Plasma YKL-40 in Inuit and Danes

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Abstract — Aims: The aim of the present study was to investigate whether there are differences in plasma levels of YKL-40 between Inuit in Greenland and in Denmark and in Danes, as well as to study the relationship between alcohol intake, plasma YKL-40 and other factors in Inuit. Methods: Plasma YKL-40 levels were measured on 1645 people from The Greenland Population Study (a cross-sectional population study of Inuit from Denmark and West Greenland) and were compared with the plasma YKL-40 levels of 8899 people from The Copenhagen City Heart Study (a population-based, prospective study of the Danish general population). Results: The plasma concentrations of YKL-40 were significantly (P = 0.001) lower in Inuit living in Greenland (median 46 µg/l, range 10–2164, n = 1164) compared with the plasma YKL-40 levels of Inuit living in Denmark (median 63 µg/l, range 20–2827, n = 481) and of Danes living in Denmark (median 55 µg/l, range 10–2099, n = 8899). In Inuit, increased alcohol intake was significantly associated with increased plasma YKL-40 levels (P < 0.001), and high plasma YKL-40 levels were associated with high values of alkaline phosphatase and low values of albumin. Smoking, gender and bilirubin were not associated with the plasma YKL-40 level. High levels of YKL-40 and alcohol were associated with where people lived. Conclusion: The plasma concentrations of YKL-40 are significantly lower in Inuit living in Greenland than Inuit and Danes living in Denmark. A number of factors, including different alcohol intake patterns, nutrition and genes may play a role in these findings.

INTRODUCTION

It has been hypothesized that Inuit in Greenland are less prone to develop chronic liver disease than Europeans despite a relatively high alcohol intake and a high prevalence (54%) of hepatitis B infection in Inuit (Skinhøj et al., 1978; Børresen et al., 2011). Transaminase levels are lower in Inuit in Greenland with high alcohol intake compared with Danes (Holmegaard and Becker, 2006) and the prevalence and incidence of liver diseases are lower in Greenland compared with Denmark (Rokkjaer et al., 2006). This finding could reflect a true lower prevalence of cirrhosis in Greenland due to a different gene pool or to different environmental factors, such as food, exercise or pollution, but it could also be due to the lack of follow-up (Rokkjaer et al., 2006). Inuit also have a low frequency of certain autoimmune disorders, such as ankylosing spondylitis (Boyer et al., 1988; Peschken and Esdaile, 1999), diabetes mellitus type 1 (Mohatt et al., 2002) and Graves’ disease (Harvard, 1989). Whether these differences are caused by lack of diagnostic evaluation or a truly lower incidence is unknown (Harvard, 1989; Andersen et al., 1999).

YKL-40 (chitinase 3 like 1, CHI3L1) is a member of ‘mammalian chitinase-like proteins’ and is a protein conserved through evolution (Johansen et al., 2009). YKL-40 is mainly produced by macrophages, neutrophils and cancer cells (Johansen et al., 2009) and by fetal and embryonic stem cells (Johansen et al., 2007; Brochner et al., 2012). IL-6 and hypoxia stimulate YKL-40 synthesis (Junker et al., 2005; Nielsen et al., 2011). YKL-40 regulates vascular endothelial growth factor and plays a role in angiogenesis, inflammation (Saidi et al., 2008; Eurich et al., 2009; Johansen et al., 2009; Shao et al., 2009; Faibish et al., 2011; Francescò et al., 2011; Lee et al., 2011; Kawada et al., 2012; Shao, 2013), cell proliferation and differentiation (Johansen et al., 2007; Brochner et al., 2012); stimulates fibroblast, remodeling of the extracellular matrix (Recklies et al., 2002), and the innate immune response (Lee et al., 2011); and protects against apoptosis (Lee et al., 2009). Recently, it was demonstrated that YKL-40 regulates cellular and tissue responses via IL-13 receptor α2 (He et al., 2013).

Plasma YKL-40 is elevated in patients with liver diseases (Johansen et al., 1997, 2000; Nojgaard et al., 2003a,b; Anttila et al., 2005; Saitou et al., 2005; Lebensztejn et al., 2007; Fontana et al., 2008, 2012; Berres et al., 2009; Malik et al., 2009; Pizano-Martínez et al., 2011; Rath et al., 2011; Eurich et al., 2013; Lee et al., 2013), and the highest levels are found in patients with alcoholic hepatitis and cirrhosis (Johansen et al., 2000; Nojgaard et al., 2003a). High plasma YKL-40 is associated with shorter survival in these patients (Nojgaard et al., 2003a). In Danes, factors like high alcohol intake, elevated liver enzymes and benign liver diseases are associated with high YKL-40 values (Kjaergaard et al., personal communication).

The aim of the present study was to determine whether there are differences in plasma levels of YKL-40 between Inuit in Greenland and in Denmark and in Danes as well as to study the relationship between alcohol intake, plasma YKL-40 and other factors in Inuit.

MATERIALS

This study was part of a large population-based cross-sectional study (The Greenland Population Study 1999), where Inuit were selected from Denmark and four areas in West Greenland. The objective was to study health-related issues among Greenlanders. The study has been described in details elsewhere (Bjerregaard et al., 2003). In short, the following locations in Greenland were chosen: Nuuk, Qasigiannguit and four villages in Uummannaq municipality (Ikerasak, Saattut, Qasrarsuit and Ukkussissat).

Nuuk, the capital of Greenland, has a population of ~16,000. The lifestyle is westernized, but traditional Greenlandic food makes up a significant proportion of the diet, and hunting and
fishing are important activities. In Nuuk, data collection was carried out by mailed questionnaires or interview by trained interviewers combined with self-administered questionnaires with questions on sensitive matters, such as alcohol use. A random sample of 1912 inhabitants was invited to participate in the study. Out of 709 interviewed participants, 443 (62%) participated in the clinical examinations.

Qasigiannguit is a small town with 975 inhabitants aged 18 years or more. Of the 842 invited residents, 618 participated in the clinical examination (73%). The diet is mainly Western, but locally caught fish, sea mammals and birds make up a significant part of the diet. Hunting and fishing are occupations. The four villages in Uummannaq have a total of 640 people who are aged 18 years or older. The eligible population of 428 was identified by house-to-house visits, and 256 (61%) of these participated in the clinical examination. Hunting and fishing are major occupations, and the diet is rich in sea mammals and fish.

In Denmark, individuals born in Greenland were identified from the Central Population Register, and a random sample of these was drawn. From this, 3513 were identified as Inuit. Data collection was based on questionnaires, interviews and clinical examinations. A random sample of 1358 interviewed participants was invited to take part in clinical examinations, and a total of 736 (54%) participated. Only some of the questions on alcohol used in this study were present in the questionnaire mailed to participants living in Denmark, but those who went through a clinical examination were asked additional questions about alcohol use.

A clinical examination was performed on 2056 participants, and plasma samples were available for determining the YKL-40 levels in 1645 participants. Blood samples were drawn from an antecubital vein, prepared and stored at -20°C for a few months. After the samples had arrived in Denmark they were stored at -80°C until analysis. The serum concentrations of bilirubin, albumin, aspartate amino transferase (ASAT) and alkaline phosphatases were determined by routine methods on an auto analyzer. All samples were analyzed using the same analytical methods although the analyses were analyzed on different laboratories, but they used the same reference limits.

The Copenhagen City Heart Study is a population-based, prospective study of the Danish general population, and the plasma YKL-40 level results used in the present paper are from the 1991–1994 study as previously described (Johansen et al., 2010). Participants aged 20 years and above were selected randomly after gender and age stratification into 10-year age groups among residents of Copenhagen; 99% were of Danish descent. Of 17,180 subjects invited, 10,135 participated, and plasma was available for YKL-40 determination in 8899 participants. The participants filled out a self-administered questionnaire, which was reviewed by the participant and an investigator on the day of participation. Participants gave information on the day of participation. Participants gave information on their usual weekly consumption of alcohol in the following groups: 0, 1–13, 14–21 and >21 drinks. Because of the limited range of consumption among women, their alcohol consumption was categorized as: 0, 1–6, 7–14 and >14 drinks per week. The highest cutoff values for men and women of 21 and 14, respectively, were based on the Danish sensible drinking limits as proposed by the National Board of Health. The total amount of daily smoking was calculated in g per day assuming one cigarette is equivalent to 1 g of tobacco, one cheroot or one cigar is equivalent to 3 g, and one pipe is equivalent to 5 g. The cumulative tobacco consumption in pack years was calculated. The body mass index (BMI) was calculated as measured weight in kg divided by squared measured height in meter.

The serum concentrations of bilirubin, albumin and alkaline phosphatases were determined by routine methods on an auto analyzer.

**YKL-40 analysis**

The plasma concentrations of YKL-40 were determined in duplicates by a commercial two-site, sandwich-type enzyme-linked immunosorbent assay (ELISA) (Quidel Corporation, San Diego, CA, USA), using streptavidin-coated microplate wells, a biotinylated-Fab monoclonal capture antibody, and an alkaline phosphatase-labeled polyclonal detection antibody. The recovery of the ELISA was 102% and the detection limit was 10 µg/l. The intra-assay coefficients of variations were 5% at 40 µg/l and 4% at 104 µg/l and 155 µg/l. The inter-assay coefficient of variation was <6%. Plasma YKL-40 is stable for at least 15 years in plasma samples stored at -80°C (Bojesen et al., 2011).

**Ethics**

The Greenland study

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

The Copenhagen city heart study

All participants gave written informed consent. The study was approved by Herlev Hospital and Copenhagen and Frederiksberg ethical committee (No. 100.2039/91 and 01-144/01) and was conducted according to the Declaration of Helsinki.

**Statistical analysis**

We used SPSS version 17.0. Two-sided P < 0.05 was considered significant. Associations between alcohol intake, plasma YKL-40 and biochemical tests were investigated by general linear models. Plasma YKL-40 and biochemical tests were log transformed to approximate normal distributions. The variables, gender, BMI, smoking (g per day) and alcohol intake (drinks per week), smoking (g per day), BMI, serum concentrations of albumin, alkaline phosphatases and bilirubin were all initially included in the model. In subsequent models, insignificant variables were excluded; additionally, the place of residence was recoded to reduce the number of categories according to results and the interaction between alcohol intake and place of living was studied. Finally, social confounding was studied, including the level of school education in a model including Inuit only because the level of school education was measured differently in Danes living in Denmark.
In the Copenhagen City Heart Study Alanine Amino Transferase (ALAT) and not ASAT was measured. Therefore, statistical analyses only include ASAT levels in the Inuit dataset.

RESULTS

Plasma YKL-40 values in Inuit living in Greenland compared with Inuit living in Denmark and Danes and association with alcohol intake

Table 1 shows the biochemical and clinical data of the Inuit and Danes. The Inuit were younger than the Danish participants. More female Inuit are represented in Inuit living in Denmark than in Inuit living in Greenland and Danes in Denmark, but otherwise there were no significant differences between groups regarding demographic variables.

Figure 1 illustrates that plasma concentrations of YKL-40 are slightly, but significantly lower in Inuit living in Greenland compared with plasma YKL-40 in Inuit living in Denmark and Danes.

Increased alcohol intake in Inuit was significantly ($P < 0.001$) associated with increasing plasma concentrations of YKL-40 in both male and female Inuit (Fig. 2A and B). Figure 3A and B illustrates the association between plasma YKL-40 and the amount of alcohol intake in male and female Inuit distributed according to their community during the study. In both men and women, the effects of alcohol intake on plasma YKL-40 levels depend on the place of residence. In small towns and villages, the level YKL-40 is lower in those drinking 15 drinks per week or more compared with large towns in Greenland and Inuit living in Denmark.

Table 2 shows the results of a general linear regression model, including gender, age, place of residence, alcohol, smoking, bilirubin, alkaline phosphatase, albumin and BMI as covariates. There was a significant association between plasma YKL-40 (log), age, alcohol intake, smoking, place of residence, albumin (log) and alkaline phosphatase (log). Increasing age of Inuit and Danes is associated with increasing plasma YKL-40. BMI was not a significant factor and gender only borderline significant but we kept gender in the subsequent analyses.

The estimates from Inuit in Denmark and in Nuuk as well as estimates in small villages and towns in Greenland (Qasigiannguit and Uummannaq) were similar, and these variables were collapsed into two categories. We recoded categories as well as an interaction variable between alcohol intake and the place of residence in a subsequent model that excluded BMI because this variable was insignificant. As seen in Table 3 we observed a significant association between YKL-40 levels and alcohol intake; the YKL-40 levels generally increased with increased alcohol intake. We also observed a significant interaction between place of residence and alcohol intake and this interaction was significant in Inuit living in Nuuk and Denmark but not in those living in the smaller communities in Greenland.
This was confirmed in final analyses (data not shown), where alcohol intake and place of residence were combined in three new variables. Including these variables revealed that there was only a significant association between alcohol intake and YKL-40 levels among Danes in Denmark and Inuit living in Nuuk or Denmark, while there was no association between alcohol intake and YKL-40 in Inuit living in the small towns and settlements in Qasigiannguit and Uummannaq.

A general linear regression model, including the level of school education in the Inuit dataset alone showed that school education was not a confounder (not shown).

Finally, ASAT was included in analyses of the Inuit dataset alone and we found in the multivariate general linear model that bilirubin was no longer significant, while ASAT had a positive significant association with YKL-40 (data not shown). We did not find any significant interaction between place of residence and ASAT, while we again found a borderline interaction between alcohol intake and the place of residence with a significant association between alcohol intake and YKL-40 in Inuit living in Nuuk and Denmark but not Inuit living in the smaller settlements and towns of Uummannaq and Qasigiannguit.

DISCUSSION

We found that the plasma concentrations of YKL-40 in Inuit living in Greenland were lower than the values in Inuit living in Denmark, but the YKL-40 levels in Inuit were not significantly different from those in Danes. In accordance with Danes (Johansen et al., 2010; Bojesen et al., 2011), plasma YKL-40 increased in Inuit with age and alcohol consumption. High alcohol intake in Inuit living in Denmark and Nuuk was associated with high plasma YKL-40 in a dose-dependent manner, while there was no association between alcohol intake and YKL-40 in Inuit living in small towns and settlements in Greenland. High plasma YKL-40 was associated with high alkaline phosphatase, bilirubin, ASAT and low albumin.

The age-specific mortality rates of cirrhosis in Greenland are 8.9 per 100,000 inhabitants per year for both men and women. In comparison, the mortality rates in Denmark are 9.4 for men and 8.7 for women per 100,000 inhabitants per year (Skinhøj et al., 1978). In a small autopsy study, no cases of liver cirrhosis or fibrosis were found among 58 autopsies in Inuit (Pedersen HS, personal communication), and a study of discharge diagnoses showed that the hospital prevalence and incidence of liver discharge diagnoses were lower in Greenland than in Denmark (Rokkjaer et al., 2006). This presumably low prevalence of chronic liver disease was observed in spite of a high per capita alcohol intake and a high prevalence of hepatitis B (Skinhøj et al., 1978). In another study, we demonstrated lower prevalence of biochemical signs of liver disease in Inuit than Danes with high alcohol intake (Holmegaard and Becker, 2006).
Danes overall have an average alcohol intake similar to Inuit, but there are significantly more abstainers and more binge drinkers in Inuit in Greenland compared with Inuit in Denmark (Bjerregaard et al., 2003; Madsen et al., 2005). Furthermore, Inuit have drinking patterns that are associated with social position (Bjerregaard and Jeppesen, 2010), migration and urbanization, and sense of coherence (Madsen et al., 2005). The alcohol consumption in Greenland has changed dramatically over the last 50 years from an average of 6 l per year in 1960, to 22 l in 1982 and now an average of ~10 l pure alcohol per year for all adults aged 15 years or higher (Statistics Greenland). During the same period, profound changes have taken place in the society, explaining the fluctuation (Roussau and Svendsen, 2008), although no simple model has been proposed. In this study, we observed an association between urbanization and alcohol intake: the highest

<table>
<thead>
<tr>
<th>Source</th>
<th>β</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.429</td>
<td>1.103 to 1.756</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.009</td>
<td>0.008 to 0.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (women – reference)</td>
<td>−0.011</td>
<td>−0.023 to 7.897E-5</td>
<td>0.052</td>
</tr>
<tr>
<td>Place of living:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inuit in Denmark</td>
<td>−0.367</td>
<td>−0.500 to −0.234</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nuuk</td>
<td>−0.468</td>
<td>−0.602 to −0.333</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qasigiannguit</td>
<td>−0.510</td>
<td>−0.644 to −0.375</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Uummannaq</td>
<td>−0.532</td>
<td>−0.670 to −0.394</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Danes in Denmark</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drinks per week (alcohol)</td>
<td>0.007</td>
<td>0.006 to 0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco (g/day)</td>
<td>0.001</td>
<td>0.001 to 0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (log)</td>
<td>−0.191</td>
<td>−0.239 to −0.142</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alkaline phosphatase (log)</td>
<td>0.194</td>
<td>0.176 to 0.212</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilirubin (log)</td>
<td>0.055</td>
<td>0.041 to 0.069</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.000</td>
<td>−0.001 to 0.001</td>
<td>0.729</td>
</tr>
</tbody>
</table>

The dependent variable is plasma YKL-40 (log transformed) and the covariates are age, sex, alcohol, tobacco, albumin, alkaline phosphatase and bilirubin. For each variable, β depicts the change in the YKL-40 level for each unit of increase in the variable in question (for example, for an increase of one drink per week or an increase of 1 g tobacco per day, etc.). For classification variables, β depicts the change in YKL-40 through a shift in place of residence from the reference group (for example shift from Danes living in Denmark to Inuit living in Nuuk, etc.). For log transformed variables β is not back transformed.

<table>
<thead>
<tr>
<th>Source</th>
<th>β</th>
<th>95% CI</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>1.373</td>
<td>1.051 to 1.696</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>0.009</td>
<td>0.009 to 0.009</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Men (women – reference)</td>
<td>−0.13</td>
<td>−0.024 to −0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Place of living:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inuit in Denmark + Nuuk</td>
<td>−0.412</td>
<td>−0.543 to −0.280</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Qasigiannguit + Uummannaq</td>
<td>−0.504</td>
<td>−0.637 to −0.371</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Danes in Denmark (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of drinks per week (alcohol)</td>
<td>0.007</td>
<td>0.006 to 0.007</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tobacco (g/day)</td>
<td>0.001</td>
<td>0.001 to 0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin (log)</td>
<td>−0.188</td>
<td>−0.236 to −0.140</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alkaline phosphatase (log)</td>
<td>0.202</td>
<td>0.184 to 0.219</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilirubin (log)</td>
<td>0.054</td>
<td>0.040 to 0.067</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interaction</td>
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<tr>
<td>Alcohol intake × place of living:</td>
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<td></td>
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</tr>
<tr>
<td>Inuit in Denmark + Nuuk</td>
<td>−0.003</td>
<td>−0.006 to −0.001</td>
<td>0.593</td>
</tr>
<tr>
<td>Qasigiannguit + Uummannaq</td>
<td>−0.003</td>
<td>−0.006 to −0.001</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Danes in Denmark (reference)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The dependent variable is plasma YKL-40 (log transformed). The covariates included the following: gender, age, alcohol intake, smoking, albumin (log), alkaline phosphatase (log), place of residence in three categories (Qasigiannguit + Uummannaq; Nuuk + Inuit in Denmark; and Danes in Denmark), and interaction between the place of residence and alcohol intake. For each variable, β depicts the change in the YKL-40 level for each unit of increase in the variable in question (for example, for an increase of one drink per week or an increase of 1 g tobacco per day, etc.). For classification variables, β depicts the change in YKL-40 by a shift in place of residence from the reference group (for example, shift from Danes living in Denmark to Inuit living in Nuuk, etc.). For log transformed variables β is not back transformed.
alcohol intake and plasma YKL-40 was found in Inuit in Nuuk in Denmark, and the lowest in the smaller villages in Uummannaq and Qasigiannguit municipality. This may be explained by environmental factors; people stick together more in small societies and take more care of each other because of social dependency leading to personal safety and confidence as well as less addiction to alcohol.

Many studies have shown that plasma (or serum) concentrations of YKL-40 are elevated in patients with different types of chronic liver diseases, including alcoholic liver diseases and hepatitis (Johansen et al., 1997, 2000; Nøjgaard et al., 2003a,b; Anttila et al., 2005; Saitou et al., 2005; Lebensztejn et al., 2007; Fontana et al., 2008, 2012; Berres et al., 2009; Malik et al., 2009; Pizano-Martínez et al., 2011; Rath et al., 2011; Eurich et al., 2013), liver fibrosis and cirrhosis (Johansen et al., 1997, 2000), and hepatitis C virus infection (Nøjgaard et al., 2003a,b; Lebensztejn et al., 2007; Rath et al., 2011; Fontana et al., 2012). Furthermore, YKL-40 levels have been shown to be associated with risk of ischemic stroke and asthma as well as YKL-40 seems to be inversely related to ischemic heart disease (Rathcke et al., 2009, 2012). The highest levels, up to 3–5 fold increased, are found in patients with alcoholic cirrhosis in combination with alcoholic hepatitis (Johansen et al., 1997, 2000; He et al., 2013). It has been hypothesized that high plasma YKL-40 in alcoholics are caused by alcoholic liver damage processes. It has been demonstrated that the plasma YKL-40 levels are related to the degree of fibrosis, confirmed histologically, with the highest levels in patients with moderate to severe fibrosis, and these changes were independent of the etiology of the liver disease (Johansen et al., 1997, 2000; Nøjgaard et al., 2003a,b; Saitou et al., 2005; Lebensztejn et al., 2007; He et al., 2013). Rath et al. showed in patients with liver diseases that plasma YKL-40 could improve the diagnostic accuracy of other modalities such as transient elastography (Rath et al., 2011). However, the results are conflicting, and others found that plasma YKL-40 levels were not predictive of advanced liver fibrosis (Lebensztejn et al., 2007; Berres et al., 2009).

A single nucleotide polymorphism (SNP) in the proximal promoter of CHI3L1 accounts for some of the variance in plasma concentrations of YKL-40 (Kjærgaard et al., 2013). Some of these SNPs have been shown to be associated with the degree of fibrosis in HCV, which responds to antiviral treatment, to rejection after liver transplantation (Berres et al., 2009; Eurich et al., 2013), and asthma and atopy (Rathcke et al., 2009). In other trials, not all these findings were confirmed (Fontana et al., 2012). The distribution of these SNPs in Inuit is not known.

YKL-40 is produced in tissues with increased remodeling/degradation or inflammation of the extracellular matrix (Johansen et al., 2009; Lee et al., 2011), and YKL-40 is a growth factor for fibroblasts (Kawada et al., 2012) and stimulates VEGF (Saïdi et al., 2008; Shao et al., 2009; Faibish et al., 2011; Francescone et al., 2011; Shao, 2013). The cellular sources of YKL-40 in the liver are unknown, but YKL-40 may be secreted by hepatic CD14+ cells, including Kupffer cells during acute and chronic liver injury (Pizano-Martínez et al., 2011). Several factors, including YKL-40, will rise because of inflammation and apoptosis in the liver and by the remodeling of the extracellular matrix as it tries to heal the tissue damage. In a previous study, we speculated why some patients with alcoholic fatty liver but without fibrosis/cirrhosis/hepatitis had very high YKL-40 values (Johansen et al., 1997, 2000; Nøjgaard et al., 2003a). Normally, patients with fibrosis, cirrhosis or alcoholic hepatitis have higher levels of plasma YKL-40 than patients with fatty liver. We presumed that it could be because of sampling error of the liver biopsies, but we might speculate that a more likely explanation is that these patients had high alcohol consumption and therefore high YKL-40 values. Anttila et al. (2005) found a strong correlation between PIINP values and alcohol consumption, suggesting that the activation of hepatic stellate cells and initiation of fibrogenesis occur as early events in response to hazardous drinking practices. PIINP is the cleavage product of procollagen III into collagen III as well as a component of the ECM deposited in the space of Disse and produced by the HSCs as are the other ECM components in the liver. PIINP and YKL-40 are correlated, but it is not known if YKL-40 has a direct effect on PIINP production. Serum PIINP may indicate activation of fibrogenesis even before the development of severe liver disease, which could also be of value in the assessment of prognosis in alcoholic patients (Nøjgaard et al., 2003a).

It is interesting that we found a lack of association between plasma YKL-40 and alcohol intake in Inuit in small towns and settlements, while there was an association in Inuit in Nuuk and Denmark, where the association was similar to that found in Danes in Denmark. This observation may be in accordance with the hypotheses that Inuit have a lower sensitivity for alcohol in the context of developing alcohol related liver disease as mentioned above. This may in turn be explained by differences in living conditions, such as differences in diet, but our study could not evaluate whether the higher plasma YKL-40 levels in Inuit living in Denmark compared with those of Inuit living in Greenland are due to differences in nutrition. Inuit in small towns and settlements in Greenland have a higher intake of sea mammals, fish and sea food than Inuit in Nuuk and in Denmark (Bjerregaard and Jeppesen, 2010), but no studies have tested the influence of nutrition on circulating YKL-40 levels.

In conclusion, this study showed that plasma concentrations of YKL-40 are significantly lower in Inuit living in small towns and settlements in Greenland than Inuit living in Nuuk and Denmark. Furthermore, we observed no association between alcohol intake and plasma YKL-40 levels in Inuit in small towns and settlements in Greenland in contrast to Inuit in Nuuk and Denmark. Several factors including different alcohol intake pattern and nutrition, may play a role for these findings.

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