ASSOCIATION OF SELF-REPORTED DISEASES AND HEALTH CARE USE WITH COMMONLY USED LABORATORY MARKERS FOR ALCOHOL CONSUMPTION

PEKKA SILLANAUKEE*, NURIA STRID1, PEKKA JOUSILAHTI1,2, ERKKI VARTAINEN2, KARI POIKOLAINEN3,4, SEppo NIKKARI5, JOHN P. ALLEN6,7 and HANNU ALHO8,9

FIT Biotech Oyj Plc, Tampere, Finland, 1NS Associates, Vatholma, Sweden, 2National Public Health Institute, Department of Epidemiology and Health Promotion, Helsinki, 3Tampere School of Public Health, Tampere, 4Järvenpää Addiction Hospital, 5National Public Health Institute, Department of Mental Health and Alcohol Research, Helsinki, 6University of Tampere Medical School, Department of Medical Biochemistry, Tampere, Finland, 7National Institute on Alcohol Abuse and Alcoholism, Rockville, MD, USA, 8National Public Health Institute, Alcohol Research Centre, Helsinki and 9Research Unit of Alcohol Diseases, University of Helsinki, Finland

(Received 11 September 2000; in revised form 25 January 2001; accepted 12 February 2001)

Abstract — The relationships of carbohydrate-deficient transferrin (CDT), gamma-glutamyltransferase (GGT) and their mathematical combination (γ-CDT) with self-reported diseases were evaluated in a large cross-sectional risk factor survey. Significant gender effects were observed in associations of the markers with several medical conditions as well as with general health care utilization. In men, CDT was associated with rheumatoid arthritis. In both genders, GGT was positively associated with hypertension and diabetes. γ-CDT was positively associated with hypertension in males and with asthma in females. This general population study demonstrates that these markers, although most commonly used to assess alcohol misuse, might also serve as health risk indicators.

INTRODUCTION

Despite the association of light to moderate alcohol consumption with reduced risk for coronary heart disease (CHD) and subsequent reduction in total mortality (Boffetta and Garfinkel, 1990; Shaper et al., 1994; Mantarri et al., 1997), the cardiovascular system is vulnerable to heavy and chronic alcohol intake. The consequences include hypertension, cardiomyopathy, haemorrhagic stroke and arrhythmias. It is, in fact, quite possible that the effect of alcohol consumption on overall disease is dose dependent, and a J-shaped association of alcohol consumption (Simpura, 1987), laboratory tests in high alcohol consumers might prove more predictive of subsequent risk of disease. Carbohydrate-deficient transferrin (CDT) and gamma-glutamyltransferase (GGT) are commonly used markers of high alcohol consumption and have reasonable sensitivities. False-positive CDT values are rare and arise primarily from a genetic D-variant of transferrin (Stibler et al., 1988), an inborn error of glycoprotein metabolism (Hagberg et al., 1993), severe liver disease, such as advanced cirrhosis with ascites (Takase et al., 1985), primary biliary cirrhosis (Behrens et al., 1988), chronic active hepatitis (Stauber et al., 1995) and chronic viral hepatitis (Perret et al., 1997). Chronic iron deficiency and pregnancy (La Grange et al., 1995; Stauber et al., 1996) may also influence the response of CDT to heavy alcohol consumption.

High levels of GGT are not only associated with excessive alcohol consumption, but also with a variety of other conditions, including hypertriglyceridaemia, use of microsomal enzyme-inducing drugs, most hepatobiliary disorders, diabetes mellitus, obesity, pancreatitis, congestive heart failure, acute renal insufficiency, coronary heart disease, severe trauma and smoking (Whitfield et al., 1972; Ellis et al., 1979; Kristenson et al., 1980; Salaspuro, 1989; Sillanaukee, 1996). Several studies in general populations have reported an association between GGT and blood pressure and lipid metabolism (Van Barneveld et al., 1989; Nilssen et al., 1990), which suggests a predictive value of GGT in ischaemic heart disease. In fact, an association between GGT and mortality from ischaemic heart disease, independent of biological variables, such as body mass index (BMI), diabetes mellitus, smoking and blood pressure, was found in a general population study (Wannamethee et al., 1995).

In a recent study, we showed that the diagnostic utility of CDT and GGT as indices of high alcohol consumption could be improved by combining them according to a simple mathematical model (Sillanaukee and Olsson, 2001). This combination, named ‘γ-CDT’ (γ-CDT = 0.8·In GGT + 1.3·In CDT) reduces the total number of false positives and negatives as compared with GGT alone or CDT alone.

Several previous papers have studied in some detail the association of GGT with medical disorders and health care utilization (Kristenson et al., 1982; Kristenson and Johnell, 1986; Conigrave et al., 1993; Spies et al., 1996). Few articles, however, have evaluated these associations with CDT (Spies et al., 1996). To our knowledge, the current project is the first to evaluate in some detail the association of CDT and γ-CDT with selected indicators of health care use and self-reported diseases in general population settings.

MATERIALS AND METHODS

Study population

A large cross-sectional risk factor survey was performed in Finland at the beginning of 1997 to assess the levels of behavioural and biological health-related factors among the population. The study was conducted in accordance with the guidelines of the Helsinki Declaration of 1975 on Human Experimentation and was approved by the Ethical Committee of the National Health Institute of Finland. All participants
provided informed consent about the scientific use of the data and samples collected in the study.

The investigation was conducted in five geographical areas: Helsinki-Vantaa region in southern Finland, Turku-Loimaa region in southwestern Finland, Kuopio and North Karelia provinces in eastern Finland and Oulu province in northern Finland. In each study area, an age- and gender-stratified random sample of 2000 subjects was drawn from the population aged between 25 and 64 years. In addition, a sample of 250 women and 500 men aged 65–74 years was drawn in North Karelia and in Helsinki-Vantaa region rendering a total sample size of 11 500 subjects (5500 women and 6000 men). The participation rate was 76% among women and 71% among men and complete data on CDT and GGT values were available for 4011 women and 4014 men. Women who were pregnant (n = 76), those treated with hormones in the past (including the use of oral contraceptives; n = 197) and those presently using any hormone treatment (n = 656) were excluded. Due to missing data on alcohol consumption 40 men and 94 women were also excluded. Thus, 2988 women and 3974 men were considered in the present study.

The survey included a self-administered questionnaire mailed to the subjects in advance of their medical appointments. The questionnaire included 156 questions about previous and existing diseases, smoking habits and alcohol use. The questionnaires were returned to the survey site and study nurses scanned them to ensure that they were fully completed. The nurse also measured the patient’s height, weight, blood pressure and other parameters. Body mass index (BMI) was calculated as the ratio of weight (kg) to height squared (m²) and blood pressure was assessed using standard procedures. A venous blood specimen was drawn for determination of CDT, GGT and other biochemical parameters.

Quantitative estimation of alcohol intake was based on a set of 13 structured questions inquiring about the level and frequency of drinking during the past year. The average weekly alcohol intake included the following beverage types: spirits, beer, wine, cider and light wine. The measure of average alcohol consumption considered that standard units of beer, mixed drinks, spirits and wine contain 12 g of pure alcohol each, whereas cider and low alcoholic wine have 4 g of pure alcohol. Intake in the preceding week and mean alcohol consumption during the past year was calculated and expressed as g of pure ethanol/week.

Biochemical analyses

During the 4 h prior to sample collection, the subjects refrained from eating. Serum samples were collected according to routine clinical practice and stored at −70°C until analyses. The samples were analysed by a double antibody kit (CDTect™, AXIS-SHIELD, Oslo, Norway) according to the manufacturer’s instructions. This test is based on anion exchange chromatography and radioimmunoassay and offers a detection limit of 1 U/l and a measuring range of 5–300 U/l. Levels of GGT were measured by the kinetic method (Oy Medix Biochemica AB, Kauniainen, Finland) based on the recommendations of the European Committee for Clinical Laboratory Standards (ECCLS) (Leino et al., 1995).

Indicators of health care use and self-reported diseases

The following health indicators were assessed: (1) health care use (visits to the doctor and to nurses, and absence from work); (2) self-reported diseases (cancer, diabetes, angina pectoris, stroke, asthma, heart attack, cardiac insufficiency, emphysema, rheumatoid arthritis, urolgy and kidney diseases).

Statistical methods

Based on the manufacturer’s recommendations, the cut-off values for CDT were set at 20 U/l for men and 26 U/l for women. The cut-off values for GGT were 80 U/l and 50 U/l for males and females, respectively, according to the ECCLS (Leino et al., 1995). The limits for γ-CDT were based on the results of a previous study and were 7.2 for both males and females (Sillanaukee et al., 2000).

Analyses were performed separately for males and females using SPSS for Windows 9.0 (1999) software. Because the distribution of alcohol consumption and blood tests was positively skewed, logarithmic transformations of the data were employed. Groups were contrasted according to odds ratios (OR) and confidence intervals, which were considered to differ from each other if the 95% confidence interval did not include the value 1.0. Logistic regression models were also employed to adjust the OR for age, BMI, smoking and alcohol consumption.

RESULTS

OR for self-reported diseases and health care utilization between subjects with high vs low CDT are summarized in Table 1. In males, high CDT values were associated with higher risk for rheumatoid arthritis (P = 0.0137) even after adjusting for age, BMI, smoking and alcohol consumption (P = 0.0354 by logistic regression). In females, high CDT values reflected fewer visits to a nurse, less self-reported hypertension and fewer urology problems. When adjusting for age, BMI, smoking and alcohol consumption, only the association between high CDT and fewer urology problems remained significant (P = 0.0408) for females.

Table 2 shows the OR by GGT for self-reported diseases and health care use between subjects with high or low GGT. In both genders, high GGT levels were associated with higher risk for diabetes (P = 0.0274 for males and P = 0.0294 for females).

In males, high GGT values also correlated positively with prevalence of angina pectoris and self-reported hypertension. Following statistical adjustment for age, BMI, smoking and alcohol consumption, only the association between GGT and hypertension remained significant (P = 0.0006). In females, GGT levels were associated with cardiac insufficiency, asthma, back problems and self-reported hypertension, although, after adjustment for age, BMI, smoking and alcohol consumption, only the OR for self-reported hypertension remained significant (P = 0.0285). Also, associations between high GGT values and lower risks for urology problems (P = 0.0312) and gallstones and inflammation (P = 0.04) were observed following adjustment for age, BMI, smoking and alcohol consumption.

Table 3 displays the OR by γ-CDT for self-reported diseases and health care use. In males, high γ-CDT was associated with higher risk for cardiac insufficiency (P = 0.0337) and with self-reported hypertension (P = 0.0042). These relationships were independent of age, BMI, smoking and/or alcohol consumption.
In females, γ-CDT was associated with higher prevalence of asthma ($P = 0.0137$), and the risk was independent of age, BMI, smoking and alcohol consumption.

**DISCUSSION**

Self-report of alcohol intake tends to underestimate actual intake (Pernanen, 1974; Polich, 1981; Alanko, 1984; Simpura, 1987), thereby over-emphasizing the apparent relative health risk estimates. Nevertheless, a comparison of retrospective vs prospective alcohol and cigarette consumption data has shown that information bias is unlikely to exert much impact on effect size estimates based on retrospective information (Giovannucci et al., 1993).

Our results demonstrate that the biochemical markers of alcohol abuse, CDT, GGT and their combination, may prove useful as indicators of health risks in a general population. Although to-date the use of these two markers has been largely restricted to identifying alcohol-specific diseases, values on the tests may also portend risk of other diseases.

In males, we found an association between high CDT values and a higher risk for rheumatoid arthritis (OR = 2.7). Iron-deficiency anaemia (Hansen et al., 1983; Vreugdenhil et al., 1990) and the anaemia of chronic disease (Cartwright and Lee, 1971) are frequently associated with active rheumatoid arthritis. In acute and chronic inflammatory conditions, alterations in the glycosylation pattern of a number of glycoproteins have been described (Raynes, 1982; Mackiewicz et al., 1987a,b; Lejeune et al., 1989; Thompson et al., 1989). Our results disagree with several studies that have reported a shift in the micro-heterogeneity pattern of transferrin among subjects with rheumatoid arthritis resulting in an increased synthesis of transferrin with highly branched glycan chains, and
In this study, GGT and, to an even greater extent, g-CDT, were associated with heightened risk for cardiac-related diseases and self-reported hypertension. The association between GGT and cardiac-related diseases (angina pectoris and cardiac insufficiency) was BMI dependent, whereas the association with self-reported hypertension was not influenced by age, BMI, smoking or alcohol consumption. Hypertension is a major risk factor for cerebrovascular haemorrhage as well as myocardial infarction (Buckley and Miller, 1988). Numerous studies have related alcohol consumption with exacerbated risk for hypertension (MacMahon, 1987). Moreover, it has previously been demonstrated that GGT predicts hypertension among male drinkers (Miura et al., 1994). Our results are in agreement with those of Pohorecky (1990), who reported that the risk for hypertension among subjects drinking three to four drinks per day was 50% higher than among non-drinkers.

Although the exact mechanism of the association between GGT and hypertension remains as yet unclear, it has been related to hepatic cell membrane injury, rather than to enzyme induction (Yamada et al., 1991). However, the alcohol-induced effect on blood pressure can be seen after an alcohol intake exceeding three drinks per day (Moore et al., 1990), a level insufficient to induce cell membrane damage. Because the population under study is characterized by relatively low alcohol intake levels, further studies are needed to clarify the mechanism of the association between GGT and hypertension.

<table>
<thead>
<tr>
<th>Gender and diseases</th>
<th>Unadjusted</th>
<th>Adjusted*</th>
<th>Adjustedb</th>
<th>Adjustedc</th>
<th>Adjustedd</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit to doctor</td>
<td><strong>1.05 (1.02–1.08)</strong></td>
<td><strong>1.04 (1.01–1.07)</strong></td>
<td><strong>1.03 (1.01–1.06)</strong></td>
<td><strong>1.03 (1.01–1.06)</strong></td>
<td><strong>1.04 (1.00–1.07)</strong></td>
</tr>
<tr>
<td>Visit to nurse</td>
<td><strong>1.02 (1.00–1.04)</strong></td>
<td><strong>1.02 (1.00–1.04)</strong></td>
<td><strong>1.01 (0.99–1.03)</strong></td>
<td><strong>1.01 (0.99–1.03)</strong></td>
<td><strong>1.02 (0.99–1.04)</strong></td>
</tr>
<tr>
<td>Absence from work</td>
<td><strong>1.00 (1.00–1.01)</strong></td>
<td><strong>1.00 (1.00–1.01)</strong></td>
<td><strong>1.00 (1.00–1.00)</strong></td>
<td><strong>1.00 (1.00–1.00)</strong></td>
<td><strong>1.00 (1.00–1.00)</strong></td>
</tr>
<tr>
<td><strong>Self-reported diseases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td><strong>2.27 (1.78–2.90)</strong>***</td>
<td><strong>2.19 (1.70–2.83)</strong>***</td>
<td><strong>1.66 (1.27–2.16)</strong>***</td>
<td><strong>1.68 (1.29–2.19)</strong>***</td>
<td><strong>1.61 (1.22–2.11)</strong>***</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td><strong>1.31 (0.80–2.15)</strong></td>
<td><strong>1.30 (0.79–2.12)</strong></td>
<td><strong>1.19 (0.72–1.97)</strong></td>
<td><strong>1.15 (0.69–1.92)</strong></td>
<td><strong>1.23 (0.73–2.07)</strong></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td><strong>1.62 (1.07–2.46)</strong>*</td>
<td><strong>1.57 (1.03–2.38)</strong>*</td>
<td><strong>1.43 (0.93–2.20)</strong></td>
<td><strong>1.46 (0.95–2.25)</strong></td>
<td><strong>1.54 (0.99–2.41)</strong></td>
</tr>
<tr>
<td>Heart attack</td>
<td><strong>1.42 (0.92–2.20)</strong></td>
<td><strong>1.23 (0.78–1.93)</strong></td>
<td><strong>1.12 (0.71–1.78)</strong></td>
<td><strong>1.05 (0.66–1.66)</strong></td>
<td><strong>1.22 (0.76–1.94)</strong></td>
</tr>
<tr>
<td>Stroke</td>
<td><strong>1.45 (0.81–2.60)</strong></td>
<td><strong>1.35 (0.75–2.40)</strong></td>
<td><strong>1.16 (0.63–2.13)</strong></td>
<td><strong>1.07 (0.58–1.98)</strong></td>
<td><strong>1.20 (0.64–2.25)</strong></td>
</tr>
<tr>
<td>Asthma</td>
<td><strong>0.74 (0.37–1.49)</strong></td>
<td><strong>0.73 (0.36–1.46)</strong></td>
<td><strong>0.60 (0.29–1.24)</strong></td>
<td><strong>0.58 (0.28–1.20)</strong></td>
<td><strong>0.61 (0.29–1.27)</strong></td>
</tr>
<tr>
<td>Back problems</td>
<td><strong>1.12 (0.86–1.48)</strong></td>
<td><strong>1.10 (0.84–1.45)</strong></td>
<td><strong>1.01 (0.77–1.34)</strong></td>
<td><strong>0.98 (0.74–1.30)</strong></td>
<td><strong>1.03 (0.77–1.38)</strong></td>
</tr>
<tr>
<td>Cancer</td>
<td><strong>1.22 (0.51–2.94)</strong></td>
<td><strong>1.07 (0.44–2.58)</strong></td>
<td><strong>1.19 (0.48–2.90)</strong></td>
<td><strong>1.16 (0.47–2.85)</strong></td>
<td><strong>1.24 (0.50–3.08)</strong></td>
</tr>
<tr>
<td>Urology problems</td>
<td><strong>0.96 (0.44–2.07)</strong></td>
<td><strong>0.94 (0.44–2.04)</strong></td>
<td><strong>1.00 (0.45–2.23)</strong></td>
<td><strong>1.05 (0.47–2.34)</strong></td>
<td><strong>1.10 (0.49–2.47)</strong></td>
</tr>
<tr>
<td>Gallstones</td>
<td><strong>1.13 (0.53–2.42)</strong></td>
<td><strong>1.08 (0.50–2.32)</strong></td>
<td><strong>1.14 (0.52–2.51)</strong></td>
<td><strong>1.22 (0.55–2.71)</strong></td>
<td><strong>1.26 (0.57–2.80)</strong></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td><strong>1.08 (0.38–3.09)</strong></td>
<td><strong>0.99 (0.35–2.83)</strong></td>
<td><strong>0.93 (0.32–2.71)</strong></td>
<td><strong>0.87 (0.30–2.55)</strong></td>
<td><strong>1.05 (0.35–3.10)</strong></td>
</tr>
<tr>
<td>Emphysema</td>
<td><strong>1.24 (0.82–1.87)</strong></td>
<td><strong>1.20 (0.79–1.81)</strong></td>
<td><strong>1.02 (0.66–1.56)</strong></td>
<td><strong>0.97 (0.63–1.49)</strong></td>
<td><strong>1.12 (0.73–1.73)</strong></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td><strong>1.48 (1.19–1.83)</strong>***</td>
<td><strong>1.42 (1.14–1.76)</strong>**</td>
<td><strong>1.27 (1.02–1.59)</strong>**</td>
<td><strong>1.29 (1.03–1.61)</strong>*</td>
<td><strong>1.30 (1.03–1.64)</strong>*</td>
</tr>
</tbody>
</table>

The cut-off values were 80 U/l for males and 50 U/l for females. The sample was divided into two groups, above and below the cut-off point: 9.7% of the males and 7% of females had GGT > cut-off.

*Adjusted by age; **Adjusted by age and BMI; ***Adjusted by age, BMI and smoking; ****Adjusted by age, BMI, smoking and alcohol consumption.

p < 0.05, *p < 0.01, ***p < 0.001 by logistic regression. The significance of the associations is indicated in bold.

BMI, body mass index.
Betw een alcohol consumption and BMI (Poikolainen and Raether than simply by alcohol intake. Vartiainen, 1997). Thus, the association of GGT with hyper tension could be explained by an alcohol-induced obesity damage is not involved. Earlier studies have found a positive association between GGT and alcohol intake and BMI, and between alcohol consumption, the mechanism of the association observed between GGT and hypertension is unlikely to entail induced cell membrane damage. Moreover, alcohol-induced hypertension has been reported to be reversible after abstinence from alcohol (Klatsky, 1990), which also suggests that liver damage is not involved. Earlier studies have found a positive association between GGT and alcohol intake and BMI, and between alcohol consumption and BMI (Poikolainen and Vartiainen, 1997). Thus, the association of GGT with hypertension could be explained by an alcohol-induced obesity rather than simply by alcohol intake.

The association between high GGT levels and heightened risk for diabetes observed in both genders concurs with findings of previous studies, in which elevated levels of GGT among diabetic subjects were reported (Goldburg et al., 1963; Jacobs, 1972; Boone et al., 1974; Rosalki, 1975; Foster et al., 1980; Oli et al., 1983; Salmela et al., 1984), and this association was independent of serum glucose and BMI (Perry et al., 1998). In the light of findings across a range of studies, it seems that the increase in GGT observed in diabetes is not due to diabetes itself, but rather, to diabetes-associated pathologies, such as those resultant from poly-medication frequent among diabetic subjects (Oli et al., 1983; Barbieux et al., 1990). As concluded by Perry et al. (1998), the serum GGT level may be a marker of visceral and hepatic fat and, by inference, of hepatic insulin resistance.

The risk of asthma was two-fold in female subjects with high γ-CDT, as contrasted with those having low γ-CDT values. It is known that chronic alcohol misuse depresses the immune system and predisposes to infectious diseases, including respiratory infections, pneumonia and tuberculosis, as well as cancer (Adams and Jordan, 1984; Bautista et al., 1991a,b; Jerrels, 1991a,b). Vulnerability to respiratory infections may exacerbate existing asthma. Because women have a lower body
mass and metabolize ethanol less efficiently than men, and thereby experience higher blood-alcohol concentrations in a shorter time (Frezza et al., 1990), they may be more liable for alcohol-induced damage in body systems and this may account for the association between GGT and asthma being seen only in females. Nevertheless, some residual confounding caused by under-reporting of smoking in female drinkers may also be a cause.

In conclusion, this project demonstrates that commonly used laboratory markers of alcohol misuse may also serve as useful indicators of health status. Rheumatoid arthritis and, possibly, other inflammatory conditions, however, must be taken into account as potential sources of false positives when CDT is being used as a screening instrument for alcohol problems.

Acknowledgement — This study was supported by the Medical Research Fund of Tampere University Hospital (Tampere, Finland).

REFERENCES


forms of alpha-1-acid glycoprotein as indicators of rheumatoid arthritis activity. *Clinica Chimica Acta* 163, 185–190.


