Etiology and Risk Factors of Acute and Chronic Pancreatitis

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Keywords

Pancreatitis · Etiologic factors · Alcohol abuse · Genetic risk

Abstract

Based on the recognition of common etiological and genetic risk factors, acute and chronic pancreatitis are increasingly regarded as a continuum of the same disease, with a significant overlap of clinical manifestations and phenotypes but distinct morphological and imaging appearances. Recent population-based and cohort studies have found that tobacco smoke conveys a greater risk than immoderate alcohol consumption for the development of chronic pancreatitis, and hypertriglyceridemia has been identified as a risk factor for acute pancreatitis – even when plasma levels are only mildly elevated. Hereditary pancreatitis, in its autosomal dominant form, is associated with mutations in the cationic trypsinogen gene (*PRSS1*), whereas a number of germline variations in other genes have been found to represent risk factors for chronic as well as acute pancreatitis. For now, most of these involve the pancreatic digestive protease/antiprotease system. Oftentimes, affected patients are burdened with multiple or accumulating risk factors, and genetic traits when combined with environmental toxins compound the chance of developing the disease. Determining the underlying etiology of pancreatitis is worth the effort since formerly intractable varieties such as autoimmune pancreatitis are now becoming increasingly treatable, and subtype-specific therapeutic modalities may become available.

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Introduction

Pancreatitis, an inflammatory condition of the pancreas, is generally not caused by infectious agents, but triggered by initiating factors like gallstones and immoderate alcohol consumption. Complex gene-environment interactions may trigger or affect the pathogenesis and course of the disease (see Table 1). The widely accepted paradigm that acute, recurrent, and chronic pancreatitis are different disease entities has been replaced by the concept of a disease continuum: 30% of patients with acute pancreatitis will develop a chronic disease form, often with an overlap as recurrent pancreatitis in the years between. This review focuses on the etiologic factors that associate with the different disease phenotypes and the triggering factors involved in the progression from acute to chronic disease.

Acute Pancreatitis: Definition and Etiology

With an incidence of 13–45/100,000 acute pancreatitis is one of the most common ICD diagnoses for contacting emergency services and for hospitalization in Europe and the USA [1]. Based on the revised Atlanta classification acute pancreatitis is defined by two of three criteria – typical belt-like abdominal pain, elevated serum lipase level three times above the normal threshold, or radiological imaging signs of pancreatitis. Every year 54,000 patients with acute pancreatitis are treated in German hospitals [2]. Based on the total number of pancreatitis patients no gender predominance is found, albeit male sex is more often associated with an alcoholic etiology, whereas wom-

Table 1. Overview of known risk factors of acute pancreatitis, their involved pathomechanism, and the associated risk for chronicity of the disease

Risk factors for acute pancreatitis	Assumed pathomechanism	Risk for disease chronicity
Alcohol abuse	dose-dependent cell injury	high*
Smoking	dose-dependent cell toxicity	high*
Gallstones	pancreatic duct obstruction	–
Hypertriglycerides	blood viscosity, local tissue ischemia	high (in familial hypertriglyceridemia)
Endoscopic procedures (ERCP)	cell injury, increased duct pressure	–
Abdominal trauma	pancreatic tissue damage	high (for disrupted duct syndrome)
Drugs	cell toxic or metabolic effects	–
Autoimmune diseases	immune cell infiltration	high
Dominant <i>PRSS1</i> mutations	elevated trypsin activity	very high
Predisposing genetic mutations	protease activation, ER stress	high
Infections	direct tissue injury	–

Of note, complex gene-environment interactions may constitute the individual risk. ER, endoplasmic reticulum. * In cases of long-persisting abuse.

en tend to have more often biliary pancreatitis. The peak incidence of alcoholic acute pancreatitis in woman is between 25 and 34 years and in men 10 years later [3]. The overall pancreatitis risk, which includes all etiologies, increases continuously with age. Typically, individuals are affected in their sixth decade of life [4]. Black people have a two- to three-fold elevated pancreatitis risk compared to whites [5]. The mortality depends on the subtype of acute pancreatitis. Mild, edematous pancreatitis shows a mortality of only 1%, whereas the severe, necrotizing form is associated with a death toll of up to 25% [3]. Characteristically, 20–30% of patients with acute pancreatitis experience recurrent pancreatitis attacks and of these 10% develop chronic pancreatitis.

Etiology of Acute Pancreatitis

Gallstones

Gallstones and alcohol abuse are the most common causes of acute pancreatitis and each account for the underlying etiology in 30–50% of cases. Cross-sectional studies of pancreatitis patients demonstrate that 50% of women and only 15% of men have stones in the gallbladder, explaining why the female sex predominates the biliary etiology of pancreatitis. Up to 20% of an adult population carries gallstones [6, 7]. Either stones in the gallbladder or in the biliary tract predispose to pancreatitis. While 75% of gallbladder stone carriers remain asymptomatic, 8% of patients with gallstones will ultimately develop acute pancreatitis [8]. Often, acute pancreatitis is the first manifestation of biliary stones, independent of their original location. While the majority of patients with biliary acute pancreatitis recover completely after a mild edematous pancreatitis episode, 15–30% develop severe necrotizing pancreatitis, requiring intensive care and multidisciplinary treatment strategies. Gallstones trigger

acute pancreatitis when they become impacted at the duodenal papilla and obstruct the outflow from the pancreatic duct [9, 10]. This leads to increased pancreatic pressure, sometimes only transiently, but induces acinar cell injury and triggers the disease onset [10].

Alcohol in Acute Pancreatitis

Next to gallstones, alcohol is the most common factor associated with acute pancreatitis. For more than a century alcohol has been known as an etiology of pancreatitis and it is now well established that immoderate alcohol consumption can initiate an episode of acute pancreatitis and increase the susceptibility to chronic pancreatitis. The peak incidence age of alcohol-associated acute pancreatitis is between 35 and 44 years in men and between 25 and 34 years in women [2]. It was postulated that consumption of between 50 and 80 g or 4–7 drinks per day injure the gland, although individual differences must be considered. While the association between alcohol and pancreatitis is epidemiologically evident, only a minority of alcoholics ever develop acute or chronic pancreatitis. This implies that alcohol consumption alone is rarely the sole precipitating factor for pancreatitis, rather alcohol sensitizes the pancreas for co-factors such as a high lipid diet, infectious agents, or tobacco smoke, the latter being an independent and probably stronger risk factor than alcohol alone – at least for chronic pancreatitis. Alcohol is eliminated from the body by various metabolic processes. The primary enzymes involved are aldehyde dehydrogenase (ALDH), alcohol dehydrogenase (ADH), cytochrome P450 (CYP2E1), and catalase. Variations in the genes for these enzymes have been found to influence alcohol consumption, alcohol-related tissue damage, and alcohol dependence. Based on a developmental relation, the pancreas, like the liver, can metabolize alcohol, and

both oxidative and non-oxidative pathways are functional in the pancreas. Via the oxidative pathway ADH and CYP2E1 metabolize ethanol to acetaldehyde and reactive oxygen species. Metabolites of the nonoxidative ethanol metabolism are fatty ester ethyl esters which can harm the gland [11]. Triggered by ethanol and its metabolites, pancreatic acini undergo complex changes in cellular homeostasis like intracellular calcium levels [12], endoplasmic reticulum stress, increase of mitochondrial permeability [13], impairment in autophagy, or co-localization and activation of lysosomal and pancreatic digestive enzymes [14].

Hypertriglyceridemia

The incidence of acute pancreatitis is related to elevated triglycerides in an estimated 10% of cases [15]. Most subjects with elevated triglycerides experience no symptoms. It is assumed that elevated plasma levels of triglycerides and chylomicrons increase the blood viscosity leading to local ischemia in tissue [13]. During tissue ischemia, the metabolism changes from aerobic to anaerobic and cells depend upon anaerobic glycolysis, the final product of which is L-lactate. Local ischemia elicits lactate levels and acidosis; the latter increases the toxicity of free fatty acids and is the premise for autoactivation of trypsinogen. In combination with other risk factors like alcohol, tobacco, or pharmaceutical drugs ischemia can turn into a local inducer of acute pancreatitis [16]. Patients with familial lipoprotein lipase deficiency have an idiosyncratic risk for recurrent episodes of acute pancreatitis [17]. Also, pregnant women have an inherent risk for hypertriglyceridemia-induced acute pancreatitis, based on a hormone triggered elevation of cholesterol and triglyceride levels [18]. Specific differences have been reported between primary and secondary hypertriglyceridemia. The Fredrickson classification distinguishes between five types of primary hyperlipidemia, of which types I, IV, and V are associated with an increased risk for acute pancreatitis. Type I is mainly characterized by elevated chylomicrons like in lipoprotein lipase deficiency and type IV shows high very-low-density lipoproteins (VLDLs), whereas type V has increased plasma levels of both VLDL and chylomicrons. Primary hypertriglyceridemia is based on genetic aberrations with recessive (type I) or dominant (type IV and V) autosomal inheritance [19, 20]. Secondary hypertriglyceridemia is associated with obesity, pregnancy, insufficiently controlled diabetes, medications, or chronic and acute alcohol abuse. According to the Atlanta classification system the diagnosis of hypertriglyceridemia-induced acute pancreatitis requires a serum triglyceride level of over 1,000 mg/dL. The elevated risk for the development of at least 1 attack of acute pancreatitis is ~20% in a population with triglyceride levels above 1,000 mg/dL [19]. Murphy et al. [21] reported a risk in-

crease of 4% for acute pancreatitis with every rise of 100 mg/dL serum triglycerides, even at elevations much lower than 1,000 mg/dL.

Endoscopic Procedures

Pathologies of the pancreatic or biliary tract are frequent indications for performing endoscopic retrograde cholangiopancreatography (ERCP). A feared complication of ERCP is the induction of post-ERCP acute pancreatitis. Severe post-ERCP pancreatitis is a rare event (~0.5% of pancreatitis cases, 5% of ERCPs), but compared with other etiologies the severity is often high. The reasons for the post-ERCP acute pancreatitis include patient-related, operator-related, and procedure-related factors. Sex, age, anomalies of the sphincter Oddi or the gland, like pancreas divisum, preexisting pancreatitis, and biliary pancreatitis as an indication for ERCP, are patient-related factors. Operator-related complications are associated with the experience of the endoscopist and overlap with procedure-related complications. A difficult cannulation of the papilla Vateri may lead to edema, sphincter spasm, and pancreatic duct obstruction [22]. The osmolarity, pH, and composition of the contrast medium may contribute to chemical and hydrostatic damage. Equally, the increased pressure while injecting the contrast media can cause the activation of digestive enzymes which then trigger pancreatic autodigestion and the initiation of local inflammation [23].

Trauma

The incidence of abdominal trauma in poly-traumatized patients is 20% in Germany; 95% of these cases involve blunt force trauma. Usually parenchymatous organs like the liver and spleen are affected, and traumatic injury to the pancreas is rare (6%) due to its retroperitoneal location. Still, there is no association between the force effect and the extent of pancreatic damage. Common consequences of traumatic damage to the pancreas are pancreatitis, fissures, lacerations, and a disconnected duct, or a combination of them, which already indicates the complexity of management for traumatic pancreatic injuries. Abdominal traumata are associated with a high mortality, the reason being a potential for severe bleeding, septic complications, and an increased rate of multi-organ failure [24].

Rare Causes

The diagnosis of medication-induced acute pancreatitis is rare (0.1–2%). In the context of polypharmacy of an aging population the number of drug-induced cases of pancreatitis will rise and may be underestimated. The pathomechanism is largely drug-specific but can include sphincter spasm, cytotoxic and metabolic effects, hypersensitivity reactions, localized angioedema, or arteriolar

thrombosis [25, 26]. The diagnosis is laborious and based on ruling out other, more common etiologies. Commonly prescribed drugs which are known to be associated with acute pancreatitis are angiotensin-converting enzyme (localized angioedema), statins (direct and accumulation toxicity), oral contraceptives or hormone replacement therapy, especially estrogen (hypertriglyceridemia, local arteriolar thrombosis), diuretics, antiviral therapy (HIV), valproic acid, and antidiabetic agents such as GLP-1 mimetic [25–28]. Interestingly, while it was shown that being the carrier of ABO blood type B increases the risk of developing chronic pancreatitis [29], a recent study has found that the same association exists for drug-induced (i.e., azathioprine-induced) acute pancreatitis in patients with inflammatory bowel disease [30].

Recurrent Acute and Chronic Pancreatitis: Distinction and Etiology

Recurrent acute pancreatitis is characterized by relapsing episodes of acute pancreatitis and morphological signs of a normal gland in asymptomatic intervals [31]. The diagnosis of recurrent acute pancreatitis is made retrospectively after the second episode of acute pancreatitis. Often, signs of chronic pancreatitis are found after the first attack of pancreatitis or during follow-up, suggesting that the junction between recurrent and chronic pancreatitis is fluent [32]. Sankaran et al. [33] point out in a systematic review that the risk of recurrence after a first attack of acute pancreatitis is 20%, and 35% of patients with at least 1 recurrence will progress to chronic pancreatitis. While acute pancreatitis befalls patients in their sixth decade of life, individuals with recurrent acute pancreatitis are younger and diagnosed between 30 and 40 years of age with a predominance of the male sex. Andersson et al. [34] demonstrated in a retrospective study of a single Swedish hospital that patients with admission for acute pancreatitis were 5 years older than patients with a recurrent subtype. The difference in distribution of age and sex in patients with recurrent pancreatitis compared with those with a single event of acute pancreatitis is related to the underlying etiologies (less gallstones, more intensive drinking behavior). Younger patients in particular show a higher risk of alcohol-induced recurrent pancreatitis and chronicity based on continued alcohol consumption.

Chronic Pancreatitis

Chronic pancreatitis has an incidence of 4–14/100,000 per year and a prevalence of 13–52/100,000 [2, 35]. Chronic pancreatitis is defined as a continuous inflammatory degeneration of the exocrine and endocrine pancreatic tissue with irreversible morphological changes [36]. Typical morphological alterations include areas of

inflammation, calcium deposits, duct changes, or pseudocysts. Next to an exocrine (steatorrhea, weight loss) and endocrine (type IIIc diabetes) insufficiency, recurrent pain attacks agonize patients with chronic pancreatitis [37]. Patients with chronic pancreatitis are predominantly male and diagnosed between the fifth and sixth decade of life. The peak incidence of acute alcohol-induced pancreatitis is a decade earlier than for chronic alcohol-related pancreatitis [2, 3]. In hereditary pancreatitis, a rare form which is associated with autosomal dominant mutations in the cationic trypsinogen gene (*PRSS1*), the disease starts in childhood and progresses through variable clinical recurrences to chronic pancreatitis in the second or third decade of life [38]. While acute idiopathic pancreatitis shows an increasing incidence with age which plateaus after 65 years independently of the sex, chronic idiopathic pancreatitis is characterized by a dual age distribution. Early-onset idiopathic chronic pancreatitis appears during the third decade of life, while a late-onset subtype peaks during the sixth to seventh decade [2, 3, 39].

Alcohol in Chronic Pancreatitis

Alcohol abuse is the most common etiology associated with chronic pancreatitis, which accounts for approximately 65% of all cases. In 2009, a systematic review and meta-analysis analyzed the association between alcohol consumption and pancreatitis and found a monotonically increasing dose-response relationship [40]. The dose-response relationship between alcohol and chronic disease typically varies by sex, with women experiencing higher risks at comparatively lower levels of intake [41]. There are individual variations between the duration of abuse and the amount of daily consumed alcohol until the first attack of pancreatitis or the grade of pancreatic impairment. The pathomechanism of alcohol-induced injury of the pancreatic gland is not fully understood. One theory proposes that oxidative stress induced by alcohol metabolites damage the gland directly. Long-term abuse induces the alcohol detoxifying enzyme cytochrome P450 2E1 in pancreatic acinar cells, increasing acetate within the pancreas and inhibiting cellular processes and defense mechanisms [42, 43]. Although it is a minor pathway, fatty ester ethyl esters formed by nonoxidative elimination of ethanol harm the gland and are produced to a greater extent in the pancreas than in other organs [11]. Another theory rests in the experimental and clinical observation that ethanol has a direct effect on fluid secretion from the pancreatic duct via impairment of the cystic fibrosis transmembrane regulator [44]. Although there is strong association between alcohol abuse and pancreatitis, relatively few individuals who abuse alcohol develop chronic pancreatitis. This fact indicates that alcoholic pancreatitis is not caused by alcohol abuse alone [45, 46]. Instead, the

Fig. 1. Pancreatitis-associated genetic risk factors (sequence variants) influence activation, auto-activation, inhibition, or degradation processes of proteases and change the protease/anti-protease equilibrium in pancreatic acinar cells.

pancreas may be sensitized to injury by alcohol consumption, and external or environmental factors stimulate the initiation of the disease. A number of mechanisms by which ethanol and both its oxidative and nonoxidative metabolites damage pancreatic cells are currently discussed. Several factors are believed to be involved in the pathogenesis including genetic predisposition, high lipid diet, cigarette smoking, and infectious agents [47].

Genetic Risk

Genetic variants in several genes have been identified as being associated with susceptibility to chronic pancreatitis and replicated in multiple cohorts [38, 48, 49]. The most relevant genes include the cationic trypsinogen gene (*PRSS1*), the pancreatic secretory trypsin inhibitor gene (*SPINK1*), the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), the chymotrypsinogen gene (*CTRC*), and the carboxy peptidase A1 gene (*CPA1*). These major genetic susceptibility factors were identified as candidate genes linked to intrapancreatic trypsin activity regulation within the pancreas or reduced ductal fluid flow [44, 50]. Within the “trypsin-dependent pathological pathway” variants in susceptibility genes *PRSS1*, *SPINK1*, and *CTRC* increase pancreatitis risk by promoting harmful trypsinogen activation or by impairing protective trypsinogen degradation and/or trypsin inhibition (Fig. 1). Activation of *PRSS1* trypsinogen to active trypsin within the pancreas is responsible for disease onset and progression. Protective mechanisms to control trypsinogen activation include trypsin inhibition by *SPINK1* and trypsinogen degradation by chymotrypsin C (*CTRC*) and trypsin. Other *PRSS1* variants, such as the activation peptide mutants p.D22G, p.K23R, and p.K23_I24insIDK, are

clinically rare and tend to associate primarily with sporadic idiopathic disease. These mutants all exhibit reduced secretion because trypsinogen becomes intracellularly autoactivated and degraded [51–53]. It appears likely that inside the endoplasmic reticulum active trypsin is sensed as a misfolded state of trypsinogen, which prompts degradation. In addition, the intracellular levels of the misfolded protein should depend on how efficiently the cell is capable of disposing them. Mutations in digestive enzymes that induce misfolding and endoplasmic reticulum stress represent a highly relevant pathological concept and a potential therapeutic target in chronic pancreatitis. Mutations in *PRSS1* and *CPA1* are the best studied examples. Strong risk factors are occasionally associated with hereditary forms of pancreatitis.

Significant association with pancreatitis has also been demonstrated for sequence variants in *CASR* [54], *CLDN2* [55–57], and *CEL* [58, 59]. Preliminary reports which await further validation include *CTSB* [60], *MYO9B* [61], and *UBR1* [62], or the association of an increased pancreatitis risk with ABO blood group and the so-called “secretor status,” which is determined by a mutation of the fucosyltransferase gene *FUT2* [29, 63]. Additional genetic variants are being evaluated and will likely be added to this list in the future. A single factor alone rarely causes pancreatitis, and the majority of patients with recurrent acute and chronic pancreatitis carry multiple variants in one or multiple genes, coupled with environmental stressors. So far only *PRSS1* mutations are inherited in an autosomal dominant pattern, giving rise to a hereditary form of pancreatitis that runs in families. Other genetic variants, as well as different environmental factors, can be strong risk factors for susceptibility and

Fig. 2. **A** CT scan of patient with SPINK1-p.N34S/CTRC-p.G60G mutation. Note enlargement of the head of the pancreas and multiple calcifications. **B** CT scan of patient with autoimmune pancreatitis type 1 (IgG4 related) with a homogenous (sausage-shaped) enlargement of the entire gland and an enhanced rim.

progression of acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis. In a multinational cross-sectional study (INSPPIRE consortium) of 301 children with recurrent acute and chronic pancreatitis 84% of children with chronic pancreatitis reported prior recurrent episodes of acute pancreatitis [64]. Sequencing analysis identified at least one mutation in pancreatitis-related genes in 48% of patients with recurrent acute pancreatitis versus 73% of patients with chronic pancreatitis. Children with *PRSS1* or *SPINK1* mutations were more likely to develop chronic pancreatitis, but ethnic differences also seemed to influence the disease phenotype as well as disease progression.

Genome-wide association analyses and next generation sequencing studies are powerful new technologies that are capable of identifying genetic risk factors outside of candidate gene-driven screening approaches. A few genome-wide association studies have been performed to date, mainly in chronic pancreatitis and recurrent acute pancreatitis patients. Studies by Whitcomb et al. [55] and Rosendahl et al. [65] were able to identify new susceptibility loci in the claudin-2 gene (*CLDN2*), as well as a gene conversion event in the chymotrypsin B *CTRB1-2* locus, which modifies the risk for alcoholic and nonalcoholic chronic pancreatitis [65].

Hereditary Pancreatitis

Hereditary pancreatitis is a rare autosomal dominant genetic disorder of the pancreas with incomplete penetrance. In most cases recurrent episodes of acute pancreatitis start in childhood (median age of onset, 10 years) [66]. Chronic pancreatitis develops in young adulthood and results in an elevated risk of pancreatic cancer beginning in the fifth decade of life [48]. Typically, hereditary pancreatitis is associated with a limited number of gain-

of-function mutations in the cationic trypsinogen gene (*PRSS1*), the most common of which are p.A16V, p.N29I, and p.R122H. The clinical features are similar to those seen in other causes of chronic pancreatitis. Primary manifestations are abdominal pain, maldigestion as a consequence of pancreatic exocrine dysfunction, and diabetes mellitus due to islet cell damage. In a national series of 418 patients with hereditary pancreatitis from 112 families in 14 European countries, exocrine pancreatic insufficiency eventually developed in 37% and diabetes mellitus eventually developed in 48% of cases [38]. The most common presentation of autosomal dominant hereditary pancreatitis is recurrent acute pancreatitis. However, some patients may present with chronic pancreatitis without experiencing prior episodes of acute pancreatitis.

Rare Causes

The pancreas divisum or annulare are congenital abnormalities which have been associated with chronic pancreatitis. Usually these congenital aberrations do not cause chronic pancreatitis by themselves. A second risk factor is required like smoking, alcohol abuse, or genetic predisposition. A biliary pathogenesis for chronic pancreatitis is an extremely rare event and based either on noncompliance concerning a needed cholecystectomy or an underdeveloped medical infrastructure. In rare cases pancreatitis may be caused by viral infections such as mumps, coxsackie B, mycoplasma pneumonia, and campylobacter, but these are mostly acute and not chronic episodes. In approximately 5–6% of patients, chronic pancreatitis is caused by autoimmune inflammation [67]. Symptoms can be mild, but half of the patients with autoimmune pancreatitis (type 1) show elevated levels of immunoglobulin G4 (IgG4) and rarely develop pancreatic calcifications [68, 69] (Fig. 2). Additional character-

istics of autoimmune pancreatitis include main pancreatic duct changes, scarring of the pancreatic tissue, and presence of elevated numbers of inflammatory cells. Autoimmune pancreatitis can occur by itself or in association with other autoimmune diseases such as primary sclerosing cholangitis, primary biliary cholangitis, retroperitoneal fibrosis, rheumatoid arthritis, sarcoidosis, and Sjögren's syndrome [70].

Cancer Risk

Chronic pancreatitis and carcinoma of the pancreas are equally common in Western countries. Incidence rates for both are around 10 per 100,000 [71]. The incidence rates for pancreatic cancer in both sexes increase with age, the highest being in the age group over 70 years [72]. Pancreatic cancer is predominantly a disease of the elderly, and almost 90% of all cases are diagnosed after the age of 55 years [72]. Chronic pancreatitis is regarded as a precancerous lesion in this context. It is generally accepted that persisting inflammation can cause repeated DNA damage and a progressive accumulation of genetic mutations. A sequential accumulation of genetic defects has been suggested to associate in the pancreas with precancerous histologic changes. These pancreatic intra-epithelial neoplasms (PanIN) are present in sporadic pancreatic adenocarcinomas as well as in patients with a history of chronic pancreatitis. Histologically, PanINs progress through stages of increasing architectural and cytological atypia, starting from low-grade dysplasia (PanIN-1A, PanIN-1B) to moderate dysplasia (PanIN-2) to high-grade dysplasia (PanIN-3). The first genetic mutations seen in the early stages include K-RAS mutations, followed by p16/CDKN2A, TP53, and SMAD4/DPC4 [73]. Mutations in all four genes have been recognized as driver mutations that trigger neoplastic transformation and tumor progression [74]. Importantly, chronic pancreatitis rarely develops into cancer, even not in the very long-standing cases, and the majority of patients presenting

with pancreatic carcinoma have no history of chronic pancreatitis (less than 1% in population-based studies). The prognosis of chronic pancreatitis depends on the age at diagnosis and continuing alcohol or tobacco abuse.

Conclusion

Pancreatitis is a syndrome of various causes, symptoms, and outcomes [75]. Our understanding of the natural history of the disease and how treatment can effectively limit acute attacks or prevent disease progression and chronicity is still limited. Long-term follow-up and well-designed, preferably randomized, studies with adequate sample size are needed to improve our understanding of how complex gene-environment interactions shape the disease phenotype. Also, next generation sequencing technologies can elucidate the genetic risk outside of the established candidate gene-driven screening approaches. Both will improve our understanding of the pathophysiology of pancreatitis and help to develop new and successful therapeutic concepts for the benefit our patients.

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In reference to this review, all authors have no conflicts of interest to report.

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