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). In contrast, alcoholic pancreatitis is not so straightforwardly treated and as many as 46% of patients suffer from recurrent attacks within 10–20 years with 80% of the first relapses occurring during the first 4 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, 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 also be considered a risk factor for acute non-gallstone-related pancreatitis, 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 with 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 the 2-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 9 years of follow-up. Smoking and body mass index (BMI) were also recorded.

MATERIALS AND METHODS

A total of 118 patients who participated in 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 9 years.

Alcohol was determined as the cause of pancreatitis due to heavy consumption and dependency elicited by interview, the Alcohol Use Disorders Identification Test (AUDIT), Short Alcohol Dependence Data (SADD) and several laboratory markers. The 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 and 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 2 years. Otherwise, there were no differences between the two study groups.

Pancreatic function and alcohol consumption were evaluated at baseline and at 2 years and annually thereafter for up to 9 years. Laboratory tests and hospital records were also analysed from patient files. Self-estimated alcohol consumption was calculated in grams from prior to 2 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’ BMI was also measured.

Our criterion for abstinence was self-estimated alcohol consumption <24 g per 2 months, which concurs with questionnaires eliciting alcohol consumption and dependency (AUDIT < 8 and 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.

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

RESULTS
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 the follow-up at 2 years. Of the three patients who developed impaired pancreatic function according to the Atlanta criteria.

Of the remaining 100 non-abstinent patients in the study, 34% had at least one recurrence during the 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 <150 μg/g. Only one patient (6%) maintained low elastase-1 activity during the abstinence follow-up. In the remaining patients, faecal elastase-1 levels returned to normal during abstinence of 2 years or in two cases 1 year after. Vitamin A concentration was low (<1.0 μmol/l) at baseline in 28% (5 of 18) of the patients but returned to normal within 2 years in all patients. Vitamin E concentration was low (<12 μmol/l) at baseline in 17% (3 of 18) of the patients and also returned to normal in all patients within 2 years.

Endocrine function
Two patients had diabetes prior to their first acute alcoholic pancreatitis. One patient was diagnosed with diabetes during hospitalization. During the follow-up, there were no patients with new-onset diabetes. One patient (7%, 1 of 15) had impaired glucose metabolism at 2 years. Two patients (13%, 2 of 15) had insulin insufficiency in glucagon-C-peptide test, one at 4 and other at 5 years. One patient showed relative insulin insufficiency in glucagon-C-peptide test at 5 years. All three patients with insulin insufficiency or relative insulin insufficiency had normal fasting glucose values. One patient had slightly elevated fasting glucose during the follow-up at 2 years. The remaining non-diabetic patients (67%, 10 of 15) had normal values for endocrine function throughout the abstinence follow-up.

Alcohol consumption and dependency on alcohol
The mean value of AUDIT points at baseline was 21.2 (7–37) and the mean value of SADD points was 15.1 (1–31). Mean alcohol consumption at baseline was 4298 (768–9216) g per 2 months (one patient’s data missing), which equals six doses of alcohol (one dose is 12 g) per day. At 2 years, mean AUDIT points were 1.6 (0–6) and mean SADD points 0.3 (0–3). Mean alcohol consumption at 2 years was 0.75 (0–12) g per 2 months (Table 1).

Compared with the whole study group, mean alcohol consumption of all patients in the study at baseline was 3862 (288–16128) g per 2 months (data available on 116 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 of 118).

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 the 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 4 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 Borgstrom 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,b). In a prospective study, patients with first alcoholic pancreatitis were followed-up for 2 years to map risk factors for alcoholic pancreatitis. Thirteen patients reported abstinence at 2 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 6–18 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 2-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 2 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 faecal elastase-1 activity after 3 years of the follow-up. This was the same patient showing impaired glucose metabolism at 1.5 years. Rest of the patients did not show clinical signs indicating development of chronic pancreatitis during the abstinence follow-up.

All the patients in this study were men. 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 self-estimated alcohol consumption both 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 intervention strategies in order to reduce recurrences and to treat patients with alcohol problems. A randomized controlled trial published in 2009 showed that, compared with 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 2 years compared with 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 in 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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REFERENCES


