Abstinence after First Acute Alcohol-Associated Pancreatitis Protects Against Recurrent Pancreatitis and Minimizes the Risk of Pancreatic Dysfunction

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TIIVISTELMÄ

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Tutkimuksen tavoitteena oli tutkia haimatulehduksen uusimien ja haiman vajaatoiminnan ilmaantuvuutta potilailla, jotka lopettavat alkoholin käytön ensimmäisen alkoholiperäisen haimatulehduksen jälkeen.

Prospektiivisessa seurannassa oli mukana 118 ensimmäisen alkoholihaimatulehduksen sairastanutta potilasta. Näistä 18 (kaikki miehiä, iän mediaani 47 (27-71) vuotta) pystyivät pidättäytymään alkoholin käytöstä ainakin puolentoista vuoden ajan sairastumisen jälkeen. Kriteereinä alkoholin käytön lopettamiselle pidettiin alle 24 gramman itsearvioitua kulutusta kahden kuukauden ajalta yhdenmukaisena AUDIT-pisteiden (Alcohol Use Disorders Identification Test, <8), SADD-pisteiden (Short Alcohol Dependence Data, <9) ja alkoholinkulutusta mittaavien laboratoriokokeiden kanssa. Haimatulehduksen uusimat selvitettiin. Haiman mahdollista endo- ja eksokriinistä vajaatoimintaa arviointiin aluksi puolen vuoden välein ja kahden vuoden jälkeen vuoden välein aina yhdeksään vuoteen saakka haiman toimintaa kuvaavin merkkiainein. Lisäksi potilaiden tupakointi ja painoindeksi tilastoitiin.

Seuranta-ajan keskiarvo alkoholista pidättäytymiselle oli 5.15 (1.83-9.13) vuotta ja yhteensä 92.7 potilasvuotta. Seurannan aikana alkoholista pidättäytyneet potilaat eivät sairastuneet haimatulehduksen uusimiin. Kahdella potilaalla oli diabetes ennen haimatulehdusta, yhdellä potilaista diagnosoitiin diabetes sairastumisen yhteydessä. Lopuista seurannassa mukana olleista potilaista yksikään ei sairastunut diabetekseen. Eksokriininen toiminta palautui abstinenssin aikana normaaliksi kaikilla paitsi yhdellä potilaalla (6%) arvioituna ulosteen elastaasi-1:den perusteella. Sadasta potilaasta, jotka jatkoivat alkoholin käyttöä ensimmäisen haimatulehduksen jälkeen 34% sairastui taudin uusimaan.

Koska tarkkaa mekanismia, jolla alkoholi aiheuttaa haimatulehduksen ei tiedetä, alkoholista pidättäytyminen on toistaiseksi ainoa tehokas keino estää taudin uusimista. Haiman vajaatoimintaa on myös harvinaista potilailla, jotka pidättäytyvät alkoholista sairastumisen jälkeen.

Title page

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ABSTRACT

Aims. To determine the recurrence of pancreatitis and subsequent pancreatic function in patients who stop drinking after the first episode of alcohol-associated pancreatitis.

Methods. Out of a total of 118 patients suffering their first alcohol-associated pancreatitis, 18 (all male, age median 47 (27–71) years) met the inclusion criteria for abstinence during follow-up. The criteria for abstinence was alcohol consumption less than 24 grams per two months (self-estimated) which is in line with questionnaires eliciting alcohol consumption and dependency (Alcohol Use Disorders Identification Test, AUDIT < 8 and Short Alcohol Dependence Data, SADD < 9). Recurrent attacks of acute pancreatitis were studied. Smoking, body-mass index and laboratory tests detecting heavy consumption of alcohol were recorded. Blood and faecal tests were studied to assess endocrine and exocrine pancreatic function.

Results. During a mean follow-up time of 5.15 (1.83–9.13) years and a total of 92.7 patient years there were no recurrent attacks of acute pancreatitis among the 18 abstainers. Two patients had diabetes prior to and one was diagnosed immediately after the first episode of acute pancreatitis. One patient had impaired glucose metabolism at two years. Two patients had low insulin secretion in glucagon-C-peptide test, one at four and the other at five years. Only one patient (6%) maintained low elastase-1 activity during abstinence follow-up. Out of the 100 non-abstainers 34% had at least one recurrence during follow-up.

Conclusions. Regardless of the mediator mechanisms of acute alcoholic pancreatitis, abstinence after the first episode protects against recurrent attacks. Pancreatic dysfunction is also rare among abstinent patients.

INTRODUCTION

Alcohol and gallstones are two major aetiological factors associated with acute pancreatitis. The recommended treatment for biliary pancreatitis is early cholecystectomy or endoscopic sphincterotomy if cholecystectomy is not feasible. This usually prevents relapses (Uhl *et al.,* 2002; Banks *et al.,* 2006). By contrast alcoholic pancreatitis is not so straightforwardly treated and as many as 46% of patients suffer recurrent attacks within 10-20 years with 80% of the first relapses occurring during the first four years (Pelli *et al.,* 2000). The risk factors for recurrences include increased dependency on alcohol, mild first attack, persistent pseudocysts and young age at the time of the first attack. Alcohol consumed after the first attack has been identified as a dose-dependent risk factor and total abstinence has been suggested to protect against recurrences according to a preliminary short-term follow-up (Pelli *et al.,* 2008; Pelli *et al.,* 2009). Both alcohol consumption and smoking are known to be risk factors for transition from acute to chronic pancreatitis. Recent studies provide evidence that smoking should be considered a risk factor for acute non-gallstone-related pancreatitis as well, but the effects of smoking on recurrences are not known (Lankisch *et al.,* 2009; Sadr-Azodi *et al.,* 2012).

In a randomized controlled trial an intervention programme with 6-monthly visits to an anti-addiction outpatient clinic reduced recurrences by 50% compared to an initial intervention only (Nordback *et al.,* 2009). Despite this, not many international or national guidelines include any recommendations for preventing recurrent attacks in alcoholic pancreatitis, even though in many countries it is at least as common as biliary pancreatitis (Sand *et al.,* 2007).

Acute pancreatitis often causes worsening in pancreatic endocrine and exocrine function. Initially the exocrine function is more usually impaired but improves over time in many patients. New-onset diabetes or impaired glucose metabolism has been found to develop in up to 37% of patients in two-year prospective follow-up (Pelli *et al.,* 2009).

In this study we studied recurrence of pancreatitis and later pancreatic function in patients who stop drinking after the first episode of alcohol-associated pancreatitis. We aimed to ascertain the importance of abstinence in long term, in up to nine years of follow-up. Smoking and BMI were also recorded.

METHODS

A total of 118 patients who participated the randomized study after their first attack of acute alcohol-induced pancreatitis between 11 January 2001 and 4 March 2005 (Nordback *et al.,* 2009) were monitored in a prospective on-going programme for up to nine years.

Alcohol was determined as the cause of pancreatitis due heavy consumption and dependency elicited by interview, the Alcohol Use Disorders Identification Test (AUDIT), Short Alcohol Dependence Data (SADD) and several laboratory markers. AUDIT score over 8/40 was considered as probably heavy drinking. Laboratory markers included serum glutamyl transferase, desialotransferrin and mean red blood cell corpuscular volume. Other aetiologies (gallstones, tumour, hypertriglyceridaemia, pancreas divisum, hypercalcaemia, heredity, trauma, medication) were excluded by history, laboratory tests and imaging.

All the study subjects received an intervention against alcohol consumption before their discharge from hospital. The consequences of continuing heavy alcohol consumption were introduced to the patients. They were all encouraged and supported to take personal responsibility to stop drinking in order to avoid recurrences of the disease. Fifty-eight of the 118 patients were randomized to a repeated intervention study arm (Nordback *et al.,* 2009). These patients underwent similar interventions at 6-month intervals in the gastrointestinal outpatient clinic for two years. Otherwise there were no differences between the two study groups.

Pancreatic function and alcohol consumption were evaluated at baseline and at two years and annually thereafter for up to nine years. Laboratory tests and hospital records were also analysed from patient files. Self-estimated alcohol consumption was calculated in grams from prior two months in an interview. Fasting blood glucose and plasma glycosylated haemoglobin were used to measure the endocrine function of the pancreas. Oral glucose tolerance test and/or glucagon-C-peptide test was performed for patients not diagnosed with diabetes. Exocrine pancreatic function was tested using faecal elastase-1 concentration and plasma concentrations of vitamins A and E. Smoking habits were evaluated through interview by the number of cigarettes per average day. Patients' body mass index (BMI) was also measured.

Our criterion for abstinence was self-estimated alcohol consumption less than 24 grams per two months, which concurs with questionnaires eliciting alcohol consumption and dependency (Alcohol Use Disorders Identification Test, AUDIT < 8 and Short Alcohol Dependence Data, SADD < 9). Patient-years were recorded for the period the patient managed to stay abstinent. If larger amounts of alcohol were consumed or scores from questionnaires were not consistent with abstinence, the patient was excluded from further analyses. We also measured patients' glutamyl

transferase, mean red blood cell corpuscular volume and desialotransferrin in order to obtain reliable results on alcohol use.

Ethics

This study was approved by the ethics committee of Tampere University Hospital (R00126). All patients approved attendance by written consent.

RESULTS

Out of the 118 patients initially recruited, 18 (7%) managed to maintain abstinence for at least one and a half years after the initial attack. The mean follow-up time for abstinence in these patients was 5.15 (1.83-9.13) years (92.7 person years). None of the patients had recurrent attacks during follow-up. Initially one of the patients had had severe pancreatitis according to the Atlanta criteria.

Of the remaining 100 non-abstinent patients in the study 34% had at least one recurrence during follow-up. The average time to first recurrence was 23.4 months.

Exocrine function

At baseline, shortly after the initial acute pancreatitis, 47% (7 of 15) of the patients had faecal elastase-1 concentrations below 150 µg/g. Only one patient (6%) maintained low elastase-1 activity during abstinence follow-up. In the remaining patients faecal elastase-1 levels returned to normal during abstinence of two years or in two cases one year after. Vitamin A concentration was low (<1.0 µmol/l) at baseline in 28% (5 of 18) patients but returned to normal within two years in all patients. Vitamin E concentration was low (<12 µmol/l) at baseline in 17% (3 of 18) patients and also returned to normal in all patients within two years.

Endocrine function

Two patients had diabetes prior to their first acute alcoholic pancreatitis. One patient was diagnosed with diabetes during hospitalization. During follow-up there were no patients with new-onset diabetes. One patient (7%, 1 of 15) had impaired glucose metabolism at two years. Two patients (13%, 2 of 15) had insulin insufficiency in glucagon-C-peptide test, one at four and other at five years. One patient showed relative insulin insufficiency in glucagon-C-peptide test at five years. All three patients with insulin insufficiency or relative insulin insufficiency had normal fast-

ing glucose values. One patient had slightly elevated fasting glucose during follow-up at two years. The remaining non-diabetic patients (67%, 10 of 15) had normal values for endocrine function throughout abstinence follow-up.

Alcohol consumption and dependency on alcohol

Mean value of AUDIT points at baseline was 21.2 (7-37) and mean value of SADD points was 15.1 (1-31). Mean alcohol consumption at baseline was 4298 (768-9216) grams per two months (one patient's data missing), which equals six doses of alcohol (one dose is 12g) per day. At two years mean AUDIT points were 1.6 (0-6) and mean SADD points 0.3 (0-3). Mean alcohol consumption at two years was 0.75 (0-12) grams per two months (table 1).

Compared to the whole study group mean alcohol consumption of all patients in the study at baseline was 3862 (288-16128) grams per two months (data available on 116 out of 118). Mean AUDIT points at baseline were 21.2 (5-38) and mean SADD points were 13.8 (0-36) (data available on 117 out of 118).

Table 1 Descriptions of baseline and two-year follow-up status of abstinent patients

	Baseline (n=18)	Two years (n=16)
Alcohol consumption: mean (grams/2 months)	4298 (768-9216)	0.75 (0-12)
AUDIT: mean	21.2 (7-37)	1.6 (0-6)
SADD: mean	15.1 (1-31)	0.3 (0-3)
BMI: mean	29.6 (23.7-35.3)	28.9 (22.6-41.5)
Smoking		
Yes (%)	11 (61)	10 (63)
No (%)	7 (39)	6 (37)

Smoking and BMI

At baseline mean BMI value was 29.6 (23.7-35.3). Eleven (61%) of the patients were smokers, smoking mean 15.9 (6-23) cigarettes per day. BMI values and smoking status showed no statistically significant changes during follow-up. Of the three patients who developed new impaired glucose metabolism or insulin insufficiency two were smokers. The patient who developed new impaired glucose metabolism had BMI 33. The only patient with exocrine insufficiency was a smoker with BMI 27.5.

DISCUSSION

In this study, abstinence protected against recurrent attacks of acute alcoholic pancreatitis. The mean follow-up time of 5.15 years was probably long enough to detect recurrent episodes because 80% of first recurrences have been reported to occur during the first four years after the initial acute pancreatitis (Pelli *et al.,* 2000).

Recurrent pancreatitis is most commonly related to alcohol aetiology. In earlier follow-up studies recurrence rates of alcoholic pancreatitis have been high. In Finland 562 patients with their first episode of acute alcohol associated pancreatitis were followed-up for 10-20 years. The recurrence rate of the disease was 46% (Pelli *et al.,* 2000). In Scandinavia there have been similar results in long-term follow-ups with 41-48% recurrence rates (Appelros and Borgström 1999; Gislason *et al.,* 2004; Lund *et al.,* 2006). A study of five European countries reported recurrent episodes in 37% patients with alcoholic pancreatitis (Gullo *et al.,* 2002a; Gullo *et al.,* 2002b). In a prospective study patients with first alcoholic pancreatitis were followed-up for two years to map risk factors for alcoholic pancreatitis. Thirteen patients reported abstinence at two years and none of them had had a recurrence (Pelli *et al.,* 2008).

The role of alcohol in the pathogenesis of pancreatitis is not well known. It is uncertain why only a minority of alcohol abusers develop pancreatitis. However, regardless of the mechanisms, there is a clear connection between alcohol consumption and risk of pancreatitis (Apte *et al.,* 2010). The fact that abstinence seems to prevent from recurrences also supports this view.

Exocrine insufficiency usually improves after the first 6 to 18 months. The degree of dysfunction is related to the severity of the pancreatitis (Andersson and Andersson, 2004). In our study only one patient had severe pancreatitis, but in this case exocrine insufficiency was not diagnosed

during abstinence. Only one patient (7%) maintained low elastase-1 concentration. This is slightly less than reported in an earlier study with 9% of patients having exocrine insufficiency at two-year follow-up (Pelli *et al.,* 2009). Impaired exocrine function is much more common in patients with severe necrotizing pancreatitis. About 25% of the patients who undergo necrosectomy have impaired exocrine function for 2-5 years afterwards (Sand and Nordback, 2009).

In the previously mentioned prospective study 11% of the patients without previous diagnosis of diabetes developed new-onset diabetes and a total of 37% developed new impaired glucose metabolism within two years. The severity of pancreatitis did not correlate with the findings (Pelli *et al.,* 2009). The present study suggests that abstinence may prevent pancreatitis patients from developing diabetes with no new cases of the disease. However, five patients showed signs of some disruptions in endocrine function.

Imaging studies were not routinely performed in this study. Possible progression to chronic pancreatitis was mainly evaluated with laboratory tests detecting endocrine and exocrine function. There was only one patient showing low feacal elastase-1 activity after three years of follow-up. This was the same patient showing impaired glucose metabolism at 1.5 years. Rest of the patients didn't show clinical signs indicating development of chronic pancreatitis during abstinence follow-up.

All the patients in this study were male. This is mainly because acute alcoholic pancreatitis is much more common among men. There is no reason why these results should not apply to women as well.

Complete abstinence is not easily achieved. Only 7% of the patients initially recruited managed to stay abstinent for at least one and a half years. Our criteria for abstinence were, of course, quite strict. To the best of our knowledge this is the first prospective follow-up study focusing solely on patients who stop drinking after their first episode of acute alcoholic pancreatitis. Evaluating alcohol consumption is a difficult task. Studying both self-estimated alcohol consumption through scheduled interviews and using questionnaires such as AUDIT and SADD is likely to yield reliable results on abstinence. These were accompanied by laboratory tests such as CDT, GT and MCV, which did not suggest heavy alcohol consumption in patients reporting abstinence.

Treating and diagnosing patients with alcohol problems is often considered difficult and time consuming (Lappalainen-Lehto *et al.,* 2005). These results should encourage the start-up of in-

tervention strategies in order to reduce recurrences and to treat patients with alcohol problems. A randomized controlled trial published in 2009 showed that, compared to an initial intervention only, a repeated intervention at 6-month intervals protects against recurrences and helps to reduce patients' alcohol dependency. In the repeated intervention group 8% of the patients had a recurrence within two years compared to 21% in the group with initial intervention only (Nordback *et al.,* 2009). However, these particular abstinent patients divided equally between the initial intervention only and repeated intervention groups. There are also other alcohol intervention studies reporting reduction of alcohol intake among primary health care and hospital patients (Babor *et al.,* 1994; Gentilello *et al.,* 2005).

CONCLUSION

Given the lack of knowledge about the mechanisms of acute alcoholic pancreatitis, alcohol is the only variable that can be targeted in preventing relapses. An earlier randomized trial (Nordback *et al.,* 2009) demonstrated that it is effective in the short term. This study suggests that abstinence seems to be an excellent way to prevent recurrences of acute alcoholic pancreatitis, also in the long term. Pancreatic dysfunction is also rare among abstinent patients. Total abstinence should be considered a goal for patients with alcoholic pancreatitis. Patients with high dependency on alcohol should be identified and guided to appropriate intervention programmes.

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