Alcohol Consumption and Pancreatitis

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Contributor: Jia Luo

Pancreatitis is a common inflammatory disorder of the pancreas, associated with high mortality and healthcare burdens worldwide. It mainly consists of two forms: acute pancreatitis (AP) and chronic pancreatitis (CP). Alcohol exposure is a known etiological factor for both AP and CP.

Keywords: alcohol abuse ; endoplasmic reticulum stress ; unfolded protein response ; pancreatitis

1. Acute and Chronic Pancreatitis

Pancreatitis is a common inflammatory disorder of the pancreas, associated with high mortality and healthcare burdens worldwide [1][2]. It mainly consists of two forms: acute pancreatitis (AP) and chronic pancreatitis (CP). AP is the most frequent cause of gastrointestinal disorders requiring hospitalization in the US, and its associated inpatient care cost is approximately USD 2.6 billion annually [2][3][4]. Although less frequent, CP also causes significant morbidity and financial burden [3]. Additionally, the incidence of pancreatitis differs with age and gender. The risk of developing AP increases with age [5][6], whereas CP is more common in middle-aged individuals [2]. Furthermore, AP does not appear to differ between men and women [6]; however, CP is more common in men than in women [2][7]. AP and CP share a significant portion of clinical manifestations and phenotypes, but also have distinct morphological and imaging features.

AP is characterized by sudden abdominal pain, elevated levels of pancreatic enzymes in the blood, and pancreatic inflammation [8][9]. Depending on the clinical features, AP can be classified into mild, moderate, or severe forms. The most common form of AP is mild AP, which can be self-treated within weeks. However, the moderate and severe forms can progress into necrotizing pancreatitis, which has a 20–40% mortality rate [10]. A variety of long-term sequelae have been reported that can persist beyond hospital admission for AP. AP may increase the risk of other pancreatic disorders, including CP, exocrine pancreatic insufficiency (EPI), pancreatic cancer (PC) and diabetes mellitus (DM). In total, 17% of AP patients are re-admitted after their first episode for recurrent pancreatitis with about 8% of patients developing CP [11][12]. Approximately one quarter to one third of AP patients develop EPI during the follow-up period [13][14]. The prevalence of EPI following AP is higher with the severe form than with the mild form, and it is higher in patients with an etiology of alcohol than one of gallstones [14]. AP patients often develop prediabetes and/or DM after being discharged from the hospital [15][16]. The diagnosis of AP increases the risk of PC, which in turn increases the number of recurrent episodes of AP [17][18].

CP is believed to result from the recurrence of AP, leading to chronic pain, pancreatic atrophy, duct strictures and calcifications [19][20]. Although less common than AP, CP significantly affects patients' quality of life due to irreversible, debilitating injury to the function of the pancreas. CP is also associated with other pancreatic diseases. It has been reported that CP increases the risk of EPI [21][22], PC [23][24] and DM [25][26]. The high disease burden of AP and CP emphasizes the importance of identifying predisposing factors, understanding pathogenesis, and developing therapeutic intervention for these diseases.

2. Alcohol Consumption and Pancreatitis

Alcohol exposure is a known etiological factor for both AP and CP. Epidemiological studies have shown that excessive alcohol consumption is the second leading cause of AP after gallstones [1][27] and is the most prevalent risk factor for CP [28]. Alcohol abuse is also a risk factor for the recurrence of AP and increases the chance of the progression of AP into CP [11][29]. Although alcohol can contribute to the initiation and progression of pancreatitis, only a small number of heavy alcohol drinkers develop the disease, suggesting that other disposing factors are involved in the development of alcohol-related pancreatitis [7][30][31][32].

The association between alcohol consumption and pancreatitis is evaluated predominantly by self-reported survey studies. Corrao et al. conducted a meta-analysis of studies published from 1966 to 1995 and showed that the risk of

pancreatitis monotonically increased with increasing alcohol consumption [33]. Consistent with this finding, Irving et al. analyzed research published from 1980 to 2008 and confirmed a monotonic dose–response relationship between alcohol consumption and the risk of pancreatitis, with a threshold of four drinks daily that significantly increased the risk of pancreatitis [34]. Similarly, more recent studies indicated that prolonged use of alcohol with a threshold level of 4–5 drinks per day was required for an increased risk of pancreatitis [19][31][34][35][36]. In addition, the amount of recently consumed alcohol was shown to determine the severity of the first episode of acute alcoholic pancreatitis [37]. In the absence of long-term use, binge drinking alone did not increase the incidence of AP [38]. Regular consumption of alcohol at lower levels, however, appeared to have an inconsistent effect on pancreatitis. Some reported that low levels of alcohol drinking (<50 g per day) increased the recurrence of AP and accelerated the progression of CP [39][40]. Others found that mild or moderate drinking was inversely associated with an increased risk of pancreatitis [41].

In contrast to prolonged heavy alcohol consumption, which has been known as a risk factor for pancreatitis, alcohol abstinence has been shown to slow down the progression of pancreatitis and reduce the recurrence of AP. For example, withholding from drinking resolved abdominal pain and slowed the deterioration of pancreatic function in chronic heavy drinkers [42]. Abstinence after the first episode of AP minimized the number of recurrent attacks [43]. Similarly, in an effort to determine the risk factors associated with recurrent pancreatitis, Pelli et al. (2008) showed that abstinence from alcohol protected against the recurrence of AP [44].

Alcohol can also act as a co-factor to increase the sensitivity of the pancreas to the detrimental effect of other risk factors, including environmental and dietary factors [45]. Cigarette smoking is an independent risk factor for a number of pancreatic disorders, including AP [46], CP [47] and PC [48][49]. Alcohol drinking can accelerate the progression of cigarette-smoking-related pancreatitis and vice versa, suggesting a synergistic interaction between alcohol and smoking in the development of the disease [36][50][51][52]. Hypertriglyceridemia, referring to an elevated blood level of triglycerides often resulting from high dietary fats, is another important cause for pancreatitis [53][54][55] and is present in many alcoholics [56][57]. Excessive alcohol consumption has been suggested to be associated with hypertriglyceridemia-induced pancreatitis [58][59].

The risk of alcoholic pancreatitis can also be altered by genetic modifiers. The *CLDN2* (Clauding 2) gene encodes a tight junction protein-regulating cation and water transport of epithelial cells. It is normally expressed in pancreatic duct cells but not acinar cells [60][61]. In a genome-wide study, a *CLDN2* risk allele, which is associated with an abnormal expression of CLDN2 protein in pancreatic acinar cells, was identified as a risk factor that interacted with alcohol consumption to accelerate the progression of chronic pancreatitis [62]. In another genome-wide association study, an inversion of the *CTRB1–CTRB2* (chymotrypsin B1 and B2) locus led to both the imbalanced expression of CTRB1 and CTRB2 and an increased risk for both alcoholic CP and non-alcoholic CP [63].

Racial/ethnic differences are another susceptibility factor that can alter the risk of alcoholic pancreatitis. A population study using nationwide inpatient samples from the racially diverse US population between 1988 and 2004 demonstrated that Black people had the highest frequency of alcohol-related pancreatitis [64]. Another study using data collected by the North American Pancreatitis Study Group from 2000 to 2014 found that Black people were more likely to be diagnosed with CP than White people, likely because of alcohol consumption and smoking being more frequent in Black people [65]. In a number of studies conducted in the Asian population, a dose–response relationship between alcohol and pancreatitis was revealed [66][67][68]. The impact of ethnicity on the risk of alcoholic pancreatitis in these Asian studies was suggested to be related to the genetic polymorphism of alcohol metabolism enzymes. Genetic variant alleles of the aldehyde dehydrogenase-2 gene (ALDH2*2) and alcohol dehydrogenase-1B gene (ADH1B*2), which are associated with the accumulation of toxic acetaldehyde after alcohol drinking, were predominantly found in East Asians [69][70][71].

3. Animal and Cell Culture Models for Alcoholic Pancreatitis

Epidemiologic studies have indicated that alcohol can act as a mild initiator or a robust modifier that sensitizes the pancreas to the insult of other risk factors during the development of pancreatitis. To understand the mechanisms underlying the pathogenesis of alcohol-related pancreatitis, many animal and cell culture models have been established. These experimental models have recapitulated the clinical features of alcohol-related pancreatitis, facilitated our understanding of the pathology, and provided opportunities to test potential therapeutic treatments for the disease.

Consistent with epidemiologic studies, alcohol alone, either by acute exposure (77) or by chronic feeding [72][73][74], is not sufficient in inducing pancreatitis-like features in rodent models. Recent studies have combined chronic exposure with binge drinking and found that alcohol, when acting as both the initiation and susceptibility factor, can cause pancreatic injury, mimicking pancreatitis. Binge alcohol exposure by intragastric intubation for 10 consecutive days (5 g/kg/day, 25% ethanol *w*/*v*) caused pancreatic edema, acinar cell death and moderate fibrosis in C57BL mice [75]. Mice receiving a liquid

alcohol diet for two weeks followed by binge alcohol exposure by oral gavage for 3 days (5 g/kg/day, 25% ethanol *w*/*v*) displayed more severe injury and inflammation in the pancreas [76]. A 10-day feeding of a liquid alcohol diet plus a single binge ethanol exposure was found to lead to pancreatic edema and inflammation in C57Bl/6 mice [77][78]. The chronic plus binge model may be of clinical relevance due to the similarity of the drinking pattern to that of many alcoholic patients who have a history of chronic alcohol consumption and tend towards heavy episodic drinking [79][80][81]. In fact, the chronic plus binge exposure has also been used in animal models for alcoholic liver disease (ALD), as it causes significantly higher elevation of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and hepatic histological features, compared with chronic alcohol feeding or binge exposure alone [77][82][83].

The detrimental effects of alcohol on the pancreas can result from the direct actions of toxic metabolites, acetaldehyde and fatty acid ethyl esters (FAEEs), via the oxidative and non-oxidative pathways, respectively. The oxidative metabolism of ethanol mainly occurs in the liver [84][85][86] and the level of acetaldehyde in the circulation is typically low [87][88], meaning organ damage in the pancreas by acetaldehyde is considered insignificant. In contrast, non-oxidative metabolism of ethanol by esterification with fatty acids, resulting in the formation of FAEEs, has been implicated in alcohol-induced damage to the pancreas. An autopsy study showed that the level of FAEEs and the activity of FAEEs synthase (enzymes responsible for the synthesis of FAEEs) are highest in the pancreas among all ethanol-damaged organs in acutely intoxicated individuals [89]. In fact, intra-arteria infusion of FAEEs in rats at concentrations comparable to those in human plasma only caused AP-like injury in the pancreas but not in other organs that are known to be susceptible to ethanol-induced damage, implying a role of FAEEs as a mediator in ethanol-induced pancreas-specific toxicity [90]. In a ethanol-induced AP rat model, the inhibition of oxidative ethanol metabolism increased FAEEs concentration in the plasma and pancreas and exacerbated pancreatitis-like injury, suggesting FAEEs are responsible for pancreatic damage in alcohol-related AP [91]. With in vitro and in vivo models for AP induced by low ethanol and fat, Huang et al. (2014) showed that 3-benzyl-6-chloro-2-pyrone (3-BCP), an inhibitor of carboxylester lipase (a FAEE synthase produced by pancreatic acinar cells), reduced FAEEs formation and alleviated exocrine pancreatic damage, demonstrating a crucial role of FAEEs in alcohol-related AP [92].

Alcohol can also act as a co-factor to sensitize the pancreas to the adverse effects of other susceptibility factors in the progression of pancreatitis. One physiologically relevant animal model for alcohol-related pancreatitis is the co-exposure of cholecystokinin (CCK) analogs and alcohol. CCK, an intestine hormone, is one of the most commonly used models to induce mild AP in rats [93][94][95][96] and a more severe form in mice [97][98][99][100], with a dose that is at least 10 times higher than physiological conditions. CCK analog-induced AP can recapitulate the pathologic features of human AP caused by scorpion venom and cholinergic toxins [101][102][103][104]. The co-treatment of alcohol can either reduce the threshold concentration of CCK analogs required to elicit a pancreatitis response or intensify the pathologic response of the pancreas. Pandol et al. (1999) demonstrated that alcohol exposure sensitized rats to pancreatitis induced by CCK-8 at physiological concentration, which by itself did not cause pancreatitis [95]. Quon et al. (1992) showed that chronic feeding with an alcohol diet exacerbated CCK analog caerulein-induced pancreatitis in rats, signified by greater increases in serum lipase level, interstitial edema and acinar vacuolization compared with animals treated with caerulein alone [105]. Repeated use of caerulein over time induced pathological features of the pancreas in rodents that mimicked human CP [106][107][108]. Alcohol exposure accelerated the progression of caerulein-induced CP in rats [108] and mice [109].

Another clinically relevant animal model is lipopolysaccharides (LPS)-induced alcoholic pancreatitis in rodents [110]. LPS are endotoxins derived from Gram-negative bacteria in the gut, which can be released to the blood to cause LPS-associated toxicity [111]. There have been reports of higher plasma levels of LPS in alcoholics [112][113] and an association between plasma endotoxin concentrations and the severity of human AP [114]. In rat models, LPS and alcohol exposure have been shown to cause a more severe pancreatic injury than LPS alone [110][115]. Withdrawal of alcohol after manifestation of LPS-induced pancreatitis in rats resulted in the resolution of pancreatic lesions, including fibrosis and cell death, whereas continued alcohol administration aggravated the injury [116]. In a rat model of alcoholic AP, alcohol increased the expression of LPS-induced proinflammatory factors in acinar cells, including TNFα, IL-6, IL-10 and IL-18 [117]. The elevated expression of these inflammatory mediators was also observed in human AP and recurrent AP patient samples, suggesting an involvement of inflammation in alcoholic pancreatitis [117].

There are other susceptibility factors that have been identified in experimental models and shown to be associated with alcoholic pancreatitis. Pancreatic duct obstruction, which causes minimal pancreatic damage independently, induced pancreatitis in a rat model when combined with alcohol feeding [118] and worsened the canine model of alcoholic CP [119]. Genetic mutations, as exemplified by a pathogenic human p.N256K *CPA1* (Carboxypeptidase A1) mutant when expressed in mice, caused protein misfolding, ER stress and progressive CP, which was aggravated by alcohol exposure [120]. A severe pancreatitis phenotype manifested in knock-out mice for nuclear factor erythroid 2 like 2 (NRF2), a regulator

of cellular antioxidant response and ethanol metabolism, was worsened by acute binge alcohol exposure, suggesting the involvement of oxidative stress or ethanol metabolites in alcoholic pancreatitis [121].

In addition to animal models, many in vitro models have been proposed to address the mechanisms underlying the pathology of alcoholic pancreatitis. The exocrine compartment of the pancreas is mainly composed of acinar and ductal cells. The pancreatic acinar cells are the functional unit of the exocrine pancreas, constituting about 80% of the pancreas. Their function is to synthesize, store and secrete digestive enzymes. Acinar cells are believed by many to be the initiation site of pancreatic injury, as molecular and cellular events linked to acinar cell dysfunction have been shown to occur early in pancreatitis [122][123][124][125]. Similar to animal models, pancreatic acinar cells, when treated by alcohol alone, appeared to display minimal damages. Chronic alcohol exposure at a clinically relevant concentration (50 mM equivalent to 230 mg/dL, 96 h) reduced the cellular uptake of thiamine pyrophosphate (TPP) in rat primary acini, rat pancreatic AR42J acinar cells [126] and mouse pancreatic 266-6 acinar cells [127], indicative of alcohol's damaging effects on pancreatic thiamine-dependent functions [128][129][130]. Alcohol exposure at concentrations from 200 to 800 mg/dL for 6 h caused mild apoptosis of AR42J cells and minimal effect on the activity of lipase or amylase [131]. Lugea et al. (2017) showed that alcohol treatment (50 mM equivalent to 230 mg/dL) for 4 days decreased the viability of AR42J cells only in combination with cigarette smoke extracts but not independently [132]. In CCK-8-stimulated primary mouse pancreatic acini, alcohol treatment altered Ca^{2+} homeostasis [133], increased reactive oxygen species (ROS) production [134] and reduced CCK-8-evoked amylase secretion [135]. In rat pancreatic acini, alcohol treatment exacerbated the pathological intra-acinar protease activation induced by muscarinic agonist carbachol [136].

Pancreatic ductal cells, which are responsible for transporting the acini-produced digestive enzymes into the duodenum and secreting bicarbonate-rich fluid to neutralize stomach acid, have also been proposed to be involved in the pathology of pancreatitis [137][138][139]. Alteration of ductal cell function may cause insufficient transportation or precipitation of digestive enzymes in the ducal lumen, potentially leading to obstruction and damage. Sarles et al. (1965) showed that the formation of mucoprotein plugs in the pancreatic ducts was an early lesion in the pathology of alcohol-induced chronic calcifying pancreatitis [140]. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), an ion channel protein highly expressed in pancreatic duct cells, were found to be associated with CP [141]. Maleth et al. (2015) showed ethanol exposure reduced the expression of CFTR and disrupted the folding of CFTR at the endoplasmic reticulum (ER) in a number of human pancreatic cell lines and the pancreatic tissues of mice and guinea pigs [142]. In addition, CFTR knockout mice developed more severe pancreatitis when given ethanol than *WT* control mice [142].

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