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A comprehensive review of recent advances in chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a multifaceted disorder influenced by environmental and genetic factors, with smoking and alcohol consumption being major contributors. Recent developments encompass the advent of innovative transgenic models and the identification of susceptibility genes, shedding light on the genetic aspect of CP. The pathogenesis of this disease involves a complex interplay of pancreatic acinar cell dysfunction, inflammatory reactions, and fibrosis. Current research delves into understanding these molecular mechanisms. Pain, a pivotal symptom of CP, has been increasingly studied to develop effective therapeutic interventions. Diagnostic advancements, including endoscopic ultrasound, radiomics, and blood-based markers, have shown potential in enhancing early CP detection. Moreover, recent clinical trials have optimized treatment approaches, such as pancreatic stone fragmentation, stent placement, and decision-making between endoscopic and surgical procedures. Emerging therapies, including chemical pancreatectomy and gene therapy, present promising opportunities for improved CP management.

Keywords: Chronic pancreatitis, Diagnosis, Endoscopy, Etiology, Mechanism, Surgery

Introduction

Chronic pancreatitis (CP) is a progressive fibrotic inflammatory disease of the pancreas, which is associated with environmental factors such as alcohol consumption and smoking, as well as certain gene mutations. In this condition, the pancreatic tissue undergoes repeated inflammation due to various stimuli, leading to progressive pathological alterations including pancreatic atrophy, calcification, fibrosis, and ductal changes.[1] The pathophysiological process involves the damage and dysfunction of pancreatic acinar cells, secondary inflammatory reactions, and activation of pancreatic stellate cells (PSCs). Patients with CP often experience recurrent or persistent abdominal pain, along with troublesome complications like pancreatic endocrine and exocrine insufficiency, manifested as diabetes and steatorrhea.[2] The global incidence of CP is approximately 4.4 to 14 cases per 100,000 persons per year, the prevalence is 36 to 125 per 100,000 persons. These numbers have been on the rise in recent years, imposing a substantial social and economic burden.[2,3] Therefore, it is crucial to further explore the pathogenesis of CP and develop novel methods for early diagnosis and curative treatment. In recent years, extensive studies have been conducted to enhance our understanding of the etiology, pathogenesis, clinical features, diagnosis, and treatment options for CP. This review aims to provide an overview of the recent progress in both basic and clinical research in this field.

Database and literature searching strategy

We searched PubMed, MEDLINE, Embase, and Web of Science for articles on CP published until December 1, 2023, using keywords connected with Boolean operators. Inclusion criteria encompassed primary studies in etiology, pathogenesis, diagnosis, and treatments. Exclusion criteria included case reports, commentary/editorials, duplicate articles, studies where full text was not available or could not be accessed, and non-English publications. Study selection was performed in 2 stages: Initial screening of titles and abstracts was conducted by 2 reviewers independently, and discrepancies were resolved by consensus. The second phase involved full-text evaluation of the shortlisted items.

Etiology of CP

Environmental factors

Alcohol consumption and smoking are 2 significant environmental factors associated with the occurrence and progression of CP. Daily alcohol intake within the range of 25 to 50 g increases the possibility of developing CP by approximately 1.5 times, while smoking 15 to 25 cigarettes per day can double the risk of CP.[4] Alcohol has traditionally been recognized as the primary risk factor for CP, with a significant attributable risk of 40%.[5] However, the role of tobacco in this disease may have been underestimated. An observational study highlighted that smoking emerged as the major factor for CP in the general population, with population-attributable fractions of 38% for males and 31% for females. These numbers surpassed the proportions attributed to alcohol consumption, which were 7% for men and 3% for women, respectively.[6] Moreover, the clinical course of CP can also be influenced by tobacco and alcohol. In advanced stages of CP, patients may develop various complications, including pseudocysts and pancreatic endocrine and exocrine insufficiency.[1] Numerous studies have provided evidence of the relationship between these factors and the occurrence of CP complications. Tobacco and alcohol have recently been proven to accelerate the progress of pancreatic endocrine

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and exocrine insufficiency, and have a dose-dependent relationship with calcifications, underweight, pain, and pseudocysts.[7,8] Specifically, smoking increases the odds of fibrotic complications and pancreatic insufficiency, while patients with alcoholic etiologies are more susceptible to inflammatory complications.[9]

It is well-established that alcohol and its oxidative and non-oxidative metabolites exert toxic effects on acinar cells, resulting in disruption of cellular functions and induction of endoplasmic reticulum (ER) stress and oxidative stress.[10–12] One prominent component found in tobacco, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, exacerbates the damage to acinar cells by binding to nicotine acetylcholine receptors.[13] Additionally, a recent study[14] demonstrated that exposure to combined alcohol and tobacco in mice resulted in the formation of malondialdehyde-acetaldehyde (MAA) adducts in the pancreatic extracellular matrix (ECM) proteins. This adduct formation inhibited the unfolded protein response of acinar cells, induced ER stress, and impeded acinar cell regeneration. Importantly, even after the removal of stimuli, the MAA adducts and their deleterious effects persisted, suggesting persistent pancreatic damage caused by the combination of tobacco and alcohol.

Genetic factors

Currently, it has been discovered that mutations in genes encoding cationic trypsinogen (*PRSS1*), serine protease inhibitor Kazal type 1 (*SPINK1*), chymotrypsin C (*CTRC*), cystic fibrosis transmembrane conductance regulator (*CFTR*), and other genes can modify the risk of CP through trypsin-dependent, misfolding-dependent, and ductal pathways.[15] The premature activation of trypsinogen in pancreatic acinar cells is considered a pivotal event in the development of CP.[16] *PRSS1* and *SPINK1* are among the genes involved in trypsinogen activation. Specific mutations in *PRSS1*, such as R122H and K23R, have been shown to increase sensitivity to inflammatory stimuli by elevating trypsin activity. This has been confirmed in novel transgenic animal models, shedding light on the in vivo mechanism of *PRSS1* mutations in hereditary pancreatitis.[17–19] SPINK1, a protein secreted by acinar cells, plays a role in mitigating the detrimental effects of excessive trypsinogen activation by inhibiting trypsin activity.[20] Mutations that trigger loss of function of SPINK1 are also implicated in the development of CP. In a study by Sun et al,[21] a heterozygous *Spink1* c.194+2t>c mutant mouse model was constructed, which directly developed CP without the presence of any cofactors. This model offers an ideal platform for further investigation into the pathogenesis of CP and the identification of potential therapeutic targets.

In addition to genes associated with proteases and their inhibitors, the pathogenesis of CP also involves genes encoding lipases. The carboxyl ester lipase (*CEL*) gene can undergo homologous recombination with its tandem pseudogene (*CELP*) to form a hybrid allele called *CEL-HYB1*. This hybrid allele which induces defective protein secretion and secondary autophagy has been found to be significantly enriched in European patients with nonalcoholic CP (NACP).[22] Our team[23] further investigated the underlying mechanism of this variant in vivo and observed that the mutant protein induces ER stress in acinar cells at an early stage, followed by deficient autophagy at a later stage. These events are likely associated with the observed spontaneous focal lesions in the pancreas and an increased risk of CP in coordination with environmental factors. Variants in the gene encoding pancreatic lipase (*PNLIP*) have also been linked to CP risk. This was initially reported in 2 brothers with homozygous *PNLIP* T221M mutations, who exhibited pancreatic exocrine insufficiency (PEI).[24] Zhu et al[25] provided evidence for the potential mechanism by generating mice with homozygous human *PNLIP* T221M mutations, which led to spontaneous CP changes through protein misfolding and ER stress in vivo. Furthermore, a recent study in several European NACP cohorts[26] discovered missense mutations in *PNLIP* that enhance protein degradation by proteases. These mutations may also contribute to the risk of CP, although further investigation is needed to elucidate the underlying mechanisms.

Continuous efforts have led to the identification of additional candidate genes associated with susceptibility to CP. Masamune et al[27] and our team[28] discovered that loss-of-function mutations in transient receptor potential vanilloid subfamily member 6 (*TRPV6*), a calcium channel protein, may disrupt the balance of Ca^{2+} in pancreatic cells and influence CP susceptibility. Furthermore, mutations in chymotrypsin-like elastase 3B (*CELA3B*) have been confirmed to increase the risk of CP,[29,30] although further studies are needed to establish the exact causal mechanisms. It is widely recognized that genetic factors interact with environmental factors and collectively contribute to the progression of CP. This concept was validated by 2 studies conducted by Hegyi et al[31] and our team,[12] which demonstrated that variations in the *PRSS1-PRSS2* locus exhibit an alcohol-dependence effect on CP risk. These new discoveries have proposed more comprehensive insights into the complex etiology of CP and its implications.

Molecular pathogenesis of CP

The development of CP is a complex process, primarily characterized by pancreatic acinar cell damage, inflammatory reactions, and fibrosis.[2] Recent studies have provided novel insights into the molecular mechanisms underlying these aspects (Fig. 1). The following sections outline the main findings in detail.

Pancreatic acinar cell damage

Acinar cell injuries attributable to various pathological stimuli are considered as the initial events in the development of CP. The stability of acinar cells requires the coordinated maintenance of various cell structures and molecules, among which mitochondria serve as the source of the large amount of energy demand from acinar cells, and mitochondrial dysfunction can disrupt cell homeostasis and result in pancreatitis.[32] The transcriptional regulation of mitochondrial genes by estrogen-related receptor γ (ERRγ) in relation to maintaining mitochondrial function was examined. However, there is conflicting evidence regarding the role of ERRγ in CP. Choi et al[33] observed downregulated ERRγ expression in CP patients, resulting in reduced expression of genes related to mitochondrial oxidative phosphorylation, increased reactive oxygen species (ROS) formation, acinar cell death, and pancreatitis. Conversely, Chanda et al[34] reported upregulated ERRγ expression in mouse models of pancreatitis and CP patients' pancreas. Increased ERRγ expression led to enhanced expression and oligomerization of voltage-dependent anion channel 1, leading to elevated levels of Ca^{2+} and ROS in mitochondria and acinar cell damage. Thus, the exact effect of ERRγ in CP remains controversial. Autophagy is crucial in maintaining acinar cell homeostasis by removing damaged structures. Disruptions in molecules that regulate autophagy have been implicated in the development of CP.[35] Vacuole membrane protein 1, an ER membrane protein involved in autophagosome formation, was found to be downregulated in CP, leading to defective autophagy, ER stress, and activation of the nuclear factor erythroid 2-like 2 pathway, potentially contributing to CP pathogenesis.[36] Farnesoid X receptor (FXR) has recently been implicated in the restoration of effective autophagy. As a transcription factor, FXR acts on its target gene oxidative stress-induced growth inhibitor 1 (OSGIN1), increasing autophagy flux through the FXR-OSGIN1 axis and exerting a protective effect on CP.[37] Given that acinar cells produce a large number of digestive enzymes, regulatory mechanisms are necessary to manage their secretion and prevent ER stress. Fibroblast growth factor 21 (FGF21) stimulates acinar cells to

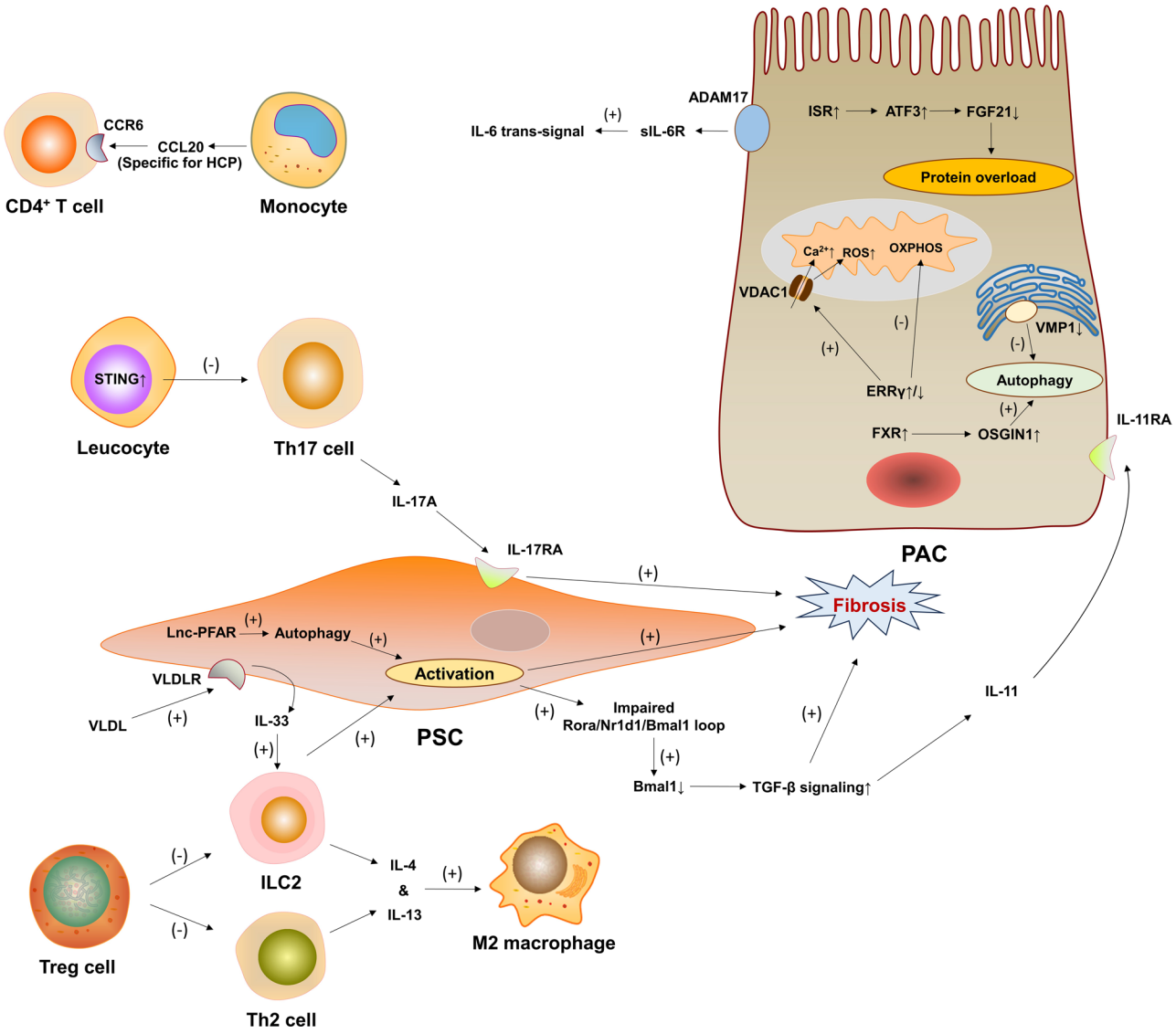

Figure 1. Illustration for the recent progress in the molecular pathogenesis of CP. ADAM17 = the protease A disintegrin and metalloproteinase 17, Bmal1 = aryl hydrocarbon receptor nuclear translocator-like, CP = chronic pancreatitis, ERRγ = estrogen-related receptor γ, FGF21 = fibroblast growth factor 21, FXR = farnesoid X receptor, ILC2 = group 2 innate lymphoid cell, ISR = integrated stress response, Nr1d1 = nuclear receptor subfamily 1, group D, member 1, OSGIN1 = oxidative stress–induced growth inhibitor 1, OXPHOS = oxidative phosphorylation, PAC = pancreatic acinar cell, PSC = pancreatic stellate cell, Rora = retinoic acid receptor–related orphan receptor A, ROS = reactive oxygen species, sIL-6R = soluble interleukin-6 receptor, STING = stimulator of interference genes, TGF-β = transforming growth factor-β, Treg = regulatory T cell, VDAC1 = voltage-dependent anion channel 1, VLDL = very low-density lipoprotein, VLDLR = very low-density lipoprotein receptor, VMP1 = vacuole membrane protein 1.

secrete digestive enzymes and maintain intracellular protein stability, which is disturbed in CP. The activation of the integrated stress response pathway in CP results in increased expression of the transcriptional inhibitor ATF3, leading to decreased FGF21 expression and subsequent intracellular protein overload.[38] In summary, the pathways involved in acinar cell damage in CP have been further elucidated.

Inflammatory reaction

There are complex and diverse innate and adaptive immune responses involved in the progression of CP. The interactions between inflammatory cells and pancreatic cells contribute to the chronic injury of the pancreas.[35] Various inflammatory mediators form a complex immune regulatory network with specific molecular mechanisms. The protease A disintegrin and metalloproteinase 17 (ADAM17) has been observed to exacerbate CP progression. ADAM17 is capable of shedding bioactive inflammatory mediators, including soluble interleukin (IL)-6 receptor, which activates the IL-6 trans signaling pathway and downstream signal transducer and activator of transcription 3.[39] Additionally, the activation of the stimulator of interferon genes signaling pathway in leukocytes has been found to inhibit the differentiation of IL-17A⁺ cells, production of IL-17A, as well as downstream signals, resulting in a protective effect on CP.[40] The immune characteristics of CP with different etiologies have also been investigated. Lee et al[41,42] identified distinct immunological responses in hereditary CP (HCP) and idiopathic CP (ICP). HCP showed a higher proportion of CD3⁺ T cells, while ICP had a higher proportion of CD68⁺ macrophages. Specifically, HCP exhibited a higher enrichment of CCR6⁺CD4⁺ T cells compared to ICP. Moreover, the expression of CCR6 ligand CCL20 on monocytes was significantly higher in HCP, indicating the pancreatic-specific immune crosstalk mediated by the CCR6-CCL20 axis.[41,42] Furthermore, a recent study using serum samples from a large pancreatitis cohort revealed that elevated levels of IL-17A and CCL20 are key characteristics of CP, supporting the aforementioned findings.[43] These discoveries

contribute new insights to the immune regulatory network of CP and present potential therapeutic targets for this disease.

Pancreatic fibrosis

Pancreatic fibrosis is a crucial pathological characteristic of CP, characterized by the activation of PSCs and excessive deposition of ECM in pancreatic tissue. This process ultimately leads to worsened pancreatic endocrine and exocrine dysfunction.[44] The activation of PSCs is influenced by numerous regulatory factors, including metabolites and the immune system. Lipoprotein metabolites have been identified as promoters of PSCs activation and fibrogenesis through their interaction with the very low-density lipoprotein receptor. This interaction enhances lipid metabolism in PSCs and stimulates the expression and release of IL-33, which triggers the accumulation of pancreatic group 2 innate lymphoid cells (ILC2s). Subsequently, the type 2 immune response and PSCs activation are initiated, eventually eliciting fibrosis.[45] In addition, fibrogenesis is mitigated by $FOXP3^+CD25^+$ regulatory T cells (Treg cells). Treg cells suppress the type 2 immune response by inhibiting $GATA3^+$ T helper cells, ILC2s, and $CD206^+$ M2 macrophages to prevent fibrosis.[46] Long non-coding RNAs (LncRNAs) may also contribute to PSCs activation through autophagy-related mechanisms. Specifically, a lncRNA named lnc-PFAR can enhance PSCs activation by inhibiting the maturation of pre-miR-141, which in turn promotes retinoblastoma coiled-coil protein 1–induced autophagy.[47] Furthermore, the circadian clock system in the exocrine portion of the pancreas, which regulates the circadian rhythm of pancreatic secretion, has a protective effect on pancreatic fibrosis. Jiang et al[48] emphasized the importance of the retinoic acid receptor–related orphan receptor A/nuclear receptor subfamily 1, group D, member 1/aryl hydrocarbon receptor nuclear translocator-like loop in maintaining the circadian clock and controlling fibrosis. These studies highlight potential targets for regulating fibrosis in CP, which could potentially contribute to the improvement or even reversal of this challenging irreversible disease.

Clinical assessment of abdominal pain

Abdominal pain is a common clinical symptom of CP, affecting more than 80% of patients.[2] The pain caused by CP can be categorized into intermittent or persistent patterns based on its frequency. These patterns were previously believed to be associated with different pathological entities, mechanisms, and treatment strategies.[49] However, a recent prospective longitudinal study revealed that 61% of patients experienced changes in their pain patterns during the follow-up period, transitioning from severe and persistent pain to moderate and intermittent pain.[50] It was found that the different pain patterns were not related to treatment strategies, but rather reflected the severity of the pain. These findings emphasize the importance of focusing on pain intensity rather than frequency in clinical practice. Patients with severe or persistent pain in CP are more likely to experience psychological complications such as anxiety and depression.[51] These psychiatric comorbidities have a significant impact on the disease characteristics and quality of life of CP patients, manifested as higher pain incidence, greater pain severity, and poorer quality of life.[52] The studies indicate a bidirectional relationship between CP-related pain and psychiatric disorders. Recent research conducted by Dunbar et al[53] identified several candidate gene loci associated with anxiety and post-traumatic stress disorder, which overlapped with some gene loci linked to persistent and severe CP pain. This suggests a genetic connection between mental disorders and CP-induced pain, supporting the observations of a mutual influence between the 2. CP-induced pain is thought to be associated with aberrant alterations in the peripheral and central sensory systems.[54] A comprehensive understanding of the specific pathogenesis of pain in each patient is crucial for effective pain management. In this regard, Phillips et al[55] developed an accessible clinical tool called the pancreatic quantitative sensory test for evaluating CP-induced pain. This test can classify patients into 3 pain phenotypes based on changes in central pain processing: no hyperalgesia, segmental hyperalgesia, and widespread hyperalgesia.[55] Importantly, this method's outcomes remain unaffected by potential mental disorders, providing a reliable measure of the nociceptive or pain-processing system without requiring additional psychiatric assessments.[56] Given the complex and multidimensional nature of pancreatic pain, there is a lack of inclusive and validated questionnaires specific to this condition. In response to this, the Comprehensive Pain Assessment Tool for Chronic Pancreatitis (COMPAT) was developed to address all dimensions of pancreatic pain. To enhance its clinical applicability, a short form of COMPAT (COMPAT-SF) was created. COMPAT-SF includes 5 pain dimensions: pain severity, pain pattern, pain-provoking factors, widespread pain, and a qualitative pain-describing dimension. In the future, COMPAT-SF may serve as a feasible, reliable, and effective tool for pain assessment, assisting clinicians in formulating personalized intervention strategies and improving patients' quality of life.[57,58] As mentioned earlier, pancreatic pain is influenced by heterogeneous factors, including psychological disorders and abnormalities in sensory processing. Research has shown that factors including pancreatic duct blockage, abnormal pain processing, and psychological complications often overlap, resulting in cumulative adverse effects on pain severity and quality of life. These findings underscore the importance of multidisciplinary management for pancreatic pain in CP.[59]

Diagnosis of CP

Imaging findings are routinely utilized in diagnosing CP. Noninvasive cross-sectional imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) are commonly used to visualize the typical morphological changes associated with CP, including pancreatic atrophy, calcifications, fibrosis, and ductal changes. However, these imaging modalities have limited diagnostic value in the early stages of CP. In contrast, endoscopic ultrasound (EUS) is a highly sensitive method that can detect subtle morphological changes in the pancreas, making it superior to CT or MRI for early diagnosis.[60] A diagnosis of CP using EUS is based on morphological ductal and parenchymal criteria. However, there is still controversy regarding the minimum number of EUS characteristics required to establish a diagnosis, considering both sensitivity and specificity. Moreover, there is a lack of consensus among specialists in diagnosing CP using EUS.[61] The endoscopic pancreatic function test after secretin stimulation (ePFT) is a practical tool for diagnosing PEI and is crucial in assisting with the diagnosis of suspected CP.[62] Recent studies have shown that ePFT can be safely and feasibly performed simultaneously with EUS evaluation combined with secretin injection (s-EUS).[63] Furthermore, the combined results from these integrated methods have synergistically improved the diagnostic accuracy of minimal change CP, providing valuable insights into early diagnosis. Despite its high efficacy in diagnosing early CP and PEI, the expensive cost and lengthy test duration of ePFT limit its clinical utility. In light of the evidence that the stimulated pancreatic bicarbonate excretion measured by ePFT is significantly correlated with the degree of histological fibrosis,[64] there is potential diagnostic value in using EUS elastography (EUS-E) to quantify fibrosis levels. Iglesias-Garcia et al[65] demonstrated a parallel correlation between EUS-E and ePFT ($r = 0.715$, $P < .05$), with an accuracy of 93.4% for EUS-E in diagnosing CP. Thus, EUS-E shows promise as a reliable alternative to ePFT in assisting the diagnosis of suspected CP. Regarding the diagnosis of PEI, noninvasive methods like pancreatic elastase-1 measurement and secretin-enhanced

magnetic resonance cholangiopancreatography (S-MRCP) may also be helpful.[66] Additionally, a radiomics model based on fully automated pancreas segmentation has been developed, demonstrating superb diagnostic performance in predicting PEI (area under the curve [AUC] = 0.92). This model outperforms the measurement of pancreatic flow output rate using S-MRCP.[67]

The lack of specific diagnostic markers collected from easily accessible samples such as blood has hindered the early prevention of CP. To address this limitation, a large prospective cohort study successfully identified and validated metabonomic biomarkers from plasma and serum for diagnosing CP. Eight metabolites, including β carotene and cryptoxanthin, were discovered to distinguish CP from healthy controls with respectable accuracy (AUC > 0.8). These findings form the basis for the development of the first routine laboratory indicators for CP detection.[68]

Management of CP

The primary objectives of managing CP currently are pain relief, symptom management, complication treatment, and disease progression delay. Physicians have various alternative therapeutic options at their disposal, including lifestyle modifications, medications, and invasive therapies such as endoscopy and surgery.[1] These invasive treatments can be effective in addressing distressing symptoms or complications that occur in advanced stages. Significant advancements have been made in recent years in the endoscopic and surgical management, and novel therapies for CP.

Endoscopic intervention

Endoscopic intervention is commonly employed for pain relief, intraductal stone removal, and management of pancreatic or biliary stenosis, primarily due to its minimal invasiveness. Guidelines recommend the extraction of stones in pancreatic ducts through endoscopic retrograde cholangiopancreatography (ERCP), either alone or in combination with lithotripsy for stones larger than 5 mm.[69] Lithotripsy options include extracorporeal shock wave lithotripsy (ESWL) and single-operator pancreatography with intraoperative lithotripsy (SOPIL). ESWL is widely accepted as the first-line therapy due to its effectiveness, although some patients may experience acute pancreatitis, leading to additional burden.[70,71] Our team conducted a double-blind, randomized, placebo-controlled trial that provided a solution to this predicament. It proposed that preoperative rectal administration of indomethacin was an effective and safe approach to prevent post-ESWL pancreatitis, reducing the incidence rate by 25%, shortening hospital stays, and decreasing medical costs.[72] SOPIL is considered as an alternative when ESWL cannot be utilized or when its efficacy is poor. SOPIL allows for more precise stone localization under direct visualization, minimizing damage to surrounding tissues. Prospective studies have demonstrated the efficacy and safety of SOPIL, with a complete stone clearance rate of 90% and a pain relief rate of 82.4%.[73] The latest guideline also highlights that ESWL and SOPIL are usually complementary for the management of large and/or complex stones.[69] Endoscopic pancreatic stent implantation is a treatment option for pancreatic duct stenosis and associated pain. Multiple plastic stents (MPSs) are commonly recommended for this purpose. Fully covered self-expanding metal stents (FCSEMS) are a relatively new method that offer advantages in reducing the need for stent replacement and ERCP procedures. However, emerging evidence suggests an increased risk of adverse consequences associated with FCSEMS.[74] Although efforts have been made to develop modified stents to overcome these issues, limited research has demonstrated satisfactory efficacy and safety. One reformative flared FCSEMS with an anti-migration characteristic has been observed to frequently cause stent-related duct stricture.[75,76] Based on this information, a recent prospective study evaluated a newly developed nonflared FCSEMS and confirmed its satisfactory performance. The study included 25 patients, all of whom showed resolution of pancreatic duct stenosis. Stent-induced neostenosis was not observed in any of the patients, but 1 patient experienced stent displacement, which required extra randomized controlled trials to validate its effectiveness.[77] Another study evaluated the efficacy and safety of a new "soft" FCSEMS that remained in place for 6 months. However, this stent did not yield the expected outcomes and was associated with adverse events, including stent migration.[78] Therefore, more research is needed to determine the optimal decompression strategy, FCSEMS design, and the patient population to which it is applicable. In the management of CP complicated with benign biliary stricture (BBS), both MPSs and FCSEMS are appropriate treatment options. However, MPSs may require multiple ERCP procedures, which can increase the financial burden on patients. FCSEMS, on the other hand, with its larger lumen diameter, offers long-term efficacy in unclogging the obstruction and minimizes the need for repeated interventions. A recent multicenter randomized trial confirmed that FCSEMS is as effective and safe as MPSs in the treatment of BBS.[79] Furthermore, a 5-year follow-up study demonstrated the durable effect of FCSEMS in resolving stenosis, with over 60% of patients remaining asymptomatic and stent-free, and the safety data were acceptable.[80] Moreover, a cost-effectiveness model supported the use of FCSEMS in reducing financial stress for patients.[81] Therefore, FCSEMS can be a prioritized treatment option for CP-related BBS when feasible.

In summary, for intraductal stones, ERCP combined with ESWL is prioritized. If this strategy proves ineffective or unsuitable, the utilization of SOPIL can serve as a viable alternative. It is crucial that a standardized protocol is designed to guide the choice between ESWL and SOPIL, based on existing evidence and future studies. For pain due to pancreatic ductal stricture, both MPSs and FCSEMS are effective. However, caution is advised when utilizing FCSEMS, particularly concerning the risk of adverse events. In the case of coinciding BBS in CP patients, the application of FCSEMS is a more favorable choice over MPSs where feasible, as it offers similar effectiveness but significantly reduces the need for stent exchanges during treatment.

Surgery

Although the endoscopy-first strategy is regularly considered advantageous due to its minimally invasive nature, several studies have suggested that early surgery may be more beneficial for patients with CP. It has been observed that a significant number of patients initially treated with endoscopy eventually require surgical intervention. Randomized clinical trials comparing endoscopy and surgery have assessed the clinical outcomes in obstructive and symptomatic patients (Table 1). Collectively, early surgical drainage has shown superior long-term pain improvement and reduced need for further operations compared to strategies prioritizing endoscopy.[82–85] Moreover, prompt surgical treatment has been found to be more cost-effective for patients experiencing pain.[86] Recently, a Chronic Pancreatitis Pain Relief Score (CPPR Score) has been developed to predict the likelihood of postoperative pain relief. This score incorporates various clinical and pathological manifestations such as pancreatic head enlargement, pancreatic duct dilatation, pancreatic calcification, pancreatic fibrosis, and alcohol-induced diseases. The CPPR Score has demonstrated a strong correlation with positive prognosis, which may facilitate future clinical decisions regarding the appropriate therapeutic schedule for patients.[87] These emphasize that physicians should carefully consider the potential benefits of early surgery when treating obstructive and symptomatic CP. The development of individualized treatment strategies should be based on specific clinical manifestations, pain patterns, and long-term management objectives of the patient. Utilization of tools predicting postoperative

Table 1

Randomized controlled trials comparing clinical outcomes of endoscopy and surgery for obstructive and painful chronic pancreatitis

Study	No. of patients	Follow-up period	Primary outcome	Degree of pain during follow-up	Pain relief	No. of procedures
Díte et al 2003[82]	72 (endoscopy, N = 36; surgery, N = 36)	5 y	Pain relief	NA	15% vs 34% (P = .002)	NA
Cahen et al 2007[83]	39 (endoscopy, N = 19; surgery, N = 20)	2 y	Degree of pain	51 ± 23 vs 25 ± 15 for the mean Izbicki pain score (P < .001)	32% vs 75% (P = .007)	8 vs 3 (P < .001)
Cahen et al 2011[84]	31 (endoscopy, N = 16; surgery, N = 15)	79 mo	Degree of pain	39 ± 28 vs 22 ± 31 for the mean Izbicki pain score (P = .12)	38% vs 80% (P = .042)	12 vs 4 (P = .001)
Issa et al 2020[85]	88 (endoscopy, N = 44; surgery, N = 44)	18 mo	Degree of pain	49 vs 37 for the mean AUC of the Izbicki pain score during follow-up (P = .02)	39% vs 58% (P = .10)	3 vs 1 (P < .001)

AUC = area under the curve.

effectiveness is also encouraged. Active consideration should be given to surgical interventions that will effectively alleviate symptoms and reduce long-term healthcare costs.

Novel treatment strategies

Recent advances in the treatment of CP have aroused an exploration of novel therapeutic approaches. A pivotal pathogenic mechanism of CP involves the persistently elevated levels of intracellular Ca^{2+}. As an essential calcium influx channel on the plasma membrane, Orai1 has emerged as a potential target for intervention. A reduction in intracellular Ca^{2+} overload could be achieved through the selective inhibition of Orai1, which demonstrated a promising efficacy in halting the progression of early-stage CP toward the terminal stage. Thereby Orai1 inhibitors may potentially serve as effective therapeutic agents for CP.[88] Total pancreatectomy with islet autotransplantation (TPIAT) is a viable option for refractory CP that involves the removal of inflammatory pancreatic tissue while preserving some endocrine function. However, TPIAT might be associated with a high morbidity rate and considerable loss of pancreatic islets during the process of isolation and reinfusion.[89] Recently, a novel approach utilizing acetic acid injection into the pancreatic duct, known as chemical pancreatectomy, has been developed. This promising technique has been observed to effectively ablate the exocrine pancreas while retaining the endocrine component. In experimental models of CP, chemical pancreatectomy has shown promising results, including reduced inflammation and pain, improved glucose tolerance, and enhanced insulin secretion. Consequently, in the future, minimally invasive techniques like ERCP may enable pancreatic chemical resection in humans, overcoming the limitations associated with conventional tools, such as significant trauma and islet dysfunction.[90] As indicated earlier, genetic factors are significant etiologies for CP, with the dysfunctional variants of *SPINK1* predominantly found in Asian populations. Notably, our team has established a recombinant adeno-associated virus vector facilitating *SPINK1* expression, which displayed dependable safety and effectively prevented the acute occurrence and progression of CP in vivo, providing a promising outlook for gene therapy for CP.[91]

Conclusion and prospects

This review offers a comprehensive overview of the latest advancements in the etiology, pathogenesis, pain assessment, diagnosis, and management of CP. Through animal experiments and population-based studies, several high-quality investigations have been conducted to assess the contribution of genetic and environmental factors to CP. These studies have provided valuable research models, furthered our understanding of underlying mechanisms, identified novel susceptible genes, and examined the synergistic effects of genetic and environmental factors. Additionally, there has been a focus on elucidating the molecular and cellular interactions involved in the dysfunction of pancreatic acinar cells, abnormal inflammatory reactions, and fibrosis, thereby expanding our knowledge of CP pathogenesis and potential therapeutic targets. Furthermore, this review examines the accurate evaluation, influencing factors, and related psychiatric disorders of CP-induced pain, all of which provide a foundation for more effective pain management strategies. The advancement of imaging technology and the identification of blood-based diagnostic metabolites have also contributed to improving the accuracy and convenience of early diagnosis, although innovative methods and applications are still needed in this area. Moreover, new studies and international guidelines have guided endoscopic and surgical treatments for CP, proposing novel therapeutic approaches based on existing tools. However, there is a pressing need for early preventative and curative therapies. Most studies in this field are limited to animal experimentation, and there exists a disconnect between basic and clinical research. It is crucial to develop feasible treatments based on the identified molecular targets, rigorously evaluate their efficacy and safety, expedite the transition to clinical trials, and upgrade the current treatment paradigm from symptomatic relief to complete restoration.

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Author contributions

S-HM and W-BZ contributed to collating the literature and writing the manuscript. X-TM helped in the selection and evaluation of the literature. Z-SL contributed to revising the manuscript. ZL contributed significantly to the conception of the review topic, verification of the information, and the critical editing and revision of the manuscript. All authors read and approved the final manuscript.

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Conflicts of interest

ZL is an Editorial Board member of Journal of Pancreatology. He was blinded from reviewing or making decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other authors declare that they have no conflicts of interest.

Ethics approval

Our review did not involve any clinical or animal experiments and was analyzed only using published open-source studies,

therefore did not involve the approval of the Institutional Review Board.

References

[1] Beyer G, Habtezion A, Werner J, et al. Chronic pancreatitis. Lancet (London, England). 2020;396:499–512.
[2] Singh VK, Yadav D, Garg PK. Diagnosis and management of chronic pancreatitis: a review. JAMA. 2019;322:2422–2434.
[3] Kichler A, Jang S. Chronic pancreatitis: epidemiology, diagnosis, and management updates. Drugs. 2020;80:1155–1168.
[4] Cohen SM, Kent TS. Etiology, diagnosis, and modern management of chronic pancreatitis: a systematic review. JAMA Surg. 2023;158:652–661.
[5] Yadav D, Lowenfels AB. The epidemiology of pancreatitis and pancreatic cancer. Gastroenterology. 2013;144:1252–1261.
[6] Hansen SEJ, Nordestgaard BG, Langsted A. Smoking as the most important risk factor for chronic pancreatitis in the general population. Eur J Epidemiol. 2023;38:95–107.
[7] Ru N, Xu XN, Cao Y, et al. The impacts of genetic and environmental factors on the progression of chronic pancreatitis. Clin Gastroenterol Hepatol. 2022;20:e1378–e1387.
[8] Tjora E, Dimcevski G, Haas SL, et al. Patient reported exposure to smoking and alcohol abuse are associated with pain and other complications in patients with chronic pancreatitis. Pancreatology. 2020;20:844–851.
[9] Olesen SS, Nøjgaard C, Poulsen JL, et al. Chronic pancreatitis is characterized by distinct complication clusters that associate with etiological risk factors. Am J Gastroenterol. 2019;114:656–664.
[10] Pandol SJ, Gorelick FS, Gerloff A, et al. Alcohol abuse, endoplasmic reticulum stress and pancreatitis. Dig Dis. 2010;28:776–782.
[11] Vonlaufen A, Wilson JS, Pirola RC, et al. Role of alcohol metabolism in chronic pancreatitis. Alcohol Res Health. 2007;30:48–54.
[12] Wang YC, Mao XT, Yu D, et al. Alcohol amplifies the association between common variants at PRSS1-PRSS2 locus and chronic pancreatitis in a dose-dependent manner. Gut. 2022;71:2369–2371.
[13] Alexandre M, Uduman AK, Minervini S, et al. Tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone initiates and enhances pancreatitis responses. Am J Physiol Gastrointest Liver Physiol. 2012;303:G696–G704.
[14] Bhatia R, Thompson CM, Clement EJ, et al. Malondialdehyde-acetaldehyde extracellular matrix protein adducts attenuate unfolded protein response during alcohol and smoking-induced pancreatitis. Gastroenterology. 2022;163:1064–1078.e10.
[15] Mayerle J, Sendler M, Hegyi E, et al. Genetics, cell biology, and pathophysiology of pancreatitis. Gastroenterology. 2019;156:1951–1968.e1.
[16] Saluja A, Dudeja V, Dawra R, et al. Early intra-acinar events in pathogenesis of pancreatitis. Gastroenterology. 2019;156:1979–1993.
[17] Gui F, Zhang Y, Wan J, et al. Trypsin activity governs increased susceptibility to pancreatitis in mice expressing human PRSS1R122H. J Clin Invest. 2020;130:189–202.
[18] Huang H, Swidnicka-Siergiejko AK, Daniluk J, et al. Transgenic expression of PRSS1(R122H) sensitizes mice to pancreatitis. Gastroenterology. 2020;158:1072–1082.e7.
[19] Jancsó Z, Sahin-Tóth M. Mutation that promotes activation of trypsinogen increases severity of secretagogue-induced pancreatitis in mice. Gastroenterology. 2020;158:1083–1094.
[20] Hegyi E, Sahin-Tóth M. Genetic risk in chronic pancreatitis: the trypsin-dependent pathway. Dig Dis Sci. 2017;62:1692–1701.
[21] Sun C, Liu M, An W, et al. Heterozygous Spink1 c194+2T>C mutant mice spontaneously develop chronic pancreatitis. Gut. 2020;69:967–968.
[22] Fjeld K, Weiss FU, Lasher D, et al. A recombined allele of the lipase gene CEL and its pseudogene CELP confers susceptibility to chronic pancreatitis. Nat Genet. 2015;47:518–522.
[23] Mao XT, Zou WB, Cao Y, et al. The CEL-HYB1 hybrid allele promotes digestive enzyme misfolding and pancreatitis in mice. Cell Mol Gastroenterol Hepatol. 2022;14:55–74.
[24] Behar DM, Basel-Vanagaite L, Glaser F, et al. Identification of a novel mutation in the PNLIP gene in two brothers with congenital pancreatic lipase deficiency. J Lipid Res. 2014;55:307–312.
[25] Zhu G, Wilhelm SJ, George LG, et al. Preclinical mouse model of a misfolded PNLIP variant develops chronic pancreatitis. Gut. 2023;72:1340–1354
[26] Lasher D, Szabó A, Masamune A, et al. Protease-sensitive pancreatic lipase variants are associated with early onset chronic pancreatitis. Am J Gastroenterol. 2019;114:974–983.
[27] Masamune A, Kotani H, Sörgel FL, et al. Variants that affect function of calcium channel TRPV6 are associated with early-onset chronic pancreatitis. Gastroenterology. 2020;158:1626–1641.e8.
[28] Zou WB, Wang YC, Ren XL, et al. TRPV6 variants confer susceptibility to chronic pancreatitis in the Chinese population. Hum Mutat. 2020;41:1351–1357.
[29] Moore PC, Cortez JT, Chamberlain CE, et al. Elastase 3B mutation links to familial pancreatitis with diabetes and pancreatic adenocarcinoma. J Clin Invest. 2019;129:4676–4681.
[30] Tóth A, Demcsák A, Zankl F, et al. Loss-of-function variant in chymotrypsin like elastase 3B (CELA3B) is associated with non-alcoholic chronic pancreatitis. Pancreatology. 2022;22:713–718.
[31] Hegyi E, Tóth AZ, Vincze A, et al. Alcohol-dependent effect of PRSS1-PRSS2 haplotype in chronic pancreatitis. Gut. 2020;69:1713–1715.
[32] Gukovsky I, Pandol SJ, Gukovskaya AS. Organellar dysfunction in the pathogenesis of pancreatitis. Antioxid Redox Signal. 2011;15:2699–2710.
[33] Choi J, Oh TG, Jung HW, et al. Estrogen-related receptor γ maintains pancreatic acinar cell function and identity by regulating cellular metabolism. Gastroenterology. 2022;163:239–256.
[34] Chanda D, Thoudam T, Sinam IS, et al. Upregulation of the ERRγ-VDAC1 axis underlies the molecular pathogenesis of pancreatitis. Proc Natl Acad Sci U S A. 2023;120:e2219644120.
[35] Gukovskaya AS, Gukovsky I, Algül H, et al. Autophagy, inflammation, and immune dysfunction in the pathogenesis of pancreatitis. Gastroenterology. 2017;153:1212–1226.
[36] Wang S, Chao X, Jiang X, et al. Loss of acinar cell VMP1 triggers spontaneous pancreatitis in mice. Autophagy. 2022;18:1572–1582.
[37] Zheng Y, Sun W, Wang Z, et al. Activation of pancreatic acinar FXR protects against pancreatitis via Osgin1-Mediated restoration of efficient autophagy. Research (Wash D C). 2022;2022:9784081.
[38] Hernandez G, Luo T, Javed TA, et al. Pancreatitis is an FGF21-deficient state that is corrected by replacement therapy. Sci Transl Med. 2020;12:eaay5186.
[39] Saad MI, Weng T, Lundy J, et al. Blockade of the protease ADAM17 ameliorates experimental pancreatitis. Proc Natl Acad Sci U S A. 2022;119:e2213744119.
[40] Zhao Q, Manohar M, Wei Y, et al. STING signalling protects against chronic pancreatitis by modulating Th17 response. Gut. 2019;68:1827–1837.
[41] Lee B, Adamska JZ, Namkoong H, et al. Distinct immune characteristics distinguish hereditary and idiopathic chronic pancreatitis. J Clin Invest. 2020;130:2705–2711.
[42] Lee B, Namkoong H, Yang Y, et al. Single-cell sequencing unveils distinct immune microenvironments with CCR6-CCL20 crosstalk in human chronic pancreatitis. Gut. 2022;71:1831–1842.
[43] Lee B, Jones EK, Manohar M, et al. Distinct serum immune profiles define the spectrum of acute and chronic pancreatitis from the multicenter prospective evaluation of chronic pancreatitis for epidemiologic and translational studies (PROCEED) study. Gastroenterology. 2023;165:173–186.
[44] Apte M, Pirola R, Wilson J. The fibrosis of chronic pancreatitis: new insights into the role of pancreatic stellate cells. Antioxid Redox Signal. 2011;15:2711–2722.
[45] Yang X, Chen J, Wang J, et al. Very-low-density lipoprotein receptor-enhanced lipid metabolism in pancreatic stellate cells promotes pancreatic fibrosis. Immunity. 2022;55:1185–1199.e8.
[46] Glaubitz J, Wilden A, Golchert J, et al. In mouse chronic pancreatitis CD25(+)FOXP3(+) regulatory T cells control pancreatic fibrosis by suppression of the type 2 immune response. Nat Commun. 2022;13:4502.
[47] Zhang T, Zhang G, Yang W, et al. Lnc-PFAR facilitates autophagy and exacerbates pancreatic fibrosis by reducing pre-miR-141 maturation in chronic pancreatitis. Cell Death Dis. 2021;12:996.
[48] Jiang W, Jin L, Ju D, et al. The pancreatic clock is a key determinant of pancreatic fibrosis progression and exocrine dysfunction. Sci Transl Med. 2022;14:eabn3586.
[49] Mullady DK, Yadav D, Amann ST, et al. Type of pain, pain-associated complications, quality of life, disability and resource utilisation in chronic pancreatitis: a prospective cohort study. Gut. 2011;60:77–84.
[50] Kempeneers MA, Issa Y, Verdonk RC, et al. Pain patterns in chronic pancreatitis: a nationwide longitudinal cohort study. Gut. 2021;70:1724–1733.
[51] Yadav D, Askew RL, Palermo T, et al. Association of chronic pancreatitis pain features with physical, mental, and social health. Clin Gastroenterol Hepatol. 2022;21:1781–1791.e4.
[52] Phillips AE, Faghih M, Drewes AM, et al. Psychiatric comorbidity in patients with chronic pancreatitis associates with pain and reduced quality of life. Am J Gastroenterol. 2020;115:2077–2085.

[53] Dunbar EK, Greer PJ, Amann ST, et al. Pain experience in pancreatitis: strong association of genetic risk loci for anxiety and PTSD in patients with severe, constant, and constant-severe pain. Am J Gastroenterol. 2021;116:2128–2136.
[54] Olesen SS, Krauss T, Demir IE, et al. Towards a neurobiological understanding of pain in chronic pancreatitis: mechanisms and implications for treatment. Pain Rep. 2017;2:e625.
[55] Phillips AE, Faghih M, Kuhlmann L, et al. A clinically feasible method for the assessment and characterization of pain in patients with chronic pancreatitis. Pancreatology. 2020;20:25–34.
[56] Faghih M, Phillips AE, Kuhlmann L, et al. Pancreatic QST differentiates chronic pancreatitis patients into distinct pain phenotypes independent of psychiatric comorbidities. Clin Gastroenterol Hepatol. 2022;20:153–161.e2.
[57] Kuhlmann L, Teo K, Olesen SS, et al. Development of the comprehensive pain assessment tool short form for chronic pancreatitis: validity and reliability testing. Clin Gastroenterol Hepatol. 2022;20:e770–e783.
[58] Teo K, Johnson MH, Drewes AM, et al. A comprehensive pain assessment tool (COMPAT) for chronic pancreatitis: development, face validation and pilot evaluation. Pancreatology. 2017;17:706–719.
[59] Olesen SS, Phillips AE, Faghih M, et al. Overlap and cumulative effects of pancreatic duct obstruction, abnormal pain processing and psychological distress on patient-reported outcomes in chronic pancreatitis. Gut. 2022;71:2518–2525.
[60] Frøkjær JB, Akisik F, Farooq A, et al. Guidelines for the diagnostic cross sectional imaging and severity scoring of chronic pancreatitis. Pancreatology. 2018;18:764–773.
[61] Gardner TB, Levy MJ. EUS diagnosis of chronic pancreatitis. Gastrointest Endosc. 2010;71:1280–1289.
[62] Gardner TB, Adler DG, Forsmark CE, et al. ACG clinical guideline: chronic pancreatitis. Am J Gastroenterol. 2020;115:322–339.
[63] DeWitt JM, Al-Haddad MA, Easler JJ, et al. EUS pancreatic function testing and dynamic pancreatic duct evaluation for the diagnosis of exocrine pancreatic insufficiency and chronic pancreatitis. Gastrointest Endosc. 2021;93:444–453.
[64] Albashir S, Bronner MP, Parsi MA, et al. Endoscopic ultrasound, secretin endoscopic pancreatic function test, and histology: correlation in chronic pancreatitis. Am J Gastroenterol. 2010;105:2498–2503.
[65] Iglesias-Garcia J, Larino-Noia J, Nieto Bsn L, et al. Pancreatic elastography predicts endoscopic secretin-pancreatic function test result in patients with early changes of chronic pancreatitis: a prospective, cross-sectional, observational study. Am J Gastroenterol. 2022;117:1264–1268.
[66] Löhr JM, Dominguez-Munoz E, Rosendahl J, et al. United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis (HaPanEU). United European Gastroenterol J. 2017;5:153–199.
[67] Bian Y, Zhou J, Zhu M, et al. Replacing secretin-enhanced MRCP with MRI radiomics model based on a fully automated pancreas segmentation for assessing pancreatic exocrine function in chronic pancreatitis. Eur Radiol. 2023;33:3580–3591.
[68] Adam MG, Beyer G, Christiansen N, et al. Identification and validation of a multivariable prediction model based on blood plasma and serum metabolomics for the distinction of chronic pancreatitis subjects from non-pancreas disease control subjects. Gut. 2021;70:2150–2158.
[69] Strand DS, Law RJ, Yang D, et al. AGA clinical practice update on the endoscopic approach to recurrent acute and chronic pancreatitis: expert review. Gastroenterology. 2022;163:1107–1114.
[70] Dumonceau JM, Delhaye M, Tringali A, et al. Endoscopic treatment of chronic pancreatitis: European Society of Gastrointestinal Endoscopy (ESGE) Guideline - Updated August 2018. Endoscopy. 2019;51:179–193.
[71] Seven G, Schreiner MA, Ross AS, et al. Long-term outcomes associated with pancreatic extracorporeal shock wave lithotripsy for chronic calcific pancreatitis. Gastrointest Endosc. 2012;75:997–1004.e1.
[72] Qian Y-Y, Ru N, Chen H, et al. Rectal indometacin to prevent pancreatitis after extracorporeal shock wave lithotripsy (RIPEP): a single-centre, double-blind, randomised, placebo-controlled trial. Lancet Gastroenterol Hepatol. 2022;7:238–244.
[73] Gerges C, Albers D, Schmitz L, et al. Digital single-operator pancreatoscopy for the treatment of symptomatic pancreatic duct stones: a prospective multicenter cohort trial. Endoscopy. 2023;55:150–157.
[74] Sofi AA, Khan MA, Ahmad S, et al. Comparison of clinical outcomes of multiple plastic stents and covered metal stent in refractory pancreatic ductal strictures in chronic pancreatitis—a systematic review and meta-analysis. Pancreatology. 2021;21:854–861.
[75] Moon SH, Kim MH, Park DH, et al. Modified fully covered self-expandable metal stents with antimigration features for benign pancreatic-duct strictures in advanced chronic pancreatitis, with a focus on the safety profile and reducing migration. Gastrointest Endosc. 2010;72:86–91.
[76] Tringali A, Vadalà di Prampero SF, Landi R, et al. Fully covered self-expandable metal stents to dilate persistent pancreatic strictures in chronic pancreatitis: long-term follow-up from a prospective study. Gastrointest Endosc. 2018;88:939–946.
[77] Lee YN, Moon JH, Park JK, et al. Preliminary study of a modified, non-flared, short, fully covered metal stent for refractory benign pancreatic duct strictures (with videos). Gastrointest Endosc. 2020;91:826–833.
[78] Sherman S, Kozarek RA, Costamagna G, et al. Soft self-expanding metal stent to treat painful pancreatic duct strictures secondary to chronic pancreatitis: a prospective multicenter trial. Gastrointest Endosc. 2022;97:472–481.e3.
[79] Ramchandani M, Lakhtakia S, Costamagna G, et al. Fully covered self-expanding metal stent vs multiple plastic stents to treat benign biliary strictures secondary to chronic pancreatitis: a multicenter randomized trial. Gastroenterology. 2021;161:185–195.
[80] Lakhtakia S, Reddy N, Dolak W, et al. Long-term outcomes after temporary placement of a self-expanding fully covered metal stent for benign biliary strictures secondary to chronic pancreatitis. Gastrointest Endosc. 2020;91:361–369.e3.
[81] Thiruvengadam NR, Saumoy M, Schneider Y, et al. Fully covered self-expanding stents are cost-effective at remediating biliary strictures in patients with chronic pancreatitis. Clin Gastroenterol Hepatol. 2022;21:552–554.e4.
[82] Díte P, Ruzicka M, Zboril V, et al. A prospective, randomized trial comparing endoscopic and surgical therapy for chronic pancreatitis. Endoscopy. 2003;35:553–558.
[83] Cahen DL, Gouma DJ, Nio Y, et al. Endoscopic versus surgical drainage of the pancreatic duct in chronic pancreatitis. N Engl J Med. 2007;356:676–684.
[84] Cahen DL, Gouma DJ, Laramée P, et al. Long-term outcomes of endoscopic vs surgical drainage of the pancreatic duct in patients with chronic pancreatitis. Gastroenterology. 2011;141:1690–1695.
[85] Issa Y, Kempeneers MA, Bruno MJ, et al. Effect of early surgery vs endoscopy-first approach on pain in patients with chronic pancreatitis: the ESCAPE randomized clinical trial. JAMA. 2020;323:237–247.
[86] Kempeneers MA, Issa Y, Bruno MJ, et al. Cost-effectiveness of early surgery versus endoscopy-first approach for painful chronic pancreatitis in the ESCAPE trial. Ann Surg. 2023;277:e878–e884.
[87] Bachmann K, Melling N, Groteluschen R, et al. Morphologic factors predict pain relief following pancreatic head resection in chronic pancreatitis description of the chronic pancreatitis pain relief (CPPR) score. Ann Surg. 2021;273:800–805.
[88] Szabó V, Csákány-Papp N, Görög M, et al. Orai1 calcium channel inhibition prevents progression of chronic pancreatitis. JCI Insight. 2023;8:e167645.
[89] Bellin MD, Kerdsirichairat T, Beilman GJ, et al. Total pancreatectomy with islet autotransplantation improves quality of life in patients with refractory recurrent acute pancreatitis. Clin Gastroenterol Hepatol. 2016;14:1317–1323.
[90] Saleh M, Sharma K, Kalsi R, et al. Chemical pancreatectomy treats chronic pancreatitis while preserving endocrine function in preclinical models. J Clin Invest. 2021;131:e143301.
[91] Wang YC, Zou WB, Liao Z. Recombinant AAV-8 Mediated Pancreas-Specific Expression of SPINK1 Gene in the Prevention and Treatment of Chronic Pancreatitis. In: Abstracts of Papers Submitted to the 53rd Meeting of the American Pancreatic Association. Orlando, Florida; 2022. Abstract 836–903. Pancreas. 895.

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