Alcohol and Acute Pancreatitis

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Alcohol abuse is associated with the development of both acute and chronic pancreatitis. The majority of patients who abuse alcohol will not develop pancreatitis; the reasons for different susceptibilities to alcohol are unknown. Most patients who present with acute alcoholic pancreatitis will have underlying chronic disease, but up to a third will have no evidence of chronic pancreatitis. Alcohol has a number of acute effects on the pancreas that are potentially toxic. These include increasing pancreatic duct pressure, decreasing pancreatic blood flow, generating free radicals, and stimulating pathologic zymogen activation within the pancreatic acinar cell.

INTRODUCTION

Alcohol abuse can lead to chronic pancreatitis and bouts of acute pancreatitis superimposed on chronic disease. Epidemiologic and experimental studies have investigated the acute effects of ethanol on the pancreas in human subjects and animal models. The ability of alcohol to cause acute pancreatitis in the absence of chronic disease and the mechanism of such injury are issues of discussion. However, some information on this topic does prove useful in assessing the association between alcohol consumption and acute pancreatitis.

CLINICAL SPECTRUM OF ALCOHOL-INDUCED PANCREATITIS

The natural history of those who abuse alcohol follows several patterns (Figure 1). Although most subjects who abuse alcohol do not develop pancreatitis, a fraction will develop clinical disease. Under the international classifications of pancreatic diseases as established in the Marseilles-Rome 1988 Classification [1], the Cambridge International Workshop in 1983 [2], and the Atlanta Symposium on Acute Pancreatitis in 1992 [3], alcoholic pancreatitis most often presents with chronic pancreatitis (chronic pain and/or permanent loss of pancreatic function due to destruction of gland associated with chronic inflammation and fibrosis). Less often patients develop acute pancreatitis (acute onset of abdominal pain associated with increased pancreatic enzymes in the blood or urine, pancreatic inflammation, that resolves with a return to normal pancreatic function). Patients with chronic pancreatitis may have bouts of acute disease. Although chronic pancreatitis or acute pancreatitis superimposed on established chronic pancreatitis are the most common, some alcoholics appear to develop acute pancreatitis in the absence of chronic disease. Rarely a non-alcoholic patient may develop acute pancreatitis after a short period (days or weeks) of alcohol abuse; the risk of developing severe and fatal pancreatitis may be high in this group [4]. Although Figure 1 is likely to present an accurate summary of the natural history of alcohol on the pancreas, it is difficult to quantify alcohol ingestion and to exclude underlying chronic disease. These factors have made it

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Abbreviations: AC, adenylate cyclase; CCK, cholecystokinin.
Figure 1. Potential effects of alcohol abuse on the development of pancreatitis. The natural history of patients who abuse alcohol may fall into several categories: a) in most, long-term abuse does not lead to disease, b) some subjects with long-term abuse develop chronic pancreatitis or acute pancreatitis superimposed on chronic disease, c) a few patients with long-term abuse will have acute pancreatitis in the absence of chronic disease, d) rarely, short-term alcohol abuse may lead to acute disease.

challenging to precisely define the natural history of the disease or to evaluate the importance of factors in addition to alcohol abuse.

Extent of alcohol abuse and the development of pancreatic disease

It is difficult to establish absolute risks for developing pancreatitis in the alcoholic patient because of variability in the criterion for diagnosing alcoholism and our inability to readily assess pancreatic function and pathology. However, it is said that less than 5 percent of alcoholics develop pancreatitis related to the ethanol consumption [5]. Although subclinical pancreatic injury may be much more common than overt clinical disease [6], the incidence of a clinically evident disease among alcoholics is probably quite low.

The mean ethanol intake and duration of consumption affect the risk for developing acute and chronic alcoholic pancreatitis: both groups ingest 100 to 200 g of ethanol per day [7] for a similar duration [4]. A period of consumption greater than 15 years is typical for those who develop disease. The most important criteria for estimating the risk of alcoholic pancreatitis may be the total alcohol consumption (duration times average daily intake). Often alcoholic patients report a period of excessive ethanol intake before an
attack. This has been referred to a conditioning period that often lasts 2-3 weeks [8, 9]: acute attacks of pancreatitis often appear 12 to 48 hrs after a binge [10].

There appears to be no precise threshold of toxicity above which alcoholic pancreatitis is inevitable, but a spectrum of sensitivities. Some individuals appear to be very susceptible and may develop pancreatitis after ingesting less than 20 g alcohol/day while others may drink up to 200 g/day but do not develop disease [11]. The broad range of individual susceptibilities add to the difficulty in interpreting studies on the epidemiology of alcoholic pancreatitis.

**Susceptibility to alcoholic pancreatitis**

A number of factors may influence the sensitivity of the pancreas to ethanol-induced injury. They include genetic factors such as blood groups, HLA determinants, α1-antitrypsin phenotypes, and alcohol dehydrogenase isoenzyme polymorphisms (reviewed in Ref.) [12]. In addition, factors such as diet and nutritional status, tobacco smoking, and coexisting conditions as hypertriglyceridemia, reduction of pancreatic blood flow and the anatomic relationship between the distal biliary and pancreatic ducts may affect the development of disease [13]. Gender may affect risk for developing alcoholic pancreatitis; the mean alcohol intake for men who develop pancreatitis is about twice that of women [14].

**Acute pancreatitis in patients with chronic alcoholic pancreatitis**

There is uniform agreement that patients with established chronic alcoholic pancreatitis can develop acute disease; it is estimated that 85 percent of patients with acute alcoholic pancreatitis will have underlying chronic disease [8, 9]. Once established, the natural history may follow several patterns. In most, the intensity and frequency of the acute recurrent painful attacks will decrease over time as the patients develop functional or morphological deterioration [15]. About 10 percent of patients will experience progressive decline in pancreatic function in the absence of painful crises [16]. The course of alcoholic pancreatitis is improved by abstinence; conversely, those who continue to imbibe are more likely to experience functional deterioration and to respond poorly to pain control measures [17].

**Acute pancreatitis in patients without chronic alcoholic pancreatitis**

The potential for acute alcoholic pancreatitis to develop in the absence of chronic pancreatitis has been a topic of discussion. It has been estimated that at least 15 percent of patients with acute alcoholic pancreatitis do not have chronic disease [8]. Evidence that alcohol may precipitate acute pancreatitis in the absence of chronic disease comes from functional and histologic studies. Although the functional studies have demonstrated that patients with acute alcoholic pancreatitis may not have chronic disease [18], the possibility that early disease is missed or that there is recovery over time may affect this conclusion.

The greatest support for alcoholic acute pancreatitis occurring in the absence of underlying chronic disease comes from autopsy studies. In a prospective study of alcoholics with acute pancreatitis who later died, autopsies frequently demonstrated no chronic pancreatitis [4]. In a retrospective autopsy study of patients who died with acute alcoholic pancreatitis (Table 1), less than half had histologic evidence of acute pancreatitis [19]. The validity of these observations is confirmed by the high incidence of hepatic cirrhosis in alcoholic patients compared to non-alcoholic groups. These functional and histopathological studies strongly support the hypothesis that patients may develop acute alcoholic pancreatitis in the absence of chronic disease.

**Do acute bouts of alcoholic pancreatitis lead to chronic disease?**

Acute inflammatory conditions may lead to chronic inflammation and fibrosis. It has been suggested that the natural history of alcoholic pancreatitis may follow two pathways:
Table 1. Pancreatic pathology in 405 patients dying from acute pancreatitis (adapted from Renner et al, reference 19). Note that less than 50 percent of the patients that died of acute alcoholic pancreatitis were found to have pathologic evidence of chronic pancreatitis.

| Subgroups                  | Total | Chronic alcoholic | Common duct stone | Postoperative | Misc. | Idiopathc |
|----------------------------|-------|-------------------|-------------------|--------------|-------|-----------|
| Total number               | 405   | 247               | 25                | 37           | 18    | 78        |
| Chronic pancreatic lesions | 38%   | 47%               | 32%               | 32%          | 44%   | 14%       |
| Hepatic cirrhosis          | 17%   | 25%               | 0%                | 14%          | 6%    | 0%        |

Patients may have either recurrent bouts of acute pancreatitis but not progress to chronic pancreatitis, or acute pancreatitis may lead to chronic disease. Kloppel and Maillet have hypothesized that recurrent episodes of pancreatic necrosis may lead to fibrosis [20]. However, other studies suggest that chronic pancreatitis may arise in the absence of acute bouts of disease [16]. The resolution of these differences awaits further study.

**METHODOLOGICAL ISSUES IN DIAGNOSING ALCOHOLIC PANCREATITIS**

*Epidemiologic and clinical studies*

In most series the diagnosis of alcoholic acute pancreatitis is based on the characteristic findings of acute pancreatic inflammation, a history of excessive alcohol intake obtained from the patients or their relatives and the absence of other etiologic factors. Studies of alcoholic pancreatitis have had to confront several major obstacles. First, the history of alcohol exposure is unreliable and estimates of alcohol consumption are inaccurate. Second, most investigations have lacked the histopathologic and functional information that are needed to exclude underlying chronic pancreatitis. In a patient with pancreatitis, known alcohol abuse does not exclude other etiologic factors. An additional important causative factor may be found in 10-20 percent of the patients who present with alcoholism and pancreatitis [21].

It is widely appreciated that a history of alcohol consumption is unreliable. Renner and co-workers found that although patients often denied alcoholism, a history of alcohol abuse frequently could be elicited from family members [19]. Questionnaires are often used to diagnose alcoholism; Alcohol Use Disorders Identification (AUDIT) has been widely validated and has proved useful in identifying patients with alcoholic acute pancreatitis [22]. The most effective method for obtaining a history of alcohol abuse is probably the combination of a standardized patient questionnaire and an interview of family members.

Biochemical markers may help to separate alcoholic from non-alcoholic pancreatitis. Ethanol abuse has been associated with a relative increase in the synthesis and/or secretion of chymotrypsinogen, trypsinogen and lipase compared to amylase and these changes may be reflected in serum levels of these enzymes [23]. However, the value of changes in serum trypsin levels or the serum lipase to amylase ratio as markers of alcoholism has not yet been demonstrated [22, 24].

The effects of alcohol on organs other than the pancreas have been used as markers of an alcoholic etiology in acute pancreatitis. The γ-glutamyltransferase, carbohydrate-
Figure 2. Potential mechanisms of acute ethanol toxicity in the pancreas. Based on experimental and pathologic studies, a number of mechanisms may play a role in ethanol-induced pancreatic injury. Changes in pancreatic blood flow may predispose to ischemia and reperfusion injury and oxidant stress. Other factors include the release of cytokines that induce inflammation and cell death, the pathologic activation of zymogens within the acinar cell or the interstitial space as well as other direct toxic effects on the acinar cell, increased pancreatic secretion, and dysfunction of the sphincter of Oddi that might lead to obstruction or the reflux of duodenal contents (see text for additional details).

deficient transferrin, and even the mean corpuscular volume may be increased, but are insensitive and non-specific indicators of alcohol abuse [10, 25]. Although these tests may prove useful in examining large patient populations, their utility in an individual patient appears to be limited.

MECHANISMS OF ETHANOL-INDUCED Pancreatic INJURY

This review emphasizes the ability of ethanol to cause acute pancreatic injury. The short-term effects of ethanol are likely to be relevant to this acute injury and will be discussed in detail. The chronic effects of ethanol are likely to play an important role in the pathogenesis of pancreatic injury and have been reviewed in greater detail elsewhere [9, 11].

A number of acute effects of ethanol have been related to the development of pancreatitis; the various mechanisms are summarized in Figure 2. Its effects on pancreatic duct pressures are complex and may result in both the reflux of noxious substances and increased ductal pressure. The effect of ethanol on blood flow may predispose to ischemia
and its enhancement of ductal permeability may permit the movement of pancreatic duct contents into the interstitial space. Ethanol also may be directly toxic to the acinar cell or have metabolic effects that promote acinar cell injury and pancreatic inflammation. Since it is difficult to study many of the potential effects of ethanol in humans, animals models have been frequently used. However, there is no animal model that fully recapitulates the effects of ethanol on the human pancreas.

**Pancreatic duct pressure, secretion and permeability**

Pancreatic duct pressure is a function of the viscosity of pancreatic fluid, the rate of secretion and the resistance to outflow within duct caused by sphincter of Oddi dysfunction, pancreatic duct stones or strictures. Ethanol may acutely affect several of these pathologic mechanisms.

The acute effects of alcohol in humans have been examined using either intravenous or duodenal instillation of ethanol in normal and alcoholic subjects. Two recent studies demonstrated increased basal sphincter of Oddi and pancreatic duct pressures in patients with chronic alcoholic pancreatitis compared to controls [26, 27]. Acute ethanol exposure has been reported to cause sphincter pressures to decrease [28] and to increase the number of retrograde contractions [27]. Thus, basal sphincter and pancreatic duct pressure are often elevated in patients with chronic alcoholic pancreatitis, but ethanol may transiently reduce sphincter pressure and enhance retrograde contractions. These changes may allow the temporary reflux of duodenal contents into the pancreatic duct followed by longer periods when the resistance to outflow is increased.

The epithelial lining of the pancreatic duct is a barrier that prevents the movement of pancreatic juice into the interstitial space. Pancreatic duct secretions that escape into the interstitial space may be activated and play a role in the development of pancreatitis [29]. The effects of ethanol on pancreatic ductal pressure and permeability have been examined after its intragastric and intravenous administration or using duct perfusion. Although it appears that ethanol increases the permeability of the pancreatic duct, this change alone is probably not sufficient to cause pancreatitis [30, 31].

The acute effects of ethanol on exocrine secretion may vary on the history of its use and the type of beverage. In non-alcoholics, alcohol tends to inhibit pancreatic secretion [32], but in chronic alcoholics there may be an enhanced secretory response that is mediated by cholinergic pathways [33]. However, the paucity of studies in human subjects make it difficult to conclude that acute ethanol ingestion has a predictable effect on the human exocrine pancreas.

The effects of acute ingestion or withdrawal of alcohol on the composition or viscosity of pancreatic secretions has not been carefully examined, but increased concentration of proteins in pancreatic juice are found in chronic alcoholics and may lead to the formation of protein plugs and ductal hypertension [34]. Chronic abuse also leads to increased levels of trypsinogen in pancreatic juice and decrease in trypsin inhibitor [35].

These studies suggest that the major acute effects of ethanol are to cause a relaxation and retrograde contractions of the sphincter and to increase duct permeability. It is unlikely that either of these mechanisms alone leads to pancreatitis.

**Pancreatic blood flow and oxidants**

Experimental and clinical evidence supports a relationship between pancreatic ischemia, oxygen-derived free radicals and the pathogenesis of acute pancreatitis [36, 38]. Ethanol may influence oxidant damage through a variety of mechanisms [39]. Although some experimental studies indicate that ethanol may cause oxidant stress in acute pancreatitis, the clinical relevance of these observations have not been explored.
Ethanol and cytokines

Ethanol may modulate the generation of cytokines that lead to inflammation and cell death and the most serious consequences of acute pancreatitis [40]. Tumor necrosis factor (TNF) is released by ethanol feeding [41]. TNF and interleukin-1 are determinants of the severity of acute pancreatitis [42]. Inhibition of damaging interleukins or infusing the protective interleukin-10 may provide an effective therapy for acute pancreatitis [43].

DIRECT AND INDIRECT EFFECTS OF ETHANOL
ON THE PANCREATIC ACINAR CELL

Ethanol and its metabolites may have short-term and long-term affects on acinar cell physiology and cause changes in the composition of cell membranes and membrane movement and cell signaling that may contribute to its toxic effects.

Ethanol affects cell membranes and trafficking

Ethanol has been reported to rapidly change membrane fluidity, charge, composition, and membrane integrity of acinar cell. The effects of ethanol on membrane fluidity depends on the concentration of ethanol and its metabolism. Although ethanol may directly increase membrane fluidity, some of its metabolites such as phosphatidylethanol may decrease membrane fluidity [44]. Phosphotidylethanol is generated from phosphatidylcholine by the action of phospholipase D. As a result of ethanol treatment in some tissues, phosphatidylethanol may increase from undetectable levels to comprise 2 percent of cellular phospholipid. The generation of negatively-charged phosphotidylethanol from its positively-charged precursor (phosphatidylcholine) is very likely to change membrane surface charge. These effects of ethanol have the potential to affect the interaction of membrane proteins with intra- and extracellular proteins and ligands, the movement of proteins within the bilayer, and to indirectly modify cellular signaling pathways.

Ethanol may affect membrane integrity and permit the breakdown of cellular organelles. Leakage of lysosomal enzymes from lysosomes has been reported to occur in experimental pancreatitis and attributed to increased membrane fragility [45]. Similar increases in fragility of lysosomal membranes has been reported in ethanol-fed rats [46]. This effect appears not to be due to ethanol or its metabolite, acetaldehyde, but may be the result of ethanol-induced cholesterol ester accumulation [47] or ethanol enhanced phospholipase A₂ [48]. The effects of short-term ethanol on membrane integrity have not been examined.

Physiologic studies relevant to the membrane effects of ethanol are limited. However, ethanol has been found to affect the trafficking of cell surface proteins through endocytic pathways. Reduced endocytosis of the epidermal growth factor receptor by ethanol (100 mM) in hepatocytes may be related to changes in membrane fluidity and the disruption of the clathrin coat required for endocytosis [49]. Ethanol (50 mM) reduces endocytosis of the insulin receptor from the hepatocyte [50]. Whether ethanol affects endocytic pathways or other trafficking events in the acinar cell is unknown.

Ethanol affects intracellular signaling

Ethanol has been found to influence both cyclic nucleotide and calcium messenger systems. In many systems ethanol stimulates adenylate cyclase (AC) activity; pathologic stimulation of AC activity requires very high concentrations (> 500 mM) of ethanol in most systems, including the pancreas (reviewed in [51]). However, when added in the presence of ligands that activate AC, low doses of ethanol (< 25 mM) often dramatically enhance AC activation [51]. Although the mechanism of ethanol sensitization of AC activity is unclear,
it may act by decreasing the activity of Gi, increase the efficacy of Gas in activating AC and enhance nucleotide exchange, or by affecting membrane fluidity [52].

In many cell systems, ethanol can affect intracellular calcium levels in the absence of receptor occupancy. The most common effect is a transient increase in intracellular calcium that has been linked to G protein-dependent phospholipase C activation. The increase in intracellular calcium as well as 1,4,5 inositol trisphosphate generation associated with ethanol treatment is more short-lived than that generated by natural ligands. These studies suggest that physiologically relevant concentrations of ethanol probably have little effect on acinar cell signaling, but that it may modify signalings in stimulated cells.

Ethanol enhances zymogen activation

The pathologic activation of pancreatic zymogens within the acinar cell is thought to play a role in the initiation of some forms of pancreatitis. Animals treated with high concentrations of CCK or cholinergic agonists develop pancreatitis; treatment of isolated pancreatic acini with similar concentrations of these agents results in the intracellular activation of pancreatic enzymes [53]. Ethanol dramatically sensitizes the acinar cell to the effects of cholecystokinin on zymogen activation; 25 mM ethanol, a physiologically relevant concentration, shifts the concentration-dependence for CCK two orders of magnitude to the left [53]. These findings suggest that a combination of ethanol and increased CCK levels might lead to the pathologic activation of zymogens within the acinar cell.

It is difficult to generate ethanol-induced pancreatitis experimentally

Although ethanol alone does not appear to cause pancreatic injury in experimental models of pancreatitis, it may have a synergetic effect when combined with other insults. The acute or chronic administration of ethanol in the rat resulted in increased injury when pancreatitis was induced by a combination of pancreatic duct obstruction and hyperstimulation [54, 55]. These results suggest that ethanol contributes to the development of acute pancreatitis when there are active enzymes in the pancreatic duct or when secretion is stimulated in the setting of obstruction to pancreatic outflow.

These studies emphasize the fact that ethanol-induced pancreatic injury is a multifactorial event. In addition to ethanol, a variety of host factors determine the susceptibility to ethanol. The fact that only a small per cent of alcoholics develop pancreatitis emphasizes the importance of host factors in developing this disease and may provide insight into the difficult in generating alcoholic pancreatitis in an animal model using ethanol alone.

SUMMARY

Alcohol appears to generate two distinct patterns of pancreatitis; an acute self-limiting injury and a chronic inflammatory process associated with decreased pancreatic function (Figure 1). Although most cases of acute pancreatitis will be episodes of acute inflammation in a previously damaged pancreas, some patients will develop acute injury in the absence of underlying chronic disease. The relationship between the patterns and levels of alcohol consumption and the risks for developing acute pancreatitis require further examination. However, it appears that most cases occur in the setting of long-standing heavy alcohol consumption and that acute alcoholic pancreatitis in the non-alcoholic binge drinker is rare.

The pancreatic injury induced by short-term ethanol exposure is likely to multifactorial and involve both acute and chronic effects (Figure 2); proposed mechanisms include ductal hypertension induced by increased viscosity of secretions in combination with obstruction secondary to sphincter of Oddi dysfunction, stimulation of secretion, increased
duct permeability, decreased pancreatic blood flow, inflammation and oxidant stress and direct acinar cell toxicity.

Future studies should define the factors that result in patients developing either acute bouts of pancreatitis or chronic disease. Since only a fraction of patients that abuse alcohol develop pancreatic disease, elucidation of pathophysiologic determinants that increase an individual's susceptibility to alcohol is an important topic for future studies.

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