Etiology and pathogenesis of chronic pancreatitis in adults

AUTHORS: Christopher E Forsmark, MD, Steven D Freedman, MD, PhD, Michele D Lewis, MD, MSSc
SECTION EDITOR: Douglas G Adler, MD, FACG, AGAF, FASGE
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

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Literature review current through: **Sep 2023.**
This topic last updated: **Mar 02, 2022.**

INTRODUCTION

Chronic pancreatitis is a syndrome involving inflammation, fibrosis, and loss of acinar and islet cells, which can manifest with pancreatic-type abdominal pain, steatorrhea, derangements in pancreatic function (exocrine and endocrine insufficiency), and visible pancreatic damage on imaging studies. Chronic pancreatitis has a variety of etiologies with genetic and environmental risk factors for both initiation and disease progression, variable clinical and imaging features and complications, chronic pancreatitis is an ongoing inflammatory and fibrotic condition of the pancreas [1]. Although acute pancreatitis and chronic pancreatitis were previously believed to be distinct entities, evidence suggests that acute pancreatitis, relapsing acute pancreatitis, and chronic pancreatitis appear to be on a continuum of related conditions, with overlapping and sometimes indistinguishable features. In many patients, the disease may pass from acute to acute relapsing to chronic, with no clear-cut transition points.

This topic will review the etiology and pathogenesis of chronic pancreatitis. The clinical manifestations, diagnosis, and management of chronic pancreatitis are discussed in detail separately. (See "Chronic pancreatitis: Clinical manifestations and diagnosis in adults" and "Chronic pancreatitis: Management" and "Overview of the complications of chronic pancreatitis".)

EPIDEMIOLOGY

Reliable population-based estimates of the epidemiology of chronic pancreatitis are not widely available as the diagnostic criteria for chronic pancreatitis vary widely. However, limited evidence suggests that the incidence of chronic pancreatitis ranges from 5 to 12/100,000 with a prevalence of approximately 50/100,000 persons.

There are regional differences in the prevalence of chronic pancreatitis by etiology. Alcohol-related pancreatitis is more common in the West and Japan, as compared with other Asian countries. There is wide variation in the prevalence of a form of chronic pancreatitis that is endemic to tropical countries (20 to 125/100,000 persons reported in two parts of South India) [2].

Alcohol is associated with approximately one-half of all cases of chronic pancreatitis in the United States [3]. Idiopathic chronic pancreatitis accounts for approximately 10 to 30 percent of all cases. The number of patients labeled as idiopathic depends in large part on how detailed and comprehensive the search is for an etiology. In females, idiopathic causes predominate (32 percent), followed by alcohol (30 percent), genetic (13 percent) and obstructive (12 percent). In males, alcohol- and tobacco-associated chronic pancreatitis are more common (58 percent) [3-5]. Racial differences in chronic pancreatitis patients in the United States were studied in a prospective, multicenter cohort from 2000 to 2014 and found 248 of 1159 patients (21 percent) were Black [6]. When compared with White patients, Black patients were significantly more likely to be former or current smokers and to have alcohol use as the etiology (77 versus 42 percent). Black patients were also more likely to have advanced pancreatic morphology such as calcifications, atrophy, pancreatic and common bile duct strictures, and decreased pancreatic exocrine and endocrine function.

ETIOLOGY AND RISK FACTORS

Most patients with chronic pancreatitis have more than one underlying etiology. The causes of chronic pancreatitis are commonly classified using a system termed "TIGAR-O" [7]. This refers to toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, and obstructive.

Toxic-metabolic factors

Alcohol — While there is no clear threshold, for most patients, an ingestion equivalent to

five drinks daily for at least five years is usually required [3,8,9]. Curiously, some studies suggest moderate drinking may actually be protective [9]. Occasional binge drinking alone does not appear to be sufficient to lead to chronic pancreatitis. Patients may initially present with an episode of acute pancreatitis, but even at initial presentation, some may have imaging evidence of chronic pancreatitis (eg, pancreatic calcification). Many patients have an early phase of relapsing acute pancreatitis, followed by the development of chronic symptoms (pain), steatorrhea, or diabetes. Less than 5 percent of heavy drinkers develop chronic pancreatitis, suggesting that there are other important cofactors in the development of chronic pancreatitis [3]. Potential cofactors include diet, underlying genetic background, ancestry (eg, African) or ethnicity, type of alcohol or manner of ingestion, and coexistent smoking. Of these, smoking appears to be the strongest cofactor [3,8-10]. Continued alcohol use (and continued smoking) after the initial clinical presentation increases the risk of recurrent pancreatitis and progression to exocrine and endocrine pancreatic insufficiency [11]. Smoking may be present in up to 90 percent of patients who develop chronic pancreatitis related to alcohol [3].

Smoking — Smoking accounts for approximately 25 percent of the attributable risk of chronic pancreatitis and works synergistically in a dose-dependent fashion with alcohol to damage the pancreas [3]. Smoking is associated with an increased risk of pancreatic calcifications, increased risk of exocrine and endocrine insufficiency, and an increased risk of secondary pancreatic malignancies [3,10,12,13]. Abstinence from tobacco reduces the progression of chronic pancreatitis and the risk of secondary pancreatic malignancy. There is no safe level of tobacco use in those with chronic pancreatitis. It is not known if smokeless tobacco products or other forms of nicotine (eg, "vaping") are associated with an increased risk of chronic pancreatitis.

Hypertriglyceridemia — Hypertriglyceridemia is a well-characterized risk factor for acute and chronic pancreatitis. These patients often require a fasting or postprandial level of triglycerides >1000 mg/dL to initiate an episode of pancreatitis, but subsequent episodes may be precipitated by lower level elevations (>500 mg/dL) [14]. Of note, in population-based studies, even moderate elevations in fasting serum triglycerides are a risk factor for pancreatitis [15]. Patients with hypertriglyceridemic pancreatitis frequently progress to chronic pancreatitis [16]. (See "Hypertriglyceridemia-induced acute pancreatitis", section on 'Clinical features'.)

Other — Some features of chronic pancreatitis can be seen with diabetes mellitus and possibly chronic renal failure. Longstanding diabetes appears to produce a type of pancreatic injury termed diabetic pancreatopathy [4]. Whether diabetes or chronic renal failure causes

chronic pancreatitis (the syndrome) or merely causes some modest pancreatic injury and fibrosis is not known. Medications and hypercalcemia are potential causes of acute pancreatitis. Hypercalcemia is a rare cause of chronic pancreatitis.

Injury to the pancreas from a severe ischemic event (usually associated with surgery and cardiopulmonary bypass) and years after intra-abdominal radiation (usually for testicular cancer or Hodgkin lymphoma) are very rare causes of chronic pancreatitis. (See "Clinical manifestations and diagnosis of acute pancreatitis", section on 'Disease course'.)

Genetic — Many patients with chronic pancreatitis formerly thought to be idiopathic or alcohol associated are found to have underlying genetic mutations and polymorphisms. These genetic risk factors can be divided into autosomal dominant and autosomal recessive/modifier genes, but the genetic contributions are often complex and not easily classified [17].

Hereditary pancreatitis caused by mutations in the cationic trypsinogen gene (*PRSS1*) has an autosomal dominant pattern of inheritance [17]. The gain-of-function mutation in *PRSS1* results in abnormal trypsin which activates other digestive enzymes in the pancreas, causing ongoing damage. There is strong but incomplete penetrance. These families often have early-onset chronic pancreatitis, and affected individuals often develop exocrine insufficiency and diabetes. There is an increased risk for pancreatic malignancy, especially in those who also smoke. (See "Pancreatitis associated with genetic risk factors", section on 'Genetics'.)

Other mutations in the cystic fibrosis transmembrane conductance regulator, serine protease inhibitor kazal-1, chymotrypsin C, carboxypeptidase A-1, carboxy ethyl lipase, claudins, and others have been found in patients with chronic pancreatitis. These genes serve as modifier genes, increasing susceptibility to chronic pancreatitis and/or accelerating disease progression. They often occur in various combinations as part of a complex multigenic background.

Most genetic studies in chronic pancreatitis have occurred in White patients of European ancestry. Genotyping for pathogenic variants of *PRSS1, SPINK1, CFTR,* and *CTRC* was performed on 232 prospectively enrolled Black chronic pancreatitis patients of African descent and compared with 862 White patients of European descent. Prevalence of disease-associated variants in any of the four genes tested was significantly higher in patients of European ancestry compared with African ancestry (29 versus 8.18 percent, $p<0.05$) [18].

Autoimmune — Autoimmune pancreatitis (AIP) represents two inflammatory conditions of the pancreas, and in many cases, other organs, which respond to steroid therapy [19,20].

Patients with AIP can present with chronic pancreatitis. (See "Autoimmune pancreatitis: Clinical manifestations and diagnosis".)

Type 1 AIP is one clinical manifestation of immunoglobulin G4 (IgG4)-related disease [21]. Serum levels of IgG4 are often elevated in these patients, and tissue specimens from the pancreas reveal characteristic findings of lymphoplasmacytic sclerosing pancreatitis, including dense infiltration with plasma cells and cluster of differentiation 4-positive T-cells. The most common extrapancreatic conditions include biliary strictures, hilar lymphadenopathy, sclerosing sialadenitis, retroperitoneal fibrosis, and interstitial nephritis. Biopsies of the pancreas or these other organs will reveal a similar inflammatory infiltrate rich in IgG4-positive plasma cells. Involvement of other organs occurs in at least 60 percent of patients with Type 1 AIP and may occur before, after, or at the same time as the pancreatic disease.

Type 2 AIP or idiopathic duct centric pancreatitis is limited to the pancreas and is not associated with an infiltration of IgG4-positive plasma cells in the pancreas nor with elevations in serum levels of IgG4. Type 2 AIP may, however, be seen in association with underlying inflammatory bowel disease (15 to 30 percent of patients with Type 2 AIP).

Recurrent and severe acute pancreatitis — Recurrent acute pancreatitis is one of the strongest risk factors for progression to chronic pancreatitis [3,22,23]. After an attack of acute pancreatitis, approximately 10 percent will progress to chronic pancreatitis. Those with more severe acute pancreatitis (with pancreatic necrosis), those with repeated attacks, and those that consume alcohol or smoke are most prone to progression to chronic pancreatitis. Significantly more patients progress to at least some features of chronic pancreatitis, with approximately one in three patients developing diabetes, and one in four developing exocrine pancreatic insufficiency after an attack of acute pancreatitis [3,24,25]. (See "Clinical manifestations and diagnosis of acute pancreatitis", section on 'Natural history and complications'.)

Obstructive factors — Chronic obstruction of the main pancreatic duct by tumors, scars, ductal stones, duodenal wall cysts, can produce chronic pancreatitis in the parenchyma upstream of the obstruction. Obstruction of the pancreatic ducts may also be an important contributor to other forms of chronic pancreatitis (ie, obstruction of small or large ductal branches by protein precipitates in alcohol-associated chronic pancreatitis). In children, anomalous pancreaticobiliary ductal anatomy may be a cause of chronic pancreatitis. Neither pancreas divisum nor sphincter of Oddi dysfunction should be considered as a primary cause of chronic pancreatitis in adults. Of note, those with pancreas divisum who do develop

chronic pancreatitis commonly have underlying genetic mutations, which are the etiology of the chronic pancreatitis. (See "Pancreas divisum: Clinical manifestations and diagnosis", section on 'Clinical manifestations' and "Causes and contributing risk factors for chronic pancreatitis in children and adolescents".)

Idiopathic — If a thorough evaluation fails to identify risk factors for chronic pancreatitis, the disorder is termed "idiopathic." As genetic testing has become more common, fewer cases of chronic pancreatitis fall into this category. There appear to be distinct clinical phenotypic presentations of idiopathic chronic pancreatitis [26,27].

- **Early onset** – The early-onset form has a median age of onset of 20 years, with an equal sex distribution. Pain is the dominant feature (>90 percent), and evidence of advanced pancreatic damage (eg, pancreatic calcifications) or exocrine or endocrine insufficiency is uncommon and, if present, takes several decades to develop. Almost one-half of patients with early-onset chronic pancreatitis have genetic variants in SPINK1, CFTR, or CTRC compared with approximately one-quarter of patients with late-onset disease or alcohol-related disease [27]. The early-onset form can be difficult to diagnose, as imaging and laboratory features of chronic pancreatitis can be lacking for many years.

- **Late onset** – The late-onset form has a median age of 56 years, is comparatively painless (approximately 50 percent have pain), and is more commonly associated with pancreatic calcifications or endocrine or exocrine insufficiency.

- **Fibrocalcific or tropical pancreatitis** – Classically, it described chronic pancreatitis with an age of onset most commonly in childhood in which patients typically developed fibrocalculous pancreatic diabetes and malnutrition, often culminating in early death. Fibrocalcific or tropical pancreatitis, a disease largely confined to southern India, is becoming less common even there. The demographics of tropical pancreatitis appear to be changing, and some experts believe that this represents complex genetic etiologies as seen in Western countries and that the term should be dropped [2].

PATHOGENESIS

The pathophysiology of chronic pancreatitis is incompletely understood. However, there does appear to be a common pathway of an initial insult with injury, followed by an attempt at healing through fibrosis and regeneration. All the causes of chronic pancreatitis ultimately produce similar features, including loss and injury to acinar, islet, and ductal cells, with

fibrosis and loss of pancreatic function.

The mechanisms of chronic pancreatitis vary depending on underlying etiology, genetic background, and environmental exposures. The mechanisms by which the most common causes (ie, alcohol and tobacco) cause chronic pancreatitis are also complex and not fully understood. Alcohol may produce injury through toxic alcohol metabolites, upregulation of various genes associated with cell death, direct activation of pancreatic stellate cells (which produce fibrosis), and other mechanisms [28]. The interactions of alcohol and smoking may be primarily through increased endoplasmic reticulum stress [29].

Many patients have underlying genetic mutations and polymorphisms that increase the risk of disease progression. These polymorphisms may affect primarily the acinar cell (eg, serine protease inhibitor kazal-1 or cationic trypsinogen gene), the ductal cell (cystic fibrosis transmembrane conductance regulator), or both. The mechanism of pancreatic injury varies depending on the mutation but can be grouped into those causing injury through trypsin activation, those causing injury through protein misfolding and endoplasmic reticulum stress, oxidant stress, and pancreatic injury through altered calcium signaling. (See "Pancreatitis associated with genetic risk factors", section on 'Genetics'.)

In the early stages of chronic pancreatitis, while pain may be prominent, there may be little evidence of ongoing pancreatic injury (eg, visible on a computed tomography scan). Pain is often episodic in these early stages. With more progression, features of fibrosis; loss of acinar, islet, and ductal tissue; ductal strictures; calcifications; more chronic or continuous pain; and exocrine (steatorrhea) and endocrine (diabetes) pancreatic insufficiency, dysplasia, and malignancy can develop.

APPROACH TO DETERMINE THE UNDERLYING ETIOLOGY

Determining the etiology of chronic pancreatitis requires a combination of the history of underlying risk factors and laboratory testing. However, a significant proportion of cases remain idiopathic.

History — Key elements to the history include the following:

- Past medical history – Hypertriglyceridemia, pancreatic trauma, autoimmune conditions, and diabetes can predispose to chronic pancreatitis. Long-term pancreatic duct obstruction (eg, stricture), repeated attacks of acute pancreatitis, and even single episodes of severe necrotizing pancreatitis may result in chronic pancreatitis.

- Alcohol use – Alcohol exposure requires a careful history of type, amount of ingestion, and duration of ingestion, which may require historical input from family members. Many patients with chronic pancreatitis are falsely labeled as having "alcoholic" chronic pancreatitis. For chronic pancreatitis to develop, an average of five drinks daily for five years or more is generally required, and alcohol should not be invoked as the cause with far less amounts of intake.

- Smoking – The diagnosis of smoking-associated chronic pancreatitis is based on history. Any amount of smoking can be important, including extensive second-hand exposure.

- Family history – A family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause or known mutations associated with hereditary pancreatitis (ie, cationic trypsinogen gene *PRSS1* mutations).

Laboratory testing

Routine tests in all patients — Fasting serum triglycerides should be obtained when the patient is on a normal diet. The diagnosis is based on obtaining a fasting triglyceride level after recovery from any episode of pancreatitis. Level of triglycerides >1000 mg/dL are needed to be considered a cause of acute pancreatitis. However, in patients with a history of hypertriglyceridemic pancreatitis, modest elevations in triglycerides are associated with an increased risk of recurrent acute pancreatitis [30]. (See "Hypertriglyceridemia-induced acute pancreatitis", section on 'Laboratory findings' and "Hypertriglyceridemia-induced acute pancreatitis", section on 'Diagnosis'.)

Additional testing in selected patients

- **Genetic testing** – Genetic testing for pancreatitis susceptibility genes should be performed in patients with pancreatitis who fulfill one or more of the following criteria:

  - An unexplained documented episode of acute pancreatitis as a child
  - Recurrent acute attacks of pancreatitis for which there is no identifiable cause
  - Idiopathic chronic pancreatitis, particularly when the onset of acute pancreatitis occurs before age 25 or in patients with chronic pancreatitis at a young age (<40 years)
  - A family history of recurrent acute pancreatitis, idiopathic chronic pancreatitis, or childhood pancreatitis without a known cause
  - Relatives known to carry mutations associated with hereditary pancreatitis (ie, *PRSS1 m*utations)

Genetic testing should include serine protease 1 gene, serine protease inhibitor Kazal type 1 gene, *carboxypeptidase A1*, chymotrypsin C gene (especially exon 7), *Carboxyl Ester Lipase* gene (hybrid allele only) and may include screening for variants in cystic fibrosis transmembrane conductance regulator gene. (See "Pancreatitis associated with genetic risk factors".)

- **Serum immunoglobulin G4 (IgG4)** – In patients with suspected autoimmune pancreatitis based on clinical presentation and imaging features (eg, diffusely enlarged pancreas with featureless borders and delayed enhancement), elevated serum IgG4 (≥2 times the upper limit of normal) is suggestive of autoimmune pancreatitis. (See "Autoimmune pancreatitis: Clinical manifestations and diagnosis", section on 'Clinical manifestations' and "Autoimmune pancreatitis: Clinical manifestations and diagnosis", section on 'Diagnostic approach'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Chronic pancreatitis and pancreatic exocrine insufficiency".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- (See "Patient education: Chronic pancreatitis (Beyond the Basics)".)

SUMMARY AND RECOMMENDATIONS

- Chronic pancreatitis is a syndrome involving inflammation, fibrosis, and loss of acinar and islet cells which can manifest in unrelenting pancreatic-type abdominal pain, malnutrition, derangements in pancreatic function (exocrine and endocrine insufficiency), and visible pancreatic damage on imaging studies. (See 'Introduction' above.)

- There are regional differences in the prevalence of chronic pancreatitis by etiology. Alcohol-related pancreatitis is more common in the West and Japan, as compared with other Asian countries. There is wide variation in the prevalence of a form of chronic pancreatitis that is endemic to tropical countries. Alcohol is associated with approximately one-half of all cases of chronic pancreatitis in the United States. Idiopathic chronic pancreatitis accounts for approximately 10 to 30 percent of all cases. (See 'Epidemiology' above.)

- Most patients with chronic pancreatitis have more than one underlying etiology. The causes of chronic pancreatitis are commonly classified using a system termed "TIGAR-O". This refers to toxic-metabolic, idiopathic, genetic, autoimmune, recurrent and severe acute pancreatitis, and obstructive. (See 'Etiology and risk factors' above.)

- The pathophysiology of chronic pancreatitis is incompletely understood. However, there does appear to be a common pathway of an initial insult with injury, followed by an attempt at healing through fibrosis and regeneration. All the causes of chronic pancreatitis ultimately produce similar features, including loss and injury to acinar, islet, and ductal cells, with fibrosis and loss of pancreatic function. In the early stages of chronic pancreatitis, while pain may be prominent, there may be little evidence of ongoing pancreatic injury visible on abdominal imaging. Pain is often episodic in these early stages. With more progression, features of fibrosis; loss of acinar, islet, and ductal tissue; ductal strictures; calcifications; more chronic or continuous pain; and exocrine (steatorrhea) and endocrine (diabetes) pancreatic insufficiency, dysplasia, and malignancy can develop. (See 'Pathogenesis' above.)

- The etiology of chronic pancreatitis may be determined by a history of underlying risk factors and/or laboratory testing. However, a significant proportion of cases remain idiopathic. (See 'Approach to determine the underlying etiology' above.)

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Topic 5646 Version 17.0

Contributor Disclosures

Christopher E Forsmark, MD Grant/Research/Clinical Trial Support: Abbvie - Protocol M16-142 [exocrine pancreatic insufficiency in pancreatic cancer subjects]; NIDDK and NCI through RFA-DK-14-027 - Consortium for the study of chronic pancreatitis, diabetes, and pancreatic cancer clinical centers (UO1) - UF PI and co-Chair consortium [Pancreatitis, diabetes, and pancreatic cancer]; NIH through RFA-DK-19-023 – Consortium for the study of Type 1 Diabetes After Acute Pancreatitis – Clinical Centers (UO1) – UF PI [Type 1 Diabetes after acute Pancreatitis]. Consultant/Advisory Boards: Nestlé Healthcare Nutrition [Exocrine Pancreatic Insufficiency]. All of the relevant financial relationships listed have been mitigated. **Steven D Freedman, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Michele D Lewis, MD, MSSc** No relevant financial relationship(s) with ineligible companies to disclose. **Douglas G Adler, MD, FACG, AGAF, FASGE** Consultant/Advisory Boards: Abbvie [Endoscopy]; Boston Scientific [Endoscopy]; Endorotor [Endoscopy]; Merit [Endoscopy]; Olympus [Endoscopy]. Speaker's Bureau: Abbvie [Pancreatology, general GI]. All of the relevant financial relationships listed have been mitigated. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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