxic/Metabolic

Preventive and behavioural interventions are essential to improve outcomes in CP. Alcohol cessation, in particular for alcohol-induced CP, is highly recommended as it decreases the rate of PEI, PFC occurrence, and episodes of pain exacerbations [16]. Structured cessation programs are promising, but even specialized hospitals lack a standard of procedure [17]. Currently, two randomised European multicentre trials are investigating the benefit of structured treatment compared to current practice, hopefully defining widely applicable treatment standards [18, 19].

Though prospective trials are missing, smoking cessation is strongly recommended regardless of the underlying aetiology [11, 16]. The smoking prevalence in CP (~59–70%) is higher than in the general population [20]. Even with structured programs, smoking cessation in the CP population is extremely challenging [21]. This is supported by a Cochrane analysis in that, 8.5% quit smoking with counselling, 16.3% with nicotine replacement therapy, and 18% with bupropion [22]. In a pilot study with 4 weeks of cost-free Varenicline treatment, 15% of CP patients quit smoking with a 6-month follow-up, suggesting a viable option for routine care [23]. Multimodal therapeutic concepts that address social and psychiatric aspects would be beneficial but are still far from being implemented in clinical practice.

Treatment of HTG-induced AP comprises different therapeutical strategies to reduce plasma triglyceride levels, such as fasting, insulin application and plasmapheresis. The latter is recommended by the American Society for Apheresis [24]. However, a smaller randomised controlled trial and a recent large Chinese prospective observational trial showed contradictory results, suggesting that plasmapheresis has no impact on the incidence and duration of organ failure [25, 26]. Between pancreatitis episodes fibrates, a low-fat diet, and statins are suggested. It is currently unclear whether CP patients can also benefit from these therapeutic approaches. However, treatment of HTG-induced AP generally offers the potential to influence the progression of recurrent AP into CP. A subgroup of HTG-induced pancreatitis patients suffers from underlying familial chylomicronemia, for which genetic testing can be performed. Two antisense oligonucleotide drugs, Olezarsen and Volanesoren, have proven efficiency in placebo controlled trials, decreasing both triglyceride plasma levels and the rate of pancreatitis episodes [27, 28].

3.2 | CFTR Related Pancreatitis

CFTR variant carriers with pancreatitis are categorized into distinct groups: Cystic Fibrosis with pancreatitis, pancreatitis in CFTR-RD, or pancreatitis in CFTR carriers [29]. With the introduction of CFTR modulators, the treatment of CF patients improved dramatically with impact on the exocrine pancreas. In case series of pancreatic sufficient CF patients' treatment with modulators reduced pancreatitis attacks, whereas in pancreatic insufficient cases, an increase was reported [30, 31]. Although it seems reasonable to treat 'CFTR-associated' pancreatitis patients with these modulators, further evidence is needed [32].

3.3 | Autoimmune Pancreatitis

One ICDC diagnostic criterion for AIP is the positive response to steroid therapy [13]. However, Type I AIP is accompanied by recurrent episodes or steroid dependency, necessitating maintenance treatment with prolonged steroid therapy, azathioprine, or rituximab. In contrast, recurrences are rarely observed in AIP type 2 cases [33].

3.4 | Obstruction

Ampullary stenosis or duct strictures can be treated with endoscopic stenting. If a pancreatic cystic neoplasm causes obstruction, resection should be considered according to the current guidelines [33]. In case of pancreatic divisum, treatment options include sphincterotomy, stenting, or dilatation of the minor papilla [34].

3.5 | Chronic Pancreatitis Associated Complications

CP is associated with a range of complications that significantly impact quality of life and mortality. Therefore, structured follow-up is reasonable for most patients. While there are currently no specific guideline recommendations regarding follow-up strategies, the Chronic Pancreatitis Prognosis Score (COPPS)—a scoring system analogous to the Child-Pugh Score for liver disease - categorizes patients into three prognostic groups, which may assist to determine follow-up intervals [35]. The follow-up examinations should specifically address the early detection of PEI, DM and pancreatic cancer (Figure 3). Although there are no prospective comparative studies with other imaging modalities, the European guideline suggests transabdominal ultrasound for patients with suspected complications [11]. We favour an annual ultrasound for all CP patients to detect complications such as pseudoaneurysms or asymptomatic PFCs. Additionally, the nutritional status must be monitored and optimized. Multimodal approaches can also influence psychosocial aspects of the disease course. The following sections summarize major complications associated with CP along with their diagnostic and treatment options.

3.6 | Pancreatic Exocrine Insufficiency

PEI is considered a late complication of CP, occurring after a decline in pancreatic enzyme secretion to a level below 10%. A novel holistic approach defines PEI as a reduction in exocrine pancreatic secretion and/or intraluminal activity of pancreatic enzymes below a level that allows normal digestion of nutrients [36]. Recently, a clinical practice update of the American Gastroenterology Association was published, whereas the United European Gastroenterology (UEG) and European Pancreatic Club are currently working on new guidelines [37, 38].

A recent prospective observational trial revealed that the presence of PEI is associated with higher mortality [39]. Symptoms of PEI are heterogenous, including weight loss, cachexia, steatorrhea,

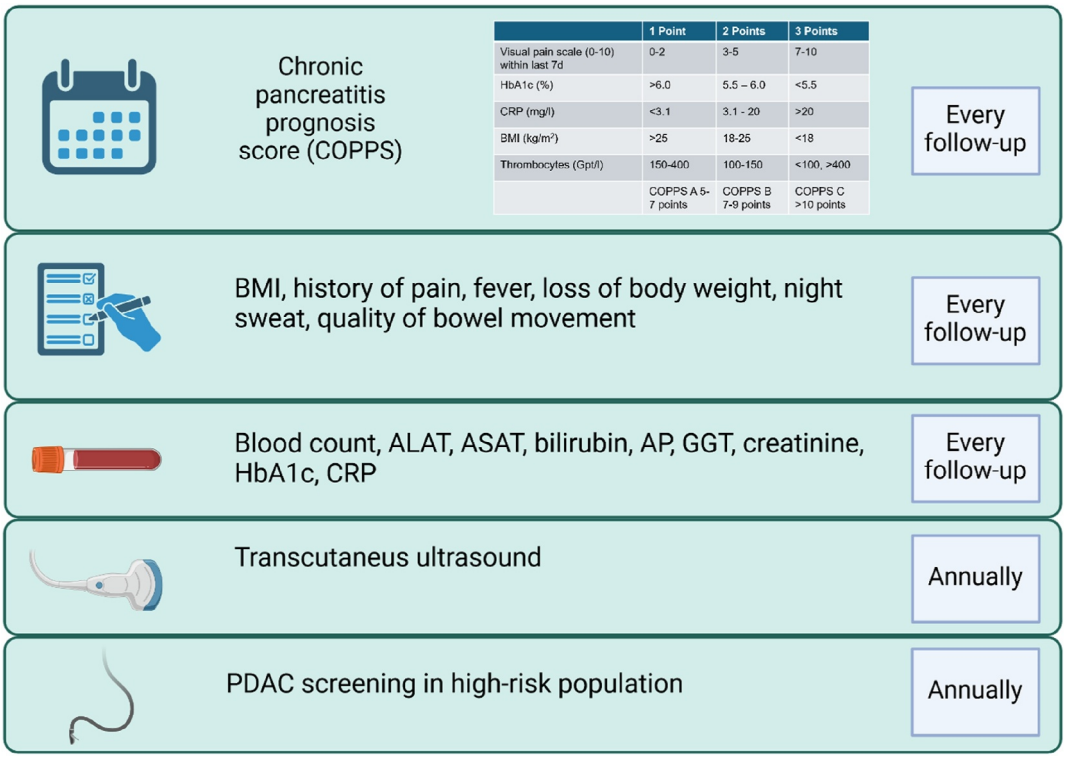

FIGURE 3 | Follow-up recommendations Risk adapted follow-up for patients with chronic pancreatitis is suggested based on the Chronic pancreatitis prognosis score (COPPS) and should include a profound anamnesis, an extended laboratory and if feasible, a regular transabdominal ultrasound. BMI = Body mass index; PDAC = Pancreatic ductal adenocarcinoma.

flatulence, abdominal pain, and hypovitaminosis (A, E, D, K). The latter can even occur in mild to moderate PEI. Faecal elastase-1 (FE) measurement is widely used as non-invasive diagnostic parameter [11]. However, it should be emphasized that FE-1 sensitivity is low in mild and moderate PEI. As an alternative, a ^{13}C-triglyceride breath test is available in specialized centres. Besides its capability to accurately diagnose mild and moderate cases. It can be used to monitor the success of pancreatic enzyme replacement therapy (PERT) [40]. For this purpose, FE-1 measurement cannot be used as it detects human FE-1, whereas PERT drugs are mostly derived from pigs.

At diagnosis and annually during follow-up, patients should be screened for PEI [11]. If clinical symptoms or laboratory signs of malnutrition are present, PERT should be initiated. In a practical approach, the initial dose is 40,000–50,000 Units (lipase activity) for main meals and half doses for snacks. It is important to educate patients about the correct intake of PERT with the meal to ensure appropriate mixing with the chyme [41]. If there is no adequate improvement in symptoms and increase in bodyweight, the PERT dosage can be doubled or even tripled. Enzymes are acid labile, and low duodenal pH can deteriorate PERT efficiency, which can be managed with an additional proton pump inhibitor treatment [11]. If the symptoms persist, further causes of malassimilation should be investigated. An important differential diagnosis of PEI is small intestinal bowel overgrowth (SIBO), which is commonly found in CP patients [42]. Mechanistically, PEI is also accompanied by a decrease of pancreas-produced antimicrobial peptides that are relevant to maintain the gut microbiome [43]. Reduced pancreatic antimicrobial peptides might lead to an overgrowth of bacteria in the large and small intestines in a preclinical model [43].

3.7 | Diabetes Mellitus

Diabetes mellitus (DM) caused by primary pancreatic disease is traditionally classified as type 3c. Since 2017, the term 'diabetes of the exocrine pancreas' (DEP) has increasingly appeared in the literature. In the case of causative pancreatitis, the term 'post-pancreatitis diabetes mellitus' (PPDM) is also used, with the suffixes '-A' and '-C' distinguishing between diabetes arising from acute and chronic pancreatitis, respectively. Up to 30% of all patients with CP develop new-onset DM and the risk increases with the duration of the disease [44]. Glycaemic control is complicated by rapid fluctuations between hyper- and hypoglycaemia, as the counter-regulatory production of glucagon and somatostatin is also impaired. Patients with PPDM are therefore at a significantly higher risk of life-threatening complications compared with those with type 2 DM. Due to the pathophysiological and clinical characteristics of PPDM, accurately diagnosing and differentiating it from type 2 DM presents a significant challenge, especially as DM may be the first clinical manifestation of CP. The basis of pharmacological treatment for PPDM currently consists of metformin and insulin. Even though the use of metformin may seem counterintuitive from a pathophysiological perspective, a survival benefit has been demonstrated for patients with PPDM [45]. Since DEP has traditionally been characterized primarily by an absolute insulin deficiency

combined with good insulin sensitivity, other classes of drugs besides insulin were not considered. Unlike in type 2 DM, calorie restriction is not recommended. Adequate PERT and replacement of fat-soluble vitamins play a crucial role in achieving good glycaemic control and maintaining nutritional status as it can improve the incretin response. In summary, overcoming the paradigm of DEP as a disease primarily caused by insulin deficiency and conducting prospective studies on DEP patients while considering their individual risk profiles may open the door to personalized treatment of these patients.

3.8 | Pain Management

Pain is the main symptom in CP patients. The pathogenesis involves local inflammatory and neuromodulatory mechanisms [45]. Recently, Transforming-growth factor b1 (TGFb1) and Glucoprotein130 (GP130) have been proposed as potential markers for phenotyping neuropathic and nociceptive pain in CP [46]. The WHO pain relief ladder forms the basis for the analgesic treatment of CP patients. Another component of treatment can be adequate PERT, particularly when pain is suspected to be due to malabsorbtion [11]. For moderate pain, non-opioid analgesics may be used, possibly in combination with co-analgesics. For more severe pain, these are combined with weak or strong opioids to achieve symptom control. Co-analgesics act through different mechanisms and play a significant role in treating pain in CP patients. In particular, the use of Pregabalin appears to offer substantial additional benefits for selected patients [47]. Cannabis and cannabinoids are relatively new players in the field of pain management. Currently, there is limited evidence for the use of cannabis and cannabinoids in non-cancer pain [48]. Regarding CP, caution is advised as cannabis use has been associated with AP in case series [49].

A significant proportion of patients cannot achieve adequate symptom control with pharmacological treatment alone. The duration of a medication only trial before considering interventional or surgical procedures remains an individual decision. If the pancreatic duct is dilated > 5 mm due to obstruction, guidelines recommend considering endoscopic-interventional or surgical measures after a maximum of 6 months of unsuccessful opioid treatment [11]. Endoscopic procedures include ERP with stone extraction from the pancreatic duct, dilatation, and stenting of the pancreatic duct. For intraductal stones, lithotripsy may be performed, potentially reducing intrapancreatic pressure and secondary inflammation. In recent years, several efforts have been made to improve the effectiveness of interventional and endoscopic treatments. For example, a recent study from India examined the combination of extracorporeal shock-wave lithotripsy (ESWL) with ERP versus a sham procedure, demonstrating at best short-term and moderate effects [50]. Here, novel extraction approaches with peroral pancreatoscopy seem to be more promising and are currently tested against ESWL [51]. Regarding direct lithotripsy another open question is whether the laser guided, or hydraulic procedure is superior. Overall, patients seem to benefit from early surgical intervention [52]. Therefore, surgery should be recommended within 3 months if endoscopic procedures do not achieve symptom control in obstructive CP [11]. Whether a primary endoscopic treatment attempt before surgery is justified for all patients requires further study. Improvements and new techniques in endoscopic-interventional treatment would be desirable to spare more patients from risky and irreversible procedures.

3.9 | Pancreatic Fluid Collection

One third of all CP patients develop at least one PFC. In case of symptoms such as pain, cholestasis, duodenal outlet obstructions or cyst related complications, like bleeding, infection, or rupture, an intervention is required. Furthermore, asymptomatic PFCs with a diameter > 5 cm without spontaneous regression within 2 months can be evaluated for drainage [11]. For endoscopic drainage, plastic pigtails or lumen-apposing metal stents (LAMS) can be placed transgastric or transduodenal. According to guidelines, the PFC wall needs to be consolidated and matured with a thickness above 3–5 mm[11]. Though current data show an advantage of LAMS compared to plastic stents regarding the drainage of walled-off necrosis, there is not enough evidence to favour one procedure in regard of pseudocysts [53]. Although LAMS are much more expensive, implantation seems technically easier due to the integrated electrocautery system. LAMS are recommended to be extracted after 4 weeks to lower the risk of complications. Four weeks of drainage might be too short as it is accompanied with a higher risk of PFC recurrence and thus a change to pigtails seems reasonable. However, a recent study showed the safety and the significantly higher efficacy of late removal compared to the 4 weeks regime [54]. Furthermore, a recent trial postulated that long-term indwelling plastic-stents are safe and harbour less recurrent fluid compartments [55]. In case of PFC recurrence, disrupted pancreatic duct syndrome needs to be excluded [11].

3.10 | Risk of Developing Pancreatic Cancer

Pancreatic adenocarcinoma (PDAC) is a late complication of CP [11]. Particularly, hereditary CP is associated with an increased risk of developing PDAC. In a French national cohort of *PRSS1* mutated gene carriers, the cumulative risk for PDAC increases with age: 10% by 50 years and 53.3% by 75 years [56]. Consequently, the risk is 80 times higher compared with the general population. Similar results are observed in a *SPINK1* mutated cohort [57]. Smoking cessation is urgently indicated in these cases [11]. For alcohol-induced CP or ICP, the risk is lower, with an adjusted hazard ratio of 6.9 after 15–20 years of disease progression [58]. The discrepancies between hereditary CP and other aetiologies are most likely due to the longer duration of disease and thus longer exposure to inflammatory processes.

Based on these epidemiological data, the German national guideline recommends PDAC screening for hereditary CP with the age of 40 or from 20 years after diagnosis onwards [59]. As a screening modality, the guideline suggests annual endoscopic ultrasound (EUS) [11]. However, differentiating between PDAC and mass-forming CP is challenging [60]. EUS is the most sensitive tool to discriminate pancreatic masses and has the advantage of acquiring histological samples. However, in CP

patients, the sensitivity is unsatisfactorily low with 50–75% [11]. Contrast-enhanced EUS/US might be useful in differential diagnosis but has to be evaluated in prospective trials [61]. However, if EUS guided biopsies and imaging cannot exclude PDAC, an oncological resection is recommended [11]. In the future, novel biomarkers and advanced imaging with the use of artificial intelligence hopefully improve prediction of PDAC in cohorts at risk.

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Conflicts of Interest

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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