Criteria for Alcoholic Pancreatitis

Results of an International Workshop in Tampere, Finland, June 2006

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Background

Alcoholic pancreatitis is a major medical problem in several countries coinciding with the amount of alcohol consumption in the country \cite{1, 2}. Depending on the area, up to 70\% of acute pancreatitis and 90\% of chronic pancreatitis are estimated to be induced by excessive alcohol consumption. However, despite that the term ‘excessive’ has been commonly used both in the scientific literature and in everyday clinical practice, it has been far from clear where the limits of alcohol consumption should be set to allow acceptance of the term alcoholic pancreatitis.

There are wide variations between the countries in the epidemiology of both acute and chronic alcoholic pancreatitis \cite{3, 4}, but this can only partly be explained by the differences in the alcohol consumption of the countries. Genetic factors have recently been proposed as relevant explanations of the differences, whereas the criteria for the diagnosis of alcoholic pancreatitis have been less in focus. When developing diagnostic and therapeutic strategies for alcoholic, biliary and idiopathic pancreatitis (just to mention the three most common categories), the same criteria should be used to allow comparison of the results of various studies and their application into clinical practice. Furthermore, in order to direct effective therapies correctly to prohibit recurrent problems of pancreatitis, and to avoid unnecessary ‘labeling’ of a patient as ‘an alcoholic’, commonly accepted criteria should be available for alcoholic pancreatitis. They should be able to be used both for the acute and the chronic variant of the disease. At the moment the criterion used might too often be expressed as ‘the patient drinks more than the doctor’.

Scientific achievements have gradually elevated the understanding of alcoholic pancreatitis and its treatment, with upgrading through some prior consensus workshops where acute and chronic dilemmas and various therapeutic options have been outlined. In the line of such consensus conferences, a consensus workshop (www.alcopancreatitis-workshop.tk) was organized in June 2006 in Tampere, Finland, aiming at finding an answer to the question ‘When will pancreatitis be considered to be caused by alcohol?’ The workshop was organized to precede the 38th European Club Meeting where the results of the workshop were also discussed. The workshop was organized without commercial conflict of interests, with the financial support of the Finnish Academy of Sciences, the Finnish Association of Gastroenterology and the Finnish Society for Digestive Surgery. In this issue of Pancreatology, the reviews of various topics are published based on of the presentations and the pre-
pared comments [5–11]. Below is a summary of the main results of the workshop to make a suggestion for criteria of alcoholic pancreatitis.

**Summary of the Reviews**

**Pathogenesis of Alcoholic Pancreatitis**

**Effects of Non-Alcoholic Compounds of Alcoholic Beverages on the Pancreas**

There are thousands of organic and anorganic compounds in alcoholic beverages, as outlined in Singer et al. [5]. Many substances have been convincingly demonstrated to have a different effect than ethanol at least on gastric acid secretion. Also pancreatic enzyme secretion is stimulated by some of the non-alcoholic constituents of beer which are generated by alcoholic fermentation of glucose. Natural phenolic compounds (e.g. quercetin, and resveratrol) of alcoholic beverages inhibit pancreatic enzyme output in vitro, activate pancreatic stellate cells and have protective effects against oxidative stress and on experimental acute pancreatitis in rats.

From this review, it may be proposed that despite the few known effects it should be anticipated that non-alcoholic compounds might also play some role in the induction of or protection against pancreatic injury, or on its repair, even though it is not probable that they are the inducer(s) of the pancreatitis. Although their role should be given more consideration in future research, the criteria for alcoholic pancreatitis cannot be based on the consumption of these non-alcoholic compounds, i.e. the types of beverages used should be omitted from the definition.

**Effects of Ethanol and Its Metabolites on the Pancreas**

Pandol and Raraty [6] emphasized the importance of ethanol metabolites rather than ethanol itself. Ethanol is metabolized not only via oxidative metabolism to acetaldehyde and acetate, but also via nonoxidative metabolism to fatty acid ethyl esters (FAEE). Actually, the pancreas has the best ability of the organs to metabolize ethanol to FAEEs, even better than the liver. There is increasing evidence that FAEEs have direct and indirect effects on cell apoptosis pathways through alterations in cell calcium metabolism leading to necrosis of pancreatic acinar cells as well as on the plasminogen system which may augment fibrosis. In addition to their direct adverse effects on the pancreas, ethanol and its metabolites sensitize the pancreas to the injury induced for example by hyperstimulation. Ethanol sensitizes the pancreas by effecting the kinase systems and transcription factors that regulate the inflammatory response, and the expression of mediators of apoptosis and necrosis. Ethanol, or acetaldehyde, may also participate in generating oxygen free radicals and thus effect both acinar and stellate cells.

From this review, it may be proposed that although the detailed mechanisms of alcoholic pancreatitis (acute and chronic) are far from clear, substantial evidence has accumulated to conclude that the metabolites of ethanol may initiate pancreatic injury under some yet not fully clear conditions. Furthermore, once the pancreatic injury has been initiated independently of the inducer, this injury may be enhanced by ethanol. Based on in vitro and in vivo experimental studies, it may be concluded that ethanol might work as a trigger or a modulator in the presence of another trigger of pancreatitis.

**Effects of Ethanol on the Inflammation Response**

The inflammation response has been largely studied in pancreatitis and has been shown to play a critical role in determining organ dysfunction – in the pancreas and in remote organs – during acute pancreatitis. Less well known are the effects of ethanol on this inflammation response. Szabo et al. [7] reviewed the effects of ethanol on the activation of inflammatory cells. Equivalent doses of ethanol simulating moderate alcohol consumption had in vitro anti-inflammatory effects on monocyte activation via inhibition of pro-inflammatory genes and NF-κB activation, inhibition of TNFα production and augmentation of anti-inflammatory IL-10. In contrast, acute treatment with ethanol augmented NF-κB activation and TNFα production and inhibited IL-10 levels in the presence of complex stimulation with combined TLR2 and TLR4 ligands. Prolonged alcohol exposure also resulted in an increase in NF-κB and TNFα production in response to TLR4 stimulation with LPS.

From this review, it may be concluded that ethanol can either attenuate or promote inflammatory responses partly depending on the length and dose of ethanol used. Thus, drinking alcohol may considerably modulate pancreatic injury, independent of its etiology.

**Summary of the Reviews on Pathogenesis**

The current knowledge on the pathogenesis of pancreatitis and the effects of alcohol (ethanol, non-ethanol compounds, and metabolites of ethanol) on the pancreas and inflammation suggests a dual role of alcohol: it may serve as a trigger of the disease, but may also mod-
ulate the disease independent of the trigger. Therefore, preceding alcohol consumption may have a role also in pancreatitis where a non-alcoholic etiology can be verified.

**Diagnosis of Non-Alcoholic Etiologies**

**Detection of Biliary Pancreatitis**

In their review, Sutton and co-workers [8] emphasized the importance of the detection of the patients with so-called biliary pancreatitis which refers to pancreatitis induced by gallstones or ‘microlithiasis’. Specific treatment with endoscopic sphincterotomy and/or cholecystectomy may ameliorate the course of the disease and prevent recurrences. Stones in the gallbladder or main bile duct verified by any imaging modality and elevated serum alanine aminotransferase documents the gallstone etiology in most cases, and should lead to endoscopic sphincterotomy in severe cases. If only large bile duct is identified without gallstones (>8 mm diameter with gallbladder in situ, or >10 mm following cholecystectomy if aged <70 years and >10 mm and >12 mm, respectively if >70 years), endoluminal ultrasonography may be performed to look for possible hidden gallstones. Another indication for endoscopic ultrasonography is when the etiology remains uncertain. Then this examination may be performed after discharge from the hospital to further investigate possible gallstones and to exclude periampullary tumors. When the etiology is still open after endoluminal ultrasonography, bile crystal analysis, an indicator of microlithiasis, is recommended. Thus, a substantial number of pancreatitis patients otherwise considered as having unknown etiology will fall into the gallstone pancreatitis category.

From this review, it may be proposed that the patient is diagnosed with biliary (gallstone) pancreatitis when gallstones or microlithiasis has been demonstrated. It is important to describe the methods used in the diagnostic work-up, because the sensitivity increases from serum liver chemistry and transabdominal ultrasonography to endoscopic ultrasonography and further to duodenal bile crystal analysis. There are no data on the prevalence of bile crystals in patients with suspected alcoholic pancreatitis. However, because gallstones and excessive alcohol consumption may coexist in a single patient the trigger of the pancreatitis cannot be proven. Alcohol may then be another trigger or just a modifier of biliary pancreatitis. Therefore, we need to accept more than one probable etiology in a single patient, not least to prevent recurrences. Furthermore, only a minority of patients who have ‘excessive alcohol consumption’ develop alcohol-induced pancreatitis. Thus, a patient with ‘excessive alcohol consumption’ should be examined in the same way as a patient without such exposure to detect other possible etiologies.

**Detection of Non-Alcoholic and Non-Biliary Etiologies**

Numerous reasons besides alcohol and gallstones have been published as potential etiologies for pancreatitis. In their review, Kemppainen and Puolakkainen [9] outlined the most important etiologies to be ruled out in clinical practice.

Serum triglyceride measurement should be performed routinely on admission in all patients with acute pancreatitis, because the triglyceride levels fall rapidly within 24–48 h of fasting. A level of more than 11 mmol/l (1,000 mg/dl) is considered as the requirement for a likely hypertriglyceridemic etiology, lower abnormal values possibly serving as not more than a cofactor. Decrease of triglyceride levels to less than half will efficiently prevent recurrent episodes of the disease. A confounding factor might be that alcohol consumption per se also raises the triglyceride levels in serum.

Hypercalcemia, either primary or secondary, is a rare etiology of pancreatitis. Despite that, serum calcium levels should be measured routinely on admission in all patients with acute pancreatitis, not only to detect rare hypercalcemia but more to stage the severity of the disease. Falsely low values are common in severe pancreatitis as well as in mild pancreatitis at low levels of serum albumin, explaining why later sampling is recommended in the work-up of patients with otherwise unknown disease.

The possibility of heredity, ERCP, trauma, preceding infection and medications should be investigated. When endoscopic ultrasonography is used to detect gallstones, periampullary tumors might be detected as well. Clarifying the etiology of multirecurring pancreatitis may require ERCP ± manometry to detect anatomic or functional outflow obstruction. In chronic or recurring pancreatitis with suspected pancreatic imaging findings serum IgG4 and pancreatic biopsy either endoluminally or transabdominally need to be studied to confirm the diagnosis of autoimmune pancreatitis. This is especially important before operative treatment of chronic pancreatitis without calcifications.

From this review, it may be proposed that careful history taking (medication, family history, trauma, toxins, autoimmune disorders, surgery, ERCP, pregnancy, infectious diseases), as well as serum triglycerides and serum
calcium levels, should be studied in each patient. Endoscopic ultrasonography/MRCP/ERCP/manometry with IgG4 and selected biopsy should be performed in multirecurring/chronic pancreatitis. As these conditions, similar to gallstones, may also exist with ‘excessive alcohol consumption’, they need to be examined as patients without such exposure to detect all possible etiologies.

**Alcohol Consumption of Pancreatitis Patients**

In their reviews, Sand et al. [10] outlined the available data of alcohol consumption and the difficulties in obtaining such data in patients who have developed either acute or chronic pancreatitis. They emphasized that despite the association between alcohol consumption and pancreatitis being recognized for over 100 years, it still remains unclear why clinical pancreatitis develops only in some of the high alcohol consumers. Smoking seems to be a remarkable co-factor in the development of chronic pancreatitis, whereas this association in acute pancreatitis remains to be solved. Epidemiological studies clearly show a connection between alcohol consumption in the population and the development of acute and chronic pancreatitis. At the individual level, the risk of developing either acute or chronic pancreatitis increases remarkably along with the alcohol consumption. Moreover, the risk for recurrent acute pancreatitis after the first acute pancreatitis episode also seems to be highly dependent on the level of continuing alcohol consumption. Abstaining from alcohol may prohibit recurrent acute pancreatitis and reduce pain in chronic pancreatitis. Therefore, all attempts to decrease alcohol consumption after acute pancreatitis and even after the diagnosis of chronic pancreatitis should be encouraged. Setting the limits for accepting alcohol as the etiology can, however, not be based on published data, but represents a ‘political’ agreement.

**Criteria for Alcoholic Pancreatitis**

Based on these reviews [5–11], and the discussions during the workshop and the 38th European Pancreatic Club Meeting, the following criteria are suggested to be used both in future clinical science and in treating patients with suspected alcoholic pancreatitis.

Although a single etiology is most often detectable for both acute and chronic pancreatitis, it must be accepted and an individual who has been sober for some months and feels pointed out in his social life for not adapting to the ‘normal’ life. It is therefore more practical to use three categories: probable alcoholic etiology when there is high alcohol consumption, possible alcoholic etiology when there is less alcohol consumption, and non-alcoholic etiology when there is negligible alcohol consumption.

**Detection of Alcohol Consumption**

In their review, Chick and Kemppainen [11] again emphasized the difficulties in detecting the amount of alcohol consumption. Hazardous drinking and alcohol dependence (i.e., high consumption) may be suspected when associated social, occupational, psychiatric or other medical conditions attributable to high alcohol consumption occur. The most pertinent single screening question is ‘How often do you drink more than 70 g in a day’ (translated into local preferred beverages and serving amounts). A reply of ‘at least once per week’ should lead to further enquiry. FAST and AUDIT are validated simple questionnaires for the detection of high alcohol consumption and SADD and CAGE for the detection of the dependence on alcohol. Concomitant use of sedatives increases the likelihood of the dependence.

Blood tests are not better than the questionnaires. They may be used when the history cannot be obtained either from the patient or the family member. Serum carbohydrate-deficient transferrin (CDT) is the best single laboratory test today to suggest high consumption. In the GI outpatient clinic with chronic or recurring pancreatitis patients the alcohol breath test may detect some individuals with high consumption.

From this review, it may be proposed that simple validated questionnaires (FAST, AUDIT) are available for the detection of high alcohol consumption. When these cannot be applied, serum CDT may suggest the high consumption.
that in some patients two or more possible etiologies may be present. Thus, when one etiology is found, further work-up is needed to detect or rule out other possibilities. For accepting alcohol as one such etiology, the preceding alcohol consumption needs to be categorized. This may be done simply with the WHO recommended AUDIT questionnaire ([www.who.int/substance_abuse/publications/alcohol/en/]) where 0–3 points refers to negligible alcohol consumption, 4–7 points to low alcohol consumption and 8 or more to risky (high) alcohol consumption [12], or even the simpler FAST questionnaire, where a negative answer to the first question means negligible alcohol consumption, positive to the first question but negative to the second question means low alcohol consumption, and positive to both first and second questions means high alcohol consumption [13]. In the rare case, when the questionnaires cannot be applied, serum CDT measurement may be performed [14, 15]. The cut-off values of CDT are dependent on the method used, which is why the method of measurement and the validation of this method should be announced. Independent of the method used, high alcohol consumption correlates with a probable alcoholic etiology of pancreatitis, low alcohol consumption not ruling out the alcoholic etiology of pancreatitis and negligible alcohol consumption to the non-alcoholic etiology of pancreatitis.

Participants


References