JOP. J Pancreas (Online) 2005; 6(1 Suppl.):68-72.

AISP - 28th National Congress. Verona (Italy). October 28-30, 2004.

Alcohol and Chronic Pancreatitis: Leading or Secondary Etiopathogenetic Role?

Lucio Gullo

Institute of Internal Medicine, St. Orsola Hospital, University of Bologna. Bologna, Italy

Based on the data of the numerous articles on chronic pancreatitis which have been published over the years, I will describe the role played by alcohol in the etiopathogenesis of this disease; all the available evidence shows that alcohol has a leading etiopathogenetic role in chronic pancreatitis. I will also discuss the possible etiological role of other factors in this disease, such as diet and smoking.

Etiopathogenesis of Chronic Pancreatitis

Modern knowledge of chronic pancreatitis begins with the study by Sarles *et al.* [1] published in 1965. In this study, the main etiological, histological and clinical aspects of this disease were described together for the first time. From an etiological point of view, it was reported that alcohol was the most frequent etiological factor (in more than 80% of cases) of chronic pancreatitis, that alcoholic chronic pancreatitis presented clinically in young adults (30-40 years), generally males, that, histologically, the lesions were chronic "*ab initio*" and that, clinically, the disease was characterized by recurrent attacks of abdominal pain. This study was followed by numerous others, both in France and in various European and non-European countries, which confirmed these data. In particular, as far as the etiological role of alcohol is concerned, this was confirmed by all the authors who studied chronic pancreatitis.

In France, the results of Sarles *et al.* [1] were subsequently confirmed by Gastard *et al.* [2] who found alcohol to be the etiological factor in 224 (85%) of 263 cases of chronic pancreatitis, by Bernades *et al.* [3] who demonstrated the role of alcohol in the etiology of chronic pancreatitis in 92 (77%) out of the 120 patients studied and finally by Levy *et al.* [4] who showed that in a series of 240 patients with chronic pancreatitis the etiology was alcoholic in 210 (88%) cases.

In Italy, in a multicenter study published in 1976 based on 253 cases of chronic pancreatitis [5], we found that excessive chronic intake of alcohol was the main etiological factor of the disease in 197 (78%) of the cases. In Italy, as in France, the disease appeared most frequently between the age of 30 and 40 years, the histological lesions were similar to those found by Sarles *et al.* [1] in France and pain was the main symptom.

More recently, another study [6] confirmed that, in Italy, alcohol continues to be the most frequent etiological factor (75% of cases) of the disease.

In Switzerland,, Ammann *et al.* [7] reported alcohol to be the etiological factor in 173 (71%) of 245 patients with chronic pancreatitis. In Germany, Lankisch *et al.* [8] found that alcohol was the main etiological factor in 230 (69%) out of 335 patients with chronic pancreatitis.

Outside Europe, the study by Marks *et al.* [9] from Cape Town (South Africa) demonstrated that chronic pancreatitis was caused by

alcohol in 492 (67%) of 734 cases, the study by Layer *et al.* [10] from the United States reported an alcoholic etiology in 252 (75%) out of 334 patients with chronic pancreatitis and, finally, the study by Dani *et al.* [11] from Brazil showed alcohol to be the etiological factor in 717 (90%) of the 797 cases studied. All these studies therefore show that an excessive chronic intake of alcohol is an important etiological factor in chronic pancreatitis.

Various findings also support the etiological role of alcohol in chronic pancreatitis. First of all, there is a clear relationship between the risk of developing chronic pancreatitis and alcohol consumption. Sarles *et al.* [12, 13] demonstrated that the relative risk of chronic pancreatitis increases in a linear fashion as a function of mean daily alcohol consumption. We have also seen that alcoholic chronic pancreatitis is generally more severe in heavy drinkers as compared to moderate drinkers, and that exocrine pancreatic insufficiency, and, consequently, the histological lesions of the disease, usually progress more slowly in patients who stop drinking with respect to those who continue [14].

The duration of alcohol intake before the onset of the disease is not generally very long; in Italy [5] we found an average of 15 years, similar to what has been observed in other countries. The minimum amount of alcohol necessary for the appearance of chronic pancreatitis has not been clearly established; it is nevertheless considered that even a relatively moderate level of alcohol intake (40-50 g of pure alcohol per day) can cause chronic pancreatitis [12].

The mechanism by which alcohol causes chronic pancreatitis is not known. In normal conditions alcohol is metabolized in the pancreas as it is in the liver via alcohol dehydrogenase to acetaldehyde, and an excess of alcohol intake can therefore have direct pathological effects on the pancreatic cells, as occurs in the liver. One of the first lesions in alcoholic chronic pancreatitis is the increase in protein concentration in the pancreatic juice and the consequent formation of protein plugs in the small excretory ducts with the occlusion of these ducts and perilobular fibrosis [1, 5]. An increase of protein concentration in the pancreatic juice and an excretion of protein plugs through the glass cannula which catheterizes the main pancreatic duct has also been observed in dogs subjected to chronic administration of alcohol [15]. It can be hypothesized that this protein alteration in the pancreatic juice is one of the pathological consequences of the toxic effects of excessive alcohol intake on acinar cells, but the mechanism is unknown.

In addition, numerous experimental studies [16, 17] have shown that alcohol abuse stimulates pancreatic fibrogenesis, and this could be another mechanism of the harmful effect of alcohol on the pancreas. It should, however, be remembered that alcohol abuse causes diffuse pancreatic fibrosis which is intralobular without other important lesions in the majority of chronic alcohol drinkers [18, 19]; this fibrosis is different from that seen in alcoholic chronic pancreatitis in which fibrosis is mainly perilobular at the beginning and intralobular only in more advanced stages.

In alcoholic pancreatitis [1, 5, 20], the main histological feature is the irregular, apparently lobular distribution of the lesions; different degrees of destruction can be seen in neighbouring lobules as well as normal-looking and altered lobules adjacent to one another. The lesions essentially consist of: a) perilobular and intralobular fibrosis (the fibrosis is exclusively perilobular in the initial phases of the disease when the lesions are scanty); b) the presence of protein plugs, which later calcify, in the dilated ducts; c) the presence of dilated interlobular ducts, lined by cuboidal or flattened epithelium or without epithelium; d) loss of exocrine parenchyma and atrophy of residual lobules. In the altered lobules the most constant and typical finding is the presence of a variable number of more or less dilated acini and ductules lined by cuboidal or flattened epithelium (canalicular regression). Often the lobules are replaced by irregular groups of dilated lumina, lined by flattened epithelium, lying in dense fibrous tissue.

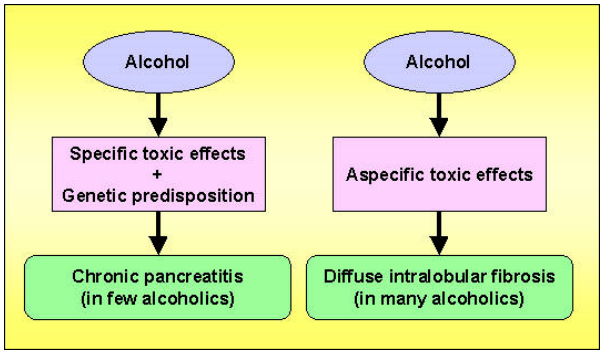

Figure 1. Pathologic effects of alcohol on the pancreas.

It would seem that alcohol abuse can lead to perilobular and subsequently intralobular fibrosis and to other lesions of chronic pancreatitis in a few genetically predisposed subjects and to diffuse aspecific intralobular fibrosis without other important lesions in many subjects (Figure 1).

Other Etiological Factors in Chronic Alcoholic Pancreatitis

In addition to alcohol, few other factors have been considered to have a role in the etiology of this form of pancreatitis; these are dietary factors and smoking.

The role of diet in the etiology of alcoholic pancreatitis was primarily studied by Sarles *et al.* [12, 13]. These investigators carried out various international multicenter studies in which they showed that a diet rich in protein and fat prior to the appearance of alcoholic chronic pancreatitis may have a role in the etiology of this disease [12, 13]. In fact, many patients with this form of pancreatitis are big eaters as well as heavy drinkers before the clinical onset of the disease, at least in France and Italy. The mechanism by which a diet rich in fat and protein can favor the development of alcoholic pancreatitis is unknown. Since a hyperconcentration of proteins in the pancreatic juice is one of the first lesions of alcoholic chronic pancreatitis, it can be hypothesized that an excess of proteins and fats in the diet can play a role in the appearance of this hyperconcentration of proteins in the pancreatic juice through an increased release of hormones which stimulate pancreatic protein secretion (cholecystokinin and neurotensin).

Table 1. Etiopathogenetic factors in chronic pancreatitis.

Exogenous factors	Endogenous factors
Alcohol (Leading role)	Genetic predisposition
Diet (Secondary role)	(Leading role)
Smoking (Secondary role)	

As far as smoking is concerned, its possible role in the etiology of alcoholic chronic pancreatitis was suggested many years ago. In our study on chronic pancreatitis in Italy [5], we noted that almost all the patients with alcoholic pancreatitis were also heavy smokers and we therefore suggested the necessity of studying this relationship. The role of smoking in the etiology of chronic pancreatitis has since been investigated by several authors [21, 22, 23] who concluded that smoking can contribute to the etiology of this disease. However, the mechanism by which this can occur is not known. I believe that if smoking does play a role in the etiology of alcoholic chronic pancreatitis, then it is certainly secondary as compared to the role of alcohol. I would like to point out that, among the numerous patients I have seen over the years who were both smokers and had chronic alcoholic pancreatitis, many of those who no longer suffered pain had stopped drinking but not smoking and, despite the fact that they continued to smoke, continued to feel well. This is a clinical observation which can further support the leading role of alcohol with respect to that played by smoking.

In conclusion, alcohol plays a leading etiopathogenetic role in chronic pancreatitis; both dietary factors and smoking, if they indeed have a role, must be considered secondary factors.

In addition to alcohol, a leading role in the etiopathogenesis of chronic pancreatitis is played by genetic predisposition (Table 1). The fact that only a few people with alcohol abuse develop chronic pancreatitis stresses the important role of genetic factors. Various studies have been carried out in recent years which emphasize the role of these factors in alcoholic pancreatitis [24, 25].

Keywords Alcohol-Related Disorders; Biological Factors; Causality; Genetic Predisposition to Disease; Histology; Pancreatic Diseases; Pancreatitis; Pancreatitis, Acute Necrotizing; Pancreatitis, Alcoholic; Toxicogenetics

Correspondence
Lucio Gullo
Institute of Internal Medicine
S.Orsola Hospital
University of Bologna
Via Massarenti, 9
40138 Bologna
Italy
Phone: +39-051.636.3615
Fax: +39-051.392.486
E-mail: gullo@med.unibo.it

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