DRINKING PATTERNS AND BIOCHEMICAL SIGNS OF ALCOHOLIC LIVER DISEASE IN DANISH AND GREENLANDIC PATIENTS WITH ALCOHOL ADDICTION

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ABSTRACT

Objectives. High alcohol intake per capita and a high prevalence of hepatitis B in the population of Greenland is well documented. However, very few studies have been concerned with alcoholic liver diseases in Greenlanders, suggesting a lower prevalence of alcoholic liver disease among Greenlanders. This study was designed to document the prevalence of alcoholic liver diseases in Greenlanders with a high alcohol intake, and to describe and compare the populations of patients with alcohol addiction in Greenland and Denmark.

Study design. Clinical cross-sectional study of patients attending alcohol treatment centres in Greenland and Denmark regarding clinical and biochemical signs of liver disease.

Methods. One hundred patients from each country answered a questionnaire about demographic variables, social conditions and alcohol consumption patterns. Each patient was examined clinically and biochemically with respect to signs of liver disease, and, when indicated, liver biopsies were taken.

Results. 42% of the Greenlanders and 91% of Danes had abnormal liver function tests. The average Serum-Aspartate amino transferase (ALAT) was 40.0 U/L in Greenlanders and 52.0 U/L in Danes. No liver biopsies with cirrhosis or fibrosis were found in Greenland, whereas three with fibrosis and ten with cirrhosis were found in Denmark.

Conclusions. There seems to be a lower prevalence of liver disease in Greenlanders with a high alcohol intake, compared to Danes with similar alcohol patterns.

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Keywords: Alcohol, ALAT, Greenland
INTRODUCTION

High alcohol intake has been a major health problem in Greenland for many years. In 1983, the average alcohol intake was 22 litres of pure alcohol per citizen aged 15 years, or older. After 1983, the alcohol intake decreased and, although the decrease in alcohol consumption in Greenland had already started in 1988, the home rule government passed new restrictions in order to further reduce the alcohol intake. In 2002, the alcohol intake had decreased to 12.3 litres alcohol for every citizen of 15 years, or older (1).

The most commonly registered alcohol-related health problems in Greenland are not chronic diseases, as for example in Denmark, but accidents, violence, murder and suicide (2-4). Few studies on alcohol-related diseases have been performed on Greenlanders. Age-specific mortality rates of cirrhosis in Greenland have previously been shown to be 8.9 per 100,000 inhabitants per year for both men and women. In comparison mortality rates in Denmark were 9.4 for men and 8.7 per 100,000 inhabitants per year (5). In a small autopsy study, no cases of liver cirrhosis or fibrosis were found among 58 autopsies (Pedersen HS et al., personal communication).

This presumably low prevalence of chronic liver disease was observed in spite of a high per capita alcohol intake (1) and a high prevalence of hepatitis B (5, 6). Therefore, we found it interesting to study drinking patterns and the severity of addiction, as well as clinical and biochemical signs of liver disease, in two high risk groups of Greenlanders and Danes attending alcohol treatment units in Greenland and Denmark, respectively.

MATERIAL AND METHODS

The study was performed as a clinical cross-sectional study of consecutive patients attending alcohol treatment centres in Nuuk, Greenland, and in Copenhagen, Denmark.

In Greenland, the study included patients from the only Greenlandic alcohol treatment centre, Qaqiffik, located in the capital of Greenland - Nuuk. Qaqiffik is based on the Minnesota treatment model and, as the patients come from all parts of Greenland, the treatment program is intensive and is run on an inpatient basis. Most patients spoke Greenlandic as their primary language and, therefore, all information and the questionnaires were translated into Greenlandic. During the clinical examination and interview, we used experienced translators from Queen Ingrid’s Hospital in Nuuk. All patients were of Greenlandic ethnicity, as defined in the population survey of 2003 (7). Here Greenlandic ethnicity was defined by self-identification as Greenlandic, or mixed Greenlandic-Danish, or if at least one grandparent, or one parent if information on the grandparents was not available, was Greenlandic. The Danish participants were recruited from the Alcohol Unit, Hvidovre Hospital, a public hospital-based outpatient clinic for alcoholics employing a primarily individual psycho-social treatment with a cognitive reference frame. In Denmark, the Minnesota Treatment Centres are not part of the public treatment system and the fees of most patients treated in the centres are paid by the patients themselves, by their employers, or by an insurance company. If we had chosen to include patients from a Danish Minnesota centre, the patients would have been highly selected compared to the Greenlandic patients.
One hundred patients from each centre were consecutively included in the study if they met the following criteria:

1) Average daily alcohol intake: more than ten units for a period of five years, or longer.

2) Age: older than 18 years.

Information was obtained by means of a semi-structured interview-based questionnaire, and the only differences between the questionnaires used in Greenland and in Denmark were questions about Greenlandic ethnicity.

In order to obtain a quantitative estimate of the individual alcohol intake as described earlier (8, 9), the participants were asked: How many units of beer, wine and spirits do you drink per week on average? A Danish unit of alcohol corresponds to 12 g pure alcohol.

In addition, we used two structured alcohol-screening tests. The first was a modification of the CAGE questionnaire - a short four-item questionnaire extensively used to detect alcoholism (10). The original CAGE questionnaire, however, has not worked optimally in a Danish population and the questions have therefore been modified to include the questions shown in Figure 1. The test has been validated in a population of hospital patients (11).

The second test was the Brief Michigan Alcoholism Screening Test (MAST). MAST is one of the most widely used measures of assessing alcohol abuse and it can be either self-administered, or administered by means of interview without training. The original MAST test contained 25 items (12). Many shorter versions of the MAST test have been developed and, among these, we used the 10-item Brief MAST (13) modified according to Martin et al. (14).

Brief MAST and CAGE screening tests have been validated and compared numerous times (15).

In addition to the questionnaire, a general health examination was performed on all patients, during which clinical signs of chronic liver disease were observed. These included jaundice, facial telangiectasia, vascular spiders, palmar erythema, white nails, ascites, abdominal wall collateral veins, fatness and peripheral edema. Different observers performed the clinical assessments. All observers were educated by means of photographs and written descriptions of the different clinical signs. The clinical observations can, to some extent, be used to diagnose cirrhosis in alcohol-abusing men with high accuracy, as demonstrated previously (16).

Serum samples were drawn from an antecubital vein, prepared and stored at –20°C until analysis. Serum bilirubin, albumin, alanine amino transferase (ALAT) and alkaline phosphatase levels were determined by routine methods on an auto analyzer. Likewise, coagulation factors 2, 7 and 10 were analyzed using
routine laboratory methods. All samples were analyzed using the same analytical methods, and the laboratories in Nuuk and in Denmark used the same reference limits.

For ethical reasons, liver biopsies were only performed if there was a clinical indication i.e. if the patients had clinical or biochemical signs suggesting liver disease.

All participants gave informed consent before entry into the study and The Danish Data Protection Agency (cpr-nr. 11-88-37-29), the Regional Scientific Ethical Committee for Copenhagen (KF 01-347/97) and the Commission for Scientific Research in Greenland (j.nr. 505-30) all approved the study.

**Statistical analyses**

The data were analysed using the SPSS statistical package. The results are presented as medians (and ranges), or as means and standard deviations when appropriate. T-test was used to test for differences between groups. The $\chi^2$ test was used to compare categorical variables. Furthermore, multivariate linear regression was used with ALAT as a dependent variable. Statistical significance was set at $p<0.05$.

**RESULTS**

The median age of the Greenlandic patients was lower (40 years; range 18 – 63 year) than that of the Danish patients (46 years; range 28 – 63 year) (table I). 56 % of the Greenlander patients were women, compared to 14 % among Danish patients. Although not significant, there was a tendency for Greenlanders to live in more stable relationships than Danes (table I).

Residents in Greenland had more rooms, and there were more people living together, and there were more children who lived at home in the Greenlandic families.

More Danish than Greenlandic patients had passed secondary school and high school, but more Greenlanders than Danes had followed one or more occupational education.

| Table I. Social data. | Greenland | Denmark |
|----------------------|-----------|---------|
| Age, median (range) years | 40 (18-63) | 46 (28-63)* |
| Sex (%) | Men (44) | (86)* |
| | Women (56) | (14)* |
| Civil status, n (%) | Not married 37 (41) | 35 (42) |
| | Married 34 (37) | 12 (14) |
| | Divorced 18 (20) | 35 (42) |
| | Widow 2 (2) | 2 (2) |

* $p<0.001$

| Table II. Result of alcohol screening tests. | Greenland | Denmark |
|---------------------------------------------|-----------|---------|
| Brief Mast, n (%) | Positive 90 (97) | 82 (98) |
| | Negative 7 (7) | 2 (2) |
| Modified CAGE | Positive 68 (99) | 50 (100) |
| | Negative 1 (1) | 0 (0) |

NS ($P > 0.05$)
The Brief MAST test and the modified CAGE showed that almost all participants exhibited harmful, or addictive alcohol abuse. There were no significant differences between the two populations (table II).

The intake of beer and spirits was higher in the Greenlandic population than in the Danish population, but the intake of wine was higher for the Danes than for the Greenlanders (table III). Drinking patterns differed in that the Greenlanders had fewer drinking days per week (mean 3.4 days) than the Danes (mean 6.8 days) (table III). As for the biochemical liver function tests, ALAT levels were significantly higher and coagulation factors 2,7 and 10 were significantly lower in the Danes than in the Greenlandic population (table IV). The average Se-ALAT was 40.0 U/L in Greenlanders and 52.0 U/l in Danes, and a higher percentage of Danish patients (35 %) had ALAT levels above upper normal reference limit, compared to Greenlandic patients (22 %). A multivariate regression analysis controlling for gender, age, alcohol intake, civil status and education, confirmed that Danes had higher levels of ALAT than Greenlanders (data not shown). Not suprisingly, we found that ALAT levels were positively associated with alcohol intake, when controlling for the above-mentioned confounders. None of the other variables reached statistical significance. In total, one or more abnormal liver function tests were observed in 91% of Danish patients, compared to 39% in the Greenlandic patients (p < 0.001)

No clear clinical signs of liver cirrhosis were found among the Greenlanders, but three patients had a liver biopsy performed, because of biochemical signs of liver disease. Two of the liver biopsies showed fatty liver, without

| Table III. Drinking pattern. |
|-----------------------------|
|                            | Greenland mean (SD) | Denmark mean (SD) |
| Drinks/week                |                   |
| beer                       | 70.6 (40.8)       | 67.2 (75.7)*      |
| wine                       | 17.7 (25.1)       | 24.0 (40.4)*      |
| Spirits                    | 31.9 (45.7)       | 16.2 (40.4)       |
| Total drinks/week          | 120.2 (42.5)      | 107.4 (35.7)*     |
| Days/week with alcohol intake | 3.4(1.7)         | 6.8(0.8)*         |

* p < 0.001

| Table IV. Biochemical parameters. |
|-----------------------------------|
|                                  | Greenland        | Denmark         |
| Blood tests mean (SD)             |                   |
| ALAT                             | 40.0 (30.4)       | 52.0 (35.3)*    |
| Alkaline fosfatases               | 181.0 (57.8)      | 175.5 (57.5)    |
| Bilirubin                        | 5.4 (3.8)         | 9.0 (4.6)*      |
| Albumin                          | 40.9 (6.1)        | 40.9 (3.5)      |
| Coagulation factors 2,7,10       | 1.2               | 0.9*            |
| Liver function test              |                   |
| outside of normal                | 42 (39)           | 77 (91)*        |
| Reference limit                  |                   |
| ALAT above normal range          | 24 (22)           | 30 (35)*        |
| ALAT within normal range         | 83 (78)           | 55 (65)         |

***p < 0.05
signs of more severe, chronic liver disease (i.e. fibrosis and alcoholic hepatitis), and one was normal.

In 25 Danish patients, liver biopsy was indicated mainly because of elevated liver enzymes. Four patients refused liver biopsy and, in one case, biopsy was contra-indicated because of severe scoliosis. Twenty-one liver biopsies were performed and showed: One biopsy was normal; seven biopsies showed pure fatty livers; fibrosis without cirrhosis was observed in three cases; and ten biopsies were diagnosed as cirrhosis. Eight Danish patients had clinical signs of chronic liver disease.

**DISCUSSION**

A higher proportion of Danish patients had abnormal liver function tests, compared to the Greenlandic population of alcohol addicted patients. Furthermore, we found that Greenlandic patients drank more than Danish patients and had a different drinking pattern in that Greenlanders were typically binge drinkers, compared with the daily drinking pattern of the Danish patients, and Greenlanders drank comparatively more beer and spirits than the Danes.

It could be argued that the average age of the Greenlandic population may have had an effect on the prevalence of cirrhosis. The prospective study of Sørensen et al. concluded that alcohol had a conditioning effect on the risk of cirrhosis and was not cumulative over time (17). According to this theory, the rate of development of liver disease will be constant over time, when the alcohol intake is above a certain threshold, thereby introducing an apparent increase in the development of liver disease with increasing age. Furthermore, Greenlanders with a high alcohol intake may have died from accidents, violence, murder, or suicide before developing liver disease (2-4). A precise estimation of the prevalence of alcoholic liver diseases would require liver biopsies of all participants, but this was not possible for ethical reasons. Instead, we used clinical signs and biochemical liver function tests, although the clinical signs have not been evaluated in the Greenlandic population as in the Danish population with regard to liver diseases (16). All the same, no Greenlandic alcoholics had clinical signs of chronic liver disease; we found no cases of cirrhosis in liver biopsies from Greenlandic patients and a lower prevalence of abnormal liver function tests among Greenlandic patients in spite of a higher alcohol intake. The prevalence of hepatitis B markers is much higher in Greenland than in Denmark (5,6). We did not analyze blood samples for hepatitis B markers, but the finding of a lower prevalence of abnormal biochemical liver function tests would not have been changed even if we had analyzed for hepatitis B markers.

Ultrasonography of the liver might have improved the study, but cannot distinguish fatty liver from more severe liver disease (i.e. cirrhosis).

Several explanations are possible for the apparently low prevalence of alcohol-related liver disease. Genetic factors are important for the development of alcoholic liver disease, as was demonstrated in twin studies, where a higher concordance was observed between monozygotic twins than between dizygotic twins (18;19). Furthermore, several studies have shown that women are at greater risk
for developing cirrhosis for a given alcohol consumption (9, 20, 21). In the present study, more Greenlanders were women – a gender distribution that does not favour a lower prevalence of liver disease.

Few earlier studies have related liver cirrhosis to ethnic differences. A study of 381 cirrhotic patients found an over-representation of South Asian non-Muslim males, compared to the local population (22). Similarly another study pointed out that Indians had a higher risk of cirrhosis than the general British population (23). In a national longitudinal Mortality Study from the United States, a higher incidence of cirrhosis was found among American Indians and Hispanic Americans (24).

Intake of polyunsaturated fat is higher in the Greenlandic population (7), but little is known about its role in the pathogenesis of cirrhosis. Oil from sea mammals and fish, which is a major part of the traditional Inuit diet, contains polyunsaturated n-3 fatty acids (PUFA). High intake of PUFA reduces the amount of inflammatory mediators, which may be involved in the pathogenesis of alcoholic liver diseases.

Furthermore, we know that other diseases related to inflammation and fibrogenesis, such as spondylolisthesis, aneurisms, atrial septal defects and osteoarthritis, have a different prevalence among Inuit in Greenland (25). The pathogenesis behind these ethnic differences in the prevalence of diseases has not been studied in detail.

The higher alcohol intake by Greenlanders in the present study favours a higher prevalence of liver disease. Few studies of the alcohol intake pattern and the risk of alcoholic liver disease have been published. In a large cross-sectional study (26), a significantly higher risk was observed in individuals drinking outside mealtimes, and two additional studies found a lower prevalence of alcoholic liver disease in binge-drinking men compared to individuals with daily alcohol intake (17, 27). These results could be in accordance with a lower prevalence of liver disease in Greenlanders, who, as we have shown, are more often binge drinkers compared with Danish participants. The higher relative intake of beer and spirits in Greenlanders would favour a higher prevalence of liver disease among Greenlanders, as it has been shown earlier that wine drinkers have a lower risk than beer and spirits drinkers of developing liver disease (28), although these findings have not been confirmed.

Regarding social conditions, we found that Greenlanders lived in more stable relationships with more children, and in homes with more rooms. They had a shorter school education, but more had completed an occupational education. It is not likely that any of these social parameters had any direct impact on the risk of developing alcoholic liver disease.

In a cross-sectional study, Hamberg et al. showed that clinical and biochemical signs in a model with regression coefficients (16), can be used to diagnose cirrhosis. However, other studies have shown physical findings to be of limited diagnostic value (29), and the diagnostic value of clinical signs of liver disease has never been tested in a population of Inuit.

Other confounders could be smoking habits. A large population survey showed that there were more cigarette smokers in the general population of Greenland than in the
Danish population (7). This difference would favour an increased prevalence of alcoholic liver disease among Danish patients, although we have no information on smoking history in the present study. (29).

In conclusion, the present small pilot study of alcoholics seem to show, in spite of the inherent flaws of the study, a lower prevalence of liver disease and abnormal liver function tests among Greenlanders seeking alcohol treatment than among Danes. A potentially lower risk of cirrhosis in Greenlanders may reflect differences in drinking pattern, nutrition, alcohol metabolism, or unknown differences in pathogenesis.

The results warrant testing the hypothesis in a large prospective study of factors predicting the risk of alcohol-related liver disease in Greenlanders, including markers of fibrogenesis and inflammation, as well as ultrasonographic examination of the liver.

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REFERENCES
1. Alcohol consumption 1987-2004 by time and specification. Statistics Greenland.
2. Jørgensen B, Johansen LG, Roed S, Andersen JF, Nielsen F, Nielsen FK et al. Accidents due to violence in Greenland. Ugeskr Læg 2004; 146: 3398-3401.
3. Pedersen OS, Olsen NK, Pedersen M, Andersen JF. Disease due to alcohol in a hospital district in Greenland. Ugeskr Læg 1984; 146:2187-2190.
4. Bjerregaard P. Disease pattern in Greenland: studies on morbidity in Upernavik. Arctic Med Res 1991; 50 suppl 4: 1-62.
5. Skinhøj P, Hansen JPH, Nielsen NH, Mikkelsen F. Occurrence of cirrhosis and primary liver cancer in an eskimo population hyperendemically infected with hepatitisB. Am J Epidemiol 1978; 108:121-125.
6. Skinhøj P, McNair A, Andersen ST. Hepatitis and hepatitis B-antigen in Greenland. Am J Epidemiol 2004; 99: 50-57.
7. Bjerregaard P, Curtis T, Borch-Johnsen K, Mulvad G, Becker U, Andersen S et al. A population survey of lifestyle and disease in Greenland and among Inuit living in Denmark. Int J Circumpolar Health 2003; 62:1-79.
8. Grønbæk M, Sørensen TIA, Becker U, Schnohr P, Jensen G. Mortality associated with moderate intakes of wine. beer or spirits. BMJ 1995; 310: 1165-1169.
9. Becker U, Deis A, Sørensen TIA. Prediction of risk of liver disease by alcohol intake, sex and age. Hepatology 1996; 5:1025-1029.
10. Mayfield D, McLeod G, Hall P. The CAGE questionnaire: Validation of a new alcoholism instrument. Am J Psychiatry 1974; 131: 1121-1123.
11. Zierau F, Hardt F, Henriksen JH, Holm SS, Jørring S, Melsen T et al. Validation of a self-administered modified CAGE test (CAGE-C) in a somatic hospital ward. Scan J Clin Lab Invest 2005; 65: 613-622.
12. Selzer ML. The Michigan Alcoholism Screening Test: The quest for a new diagnostic instrument. Am J Psychiatry 1971; 127: 1653-1658.
13. Pokorny AD, Miller BA, Kaplan HB. The Brief Mast: A shortened version of the Michigan Alcoholism Screening Test. Am J Psychiatry 1972; 129: 342-345.
14. Martin C, Liepman MR, Young CM. The Michigan Alcoholism Screening Test: False positives in a college student sample. Alcohol Clin Exp Res 1990; 14: 853-855.
15. MacKenzie DM, Langa A, Brown TM. A comparison of AUDIT, CAGE and Brief MAST. Alcohol and Alcoholism 1996; 31: 591-599.
16. Hamberg KJ, Carstensen B, Sørensen TIA, Egheøe K. Accuracy of Clinical Diagnosis of Cirrhosis Among Alcohol-Abusing Men. J Clinical Epidemiol 1996; 49(11):1295-1301.
17. Sørensen TIA, Orholm M, Bentsen KD, Hoybye G, Egheøe K, Christoffersen P. Prospective evaluation of alcohol abuse and alcoholic liver injury in men as predictors of development of cirrhosis. Lancet 1984; ii: 241-244.
18. Day CP, Bashir R, James OF, Bassandine MF, Crabb DW, Thomasson HR et al. Investigation of the role of polymorphisms at the alcohol and aldehyde dehydrogenase loci in genetic predisposition to alcohol-related end-organ damage. Hepatology 1991; 14: 798-801.
19. Arria AM, Tarter RE, Van Thiel DH. Vulnerability to alcoholic disease. Recent Dev Alcohol 1991; 9: 185-204.
20. Norton R, Batey R, MacMahon S. Alcohol consumption and the risk of alcohol related cirrhosis in women. BMJ 1987; 295: 80-82.
21. Morgan MY, Sherlock S. Sex-related differences among 100 patients with alcoholic liver disease. BMJ 1977; 1: 939-941.

22. Douds AC, Cox MA, Iqbal TH, Cooper BT. Ethnic differences in cirrhosis of the liver in a British city: alcoholic cirrhosis in South Asian men. Alcohol Alcohol 2003; 38:148-150.

23. Mckeigue PM, Karmi G. Alcohol consumption and alcohol-related problems in Afro-Carribians and south Asians in the United Kingdom. Alcohol Alcohol 1993; 28: 1-10.

24. Singh GK, Hoyert DL. Social epidemiology of chronic liver disease and cirrhosis mortality in the United States, 1935-1997: trends and differentials by ethnicity, socioeconomic status, and alcohol consumption. Hum Biol 2000; 72:801-20.

25. Fenger Hj. Sygdomsmønsteret på Grønland. Ugeskr Læg 1988; 150): 251-254.

26. Bellantani S, Saccoccio GC, Tiribelli C, Manentini F. Drinking habits as cofactors of risk for alcohol induced liver damage. Gut 1997; 41: 845-850.

27. Bourlier M, Barthet M, Berthezene P, Durbec JP, Sarles H. Is tobacco a risk factor for chronic pancreatitis and alcoholic cirrhosis. Gut 2004; 32: 1392-1395.

28. Becker U, Grønbæk M, Johansen D, Sørensen TIA. Lower risk for alcohol-induced cirrhosis in wine drinkers. Hepatology 2002; 35: 868-875.

29. Bruyn G, Graviss EA. A systematic review of the diagnostic accuracy of physical examination for the detection of cirrhosis. BMC Med Inform Decis Mak 2001; 6: 1-11.

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