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FROM ALCOHOL TO LITHIASIS - VARIED RISK FACTORS OF CHRONIC PANCREATITIS

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ABSTRACT

Introduction: Chronic pancreatitis is a growing health concern with an incidence of about 10 cases per 100,000 people per year. Alcohol-related CP is more common in men, typically appearing in their 40s or 50s, while idiopathic CP affects both sexes equally. CP is a persistent inflammatory condition of the pancreas, leading to irreversible structural damage, pain, and gradual loss of both exo- and endocrine function. Symptoms include epigastric pain, bloating, digestive issues, glucose intolerance or diabetes, and physical signs like epigastric tenderness, and abdominal mass and jaundice.
Materials and methods: A review of 47 sources from publicly available databases such as PubMed and Google Scholar was conducted. Cited publications were published mainly in English. The main topic of these publications was focused on risk factors of CP.
State of knowledge: In the following article we discuss the risk factors of CP which are described in acronym TIGAR-O. The main etiology factor of CP is alcohol consumption which is responsible for over a half the cases. Negative effect of ethanol is particularly significant in smokers. Tobacco is an inependent risk factor of CP but combined with alcohol use, risk of chronic pancreatitis is increasing. In the development of pancreatitis gene mutations play a significant role. Autoimmune pancreatitis has two subtypes and its patomechanism is complex. Acute pancreatitis and its recurrences may lead to repetitive inflammation of pancreas and its chronicisation. Obstructive chronic pancreatitis develops due to a mechanical blockage that hinders the flow of pancreatic juice.
Conclusions: Expanding access to genetic and immunological testing will help identify groups especially vulnerable to CP, potentially leading to fewer complications, lower treatment costs, and improved treatment outcomes. Understanding how modifiable risk factors affect CP can enhance both primary and secondary prevention efforts.

KEYWORDS

Chronic Pancreatitis, Alcoholic Pancreatitis, Autoimmune Pancreatitis, CFTR

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Introduction

Chronic pancreatitis remains a significant health problem. The prevalence of CP in Poland is increasing, with an annual incidence of approximately 10 per 100 000 population. Alcoholic CP affects men more frequently, usually in the 4th or 5th decade of life. The incidence of idiopathic CP is similar in both sexes. The disease can appear early, at 10-20 years of age, or late, around 50-60 years of age. Chronic pancreatitis is a long-lasting, chronic inflammatory process taking place in the pancreatic parenchyma, leading to irreversible morphological changes within this organ. The process is accompanied by abdominal pain and progressive failure of the extra- and endocrine pancreatic function. In the early stages of the disease, pancreatic changes are only visible on histological examination. In advanced cases, pancreatic fibrosis with calcification, parenchymal atrophy and dilatation of the pancreatic ducts occurs. Clinical presentation includes symptoms such as epigastric pain which may radiate to the back (painless presentation in autoimmune CP), flatulence and dispeptic symptoms, steatorrhea, abnormal glucose tolerance or diabetes mellitus and physical symptoms like epigastric tenderness during palpation, an abdominal mass (e.g., a pseudocyst) and jaundice. In the following atricle we would like to discuss risk factors of chronic pancreatitis which are contained in TIGAR-O acronym.

Materials and methods

This narrative review was conducted by systematically examining published literature on the topic of chronic pancreatitis and its risk factors. The search for source materials was conducted in medical databases such as PubMed, Scopus and Google Scholar, including publications in English and individual works in Polish. The criteria for selecting articles were their relevance (publications from the last 10 years, older articles in justified cases), scientific reliability and relevance to the topic of the article. The analysis included both clinical trials and systematic reviews, as well as guidelines from experts and scientific societies. 51 sources were analysed. The collected information was critically evaluated and synthesised in order to provide a comprehensive summary of CP risk factors.

Toxic-metabolic causes

Alcohol

The first group of chronic pancreatitis risk factors according to TIGAR-O acronym is toxic-metabolic causes. Among this group, risk factor which is responsible for the majority (55 % - 80 %) of chronic pancreatitis (CP) cases worldwide is ethyl alcohol consumption (Etemad & Whitcomb, 2001). The risk of developing pancreatitis rises with higher ethanol consumption, indicating that alcohol has a dose-dependent toxic impact on the pancreas. However, only 10 % of heavy alcohol drinkers ever suffer from clinically recognized pancreatitis. Ethanol consumption is considerd to be rather one of the components in heterogenic ethiology than only factor toxic to pancreatic tissue. Laboratory research is also uncertain because prolonged administration of high doses of alcohol to animals does not lead to the development of chronic pancreatitis, which mean that association between alcohol consumption and pancreas malfunction is not so direct (Perkins et al., 1995). Patomechanism of toxic impact of alcohol on pancreatic cells is complex and its fine details have not been established yet. Toxic impact of ethyl alcohol on pancreatic tissue is pleiotropic. Alcohol triggers an inflammatory cascade which causes releasing pro-inflammatory cytokines as IL-1, IL-2, IL-6, IL-8, IL-10, IL-18, C-reactive protein, tumor necrosis factor α (TNF-α) and its receptors, and nuclear factor κB (NK-κB) Ethanol can cause human pancreatic stellate cells to produce IL-8, a signaling molecule involved in inflammation (Huang et al., 2013; Lv et al., 2022). Both ethanol and its byproduct, acetaldehyde, also stimulate pancreatic acinar cells (PACs) to produce collagen I, which plays a key role in the inflammation seen in alcohol-related pancreatic damage. Similar to alcoholic liver disease, the fibrosis seen in chronic pancreatitis is mainly due to the activation of stellate cells. Exposure to ethanol results in swelling of pancreatic tissue and the appearance of spindle-shaped cells, which are indicators of pancreatic fibrosis.

Another mechanism of ethyl alcohol toxicity is connected with Ca^{2+} ions which are responsible for maintaining the balance of intracellular enzymes secretion. Alcoholic pancreatitis, mediated by ethanol and ethyl fatty acids (FAs), triggers a sustained elevation of Ca^{2+} levels within pancreatic acinar cells. This calcium overload activates digestive enzymes inside the cells, ultimately causing inflammation and pancreatic tissue necrosis (Gerasimenko et al., 2013). The alcohol combined with lipopolysaccharide (LPS) leads to a reduction of lysosomal-associated membrane protein 2 (LAMP-2) and other lysosomal proteins. This results in impaired fusion of autophagosomes with lysosomes, accumulation of autophagosomes, and inhibition of the cell-protective autophagy mechanism. The disruption of this process causes mitochondrial energy depletion. In cases of severe ATP shortage, acinar cells become susceptible to necrosis, which intensifies local inflammation and exacerbates tissue damage(Fortunato et al., 2009).

Ethanol exposure can cause the damage to endoplasmic reticulum, which is a significant mechanism of disrupion of PACs due to the richest ER network amongst all human body cells. The ethyl alcohol toxic infulence on ER leads to proteins to be synthesized in an unfolded or misfolded state. A study conducted in mice showed the expression level of GRP78, a key marker of ER stress, was observed to be approximately seven times higher than in the control group. Furthermore, it was showed that ethanol exposure led to a marked upregulation of several proteins involved in the unfolded protein response (UPR), including ATF6, CHOP, PERK, and eIF2α, in mouse pancreatic tissue. This was accompanied by an increase in inducible nitric oxide synthase (iNOS), suggesting that ethanol can trigger both oxidative and ER stress(Ren et al., n.d.).

Alcohol exposure impairs mitochondrial function, and the high energy demands for protein synthesis in the pancreas contribute to the development of alcoholic pancreatitis. Ethanol disrupts oxidative metabolism, as showed by a reduced NAD^+/NADH ratio, which triggers the opening of the mitochondrial permeability transition pore (MPTP). This leads to mitochondrial depolarization, a persistent loss of membrane potential in acinar cells, ATP depletion, and ultimately, necrosis of pancreatic cells. In addition, nonoxidative ethanol metabolites such as fatty acid ethyl esters (FAEEs) and fatty acids (FAs) interfere with calcium homeostasis, causing Ca^{2+} overload. This overload further activates the MPTP, impairing mitochondrial function, decreasing ATP production, and promoting cell death.(Shalbueva et al., 2013)

Tobacco smoking

According to several epidemiological studies tobacco smoking is considered to be an independent risk factor of developing chronic pancreatitis (Hansen et al., 2023; Lin et al., 2000a; Talamini et al., 1999). Based on a study conducted in Japan in 1997-1998, the odds ratios (ORs) and their 95 % confidence intervals (CIs) were estimated by multiple conditional logistic models with adjustments made for body mass index, education level, and alcohol intake. When compared to nonsmokers, the OR for all current

smokers was 7.8 (95 % CI: 2.2-27.3). The risk was notably higher among individuals who had been smoking for 25 years or more. A significant increase in the risk of chronic pancreatitis was observed with higher cumulative tobacco exposure ($p < 0.05$). When examining the combined effects of smoking and alcohol use, smoking was linked to an elevated risk of chronic pancreatitis across any level of alcohol consumption (Lin et al., 2000b). Smoking was prove to be the most important risk factor of CP. Among the population of patients with CP the most numerous group was ever tobacco smokers, wich represents 31% for women an 38% for men (Hansen et al., 2023).

Hypercalcemia

Hypercalcemia is a factor causing pancreatitis, especially when serum calcium level is > 12 mg/dL in patients suffering from hyperparathyroidism, familial hypocalciuric hypercalcemia and hyprecalcemia associated with genetic syndromes as MEN1, MEN2A. Acute pancreatitis has been linked to hypercalcemia, potentially due to its role in activating trypsinogen and stabilizing trypsin (Mithofer et al., 1995). This connection was first recognized in 1957, when Cope and al. (JACKSON, 1958) proposed that pancreatitis could serve as an indicator of hyperparathyroidism. Not long after, a link between familial hyperparathyroidism and chronic pancreatitis was identified, as 3 out of 9 affected family members were found to have the CP. Pancreatitis subsequent to primary hyperparathyroidism (PHPT) may be classified into 4 types: (a) PHPT revealed by AP, (b) PHPT revealed by recurrent AP without CP, (c) PHPT revealed by CP, and (d) PHPT complicated by AP in the postoperative period (Jacob et al., 2006). In earlier studies it was described that most common group is the one with AP which represents about 75 % of the cases, an almost 30 % of patients with CP (Bai et al., 2012) and in 2019 studies (Thareja et al., 2019) it accounts for 2 patients (40 %) in each of the first two groups and one (20 %) in the third group.

Hypertriglyceridemia

The patomechanism of pancreatitis associated with hypretriglyceridemia (HTG) is based on increased blood viscosity due to high level of triglycerides and chylomicrons (Weiss et al., 2019). When tissue experiences ischemia, its metabolism shifts from aerobic to anaerobic, relying mainly on anaerobic glycolysis, which produces L-lactate as the end product. This localized blockage of blood flow leads to elevated lactate levels and acidosis. The acidic environment exaggerates the harmful effects of free fatty acids and sets the stage for the premature activation of trypsinogen (Weidenbach et al., 1995). When combined with other risk factors such as alcohol, smoking, or certain medications, ischemia can act as a local trigger for pancreatitis. While the association of hypretriglyceridemia with acute and recurrent episodes of pancreatitis is well known, whether HTG can cause CP has not been well studied (Scherer et al., 2014). The risk of chronicity of pancreatitis is higher in patients with familial form of HTG. Chronic pancreatitis has been observed in individuals with type I and type V hyperlipidemia (Hoste et al., 1978; Krauss & Levy, 1977). In people predisposed to the condition, HTG combined with alcohol use may contribute to repeated episodes and the progression to CP over time.

Medications

Over 100 substances are prone to induce CP. There are such medications as azathioprine, thiazide diuretics, estrogens, furosemide, sulfonamides, tetracycline, cortycosteroides, statins, fenofibrate, angiotensin converting enzyme inhibitors, valproic acid, metronidazole, calcium channel blockers, methyldopa, glucagon-like peptide-1, dipeptidyl peptidase-4 (DPP-4) inhibitors, 6-mercaptopurine, 5-aminosalicylic acid compounds, isoniazid, ocreotide (Kaufman, 2013; Mallory & Kern, 1980). They are relatively rare cause of CP but increasing consumption of some of these drug may pose a significant clinical issue. Drug induced pancreatitis is often misclassified as being related to alcohol use or biliary diseases.

Genetic causes

Various genetic mutations may play a significant role in the development of pancreatitis. These involve the PRSS1 gene, which encodes cationic trypsinogen; the SPINK1 gene, which encodes the pancreatic secretory trypsin inhibitor; the CFTR gene, which encodes a protein that forms a chloride channel; the CTRC gene, encoding chymotrypsin C and the CASR gene, which encodes the calcium-sensing receptor. Below is a presentation of the involvement of the best-known genetic mutations in the development of chronic pancreatitis.

PRSS1 gene

The PRSS1 gene is located on chromosome 7q34 and encodes cationic trypsinogen, which is activated to trypsin in the pancreas. Under physiological conditions, trypsinogen is secreted by the acinar cells of the pancreas and is only activated in the lumen of the duodenum (Whitcomb et al., 1996). The human pancreas produces three isoforms of trypsinogen, encoded by separate genes: PRSS1, PRSS2, and PRSS3, commonly referred to as cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), and mesotrypsinogen (PRSS3), respectively. PRSS1 (~60 % - 70 %) and PRSS2 (~30 % - 40 %) constitute the majority of trypsinogens in pancreatic juice, while PRSS3 is secreted in relatively small amounts. The causative role of trypsinogen in pancreatitis is supported by the identification of mutations in the PRSS1 gene in patients with hereditary pancreatitis. No genetic variants of PRSS2 or PRSS3 have been associated with chronic pancreatitis (Nemoda & Sahin-Tóth, n.d.).The most common PRSS1 mutations are p.R122H (65 %), p.N29I (25 %), p.A16V and p.R122C. The mechanism of action of mutations associated with hereditary pancreatitis involves increased autoactivation of the mutated forms of trypsinogen, leading to elevated trypsin activity within the pancreas. PRSS1 mutations alter the regulation of activation and degradation of cationic trypsinogen by chymotrypsin C (CTRC), making trypsinogen resistant to CTRC-dependent degradation. As a result, the level of trypsin generated through autoactivation is increased (Schnúr et al., 2014). PRSS1 mutations are inherited in an autosomal dominant manner and are characterized by high penetrance, it is estimated that up to 80% of carriers may develop chronic pancreatitis over the course of their lifetime. The first symptoms usually appear in childhood or early adulthood (Rosendahl et al., 2008).

SPINK1 gene

The pancreatic secretory trypsin inhibitor (PSTI), which is the SPINK1 protein, plays a role in preventing the premature activation of zymogens by inhibiting up to 20 % of pancreatic trypsin activity, thereby protecting the pancreas from autodigestion. The most common mutations are N34S and P55S. Numerous studies have shown an association between the N34S mutation and chronic pancreatitis of various etiologies, with a prevalence of approximately 9.7 %. However, the exact mechanism linking the SPINK1 p.N34S mutation to pancreatitis remains unclear (Głuszek & Kozieł, 2018).

CFTR gene

The CFTR gene is located on chromosome 7q31 and encodes a transmembrane protein that plays a key role in regulating chloride ion transport across cell membranes. In the pancreas, the CFTR protein is responsible for the secretion of chloride into the lumen of the pancreatic ducts, which in turn helps maintain the proper consistency of pancreatic juice and ensures its adequate flow (Icholas et al., 1998).

As a result of mutations in the CFTR gene, chloride transport is impaired, leading to a decrease in water secretion into the lumen of the pancreatic ducts. This alters the properties of pancreatic juice, causing it to become more viscous, which in turn can lead to ductal obstruction, the formation of pancreatic stones, and damage to pancreatic cells. Additionally, it may promote the early activation of pancreatic enzymes, leading to autodigestion of pancreatic tissue, contributing to the development of chronic pancreatitis (Pelletier et al., 2010).

The CTRC protein encodes the enzyme chymotrypsin C, produced by the acinar cells of the pancreas, which aids in the degradation of trypsin. Prematurely activated trypsin can be destroyed by CTRC through its action in a calcium-dependent complex. CTRC mutations may predispose individuals to chronic pancreatitis by impairing the effective degradation of trypsin (Głuszek & Kozieł, 2018).

Autoimmune causes

Autoimmune pancreatitis (AIP) is a rare form of chronic, mild pancreatic disease.(Shimosegawa et al., 2011) There are two main types of autoimmune pancreatitis. Type 1 (AIP-1) – associated with IgG4-RD, known as lymphoplasmacytic sclerosing pancreatitis, which is the pancreatic manifestation of the disease. AIP-1 occurs in the sixth and seventh decades of life and is characterized by an elevated IgG4 serum level. IgG4-RD typically affects two or more organs, such as the salivary glands, kidneys, and biliary tract. Based on the affected organs, four phenotypes of IgG4-RD are distinguished: pancreatobiliary disease, retroperitoneal fibrosis, disease limited to the head and neck, and Mikulicz syndrome with systemic involvement.

Type 2 (AIP-2) not associated with IgG4, known as idiopathic ductal pancreatitis. It predominantly occurs in younger individuals and is more commonly associated with inflammatory bowel diseases, particularly ulcerative colitis. It is characterized by extensive inflammatory infiltration in the pancreas, consisting mainly of neutrophils, lymphocytes, and plasma cells, primarily occurring in the area of the pancreatic ducts.(Gallo et al., 2024; Löhr et al., 2022; Sah et al., 2010)

Complications of Recurrent or Severe Acute Pancreatitis

Acute pancreatitis (AP) is an acute inflammatory condition characterized by premature activation of pancreatic proenzymes and varying degrees of damage to adjacent tissues, and occasionally to distant organs (*Podręcznik Interna - Ostre Zapalenie Trzustki*, n.d.). If a patient has experienced more than one episode of acute pancreatitis, the condition is classified as recurrent acute pancreatitis (RAP). Repeated inflammatory episodes may result in irreversible changes to the structure and function of the pancreas, eventually leading to chronic pancreatitis (CP). Although not all cases of RAP progress to CP, approximately 20 % - 25 % of patients with RAP develop chronic pancreatitis (Edmiston et al., 2024). The transition from RAP to CP is complex and multifactorial.

One of the underlying mechanisms contributing to the development of chronic pancreatitis is the repetition of acute pancreatic inflammation. This results in a localized inflammatory process marked by pancreatic enzyme activation, edema, inflammatory cell infiltration, and glandular necrosis. While most patients exhibit parenchymal regeneration following the acute phase, a subset experiences persistent parenchymal injury, leading to atrophy and fibrosis of pancreatic tissue and ultimately to exocrine and endocrine insufficiency. A central component of this process is the chronic activation of pancreatic stellate cells (PSCs) (Roberts-Thomson, 2021). These cells become activated early in the course of chronic pancreatitis, regardless of whether the etiology is alcohol-related or autoimmune in nature. Upon activation, PSCs undergo phenotypic transformation from lipid-storing cells to myofibroblast-like cells. Activated PSCs produce chemokines and extracellular matrix proteins including collagen types I and III, laminin, fibronectin, and hyaluronic acid. It has been confirmed that PSC activation initiates and sustains a cascade of inflammatory responses. This includes overproduction of monocyte chemoattractant protein-1 (MCP-1), interleukin-8 (IL-8), RANTES, transforming growth factor beta 1 (TGF-β1), and activin A (*Rola Włóknienia w Przewlekłym Zapaleniu Trzustki i Raku Trzustki 2a/2018* n.d.).

The role of acinar cells in pancreatic fibrosis should also be acknowledged. In a rat model of acute pancreatitis, alcohol exposure was shown to induce TGF-β production by acinar cells, thus activating PSCs and initiating collagen deposition (Gu et al., 2013).

Another mechanism contributing to the progression from RAP to CP involves sustained immune system activation. Repeated AP episodes result in chronic macrophage activation, particularly into the M2 phenotype through alternative activation pathways. These M2 macrophages secrete cytokines that further activate PSCs, promoting collagen synthesis and fibrosis development (Glaubitz et al., 2023).

Under physiological conditions, regenerative processes follow an episode of acute pancreatitis. However, in some cases, the repair mechanisms fail, leading to chronic inflammation. An altered inflammatory response perpetuates PSC activation and fibrosis, impairing the regeneration of acinar cells and disrupting pancreatic architecture, potentially resulting in ductal strictures and calcifications (Whitcomb, 2013).

Oxidative stress is another significant mechanism involved in the pathogenesis of CP, often as a consequence of repeated AP episodes. It results from excessive production of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) and insufficient activity of antioxidant systems. In pancreatic cells, cytochrome P450 enzymes (CYP450) metabolize xenobiotics, generating free radicals. When detoxification capacity is inadequate, toxic metabolites and free radicals accumulate, leading to oxidative stress and cellular injury (Bhardwaj & and Yadav, 2013). ROS act as critical signaling molecules, modulating inflammatory cascades and recruiting inflammatory cells such as neutrophils, thereby contributing to pancreatic injury (Xia et al., 2024). Oxidative stress triggers ROS generation, which activates PSCs and induces their transformation into myofibroblast-like cells. These activated cells synthesize collagen types I and III, along with other extracellular matrix components, resulting in fibrosis. Studies have demonstrated that excessive ROS production associated with RAP-induced oxidative stress activates signaling pathways such as NF-κB and MAPK, which regulate the expression of pro-fibrotic genes, including MMP-9 and Twist (Masamune et al., 2008).

Obstructive

Obstructive chronic pancreatitis is the result of mechanical impairment in the outflow of pancreatic juice. This condition arises from increased pressure within the pancreatic ducts, damage to the glandular parenchyma, and progressive fibrosis. It should be noted that obstruction of the pancreatic duct caused by post-inflammatory strictures, benign tumors, or malignant neoplasms leads to chronic obstructive pancreatitis upstream from the site of obstruction (Forsmark & Pham, 2018). In the TIGAR-O classification, obstructive factors include structural and functional abnormalities that may contribute to the development of CP. One of the obstructive causes and simultaneously a complication of CP is pancreatic lithiasis. Pancreatic stones form

within the ductal system, usually due to chronic or recurrent inflammation of the pancreas. They are observed in approximately 90% of patients and develop progressively as the disease advances. Stones found in non-alcoholic, idiopathic CP are typically larger and denser than those found in individuals with alcohol-related CP. Obstruction of the pancreatic duct by a stone may lead to ductal blockage, resulting in upstream ductal hypertension, increased parenchymal pressure, and ischemia. These phenomena are associated with pain experienced by the patient. Removal of pancreatic stones may alleviate or reduce these symptoms. Endoscopic procedures, being less invasive than surgical interventions, are more effective in cases involving small stones located in the main pancreatic duct (Tringali et al., 2022).

Another obstructive cause of chronic pancreatitis is the presence of pancreatic duct strictures, which may arise following severe episodes of acute pancreatitis. Of particular significance are neoplasms such as pancreatic ductal adenocarcinoma, intraductal papillary mucinous neoplasms (IPMN), adenomas, or ampullary carcinomas, all of which can cause mechanical obstruction of the Wirsung duct or the common bile duct, resulting in secondary CP. When chronic pancreatitis is suspected to result from an occult malignancy, urgent diagnostic investigation is warranted, particularly in high-risk individuals.

Anatomical anomalies should also be considered among the causes of obstructive CP. In cases of pancreas divisum, the dominant dorsal part of the pancreas drains via the minor papilla, which may predispose to impaired pancreatic juice outflow. Although this congenital anomaly occurs relatively frequently in the general population (estimated in 5 % - 10 % of individuals), chronic pancreatitis in the course of pancreas divisum remains rare. Even rarer are cases where inflammatory changes are restricted solely to the dorsal part of the pancreas.

An increased incidence of pancreas divisum has been observed in patients with pancreatitis associated with CFTR gene mutations, suggesting a possible co-segregation of these two risk factors. Current evidence indicates that pancreas divisum alone is rarely a direct cause of either acute or chronic pancreatitis but may act synergistically with other predisposing conditions, particularly those of genetic origin (Forsmark & Pham, 2018).

Conclusions

In this article we presented the whole spectrum of risk factors of chronic pancreatitis. The etiology of CP is complex and not well-known. Risk factor of CP are varied and may be considered in many clinical situation. Learning about risk factors may lead to faster diagnosis and implementation of treatment in patients with chronic pancreatitis. Whereas etiology of CP United European Gastroenterology had presented the evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis**.** In pediatric patients with recurrent acute pancreatitis or chronic pancreatitis, cystic fibrosis should be considered and excluded by assessing sweat chloride levels. Genetic factors play a more significant role in the development of CP in children compared to adults. Laboratory tests should include measurements of serum calcium and triglyceride levels. Recommended imaging modalities include abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP). Cystic fibrosis should be excluded in all individuals with disease onset before the age of 20, as well as in those diagnosed with idiopathic CP, regardless of the age at onset. Genetic testing for pancreatitis-associated variants is advised for patients with a family history of CP or early onset of the disease (before age 20). If no clear cause of CP is identified, autoimmune pancreatitis should be considered and ruled out. It is also important to remember that a patient with chronic pancreatitis requires special attention and diagnosis, as the symptoms of CP are similar to those of pancreatic cancer which may occur in 4 % of CP patients and even in 44 % in patients with its hereditary form.

Increasingly widespread genetic and immunological testing will allow the identification of populations at particular risk of CP. This may allow the following group to be monitored more closely during the asymptomatic stage and applying treatment at early stage. Taking into account that no targeted treatment methods have been developed so far, genetic tests may lead to better recognition of CP etiology and patophysiology therefore it may be a next step to develope causal treatment of CP.

Diagnosis and treatment of CP is significant because, if untreated, it can cause complications such as pseudocysts, abscesses, stricture of the pancreatic or bile ducts, ascites or duodenal stenosis. These complications, along with increasing pain, are the most common cause of hospitalisations in patients with CP. Better recognition of trigger factors and causal tretment in the future may contribute in reducing complications, lowering treatment costs and increasing its effectiveness. The increasing number of people with the CFTR gene mutation and prevalence of taking drugs that may cause CP in global population will make this illness an increasingly common health problem. On the other hand, knowledge of the impact of modifiable risk factors for CP such as alcohol and cigarette smoking will allow more effective primary and secondary prevention of chronic pancreatitis.

Disclosure
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REFERENCES

1. Bai, H. X., Giefer, M., Patel, M., Orabi, A. I., & Husain, S. Z. (2012). The association of primary hyperparathyroidism with pancreatitis. In Journal of Clinical Gastroenterology (Vol. 46, Issue 8, pp. 656–661). https://doi.org/10.1097/MCG.0b013e31825c446c
2. Bhardwaj, P., & and Yadav, R. K. (2013). Chronic pancreatitis: role of oxidative stress and antioxidants. Free Radical Research, 47(11), 941–949. https://doi.org/10.3109/10715762.2013.804624
3. Edmiston, T., Kittane, V., & and Chanmugam, A. (2024). Recurrent acute pancreatitis: a harbinger for irreversible chronic pancreatitis. Hospital Practice, 52(1–2), 5–12. https://doi.org/10.1080/21548331.2024.2348990
4. Etemad, B., & Whitcomb, D. C. (2001). Chronic pancreatitis: Diagnosis, classification, and new genetic developments. Gastroenterology, 120(3), 682–707. https://doi.org/10.1053/gast.2001.22586
5. Forsmark, C., & Pham, A. (2018). Chronic pancreatitis: Review and update of etiology, risk factors, and management. In F1000Research (Vol. 7). F1000 Research Ltd. https://doi.org/10.12688/f1000research.12852.1
6. Fortunato, F., Bürgers, H., Bergmann, F., Rieger, P., Büchler, M. W., Kroemer, G., & Werner, J. (2009). Impaired Autolysosome Formation Correlates With Lamp-2 Depletion: Role of Apoptosis, Autophagy, and Necrosis in Pancreatitis. Gastroenterology, 137(1). https://doi.org/10.1053/j.gastro.2009.04.003
7. Gallo, C., Dispinzieri, G., Zucchini, N., Invernizzi, P., & Massironi, S. (2024). Autoimmune pancreatitis: Cornerstones and future perspectives. In World Journal of Gastroenterology (Vol. 30, Issue 8, pp. 817–832). Baishideng Publishing Group Inc. https://doi.org/10.3748/wjg.v30.i8.817
8. Gerasimenko, J. V., Gryshchenko, O., Ferdek, P. E., Stapleton, E., Hébert, T. O. G., Bychkova, S., Peng, S., Begg, M., Gerasimenko, O. V., & Petersen, O. H. (2013). Ca2+ release-activated Ca2+ channel blockade as a potential tool in antipancreatitis therapy. Proceedings of the National Academy of Sciences of the United States of America, 110(32), 13186–13191. https://doi.org/10.1073/pnas.1300910110
9. Glaubitz, J., Asgarbeik, S., Lange, R., Mazloum, H., Elsheikh, H., Weiss, F. U., & Sendler, M. (2023). Immune response mechanisms in acute and chronic pancreatitis: strategies for therapeutic intervention. In Frontiers in Immunology (Vol. 14). Frontiers Media SA. https://doi.org/10.3389/fimmu.2023.1279539
10. Głuszek, S., & Kozieł, D. (2018). Genetic determination of pancreatitis. Medical Studies, 34(1), 70–77. https://doi.org/10.5114/ms.2018.74823

11. Gu, H., Fortunato, F., Bergmann, F., Büchler, M. W., Whitcomb, D. C., & Werner, J. (2013). Alcohol Exacerbates LPS-Induced Fibrosis in Subclinical Acute Pancreatitis. The American Journal of Pathology, 183(5), 1508–1517. https://doi.org/10.1016/j.ajpath.2013.07.023
12. Hansen, S. E. J., Nordestgaard, B. G., & Langsted, A. (2023). Smoking as the most important risk factor for chronic pancreatitis in the general population. European Journal of Epidemiology, 38(1), 95–107. https://doi.org/10.1007/s10654-022-00945-7
13. Hoste, P., F., L., & and Rottiers, R. (1978). Chronic Relapsing Pancreatitis in Twin-Brothers with Type V Hyperlipoproteinemia. Acta Clinica Belgica, 33(5), 313–322. https://doi.org/10.1080/22953337.1978.11718649
14. Huang, H., Liu, Y., Daniluk, J., Gaiser, S., Chu, J., Wang, H., Li, Z. S., Logsdon, C. D., & Ji, B. (2013). Activation of Nuclear Factor-κB in Acinar Cells Increases the Severity of Pancreatitis in Mice. Gastroenterology, 144(1), 202–210. https://doi.org/10.1053/J.GASTRO.2012.09.059
15. Icholas, N., Harer, S., Artin, M., Chwarz, S., Eraldine, G., Alone, M., Ndrea, A., Owarth, H., Ohn, J., Ainter, P., Aurice, M., Uper, S., Oan, J., & Raganza, B. (1998). The New England Journal of Medicine MUTATIONS OF THE CYSTIC FIBROSIS GENE IN PATIENTS WITH CHRONIC PANCREATITIS A BSTRACT Background The pancreatic lesions of cystic fi (Vol. 339).
16. JACKSON, C. E. (1958). HEREDITARY HYPERPARATHYROIDISM ASSOCIATED WITH RECURRENT PANCREATITIS. Annals of Internal Medicine, 49(4), 829–836. https://doi.org/10.7326/0003-4819-49-4-829
17. Jacob, J. J., John, M., Thomas, N., Chacko, A., Cherian, R., Selvan, B., Nair, A., & Seshadri, M. S. (2006). DOES HYPERPARATHYROIDISM CAUSE PANCREATITIS? A SOUTH INDIAN EXPERIENCE AND A REVIEW OF PUBLISHED WORK. ANZ Journal of Surgery, 76(8), 740–744. https://doi.org/https://doi.org/10.1111/j.1445-2197.2006.03845.x
18. Kaufman, M. B. (2013). Drug-induced pancreatitis a potentially serious and underreported problem Pharmacovigilance Forum (Vol. 38, Issue 6). www.accessdata.fda.gov/
19. Krauss, R. M., & Levy, A. G. (1977). Subclinical chronic pancreatitis in type I hyperlipoproteinemia. The American Journal of Medicine, 62(1), 144–149. https://doi.org/10.1016/0002-9343(77)90361-8
20. Lin, Y., Tamakoshi, A., Hayakawa, T., Ogawa, M., Ohno, Y., & Diseases, R. C. on I. P. (2000a). Cigarette Smoking as a Risk Factor for Chronic Pancreatitis: A Case-Control Study in Japan. Pancreas, 21(2). https://journals.lww.com/pancreasjournal/fulltext/2000/08000/cigarette_smoking_as_a_risk_factor_for_chronic.1.aspx
21. Lin, Y., Tamakoshi, A., Hayakawa, T., Ogawa, M., Ohno, Y., & Diseases, R. C. on I. P. (2000b). Cigarette Smoking as a Risk Factor for Chronic Pancreatitis: A Case-Control Study in Japan. Pancreas, 21(2). https://journals.lww.com/pancreasjournal/fulltext/2000/08000/cigarette_smoking_as_a_risk_factor_for_chronic.1.aspx
22. Löhr, J.-M., Vujasinovic, M., Rosendahl, J., Stone, J. H., & Beuers, U. (2022). IgG4-related diseases of the digestive tract. Nature Reviews Gastroenterology & Hepatology, 19(3), 185–197. https://doi.org/10.1038/s41575-021-00529-y
23. Lv, J., Ji, L., Wang, G., Sun, B., & Tong, J. (2022). Alcohol Aggravates Acute Pancreatitis by Impairing Autophagic Flux Through Activation of AMPK Signaling Pathway. Digestive Diseases and Sciences, 67(2), 524–535. https://doi.org/10.1007/s10620-021-06870-1
24. Mallory, A., & Kern, F. (1980). Drug-induced pancreatitis: A critical review. In Gastroenterology (Vol. 78, Issue 4, pp. 813–820). https://doi.org/10.1016/0016-5085(80)90689-7
25. Masamune, A., Watanabe, T., Kikuta, K., Satoh, K., & Shimosegawa, T. (2008). NADPH oxidase plays a crucial role in the activation of pancreatic stellate cells. Am J Physiol Gastrointest Liver Phy-Siol, 294, 99–108. https://doi.org/10.1152/ajpgi.00272.2007.-Activated
26. Mithofer, K., Castillo, C. F.-D., Frick, T. W., Lewandrowski, K. B., Rattner, D. W., & Warshaw, A. L. (1995). Acute Hypercalcemia Causes Acute Pancreatitis and Ectopic Trypsinogen Activation in the Rat. In GASTROENTEROLOGY (Vol. 109).
27. Nemoda, Z., & Sahin-Tóth, M. (n.d.). CHYMOTRYPSIN C (CALDECRIN) STIMULATES AUTOACTIVATION OF HUMAN CATONIC TRYPSINOGEN. www.uni-leipzig.de/pancreasmutation
28. Pelletier, A.-L., Bienvenu, T., Rebours, V., O'Toole, D., Hentic, O., Maire, F., Hammel, P., Ruszniewski, P., & Lévy, P. (2010). CFTR Gene Mutation in Patients with Apparently Idiopathic Pancreatitis: Lack of Phenotype-Genotype Correlation. Pancreatology, 10(2), 158–164. https://doi.org/https://doi.org/10.1159/000231976
29. Perkins, P. S., Rutherford, R. E., & Pandol, S. J. (1995). Effect of chronic ethanol feeding on digestive enzyme synthesis and mRNA content in rat pancreas. Pancreas, 10(1), 14–21. https://doi.org/10.1097/00006676-199501000-00002
30. Podręcznik Interna - Medycyna Praktyczna: Ostre zapalenie trzustki. (n.d.). Retrieved April 25, 2025, from https://www.mp.pl/interna/chapter/B16.II.5.1
31. Ren, Z., Wang, X., Xu, M., Yang, F., Frank, J. A., Ke, Z.-J., & Luo, J. (n.d.). Binge ethanol exposure causes endoplasmic reticulum stress, oxidative stress and tissue injury in the pancreas (Vol. 7, Issue 34). www.impactjournals.com/oncotarget
32. Roberts-Thomson, I. C. (2021). Progression from acute to chronic pancreatitis. In JGH Open (Vol. 5, Issue 12, pp. 1321–1322). John Wiley and Sons Inc. https://doi.org/10.1002/jgh3.12698

33. Rola włóknienia w przewlekłym zapaleniu trzustki i raku trzustki** • Postępy Nauk Medycznych 2a/2018 • Czytelnia Medyczna BORGIS. (n.d.). Retrieved April 25, 2025, from https://www.czytelniamedyczna.pl/6506,rola-wlknienia-w-przewlekym-zapaleniu-trzustki-i-raku-trzustki.html#kod
34. Rosendahl, J., Witt, H., Szmola, R., Bhatia, E., Ózsvári, B., Landt, O., Schulz, H. U., Gress, T. M., Pfützer, R., Löhr, M., Kovacs, P., Blüher, M., Stumvoll, M., Choudhuri, G., Hegyi, P., Te Morsche, R. H. M., Drenth, J. P. H., Truninger, K., Macek, M., … Sahin-Tóth, M. (2008). Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nature Genetics, 40(1), 78–82. https://doi.org/10.1038/ng.2007.44
35. Sah, R. P., Chari, S. T., Pannala, R., Sugumar, A., Clain, J. E., Levy, M. J., Pearson, R. K., Smyrk, T. C., Petersen, B. T., Topazian, M. D., Takahashi, N., Farnell, M. B., & Vege, S. S. (2010). Differences in Clinical Profile and Relapse Rate of Type 1 Versus Type 2 Autoimmune Pancreatitis. Gastroenterology, 139(1), 140–148. https://doi.org/10.1053/j.gastro.2010.03.054
36. Scherer, J., Singh, V. P., Pitchumoni, C. S., & Yadav, D. (2014). Issues in hypertriglyceridemic pancreatitis: An update. In Journal of Clinical Gastroenterology (Vol. 48, Issue 3, pp. 195–203). https://doi.org/10.1097/01.mcg.0000436438.60145.5a
37. Schnúr, A., Beer, S., Witt, H., Hegyi, P., & Sahin-Tóth, M. (2014). Functional effects of 13 Rare PRSS1 variants presumed to cause chronic pancreatitis. Gut, 63(2), 337–343. https://doi.org/10.1136/gutjnl-2012-304331
38. Shalbueva, N., Mareninova, O. A., Gerloff, A., Yuan, J., Waldron, R. T., Pandol, S. J., & Gukovskaya, A. S. (2013). Effects of oxidative alcohol metabolism on the mitochondrial permeability transition pore and necrosis in a mouse model of alcoholic pancreatitis. Gastroenterology, 144(2). https://doi.org/10.1053/j.gastro.2012.10.037
39. Shimosegawa, T., Chari, S. T., Frulloni, L., Kamisawa, T., Kawa, S., Mino-Kenudson, M., Kim, M.-H., Klöppel, G., Lerch, M. M., Löhr, M., Notohara, K., Okazaki, K., Schneider, A., & Zhang, L. (2011). International Consensus Diagnostic Criteria for Autoimmune Pancreatitis Guidelines of the International Association of Pancreatology. www.pancreasjournal.com
40. Talamini, G., Bassi, C., Falconi, M., Sartori, N., Salvia, R., Rigo, L., Castagnini, A., Francesco, V. Di, Frulloni, L., Bovo, P., Vaona, B., Angelini, G., Vantini, I., Cavallini, G., & Pederzoli, P. (1999). Alcohol and Smoking as Risk Factors in Chronic Pancreatitis and Pancreatic Cancer. Digestive Diseases and Sciences, 44(7), 1303–1311. https://doi.org/10.1023/A:1026670911955
41. Thareja, S., Manrai, M., Shukla, R., Kumar Sood, A., Jha, A., Tyagi, A. K., Upreti, V., Gahlot, G. P. S., & Maggo, S. (2019). Pancreatitis and hyperparathyroidism: Still a rare association! Medical Journal Armed Forces India, 75(4), 444–449. https://doi.org/10.1016/j.mjafi.2018.11.004
42. Tringali, A., Costa, D., Rota, M., Adler, D. G., & Costamagna, G. (2022). Covered self-expandable metal stents for pancreatic duct stricture: a systematic review and meta-analysis. Endoscopy International Open, 10(09), E1311–E1321. https://doi.org/10.1055/a-1880-7430
43. Weidenbach, H., Lerch, M. M., Gress, T. M., Pfaff, D., Turi, S., & Adler, G. (1995). Vasoactive mediators and the progression from oedematous to necrotising experimental acute pancreatitis. In Gut (Vol. 37).
44. Weiss, F. U., Laemmerhirt, F., & Lerch, M. M. (2019). Etiology and risk factors of acute and chronic pancreatitis. In Visceral Medicine (Vol. 35, Issue 2, pp. 73–81). S. Karger AG. https://doi.org/10.1159/000499138
45. Whitcomb, D. C. (2013). Genetic Risk Factors for Pancreatic Disorders. Gastroenterology, 144(6), 1292–1302. https://doi.org/10.1053/j.gastro.2013.01.069
46. Whitcomb, D. C., Gorry, M. C., Preston, R. A., Furey, W., Sossenheimer, M. J., Ulrich, C. D., Martin, S. P., Gates, L. K., Amann, S. T., Toskes, P. P., Liddle, R., McGrath, K., Uomo, G., Post, J. C., & Ehrlich, G. D. (1996). Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nature Genetics, 14(2), 141–145. https://doi.org/10.1038/ng1096-141
47. Xia, C. C., Chen, H. T., Deng, H., Huang, Y. T., & Xu, G. Q. (2024). Reactive oxygen species and oxidative stress in acute pancreatitis: Pathogenesis and new therapeutic interventions. In World Journal of Gastroenterology (Vol. 30, Issue 45, pp. 4771–4780). Baishideng Publishing Group Inc. https://doi.org/10.3748/wjg.v30.i45.4771