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REVIEW

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Managing complications of chronic pancreatitis: a guide for the gastroenterologist

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ABSTRACT

Introduction: Chronic pancreatitis is a heterogeneous and complex syndrome that, in most cases, causes pain as a cardinal symptom and affects both the morphology and function of the pancreas, leading to several serious complications.

Areas covered: The present review, based on a non-systematic PubMed search updated to June 2023, aims to present the current available evidence on the role of gastroenterologists in the diagnosis and treatment of both local and systemic complications by either endoscopic or medical treatments.

Expert opinion: At diagnosis and during chronic pancreatitis follow-up, particular care is needed to consider not only the clinically manifest signs and symptoms of the disease, such as pain, jaundice, gastrointestinal obstruction, and pseudocysts, which require multidisciplinary discussion to establish the best treatment option (endoscopic or surgical), but also less evident systemic complications. Pancreatic exocrine and endocrine insufficiency, together with chronic inflammation, addiction, and dysbiosis, contribute to malnutrition, sarcopenia, and osteopathy. These complications, in turn, increase the risk of infection, thromboembolic events, and death. Patients with chronic pancreatitis also have an increased risk of psychiatric disorders and pancreatic cancer onset. Overall, patients with chronic pancreatitis should receive a holistic evaluation, considering all these aspects, possibly through multidisciplinary care in dedicated expert centers.

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KEYWORDS
Chronic pancreatitis; complications; endoscopy; pancreatic function; malnutrition; osteopathy; death; pancreatic cancer

1. Introduction

Chronic Pancreatitis (CP) is a heterogeneous disease characterized by progressive inflammation that can result in atrophy and fibrosis of the acinar tissue, with consequent insufficiency [1]. While CP is not considered a common disease, its prevalence seems increased, from some 20 per 100.000 inhabitants [2] to 40–90 per 100.000 [3,4] in more recent epidemiological studies. Data on the annual incidence of the disease are much more limited, but they are likely to be underestimated. Alcohol was classically considered the unique and most common cause of CP in the past, despite the fact that only some 30–40% of patients are heavy alcohol drinkers [5]. However, most patients had previous acute pancreatitis flares [6]. The role of smoking as the most important risk factor for CP development in the general population is being increasingly recognized [7]. Besides smoking and alcohol, other causative factors such as hypercalcemia and hypertriglyceridemia are classically enlisted as 'toxic;' other possible causes of CP are those that can lead to duct obstruction, such as necrotizing acute pancreatitis or neoplasms (Table 1). In the past two decades, the relevance of the genetic causes of CP has been increasingly recognized. Approximately 10% of cases in large CP cohorts have a defined genetic etiology [5,8]. However, the modern view of CP is more complex, and the disease is usually the result of a combination of etiological factors that are not exclusive [9]. While some dominant pathogenic mutations, such as those of PRSS1 and some CEL variants, and biallelic mutations of CFTR and SPINK1 are sufficient to cause the disease, many patients harbor monoallelic variants of CFTR, SPINK1, CTRC, or other genes that can participate in the pathogenesis of multiple etiologies or act as disease modifiers.

While the cardinal symptom of CP is pain, the disease is characterized by complications that are linked to both 'morphological' damage to the organ and 'functional' impairment of the pancreatic functions. From this perspective, both the appearance of the organ ('car body appearance') and its function ('engine') can be affected, and the correlation between these two aspects is variable [10]. The present review, based on a non-systematic PubMed search last updated in June 2023, is aimed at providing practice guidance for the management of both 'morphological' and 'functional' complications of CP.

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Article highlights

- Chronic Pancreatitis (CP) is a heterogeneous and progressive disease that represents the end-stage of an inflammation-to-fibrosis process.
- Pain is the cardinal symptom, but the disease is also characterized by complications associated with both structural damage to the organ and functional impairment of the pancreas.
- The correlation between morphology and function is limited, and gastroenterologists need to be aware of both aspects.
- Morphological complications include obstruction of the main pancreatic duct, which can cause pain. Both endoscopic and surgical treatments are available, with the latter being more effective. Endoscopic treatment is the first-line option for jaundice caused by benign stenosis and for draining pseudocysts. It can also be considered for gastric outlet obstruction in individuals who are not suitable candidates for surgery or as a bridge to surgery.
- Pancreatic exocrine insufficiency, along with other factors, contributes to malnutrition, which in turn leads to sarcopenia and osteopathy. This condition also increases the risk of extra-pancreatic complications, hospitalization, and death.
- CP patients have an increased risk of death due to infections, thromboembolic events, suicide, and a higher risk of developing pancreatic cancer.
- It is crucial for gastroenterologists to consider all of these aspects when treating patients with CP from a holistic perspective. This may be best achieved in a dedicated center with a multidisciplinary approach.

2. Morphological complications of chronic pancreatitis

CP is characterized by a progressive inflammation leading to irreversible morphological changes in the pancreas, that might result in complications with significant quality of life impairment [11]. Abdominal pain is a cardinal symptom of the disease. It might sometimes be attributable to a pancreatic duct obstruction, biliary and duodenal obstruction and pancreatic pseudocysts (PPCs), which represent some of most common morphological complications in CP patients [12]. However, it has to be recognized that pancreatic pain, especially when not promptly treated, can result in central sensitization and may become irreversible.

Managing this pain encompasses a spectrum of treatments (see Table 2), ranging from pharmacological therapy to interventional procedures [13] Painkillers following the WHO pain relief ladder, ranging from analgesics to opioids, are commonly prescribed, together with some recent evidence regarding adjuvant analgesics such as pregabalin [13]. However, the use of opioids in the long-term management of chronic pancreatitis pain is controversial, due to their addictive potential and other adverse effects such as constipation and nausea. Interventional procedures have been proposed to limit opioids consumption in this setting, such as Endoscopic Ultrasound (EUS)-guided celiac plexus block, most commonly referring to the injection of local anesthetic and/or steroids into the celiac plexus [14]. This procedure has shown conflicting results in terms of efficacy, and provides short-term pain relief, requiring repetition. More recent approaches, such as neuromodulation through spinal cord stimulation, have only been described in case series [15].

The management of the specific morphological complications has evolved over the past few years and is based on a multidisciplinary approach, involving gastroenterologists, surgeons and radiologists, and includes an accurate diagnosis with evaluation of possible modifiable exposome factors and the choice of the best-tailored treatment [16]. A common ground for all these morphological complications is that there is no indication to treat asymptomatic and uncomplicated benign CP [13].

In this section, current available evidence regarding the endoscopic management of the most common morphological complications of CP will be summarized (see Table 2).

2.1. Pancreatic duct lithiasis and strictures

The indication for the treatment of main pancreatic duct obstruction (MPD) is pain. When pain is considered due to the MPD obstruction, in the absence of a 'mass forming' CP that would pose an indication to resective surgery, possible treatments are surgical and endoscopic drainage [17].

Table 1. Causes of chronic pancreatitis.

Toxic-Metabolic
• Alcohol (only cause of CP in 30–40% of cases)
• Smoking (most common factor associated with CP development and strong influence on disease course)
• Hypercalcemia, Hypertriglyceridemia, Pancreato-toxic drugs (rather causes of acute pancreatitis, possibly becoming recurrent and then chronic)
• End-stage Chronic Kidney failure
Idiopathic (if early onset, <35 years, genetic screening indicated)
Genetic
• Autosomal dominant (PRSS1- Hereditary pancreatitis)
• Autosomal recessive (biallelic CFTR with cystic fibrosis or CFTR-related disease or SPINK1-associated familial pancreatitis)
• Others, Complex genetics, Modifier Genes (CTRC, CPA1, CLDN2, CASR, CEL)
Autoimmune
• Type I (IgG4- related disease)
• Type II (association with Inflammatory Bowel Disease)
Recurrent or Severe Acute Pancreatitis
• Acute pancreatitis (single episode with necrosis or recurrent episodes, any cause)

CP = chronic pancreatitis.

Table 2. Presentation and management of pain and morphological complications of chronic pancreatitis.

Complication	Clinical Presentation	Screening	Management
Pain	(1) Linked to MPD obstruction (→ responsive to drainage maneuvers) (2) Neuropathic/Central sensitization (especially when not treated promptly)	VAS Scales, QoL questionnaires, Izbicki pain score	(1) Painkillers: (a) Non-opioid analgesics (acetaminophen) (b) Non-Steroidal Anti-Inflammatory Drugs: not suitable for long-term use due to gastrointestinal and renal side effects. (c) Opioids (e.g. tramadol, oxycodone): long-term administration can lead to tolerance, dependency, and side effects like constipation and nausea. (d) Adjuvant analgesics (e.g. pregabalin) (2) Pancreatic enzymes: decrease of bloating symptoms related to malabsorption, that sometimes contribute to discomfort/pain. (3) Endoscopic or Surgical Treatments (see later) (4) Ancillary Therapies: (a) EUS-guided celiac plexus block (conflicting results; not permanent: require repetitions) (b) Neuromodulation with spinal cord stimulation (limited evidence, case series) (c) Alternative therapies (e.g. including cognitive-behavioral therapy)
Main pancreatic duct lithiasis and strictures	Pain	MRCP or EUS (pancreatic ductal evaluation might be impeded in the context of diffuse shadowcasting parenchymal calcifications)	(1) Surgery (a) drainage (e.g. Puestow procedure or Lateral Pancreaticojejunostomy): (in young, fit-for-surgery patients, might provide better long-term pain relief) (b) resection (e.g. pancreaticoduodenectomy): (especially in mass-forming lesions, arising concerns about neoplastic degeneration) (2) Endoscopy (as a bridge to surgery or for poor surgical candidates, but this might change with optimization of endoscopic drainage including EUS-guided maneuvers) (a) ESWL ± subsequent endoscopic clearance (for larger stones) (b) Upfront ERCP with stone clearance (for smaller stones in the head of the pancreas) (c) Pancreatoscopy and lithotripsy (d) Pancreatic stenting (for strictures)
Biliary Strictures	Jaundice, Cholangitis	MRCP + EUS + ERCP (extensive exclusion of malignant degeneration through multiparametric imaging, EUS-FNA or ERCP-guided brushing)	(1) Endoscopy (a) Fully-Covered SEMS (higher initial cost, but fewer procedure to achieve clinical success; risk of recall failure and missed malignancy during FU) (b) Multiple Plastic Stents (higher number of ERCPs to achieve clinical success, but possibility for more frequent cytopathological evaluation of the stenosis) (2) Surgery (usually resective [pancreaticoduodenectomy] versus derivative, especially in case of malignancy concern or stenosis refractory to endoscopic treatments)

(*Continued*)

Table 2. (Continued).

Complication	Clinical Presentation	Screening	Management
Duodenal stenosis	Nausea, Vomiting, Weight loss	Rx GI Follow-through or Endoscopy	(1) Surgery (a) surgical gastroenterostomy (b) pancreaticoduodenectomy (2) Endoscopy (in unfit for surgery patients, incomplete stenoses or as a bridge to surgery for restoration of nutritional status). (a) Endoscopic balloon dilation (reduced efficacy in CP versus peptic strictures) (b) Enteral SEMS (limited evidence in benign diseases) (c) EUS-guided gastroenterostomy (limited evidence in benign diseases; advantage of potential removability of the stent)
Peripancreatic Fluid Collections	(1) Symptoms (2) Abdominal pain (3) GOO, early satiety, weight loss (4) Jaundice (5) Complications: (6) superinfection (7) bleeding, rupture, fistulization (8) vascular compression and thrombosis	CT, MRCP or EUS	Step-up therapy: (1) EUS-guided drainage (Reduced complications over surgery and reduced pancreatico-cutaneous fistula and recurrences over percutaneous interventions) (a) Lumen-Apposing Metal Stents (for necrotic collections or WOPN) (b) Double-pigtail plastic stents (for pseudocysts, with long-term indwell to reduce recurrence) (2) Percutaneous interventions (usually in adjunct to endoscopic drainage, as for example in case of paracolic gutter extension) (3) Minimally-invasive surgical necrosectomy (e.g. Video-Assisted Retroperitoneal Debridement) (in case of failure of other treatments)
Pancreatic Cancer	Unexplained weight loss, new-onset diabetes, jaundice, abdominal pain, loss of appetite	CT, MRCP or EUS (parenchymal evaluation might be hampered in the context of diffuse shadowcasting calcifications, however focal, hypoechoic, hypovascular areas without calcifications or downstream to a stenosis might be sampled via EUS-FNA) CA19–9	(1) Surgical Resection (2) Chemotherapy (3) Local treatments (radiation therapy and/or EUS-guided ablation)

MPD: Main Pancreatic Duct; MRCP: Magnetic Resonance Cholangiopancreatography; EUS: Endoscopic Ultrasound; CT: Computed tomography; SEMS: Self-Expandable Metal Stents; GOO: Gastric Outlet Obstruction; VAS: Visual Analogue Scale; QoL: Quality of Life.

Evidence from randomized controlled trials suggests that surgical drainage results in better pain control and is more cost-effective [18] compared to an endoscopy-first approach [19]. Guidelines, therefore, suggest preferring derivative surgery as a long-term treatment to relieve pain in obstructive CP [13]. However, while it is reasonable to think that the surgical approach is at a steady state and there is no novel technical proposal, endoscopy techniques are in continuous development. On the other hand, EUS-guided interventions and pancreatoscopy are still in their early days. In addition, endoscopic drainage can serve as a bridge to surgery and to select patients that may benefit from decompression or be the only treatment in poor surgical candidates.

Therefore, Endoscopic Retrograde Cholangiopancreatography (ERCP) still plays a pivotal role in the management of symptomatic main pancreatic duct lithiasis and strictures [17].

The endoscopic armamentarium may involve extracorporeal shock wave lithotripsy (ESWL) and subsequent endoscopic clearance, or direct stone clearance by ERCP and the use of baskets or balloon, with or without lithotripsy. Pancreatic stones are often associated with strictures, and therefore pancreatic stenting is often needed. Newer possibilities involve EUS-guided endoscopic access to the main pancreatic duct either for ERCP rendezvous or pancreaticogastrostomy in expert centers [20–22]. Moreover, the use of single-operator pancreatoscopy with lithotripsy (either retrograde by ERCP or antegrade by EUS-guided access) can further optimize duct clearance.

Patients with small (<5 mm) pancreatic stones in the head of the pancreas, without a MPD stricture, with a short disease course and discontinuing alcohol and tobacco are usually the best responders to endoscopic treatments [13,17]. Whilst further evidence is required, in clinical practice, endoscopy therapy is usually performed first and surgery reserved for endoscopic failures [13], whereas other clinical and demographical factors should be taken into account in a personalized multidisciplinary discussion [23,24]. However, it is important to avoid multiple endoscopic treatments if not effective and to offer surgery in fit candidates.

2.2. Biliary strictures

All biliary strictures arising in the context of CP should be considered as potentially malignant and their management discussed carefully in a multidisciplinary setting.

Before endoscopic treatment, it is therefore essential to rule out the presence of a malignancy by imaging (Computed Tomography, Magnetic Resonance) and EUS, particularly in high-risk patients (e.g. weight loss, increased markers, long standing disease, hereditary CP, CA19.9 elevation) [25].

When malignancy is ruled-out, ERCP represents the first possible treatment for benign biliary stenosis. Compared with strictures from other etiologies, those from CP are usually more difficult to treat due to periductal calcification and fibrosis [12,17,24].

Endoscopic treatment usually involves either placement of multiple side-by-side plastic stents (MPSs) or one fully-covered self-expandable metal stent (FC-SEMS) (Figure 1) [17,26,27]. Based on the results of 2 RCTs and one meta-analysis [27], the two approaches are similar in terms of long-term stricture resolution and AEs, the advantage of FC-SEMS being a reduced number of procedures (as MPSs need to be exchanged every 3–4 months) to achieve clinical success at the price of a higher initial cost [28,29]. Patient compliance and recall registers are crucial to avoid fatal AEs [30]. It is important to underline that even in these trials performed in selected patients in expert centers, the rate of overlooked malignant biliary stenosis was not negligible. Therefore, even when malignancy was initially ruled out, in case of refractory biliary stenosis after one year of treatment, lack of patient compliance or suspicion of malignancy, surgery should be considered [17,26].

2.3. Duodenal stenosis

Duodenal stenosis (DS), especially in the case of groove pancreatitis, is a complication that affects about 5% of patients with CP [26,31]. Abdominal pain, nausea, vomiting and weight loss are the typical clinical manifestations.

Surgery, either surgical gastroenterostomy or pancreaticoduodenectomy depending on the clinical-morphological scenario, usually represents the most adopted option when feasible [26,32].

In the setting of poor surgical candidacy or as bridge to surgery, endoscopic treatments are possible (Figure 2). Endoscopic balloon dilation (EBD) is usually the first-line strategy in case of benign gastric outlet obstruction (GOO); however, outcomes in the setting of CP have been reported to be poorer than in peptic strictures [33,34]. Enteral SEMS (ES) might represent another endoscopic treatment in this scenario but their use in benign setting is restricted due to limited evidence [35].

EUS-guided gastroenterostomy (EUS-GE) has been more recently proposed as a viable alternative [36]. Whereas EUS-GE has demonstrated advantages over enteral stenting and surgery in the setting of malignancy [37,38] evidence in benign GOO is still limited. However, in the largest published series, EUS-GE has demonstrated to be able to prevent surgery in 83.3% of cases and, when surgery was still necessary, it was performed after an average of 270 days, allowing a more adequate nutritional status [36].

2.4. Pancreatic pseudocysts

Pancreatic Pseudocysts (PPCs) represent the third most common indication for endoscopic procedures in CP patients [26]. PPCs usually occur after acute episodes [39] and are more frequent in patients with alcoholic CP [40].

About 40% of PPCs resolve spontaneously within 6 weeks from the acute flare; in CP patients, however, this percentage is halved, probably due to the occurrence of MPD disruption and strictures.

Indications for drainage include symptoms such as abdominal pain, GOO, early satiety and weight loss or complications such as infection, bleeding, rupture, fistulization and/or compression of adjacent organs and structures (e.g. jaundice or vascular compression) [13,17,26].

Published evidence and guidelines agree on recommending endoscopic treatment as the first-line treatment of PPCs [13,17,26].

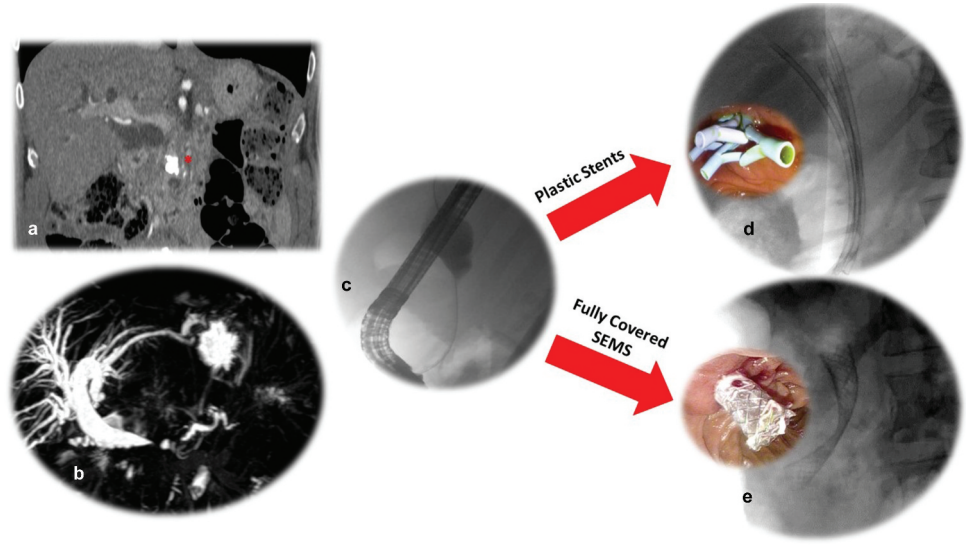

Figure 1. Management of biliary stenosis. Biliary stenosis (BS) represents one the most common morphological complications of chronic pancreatitis (CP). Imaging, including Computed Tomography (a) and Magnetic Resonance cholangiopancreatography Magnetic Resonance (b) and endoscopic ultrasound, is essential both to exclude malignancy and to plan the treatment. Periductal calcification (a, red asterisk) and fibrosis make tight BS from CP more challenging to treat compared to those from other etiologies. Endoscopic retrograde Cholangiopancreatography (c, d, e) represents the first-line treatment in this setting and involves either placement of multiple side-by-side plastic stents (d) or one Fully-covered self-expandable metal stent (FC-SEMS; e).

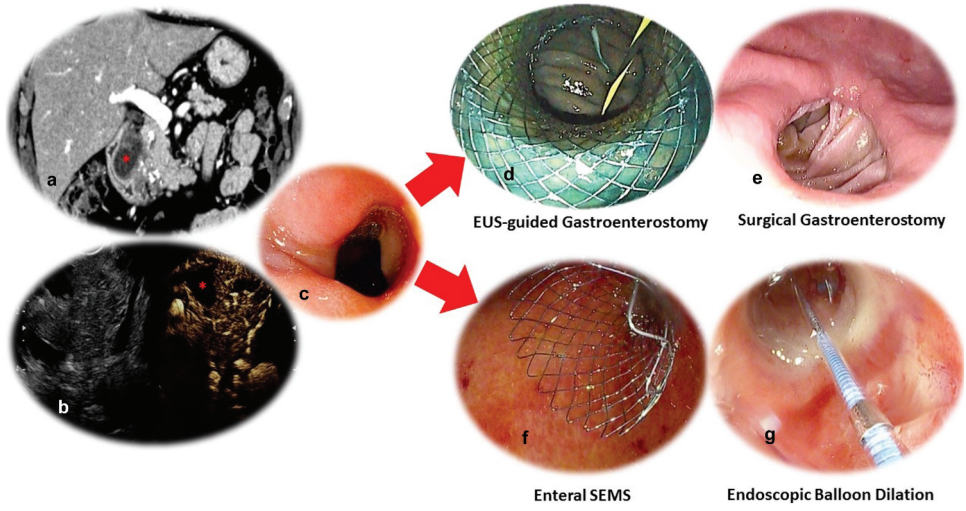

Figure 2. Management of duodenal stenosis. Approximately 5% of patients with chronic pancreatitis suffer from duodenal stenosis, mostly associated with groove pancreatitis (GP). Initially, it is necessary to rule out underlying neoplasia through imaging (Computed Tomography; a) and endoscopic ultrasound (EUS; b). Thickening of the duodenal wall with the presence of cystic formations (a–b; red asterisk) of varying sizes and collateral vessels are typical features of GP. Endoscopically, a reduction in duodenal lumen caliber can be observed, along with edematous and hyperemic mucosa (c). In patients eligible for surgery, either surgical gastroenterostomy (e) or pancreatico-duodenectomy represents the main treatment option. Endoscopy plays a pivotal role in unfit for surgery patients. Endoscopic balloon dilation (g) represents the first approach in cases of benign gastric outlet obstruction (GOO), but in the context of CP, outcomes are not optimal. Enteral self-expandable metal stents (f) are rarely used in this scenario due to limited evidence. Although evidence for EUS-guided gastroenterostomy (d) in benign GOO is limited, it has been shown to play a role in preventing surgery or as a bridge treatment to achieve a more suitable nutritional status before surgery.

Advantages over surgery include shorter hospitalization and reduced costs [41], whereas internal endoscopic versus percutaneous drainage reduces the risk of pancreato-cutaneous fistula [42] and recurrence [43].

Whilst endoscopic drainage was historically performed by direct endoscopic identification of a bulging, EUS guidance has revolutionized the endoscopic approach, allowed detailed real-time characterization of the collection and its contents and enhanced safety [42,44].

Although the use of Lumen Apposing Metal Stents (LAMS) has become very popular due to the larger connection between the cyst and the gastrointestinal tract and the easiness of deployment, available data comparing LAMS and double pigtail plastic stenting (DPPS) mostly regard necrotic collections [45] and have not yet been able to prove a definite superiority of one approach over the other [46,47]. For these reasons DPPS is still recommended for most uncomplicated PPCs [48].

Moreover, in cases where a disconnected pancreatic duct syndrome (DPDS) is likely, the risk of collection recurrence is high [49]. To date no clear evidence suggests the addition of transpapillary stenting of the MPD to transmural drainage, because the latter might contribute to the healing of the MPD rupture [50]. Finally, long-term indwelling of transmural DPPS has been suggested to reduce the recurrence risk [51], despite recent randomized data have failed to demonstrate an advantage of exchanging LAMS with DPPS [52].

3. Functional complications of chronic pancreatitis

3.1. Pancreatic exocrine insufficiency (PEI) diagnosis and treatment

The most recent guidelines [13,53,54] define PEI as a condition secondary to the impaired digestive function of pancreatic enzymes on the food that arrives in the duodenum mixed with gastric juice. This brief definition represents only the endpoints of many possible components. Indeed, PEI in patients with CP may be due to reduced pancreatic enzyme production due to parenchymal atrophy or chronic inflammatory flare-up, or to reduced secretion in the duodenum as a result of ductal stenosis or stones. Other possible less frequent causes may be altered enzyme function (in some forms of genetic mutations) or an asynchrony between the release of enzymes in the intestinal lumen and the passage of the food, as in patients undergoing resective or derivative pancreatic surgery.

The risk of developing PEI is high during the lifetime of patients with CP. It has been demonstrated that pancreatic function in patients with CP is reduced by 50–80% compared with healthy volunteers [55]. This impairment, in most cases, is not immediate, but takes several years to become clinically significant. In fact, it has been estimated that more than 90% of pancreatic exocrine function must be lost in order to develop severe PEI, with timing of PEI development differing depending on CP etiology. Patients with alcoholic CP develop PEI more rapidly (mean 13.1 years), especially if alcohol consumption persists or is associated with tobacco use, whereas patients with genetic or idiopathic CP develop it more slowly (mean 26.3 years) [56]. The discontinuation of tobacco and alcohol use slows down the evolution of CP and, consequently, the development of PEI.

Symptomatically, PEI can present with malabsorption manifestations, especially those related to fat-soluble vitamins (A-D-E-K). Symptoms can include fatigue, steatorrhea, bloating/abdominal pain, osteoporosis, changes in iron metabolism, ecchymosis, impaired night vision, xerophthalmia, ataxia, peripheral neuropathy and muscle spasms [13].

Diagnosis is not always simple, and it is based first on patient's symptoms, nutritional status and clinical history. In patients with severe CP and symptoms and signs of malabsorption, the pretest probability of PEI is extremely high, and treatment might already be started without a diagnostic test to confirm PEI diagnosis.

Several diagnostic tests are available for measuring exocrine pancreatic function [57]. Direct evaluation of pancreatic secretion through aspiration of pancreatic juice (during secretin-cholecystokinin/cerulein administration) is an invasive procedure and is only performed in clinical trials. Measurement of quantitative fecal fat excretion with calculation of the coefficient of fat absorption (CFA) requires collection of stools for 3 days after a specific diet. Although traditionally accepted as the gold standard for the diagnosis of steatorrhea it is troublesome and rarely employed.

The 13C-mixed triglyceride breath test measures labeled carbon, originating from marked fat digestion, absorption, and oxidation It is a noninvasive, accurate test that has the advantage of being able to monitor the response to pancreatic enzyme replacement treatment (PERT) [58], but it is poorly available. Therefore, fecal elastase [59] is the most commonly used method for diagnosing PEI. The most widely accepted cutoff value is 200 µg/g, but while values of elastase between 100 and 200 are considered borderline, these <100 µg/g are diagnostic for PEI.

In a meta-analysis comparing the accuracy of FE-1 to fecal fat estimation, the sensitivity was 96% with 88% specificity [60].

The treatment of PEI is based on PERT, the oral administration of pancreatic enzymes, which compensates for the lack of endogenous production or release. Most enzymes (mainly lipases of porcine origin) commercially available to date are contained within enteric-coated microspheres or minimicrospheres of <2 mm in size that are resistant to gastric acidity and are activated when they reach pH 5.5 within the duodenum. Given their function, it is essential to explain to the patient that tablets must be taken throughout the meal in order to be effective. The combination of proton pump inhibitors could favor the functioning of these capsules. Normally, the pancreas produces approximately 900,000 units of lipase each meal and, as mentioned above, the signs and symptoms of PEI usually begin to develop when there is a loss of more than 90% of pancreatic function; therefore, theoretically about 90,000 replacement enzyme units per meal would be required [61]. However, in many cases, residual enzymes make it possible to reduce the amount of PERT to be administered; therefore, current guidelines suggest administering a minimum dosage of 40,000–50000 units of enzymes per meal (half in case of snacks). The effectiveness of treatment does not require repetition of instrumental tests, and in most cases, the efficacy is based on symptoms and blood test improvement.

One of the most significant causes of EPI, affecting both adults and children, is undoubtedly cystic fibrosis (CF). This disease involves some dysfunction in the transmembrane channels that transport chloride, known as the CFTR (cystic fibrosis transmembrane conductance regulator). Chloride transport abnormalities can arise from various factors, including over 2000 known mutations of the CFTR gene, leading to issues in protein production and assembly, or in channel function. This results in an improper composition of body fluids, which become overly thick and viscous [62]. This mechanism underlies EPI in CF patients. Initially, CF patients have a normal-sized pancreas with well-represented parenchyma and ductal systems. However, the density of pancreatic juice hinders proper food digestion. Over time, a chronic inflammatory process leads to the morphological

changes typical of chronic pancreatitis. In recent years, there's been a significant shift in managing CF patients, with the development of drugs that modulate CFTR channel function, acting as correctors or enhancers of the protein [63]. Despite their recent introduction, these drugs have shown promising effects on various aspects of CF patients' daily lives. Regarding the pancreatic aspect, two literature reviews [64,65] have recently analyzed different facets of pancreatic functionality. Interestingly, about 23% of patients with EPI regained adequate pancreatic function after CFTR modulator therapy. Those who responded best to treatment were significantly younger (8.0 vs 9.8 years, $p = 0.032$), with no correlation to the type of modulator used or the specific CFTR dysfunction. This suggests the logical step of starting CFTR modulator treatment early, as once chronic pancreatitis-related parenchymal damage is established, little can be done for the etiological improvement of EPI. Similarly, CFTR modulators have been shown to improve FE-1 values and reduce the need for PERT.

Malnutrition in CP is, nonetheless, multifactorial and, besides PEI, is also associated with pain, psychological and social factors linked with alcohol and smoking abuse, chronic inflammation, pancreatogenic diabetes, delayed gastric emptying and small intestinal bacterial overgrowth [66] (Figure 3).

As malnutrition results in increased morbidity and mortality globally, gastroenterologists taking care of CP patients should proactively monitor their pancreatic exocrine function and nutritional status.

3.2. Sarcopenia and body composition in CP

At the time of diagnosis, most CP patients have already lost body weight, due to disease-related inflammation, PEI, and comorbidities [13,63,64]. While guidelines suggest assessing the nutritional status of CP patients through tools such as the community Malnutrition Universal Screening Tool (MUST) or the hospital Nutritional Risk Score NRS-2002 [13], they are not specifically designed for CP although both have a high degree of inter-related reliability for identifying patients who will benefit from nutritional intervention [13,67].

However, the capability of such methods to predict clinically relevant outcomes is limited. MUST is a pathological score with good specificity (80%) but low sensitivity (34%) to predict the risk of hospitalization during follow-up [67,68].

The Global Leadership Initiative on Malnutrition (GLIM) [69] consensus, instead, focuses on the role of skeletal muscle mass as a relevant nutritional protein regulator and endocrine organ [70]. In this view, both phenotypic criteria such as: non-voluntary weight loss, low body mass index (BMI), reduced muscle mass and etiological criteria such as reduced food intake or absorption, disease burden/inflammation should be considered. Malnutrition and undernutrition in CP based on GLIM criteria were reported to have a prevalence of 46.4% [71].

Malnutrition is often a precursor of sarcopenia, which leads to reduced physical function and unfavorable changes in body composition [67,70]. PEI can lead to progressive loss of muscle mass and area, decreased muscle strength, and even day-to-day muscle functioning [70,72,73].

As CT-scan images are often available for CP patients, most studies have employed them to estimate the prevalence of sarcopenia, resulting in approximately 32% [74]. However, a CT-scan may not be necessary in all patients during follow-up and there are no widely-accepted CT cutoff values for sarcopenia significantly associated with reduced skeletal muscle function.

In addition, while guidelines define sarcopenia as a disorder affecting both muscle strength and function [75], the common use of this classification is limited because both parameters are not regularly obtained in clinical settings.

Body composition assessment using bioelectrical impedance analysis (BIA) is a simple, easy-to-perform, noninvasive, and reproducible method that has been used to analyze body composition and hydration status. Among the BIA parameters, the Phase angle (Pha) reflects the relative contributions of fluid (resistance) and cellular membranes (capacitance) of the human body. Pha has been found to be a prognostic marker in several clinical conditions, such as liver cirrhosis and chronic obstructive pulmonary disease and correlates with

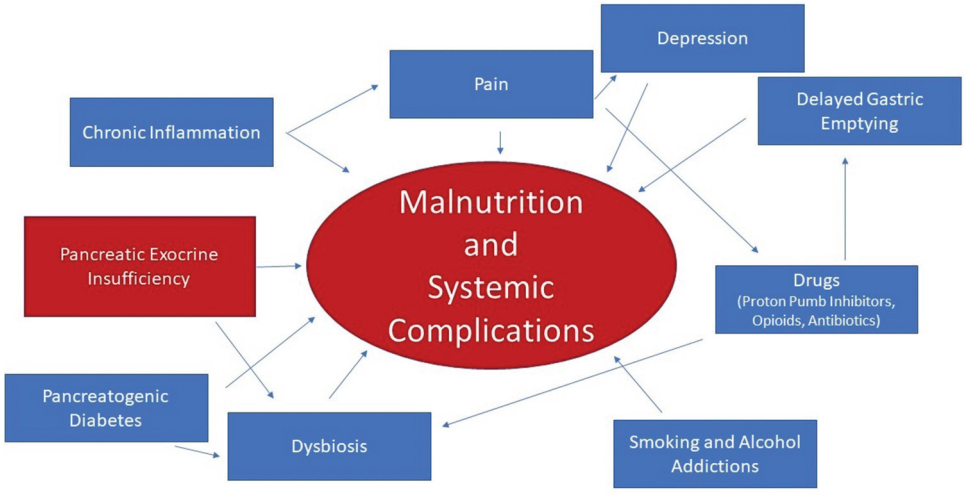

Figure 3. Malnutrition in chronic pancreatitis is multifactorial, with pancreatic exocrine insufficiency being the main cause, but many other factors concurring.

inflammatory markers and oxidative stress. Pha is correlated with muscle area and composition, and the prevalence of sarcopenia is higher in patients with low Pha [76].

However, studies employing BIA in CP patients are limited. Olesen et al. [77] investigated 182 CP patients by BIA and 17% were sarcopenic. Notably, most of them had a normal BMI, and PEI was associated with a 4-fold increased risk of sarcopenia. Sarcopenic patients also have a higher risk of hospitalization and reduced survival during follow-up.

In a recent multicentre study [70], 66 CP patients were investigated using BIA and handgrip strength evaluation. Over 60% had signs of malnutrition, but handgrip strength was not associated with it but only with muscle mass. The proportion of patients with both reduced muscle mass and handgrip strength was only 3%.

Although nutritional assessment and BIA help identify patients at risk of malnutrition, there is limited evidence on the association between body composition variables, nutritional trajectories and outcomes in CP.

Moreover, as in many other chronic diseases, such as congestive heart failure and chronic obstructive pulmonary disease, CP is associated with systemic chronic or recurrent mild-to-moderate inflammation. Although severe inflammation is generally easy to discern, clinical judgment is often required to recognize a lower degree of inflammation. Supportive proxy measures of inflammation can include laboratory indicators such as serum C-reactive protein (CRP), albumin, and prealbumin.

3.3. Osteopathy and vitamins deficiency in CP

Although most CP patients are men, osteopathy is common. A recent meta-analysis [78] showed a pooled prevalence of osteoporosis and osteopenia of 18% and 39%, respectively. Among patient-related factors, older age, female sex, smoking, and alcohol consumption are associated with lower bone mineral density (BMD). Notably, lower BMI and decreased vitamin D, K, and fecal elastase levels also affect BMD, underlining the importance of PEI and malabsorption of vitamins in causing bone damage in CP patients.

Accordingly, the risk of fractures is as high as 5.9% in CP, including low trauma fractures predominantly localized in the hip, vertebrae and distal radius [78].

Therefore, consensus guidelines recommend bone health assessment [13,54] at baseline in CP patients. However, only a quarter of CP patients are screened for bone disease, suggesting that this condition is an underrated source of morbidity [78].

Several factors including nutritional deficiencies, systemic inflammation, alcohol and smoking use and diabetes may disrupt the balance between bone formation and reabsorption [78–80].

Vitamin-D (vit-D) is an important player in bone health process [81] and can be malabsorbed due to PEI. Vit-D is a fat-soluble steroid hormone with two different forms: vit-D3 (cholecalciferol), endogenously produced in the skin of animals, and vit-D2 (ergocalciferol), produced upon ultraviolet irradiation of ergosterol in fungi or yeast [82]. After being hydroxylated in the liver and kidney vit-D3 turns into hormonally active 1,25(OH)2D3, which binds to the vit-D receptor (VDR) which functions as an obligate heterodimer with the retinoid X receptor (RXR) [82,83]. The activated heterodimer VDR/RXR translocates into the cell nucleus and binds to specific DNA sequences known as VD response elements (VDRE), which trigger the transcription of downstream genes that regulate bone and calcium homeostasis [82].

Current CP guidelines recommend assessment of fat-soluble vitamin levels in all patients [13], as the prevalence of deficit was estimated to be 16.8% for vitamin A, 29.2% for vitamin E and 57.6% for vit-D [84]. Vitamin K is also a fat-soluble vitamin playing a key role in bone metabolism and its deficiency is a frequent finding in subjects with osteoporosis and pathological fractures [85]. There are fewer studies on vitamin K levels in CP, but its role seems to be of interest.

Notably, in a large prospective cross-sectional European multicentre study, osteopenia and osteoporosis were diagnosed in 42% and in 22% of the 211 CP patients, respectively. Vitamin D and K were deficient respectively in 56% and 32%, and in male patients the only factor associated with osteoporosis was vitamin K deficiency (OR 4.23) [86].

Given the very high prevalence of vit-D deficiency in healthy subjects, findings on the rate of its deficiency in CP patients vs. controls are heterogeneous. Both Hoogenboom et al. [87] and Duggan et al. [88] found a high prevalence of vit-D deficiency in CP patients, however, without a significant difference from controls. In another study, a significantly greater proportion of CP patients than controls showed vit-D levels below 30 ng/mL [89]. The pitfalls of studying vit-D deficiency were highlighted by Olesen et al. [90], who underlined the heterogeneity of studies, the insufficient standardization of vit-D assessment among laboratories, the influence of solar exposure on vit-D levels and its role as a negative acute-phase reactant.

Bone mineral density (BMD) is usually assessed by applying dual-energy X-ray absorptiometry (DXA) to pertinent sites, a pilot study conducted by Baltar et al. found that a CT scan can be a viable tool for opportunistic osteoporosis screening in patients with CP [91].

As for bone turnover markers, in CP patients, the levels of procollagen type I N propeptide (PINP) and osteocalcin were higher than in controls; furthermore, patients with lower vit-D levels (less than 20 ng/mL) had significantly elevated levels of PINP [89].

If PEI is one of the main causes of nutritional deficiencies and, hence, of osteopathy, PERT should reduce the risk of osteopathy, but data are limited and heterogeneous.

Bang et al. showed that patients not using PERT have a higher risk of fractures, but the risk increased in patients with a longer duration of PERT, probably as a proxy for disease duration and severity [91]. In a prospective cohort of male CP patients, Haas et al. [92] also found that those who received PERT had a higher DXA score than those who did not.

In conclusion, it is recommended to perform a baseline assessment of fat-soluble vitamin levels and bone density by DXA in CP patients, followed by periodic evaluations of fat-soluble vitamins, zinc levels and DXA every two years in patients with osteopenia, in order to identify patients at risk of developing osteopenia, osteoporosis and fractures [13,54,93].

European guidelines also recommend referral to a bone specialist in case of osteoporosis for specific pharmacological supplementation [13]. Nonetheless, in the clinical setting, the assessment of bone health and adherence to guidelines seems to be low [94] and there are very limited data on the efficacy of PERT and specific pharmacological treatments on bone density and risk of fractures in CP patients.

Vitamins A and E deficiencies have also been associated with PEI [95] and their reduced levels contribute to immune system dysfunction, such as cognitive, vision and skin damage.

4. Systemic extra-pancreatic complications

4.1. Chronic pancreatitis and mortality

Several studies have investigated the risk of mortality in CP patients. As previously discussed, CP causes multiple nutritional, immunological, oncogenic, and hormonal alterations. Thus, it is not surprising that it is associated with an increased risk of death. A large prospective cohort study with a nearly 30-year follow-up period found that patients with definite CP had a 4-fold higher mortality rate than that of the background population [96]. The main causes of death among CP patients were digestive diseases (19.5%, mostly cirrhosis and CP complications), malignancies (19.5%), and cardiovascular diseases (11.3%). Additionally, 0.8% of patients committed suicide, and 3.8% died from pancreatic ductal adenocarcinoma (PDAC). Similarly, a retrospective study found that CP patients have a 5-fold increased risk of mortality compared to age- and sex-matched controls, with an 8 year-lower life expectancy [97]. Again, CP patients had an increased risk of gastrointestinal diseases, endocrine disorders, respiratory diseases, infections, or psychiatric disorders (HRs adjusted for Charlson index and socioeconomic status, respectively 26.1, 4.2, 3.3, 4.4, and 6.3). Moreover, as demonstrated in a prospective longitudinal cohort study, patients with CP and a diagnosis of PEI have an additional annual mortality rate of 2% regardless of PERT [98]. The fact that mortality in CP patients with PEI is higher than in those without PEI, regardless of PERT, suggests that enzyme deficiency alone is probably not the only cause of the increased mortality risk, being an expression of a more aggressive disease. In addition, PERT may be started too late to reduce the risks after long-standing nutritional deficiencies.

With respect to the causes of mortality in CP, Pedrazzoli et al. [99] found that the main causes of death in surgically treated patients under follow-up were smoking-related cancers and complications of ischemic heart and cerebrovascular disease. Similarly, a retrospective study including 193 CP patients, with a median follow-up of 10.1 years, found that the leading cause of death was cancer [100]. Therefore, the authors hypothesized that shared risk factors such as alcohol consumption and smoking play a fundamental role in establishing this association, but chronic inflammation, deficiencies in macro and micronutrients, and genetic susceptibility also contribute. Furthermore, a prospective longitudinal cohort study with nearly 20 years follow-up of surgically treated CP patients, found that mortality in the group of patients with non/minimal alcohol consumption did not significantly differ from that in the background population, while it was significantly increased in patients with moderate/severe alcohol consumption and in heavy smokers [101]. However, the role of lifestyle habits is still controversial, as other studies have suggested that there is no strong correlation between smoking, alcohol consumption and increased mortality rates [96,102].

4.2. Cardiovascular, infectious and mental illness risk in patients with chronic pancreatitis

Historically, the association between CP and cardiovascular (CV) and cerebrovascular diseases has been overlooked due to the presence of common risk factors such as alcohol consumption, smoking, and diabetes. However, recent studies have shown that 33% of CP patients and 9% of controls have evidence of atherosclerotic disease [103], and that CP patients have a 2.95-fold greater adjusted HR for deep vein thrombosis and a 4.51-fold greater adjusted HR for pulmonary embolism [104]. Furthermore, patients with CP have more than 3-fold higher risk of acute CV events [105]. This latter study also highlighted, for the first time, the cardioprotective role of metformin in preventing acute CV events in CP patients beyond its hypoglycemic effects, probably due to its pleiotropic, anti-inflammatory and antioxidant role [106]. Indeed, as it is well known, states of chronic inflammation like CP can lead to endothelial dysfunction, resulting in a prothrombotic state that promotes CV events [107]. Furthermore, PEI has also been demonstrated to be an independent risk factor for CV events, which is not surprising as malnutrition resulting from reduced absorption of fats, proteins, and fat-soluble vitamins, such as vit-D, is notoriously associated with an increased risk of all-cause mortality, particularly CV-related [108,109]. In conclusion, CP is associated with increased CV risk, although the exact pathogenesis remains unclear. Further research is required to better understand and address this relationship [110].

Patients with CP are prone to infections owing to various factors, including pancreatic ductal obstruction caused by fibrosis and strictures. This obstruction leads to stagnant pancreatic secretions, creating an ideal environment for bacterial overgrowth [111]. Invasive procedures, such as ERCP and pancreatic surgery, also contribute to an increased risk of infection. Moreover, pancreatic enzymes exhibit antimicrobial activity by breaking down bacterial cell walls and inhibiting the growth of pathogens. Consequently, the reduced enzyme activity in CP contributes to an impaired defense mechanism, with changes in the gut microbial composition and diversity. Such modifications can disrupt the delicate balance between commensal and pathogenic bacteria, thereby increasing the risk of gastrointestinal infections, and extrapancreatic translocation. Dysbiosis may lead to overgrowth of potentially harmful bacteria, such as *Enterobacteriaceae* and *Enterococcus* species, while reducing the abundance of beneficial bacteria that help maintain intestinal homeostasis, with an increased likelihood of pathogenic bacteria translocation from the gut to the pancreatic tissue [112]. A recent meta-analysis found a pooled prevalence of Small Intestine Bacterial Overgrowth (SIBO) of 38.6% in CP compared to 9.9% in controls, with considerable heterogeneity across studies, as PEI, diabetes,

and the type of test used to identify SIBO affect the rates [113]. This was confirmed by a further study, which also confirmed that the rate of SIBO between alcoholic CP and nonalcoholic CP was not significantly different [114]. In addition, the presence of SIBO appears to correlate with CP severity [115].

In addition to SIBO, CP and related malnutrition are associated with a compromised immune system and contribute to systemic infection susceptibility. Deficiencies in key nutrients impair immune cell production and activity. Additionally, chronic inflammation and fibrosis in the pancreas can lead to immune dysregulation, causing an imbalance between pro-inflammatory and anti-inflammatory cytokines. This imbalance impairs the ability of the immune system to mount an appropriate response against invading pathogens.

In patients with CP, several pathogens have been implicated in infections, contributing to the disease burden and complications. *Escherichia coli* and *Klebsiella pneumoniae* and other gram-negative bacteria, are frequently isolated from infected pancreatic necrosis, abscesses, and pseudocysts [116].

These pathogens can migrate and cause infections at other sites, such as the respiratory tract, the liver and skin [117,118]. Patients with CP also have a higher risk of *Clostridium Difficile* infections, with an increasing trend contributing to the development of drug resistance [119].

One of the potential causes of death in CP patients is suicide, which in most cases is associated with concomitant psychiatric conditions. CP has frequently been associated with reduced quality of life in affected patients; however, in recent years, the focus on mental health in these patients has gained more attention. A recent meta-analysis investigating the prevalence of depression in 87,136 CP patients demonstrated an overall prevalence of 36.2% [120]. Similarly, in a prospective multicentric study CP patients [121] were diagnosed with anxiety and depression in 46.8% and 38.6% of cases respectively, with an overlap of 29%. Patients with anxiety or depression also reported a higher prevalence and severity of pain, indicating bidirectional interaction between pain and psychiatric disorders. The association between pancreatic disease and suicide has also been investigated in a Taiwanese nationwide study finding a higher cumulative incidence of suicide attempts in e CP than in controls (adjusted HR = 2.72) [122].

5. Risk of pancreatic cancer

5.1. Pancreatic carcinogenesis in chronic pancreatitis

Chronic pancreatitis (CP) and pancreatic duct adenocarcinoma (PDAC) are strongly linked, as the inflammatory process occurring during CP lead to a molecular environment modification, that promotes carcinogenesis [123].

The most common process is represented by the initial activation of the oncogene KRAS (70–95% of cases), followed by the epigenetic or genetic inactivation of tumor suppressor genes such as CDKN2A, TP53 and DPC4, translated in step-up pancreatic intraepithelial (PanIN) progression to cancer [124,125]. In mice models, a previous step has been identified in the carcinogenetic process, called acinar-to-ductal metaplasia. Several inflammatory processes involved in CP pathophysiology play a key role in this process, including oxidative stress and the generation of reactive oxygen species and reactive nitrogen species, which perpetuate acinar cell necrosis and fibrosis. Furthermore, the Cox2, NK-KB and STAT3 pathways can generate sustained secondary oxidative injury, promoting inflammatory infiltration and acinar cell injury. Lastly, STAT3 promotes the de-differentiation of acinar cells, which become more vulnerable to the transformation initiated and promoted by KRAS activation [126].

5.2. Pancreatic cancer risk in individuals with chronic pancreatitis

CP is a definite risk factor for the development of PDAC. In a Danish nationwide study, a history of CP was associated with an HR for PDAC of 6.9 [97]; however, a recent meta-analysis demonstrated that PDAC risk in CP might be even higher (standardized incidence ratio from 13.3 to 22.61) [25]. Nonetheless, it is relevant to remember that studies evaluating the association between CP and the incidence of PDAC can be prone to bias due to the risk of PDAC misdiagnosis initially interpreted as CP. For this precise concern, some studies focus on the lag period between the two diagnoses. In a meta-analysis by Kirkegard et al. [127], the risk of PDAC in CP patients is highest at 2 years and decreases with longer follow-up (pooled effect estimates 16 at two years, 7.9 at five years and 3.5 at nine years).

Interestingly, the risk of PDAC onset in CP patients seems to differ according to the etiology. Concerning toxic etiologies, specific data are lacking, but it is reasonable to believe that the perpetuation of toxic habits, both heavy alcohol intake and smoking, could further increase the risk. Alcohol consumption not only independently and dose-dependently elevates the risk of CP, but also heavy alcohol consumption is an independent factor for PDAC, reaching a relative risk of 1.45 among consumers of more than three drinks per day [128,129].

Smoking independently increases the risk of both CP and PDAC, with a dose-response effect. The relative risk for CP in ever-smokers was 3, with a relative risk reaching 3.3 in those smoking one or more packs per day. Similar relative risks were associated with smoking and PDAC risk. Quitting smoking results in a reduction of this risk, with an odds ratio of 1.2 in former smokers compared to never smokers [128,129]. Clinicians should therefore stress the importance of cessation of alcohol drinking and smoking in patients with CP in order to prevent disease progression and the onset of complications, including PDAC.

For patients affected by hereditary pancreatitis, caused by a mutation of 'susceptibility' genes such as PRSS1, SPINK1, CFTR, CASR, CLDN2, CPA1, TRPV6, CEL-HYB, the risk of PDAC onset varies widely based on the gene involved: the relative risk in patients with PRSS1 mutations is dramatically higher than that of other mutations, reaching a value of up to 87 [130]. A registry study reported for these PRSS1-mutated patients a cumulative PDAC risk of 44% at 70 years from symptom onset with a standardized incidence ratio of 67 [131]. Moreover, an update of this study found PDAC cases among individuals from families with an autosomal dominant family history but without any PRSS1 mutations or deleterious

variants/mutations of the SPINK1, CFTR and CTRC genes [132], underlining the relevance of family history despite genetic testing results, as well as our incomplete understanding of the genetic background of pancreatitis. The other forms of hereditary pancreatitis also have an increased risk of developing PDAC, with a 12-fold relative risk in SPINK1 mutations [133], and 1.41 fold relative risk in CFTR mutations [134].

5.3. Should patients with CP undergo surveillance for pancreatic cancer?

The incidence of PDAC in sporadic chronic CP is not considered sufficiently high to justify screening [13,54,130]. On the other hand, as mentioned above, hereditary pancreatitis has a higher risk of developing PDAC than sporadic CP, probably because of a longer exposure to pancreatic inflammation. There is wide consensus about surveillance in PRSS1 mutations, which have the highest risk of PDAC [130,135,136], while for other forms of hereditary pancreatitis there are currently non-homogeneous indications, with some clinical studies advising surveillance in all cases of genetically determined pancreatitis [136], or others indicating surveillance for PRSS1 mutations, as well as individuals with an autosomal dominant family history without any PRSS1 mutation [130].

The topic of which screening modality should be adopted in CP cases is also debated, with most pancreatic surveillance protocols adopting MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with pancreatic-protocol CT reserved for individuals unable to undergo MRI or EUS. In the specific setting of CP, radiological diagnosis of PDAC is particularly difficult, given the parenchymal and ductal changes and numerous differential diagnoses, including mass-forming, para-duodenal or obstructive pancreatitis developing upstream of Wirsung duct stenosis [135].

In the context of the surveillance of CP patients, the role of serological biomarkers as a support for the diagnosis of PDAC has been widely studied. CA 19–9 blood test alone is extremely unspecific, especially in such 'inflammatory' setting, with a sensitivity and specificity of 82–91%. Additionally, the high prevalence of Lewis-negative patients (5–10% of the general population) [137], hampers its diagnostic utility [138]. Recently, combinations of CA 19–9 and novel serological (LRG1, TIMP1, PROZ, TNFRSF6B, sTRA, thrombospondin-2) or urine (PancRISK) biomarkers have been proposed, to increase specificity and sensitivity, with excellent results; however, these tests lack a clinical indication whatsoever [139–141].

6. Conclusion

CP is a challenging and multifaceted disease with a complex etiology, that can present with several complications and requires clinical and technical skills from a caring gastroenterologist. Morphological complications are usually suspected due to specific signs (jaundice) and symptoms (pain, GOO) and are readily assessed by imaging. In such cases, multidisciplinary discussion is mandatory to establish the indications for advanced endoscopic procedures that represent the key treatment modality. However, surgery is superior in terms of pain relief in the presence of an obstructed pancreatic duct.

Besides morphology, impaired pancreatic function (PEI and diabetes) contributes to malnutrition, sarcopenia, vitamin deficiencies, and osteopathy which in turn lead to systemic complications, increasing morbidity and mortality.

Sarcopenia is a common complication associated with adverse outcomes and a reduced quality of life. Measuring nutritional status and assessing sarcopenia using validated tools, such as BIA, is an often-overlooked part of CP care. In addition, as patients with CP seem to have much lower levels of physical activity [142], interventional studies on this topic are urgently needed. Recently, a randomized trial was designed to investigate the influence of the addition of exercise to nutritional guidance on sarcopenia in CP patients: however, the results are not yet available [143].

Osteopathy is also common in CP patients, also being often uninvestigated. Prospective interventional studies are required to comprehensively evaluate the potential long-term benefits of pharmacological supplementation in the specific clinical context of CP, with particular emphasis on the timing of PERT initiation and addition of fat-soluble vitamins. This will allow the establishment of clear guidelines regarding the indications and optimal posology of such treatments.

Malnourished CP patients are also at an increased risk of other extrapancreatic complications, especially CV and infectious events that often result in hospitalization and death.

Finally, patients with CP are at an increased risk of PDAC, although surveillance only seems justified in those with genetic etiology.

7. Expert opinion

The incidence and prevalence of CP seem to be increasing, partially due to increased knowledge of the high likelihood of developing CP after acute pancreatitis flare, and this trend will most likely further increase. One may therefore hypothesize that compared to 30 years ago, when most CP patients were cared for when the disease was already at an advanced stage with multiple complications, a larger number of patients will be seen by gastroenterologists at an earlier stage in the future. In this scenario, while on the one hand, it is important that the caring physicians keep in mind that different complications will likely arise during the disease course, stakeholders, including scientific societies, should underline the unmet needs in CP care to promote awareness and research.

Several guidelines on the clinical management of CP already have already suggested careful screening of the nutritional status and bone health of these patients not only at the time of diagnosis but also during the disease course [13,54]. However, gastroenterologists dealing with CP patients tend to focus on the management of pain or morphological complications such as duodenal or biliary stenosis, while little attention is paid to other complications that can still result in significant morbidity and mortality. The combination of malnutrition and chronic inflammation results in a plethora of systemic complications that worsen the clinical course of CP patients (Figure 3).

Table 3. Screening and management of functional, systemic complications of chronic pancreatitis.

Complication	Screening and Management
Pancreatic exocrine insufficiency (PEI), Malnutrition and Sarcopenia	Annual screening of pancreatic function and nutritional status and body composition investigation in individuals at risk of malnutrition. Treatment with pancreatic enzymes for PEI and with supplements when indicated.
Osteopathy	Bone Mineral Density evaluation at diagnosis and at subsequent intervals depending on results. Treatment for osteopathy.
Cardiovascular Events	Awareness of increased risk
Infectious Diseases	Vaccination policy and awareness of increased risk
Mental Illness	Awareness of increased risk, especially in presence of chronic pain and additions.

Notably, there is also a lack of a 'personalized approach' to CP patients, as the disease has a heterogeneous etiology, presentation, and clinical course, and there is a lack of models integrating clinical and non-clinical information, including exposome data. In this view, a better understanding of distinct underlying disease mechanisms linked to specific clusters of CP complications may help establish more appropriate therapeutic approaches [144]. In addition, a better understanding of the interaction of genetic and environmental factors in determining the disease course and its complications will allow a more tailored approach not only for pain management but also for the prevention and treatment of complications.

In this view, there is a need for prospective studies, such as disease registries, including collection of clinical, biochemical, and radiological data, and possibly biobanking. The absence of patients' associations with CP patients is a further barrier to their care, as a modern view of the disease should include patients' perspectives.

Clinicians taking care of CP patients should ideally more proactively act as an 'hub' and coordinate a multimodal care of these patients that includes evaluation not only by gastroenterologists that can also guarantee endoscopic treatments and surgeons, but also by nutritionists and physiotherapist, bone specialists, cardiologists, diabetologists and infectious disease specialists (see Table 3). Other unmet needs include support from psychiatric consultants and clinics for smoking and alcohol cessation.

CP can be considered a syndrome rather than a disease, as it represents a group of symptoms without a direct and univocal cause. Finally, when CP patients develop complications, they should be cared for in specialized, tertiary, high-volume centers, not only when surgery is necessary but also for a better treatment plan.

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