Association Between Alcohol Consumption and Subclinical Carotid Atherosclerosis

The Study of Health in Pomerania

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Background and Purpose—Epidemiologic studies have shown a J-shaped association between alcohol consumption and vascular diseases. However, only few studies have reported on the association between alcohol intake and subclinical atherosclerosis. The aim of the study was to investigate the relation between alcohol intake and carotid intima-media thickness (IMT) in participants of the population-based Study of Health in Pomerania.

Methods—In 1230 men and 1190 women, the mean IMT of the right and left common carotid arteries was measured by B-mode ultrasonography. Alcohol consumption was assessed with a computer-assisted face-to-face interview.

Results—In men, carotid IMT as a function of alcohol intake was depicted as a J-shaped curve with a nadir for the alcohol intake category of 61 to 80g/d. Linear regression models controlled for age, diabetes, systolic blood pressure, leisure time physical activity, food frequency patterns, smoking status, and education revealed a significant inverse association between IMT and alcohol intake =80g/d in men ($\beta=-0.009, P<0.02$), which became insignificant after further controlling for HDL cholesterol and fibrinogen ($\beta=-0.007, P=NS$). In women, neither a J-shaped relation nor significant differences in IMT between the drinking and nondrinking groups were found.

Conclusions—Alcohol consumption is inversely correlated with carotid IMT in men but not in women. However, the total daily level of alcohol intake that shows a maximum protective effect against atherosclerosis is above the threshold where severe alcohol related comorbidity and organ damage have been reported. (Stroke. 2005;36:1746-1752.)

Key Words: alcohol drinking ■ atherosclerosis ■ carotid arteries ■ epidemiology ■ intima-media thickness

Epidemiologic studies have shown a J-shaped or a U-shaped relation between alcohol consumption and vascular diseases.1–4 The majority of these studies focused on clinical end points, such as mortality and morbidity from coronary heart disease (CHD) or stroke. The common pathophysiologic basis for the subsequent occurrence of clinical vascular end points is atherosclerotic changes of the vessel wall. Carotid intima-media thickness (IMT) is widely considered to be a surrogate marker for the severity of atherosclerosis, and it is highly predictive for prevalent and incident CHD and stroke.5–8 In contrast to the large number of studies for clinical end points, only few studies have reported on the association between alcohol intake and subclinical atherosclerosis.9–16 Their results are incongruent. Cross-sectional studies found either no association between alcohol intake and carotid atherosclerosis11 or a J-shaped relation between alcohol consumption and carotid plaques12 or between alcohol consumption and carotid IMT in an elderly population.16 A study from Finland demonstrated that binge-drinking men had the highest progression rates of IMT during a 4-year follow-up period.15 The objective of our study was to investigate the relation between alcohol intake and carotid IMT as an indicator of asymptomatic subclinical atherosclerosis in participants of the population-based Study of Health in Pomerania (SHIP).

Methods

SHIP is a cross-sectional survey in northeastern Germany involving the 3 cities of Greifswald, Stralsund, and Anklam and 29 surrounding communities. From the total population of 212 157 living in the study area, a representative population sample totaling 7008 persons aged 20 to 79 years was selected from population registers.17 The 2-stage cluster sampling method was adopted from the WHO MONICA Project Augsburg, Germany, and yielded 12 5-year age strata (20 to 79 years) for both sexes, each including 292 individuals.18 A total of 4310 individuals (2193 women), 68.8% of all eligible subjects, took part in the study. The study was approved by the Review Board of the Federal State of Mecklenburg-Greifswald, Germany.

Drs Schminke and Luedemann contributed equally to this work.

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Stroke is available at http://www.strokeaha.org

Received January 11, 2005; final revision received April 21, 2005; accepted May 6, 2005.

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Vorpommern, and all participants gave written, informed consent to the scientific use of the collected data. Ultrasound measurements of carotid IMT were restricted in the study design to 2515 subjects between 45 and 79 years of age. Ninety-five subjects were excluded from the study because of either poor quality of the recorded ultrasound images or missing information about their alcohol consumption. Thus 2420 (49% women) subjects were included in the statistical analysis.

Sociodemographic factors, medical histories, medications, and behavioral risk factors were assessed by a computer-assisted face-to-face interview (CAPI). The beverage-specific consumption of beer, wine, and distilled spirits from the weekend and weekday before the examination was assessed by CAPI, and the mean daily alcohol consumption was calculated by assuming that 1 L of beer contains 40 g, 1 L of wine contains 100 g, and 0.02 L of distilled spirits contains 6.2 g of pure ethanol. Alcohol intake was classified into sex-specific categories of 0 g/d, 1 to 20 g/d, 21 to 40 g/d, 41 to 60 g/d, 61 to 80 g/d, >80 g/d in men and 0 g/d, 1 to 5 g/d, 6 to 10 g/d, 11 to 15 g/d, 16 to 20 g/d, >20 g/d in women. To account for former drinkers who quit drinking, we applied the Luebeck Alcohol and Abuse Screening Test (LAST) score to the group of abstainers. The LAST score is derived from 7 questions regarding problems with alcohol use and has been validated as a regional screening test for a German population. A LAST score >0 is highly specific for at-risk drinking or alcohol misuse.

Smoking status was classified as never-smoker, former smoker, or current smoker, the latter referring to smoking 1 or more cigarettes per day. Leisure time physical activity was defined by 2 questions according to the MONICA Augsburg algorithm. Physically active individuals participated in sports in summer and in winter in at least 1 season for >1 h per week. A food frequency questionnaire was applied, which classifies selected food groups. The frequencies per food category (food frequency patterns) were summarized to a summary score per subject according to the recommendations of the German Society of Nutrition. Sex-specific tertiles of this score reflected the quality of food intake: lower tertile=unfavorable dietary pattern (score <15 for men, <17 for women), medium tertile=normal dietary pattern (score 15 to 16 for men, 17 to 18 for women), and upper tertile=optimal dietary pattern (score >16 for men, >18 for women). Health-related lifestyle was summarized into 3 distinct categories based on answers to a food frequency questionnaire and leisure time physical activity questions. Physically active individuals with optimal food intake were classified as having a favorable lifestyle. Those participants being inactive and having an unfavorable food intake pattern were classified as having an unfavorable lifestyle, and all others as having a normal lifestyle. A low education level was assumed in subjects with <10 years of school education.

Hypertension was considered if the diagnosis had been established by a physician, if a subject was being treated with antihypertensive drugs, or if arterial blood pressure was >140/90 mm Hg. Diabetes was considered if the diagnosis had been established by a physician or if a subject was under antidiabetic treatment. Enzymatic methods were used to measure total serum cholesterol (CHOD-PAP), HDL cholesterol (after MgCl₂ precipitation), and LDL cholesterol (after dextran-sulfate precipitation). For γ-glutamyltransferase (GGT), serum samples were kept at 2°C to 8°C and analyzed within 8 hours (Hitachi 717 and 704, Roche Diagnostics GmbH). For carbohydrate-deficient transferrin (CDT), serum samples were stored at −20°C and analyzed within 7 days with a nephelometric immunoassay (%CDTri-TIA, Axis Biochemicals Oslo, Behring-Nephelometer BN II Version).
Ultrasound Measurements

Both carotid arteries were assessed in B-mode with a 5-MHz linear-array transducer with an axial resolution of <0.5 mm. The mean far-wall IMT of the distal straight portion of the right and left common carotid arteries proximally from the bifurcation was calculated by averaging 10 consecutive measurement points (in 1-mm steps) from the bulb. Details of the procedure have been described elsewhere.25

Statistical Methods

Kruskal-Wallis test and χ² tests were used to calculate sex-specific differences. χ² statistic and a general linear model (GLM) ANOVA were used for analysis of between-group differences stratified by daily alcohol intake. Spearman rank correlation coefficients were calculated to assess the correlation between alcohol use and GGT, CDT, HDL cholesterol, and fibrinogen levels. GLM ANOVA was applied to compare group means of IMT against the groups of nondrinking men and women after adjustment for age, systolic blood pressure, diabetes, smoking, HDL-LDL ratio, and lifestyle patterns. Linear regression analysis was used to fit different models of IMT as a function of potential cardiovascular risk factors and control variables. The analyses were performed by PROC FREQ, PROC NPAR1WAY, PROC GLM (contrast statement for trend analysis across categories), PROC REG, and PROC LOGISTIC programs of the SAS 8.2 software system.

Results

Our analysis was restricted to 1230 men and 1190 women with complete data on daily alcohol intake and carotid IMT. The distribution of alcohol intake and the sources of alcohol intake for different levels of consumption are shown in Figures 1 and 2. In women, increased alcohol consumption was usually based on an increased intake of wine. In men, higher daily alcohol intake was due to increased beer consumption. Because of sex-specific differences in alcohol metabolism and because of the markedly higher alcohol intake in men, further analysis was performed separately for both sexes. In men, CDT (r=0.22, P<0.0001) and GGT (r=0.32, P<0.0001) were directly correlated with alcohol use, indicating a sufficient prediction of real alcohol intake as described by the interview data. No significant correlation was seen in women.

Data on cardiovascular and behavioral risk factors according to levels of alcohol consumption are shown in the supplementary Tables 2 (men) and 3 (women). In men, alcohol consumption was significantly associated with higher serum CDT and GGT levels, higher diastolic blood pressure, higher HDL cholesterol levels, and lower fibrinogen levels. Furthermore, HDL cholesterol (r=0.25, P<0.0001) and fibrinogen levels (r=-0.18, P<0.0001) were significantly correlated with alcohol use. In women, alcohol consumption was significantly associated with higher GGT, higher HDL cholesterol, lower LDL cholesterol, and lower fibrinogen levels. In both sexes, a higher level of education was seen more frequently among drinkers, whereas the health-related lifestyle index including leisure time physical activity and healthful food intake was not related to alcohol use.

Alcohol Consumption and Carotid IMT

In men, carotid IMT as a function of alcohol intake was depicted as a J-shaped curve, with highest values in abstainers and a nadir at an alcohol intake category of 61 to 80 g/d (Figure 3). In abstainers with an LAST score =0, carotid IMT was 0.8896 (SD=0.212, n=189) compared with 0.8469 (SD=0.1685, n=128) in those with an LAST score >0. Thus, the higher IMT in the group of abstainers cannot be explained by inclusion of former drinkers. In the fully adjusted model including all subjects, the decrease in IMT toward the nadir followed a significant linear trend (P<0.05). More specifically, the difference in IMT between nondrinkers and drinkers in each category of alcohol intake up to 80 g/d was either significant (0 to 20 g/d vs 0 g/d, and 41 to 60 g/d vs 0 g/d; P<0.05) or of borderline significance in men (21 to 40 g/d vs 0 g/d, and 61 to 80 g/d vs 0 g/d; P=0.055). Restricting the analysis to nondiabetics did not alter the shape of the curve, whereas restriction to subjects without hypertension turned associations to insignificant levels, which is probably due to the low number of normotensive subjects. In women, no significant differences in IMT between drinking and nondrinking women were observed, regardless of whether daily alcohol intake was classified into categories of 20-g intervals (data not shown) or 5-g intervals (Figure 3).

In additional linear regression analyses, we examined the effect of HDL cholesterol and inflammation markers as potential mediators of the inverse association between IMT and an intake of alcohol <80 g/d in men (Table 1). The linear regression model (model 1) that controlled for age, diabetes, systolic blood pressure, smoking status, lifestyle patterns, and education revealed a significant decrease of 0.009 mm in IMT per 20-g increase in daily alcohol consumption for men.
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SBP indicates systolic blood pressure. Alcohol consumption was used according to the intake classification in 20-g/d units. The adjusted $R^2$ for the multivariate models 1, 2, 3, and 4 were 0.21 for all.

### TABLE 2. Demographic Data, Circulation and Blood Parameters of Men of the Study of Health in Pomerania (SHIP) Classified by Mean Daily Alcohol Intake

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Daily Alcohol Intake Categories</th>
<th>0 g/d</th>
<th>1–20 g/d</th>
<th>21–40 g/d</th>
<th>41–60 g/d</th>
<th>61–80 g/d</th>
<th>&gt;80 g/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td></td>
<td>317</td>
<td>483</td>
<td>264</td>
<td>103</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Age [years]‡</td>
<td></td>
<td>64.6 (9.6)</td>
<td>63.6 (9.1)</td>
<td>61.6 (9.6)**</td>
<td>58.5 (8.7)**</td>
<td>58.6 (8.2)**</td>
<td>54.3 (8.2)**</td>
</tr>
<tr>
<td>Low education [%]</td>
<td></td>
<td>68.4</td>
<td>60.2*</td>
<td>59.7*</td>
<td>50.5**</td>
<td>42.4**</td>
<td>60.0</td>
</tr>
<tr>
<td>Lifestyle categories</td>
<td></td>
<td>16.4</td>
<td>17.8</td>
<td>17.8</td>
<td>11.7</td>
<td>3.0</td>
<td>10.0</td>
</tr>
<tr>
<td>Optimal [%]</td>
<td></td>
<td>51.1</td>
<td>54.5</td>
<td>47.4</td>
<td>45.6</td>
<td>57.6</td>
<td>43.3</td>
</tr>
<tr>
<td>Normal [%]</td>
<td></td>
<td>32.5</td>
<td>27.7</td>
<td>34.9</td>
<td>42.9</td>
<td>37.4</td>
<td>46.7</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td>28.2 (4.0)</td>
<td>28.6 (3.8)</td>
<td>28.3 (4.0)</td>
<td>28.1 (3.9)</td>
<td>28.4 (3.1)</td>
<td>26.8 (4.5)</td>
</tr>
<tr>
<td>Hypertension [%]</td>
<td></td>
<td>73.2</td>
<td>77.3</td>
<td>75.9</td>
<td>74.1</td>
<td>87.5</td>
<td>75.9</td>
</tr>
<tr>
<td>SBP [mm Hg]</td>
<td></td>
<td>146.2 (20.3)</td>
<td>147.7 (20.1)</td>
<td>148.6 (20.6)</td>
<td>149.0 (20.3)</td>
<td>152.0 (18.1)</td>
<td>147.5 (20.8)</td>
</tr>
<tr>
<td>DBP [mm Hg]†</td>
<td></td>
<td>85.1 (11.7)</td>
<td>87.7 (11.3)**</td>
<td>88.1 (11.9)**</td>
<td>90.0 (10.6)**</td>
<td>92.1 (12.6)**</td>
<td>89.9 (11.7)**</td>
</tr>
<tr>
<td>Diabetes mellitus [%]</td>
<td></td>
<td>20.1</td>
<td>12.7**</td>
<td>9.5**</td>
<td>5.8**</td>
<td>12.5</td>
<td>6.7</td>
</tr>
<tr>
<td>CDT [%]‡</td>
<td></td>
<td>4.5 (1.3)</td>
<td>4.7 (1.4)**</td>
<td>5.0 (1.8)**</td>
<td>5.9 (2.1)**</td>
<td>5.4 (1.4)**</td>
<td>7.4 (3.9)**</td>
</tr>
<tr>
<td>GGT [μkat/l]‡</td>
<td></td>
<td>0.53 (0.52)</td>
<td>0.65 (0.73)</td>
<td>0.89 (1.95)**</td>
<td>1.4 (2.8)**</td>
<td>1.2 (1.1)*</td>
<td>2.9 (5.8)**</td>
</tr>
<tr>
<td>Fibrinogen [g/l]‡</td>
<td></td>
<td>3.3 (0.8)</td>
<td>3.1 (0.7)</td>
<td>3.0 (0.7)</td>
<td>2.9 (0.5)</td>
<td>2.9 (0.7)**</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td>Total cholesterol [mmol/l]‡</td>
<td></td>
<td>5.7 (1.2)</td>
<td>5.9 (1.3)</td>
<td>6.0 (1.2)</td>
<td>6.1 (1.1)</td>
<td>5.9 (1.4)</td>
<td>6.3 (1.6)</td>
</tr>
<tr>
<td>HDL cholesterol [mmol/l]‡</td>
<td></td>
<td>1.2 (0.3)</td>
<td>1.3 (0.4)</td>
<td>1.4 (0.4)</td>
<td>1.4 (0.3)</td>
<td>1.4 (0.4)</td>
<td>1.7 (0.5)</td>
</tr>
<tr>
<td>LDL cholesterol [mmol/l]‡</td>
<td></td>
<td>3.7 (1.2)</td>
<td>3.8 (1.2)</td>
<td>3.8 (1.0)</td>
<td>3.7 (1.0)</td>
<td>3.7 (1.4)</td>
<td>3.8 (1.4)</td>
</tr>
<tr>
<td>HDL/LDL ratio‡</td>
<td></td>
<td>0.36 (0.17)</td>
<td>0.38 (0.26)</td>
<td>0.39 (0.18)</td>
<td>0.41 (0.18)</td>
<td>0.43 (0.25)</td>
<td>0.52 (0.26)</td>
</tr>
</tbody>
</table>

Means and standard deviations (in brackets) and proportions. SBP indicates systolic blood pressure; DSP, diastolic blood pressure; CDT, carbohydrate-deficient transferrin; GGT, γ-glutamyltransferase. Differences vs the non-drinking group: *$P<0.05$, **$P<0.01$; linear trend across the categories of alcohol intake: †$P<0.05$, ‡$P<0.01$. 

($\beta=0.009$, $P<0.02$). The association remained borderline significant after further adjustment for HDL cholesterol ($\beta=-0.008$, $P=0.052$); however, the $\beta$-coefficient for alcohol consumption was slightly decreased (from $-0.009$ to $-0.008$), indicating that a small part of the alcohol effect on IMT is mediated by HDL cholesterol (model 2). Further adjustment for the inflammation marker fibrinogen (model 3) instead of HDL cholesterol revealed the same result. After combined adjustment for HDL cholesterol and fibrinogen (model 4), however, the association became insignificant.
Carotid IMT in groups classified by mean daily alcohol intake. Analysis was performed separately for the entire SHIP study population and separately for nondiabetics (ND) and normoterative subjects (NT). Each model was controlled for age, systolic blood pressure, diabetes, smoking, HDL-LDL ratio, lifestyle patterns, and in women, for hormone replacement therapy (HRT). Data are shown as mean and SEM. P for differences of IMT group means compared with the abstainer groups: $P<0.05$, $P<0.05$, $P<0.01$). $P$ for trend across categories ($P<0.05$) except the highest category in men.

$\beta=-0.007, P=NS$). In women, again no associations were seen (model 1: $\beta=-0.001, P=NS$; data not shown).

Discussion

Our data revealed a J-shaped association between alcohol consumption and subclinical atherosclerosis in men after controlling for major confounders. No association was seen in women. In men, we observed a significant decrease in carotid IMT with increased alcohol consumption up to daily intake levels of 80 g. The observed association was mediated by HDL cholesterol and fibrinogen, which supports the hypothesis that alcohol use could mitigate the influence of inflammatory processes on carotid IMT.26

In SHIP, the nadir of the J-shaped curve in men was observed at an intake of 61 to 80 g of alcohol per day, which is consistent with data from a recent meta-analysis of 28 cohort studies on alcohol use and CHD.2 This meta-analysis showed a decreasing risk function up to 20 g/d. The protective effect of alcohol intake remained statistically evident up to 72 g/d, whereas the harmful effect became significant at intake levels >89 g/d. This is considerably higher than intake levels that are commonly regarded as having a protective effect against CHD.1,3 In the Cardiovascular Health Study investigating subjects >65 years, consumers of 1 to 6 drinks per week (equaling <15 g/d) had a carotid IMT 0.07 mm lower than abstainers, whereas consumers of 14 or more drinks (equaling >30 g/d) had an IMT 0.07 mm higher than abstainers.16 Conversely, the ARIC Study and the National Heart, Lung, and Blood Institute Family Heart Study did not find any relation between alcohol drinking and carotid IMT.11,27

The evaluation of daily alcohol intake on morbidity and mortality also has to take specific drinking pattern into account, because they are associated with risks for vascular clinical end points. Both the Kaiser Permanente Medical Care Program and the Health Professionals Follow-up Study reported that wine drinking frequency was associated with a lower risk of total mortality and myocardial infarction, independent of total alcohol intake.28,29 A more moderate drinking pattern, eg, drinking alcohol regularly with meals, is expected to be related to a healthier lifestyle and higher socioeconomic status.28 In SHIP, the association between alcohol consumption and atherosclerosis remained significant after controlling for educational level and for a health-related lifestyle variable, which included healthful food intake and leisure time physical activity. This lifestyle variable was associated with carotid atherosclerosis, independent of alcohol use.21

Although questionnaire-derived estimates of self-reported alcohol intake have been criticized because of underreporting, especially by heavy drinkers, the present study validated self-reported alcohol intake against biochemical parameters of disturbed liver function, which are sensitive to increased alcohol intake.30 Therefore, the probability is low that the higher IMT in the abstinent group could be due to former heavy drinkers, who stopped drinking because of disease.

Our study is limited by the cross-sectional design, which does not allow one to establish a time sequence between the outcome examined (mean IMT) and alcohol consumption. Selective survival of those individuals whose arteries were less susceptible to unfavorable risk factor levels may have influenced the association among the elderly. The lack of associations between alcohol consumption and atherosclerosis in women may be explained by the lower amount of daily alcohol intake in women than in men. Another potential weakness is the restriction of quantitative IMT measurements to the common carotid segment. The latter is, however, justified by better reproducibility of measurements from this site and the technical difficulties in obtaining measurements from the bifurcation or the internal carotid artery.

In conclusion, in this population living in the northeast area of former East Germany, alcohol use was found to be inversely correlated with carotid IMT as a surrogate marker of generalized atherosclerosis in men but not in women. The total daily level of alcohol intake that provides a maximum protective effect against atherosclerosis, however, is higher than previously described in studies that used clinical end points and is well above the threshold for which severe alcohol-related comorbidity and organ damage have been reported.

Acknowledgments

The SHIP study is part of the Community Medicine Net (http://www.medizin.uni-greifswald.de/cm) of the University of Greifs-
walsd, which is funded by grants from the German Federal Ministry of Education and Research (BMBF, grant No. 01ZZ96030) and from the Ministry for Education, Research and Cultural Affairs and the Ministry for Social Affairs of the Federal State of Mecklenburg-Vorpommern. The contribution to the data collection made by the field workers, study physicians and ultrasound technicians, interviewers, and computer assistants is gratefully acknowledged.

References


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*Stroke*. 2005;36:1746-1752; originally published online July 7, 2005; doi: 10.1161/01.STR.0000173159.65228.68

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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