Pattern of Alcohol Drinking and Progression of Atherosclerosis

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Abstract—Most studies that examine the role of alcohol consumption in atherosclerosis and cardiovascular disease have overlooked the possible effect of drinking pattern. We investigated the association between the habit of heavy acute intake of beer and spirits (binging) and the 4-year progression of carotid atherosclerosis in a population-based sample of middle-aged Finnish men. Data from the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) were used to estimate changes in maximum and mean intima-media thickness (IMT) and the maximum plaque height in 764 KIHD participants who reported using beer and in 871 participants who used spirits. After adjustment for age, baseline carotid atherosclerosis, and average weekly alcohol consumption level, we observed the highest atherosclerosis progression in men who usually consumed a whole bottle of vodka or more in 1 session. For beer binging (>6 beers at a time), the magnitude of IMT progression was even higher, although this association was only marginally significant ($P<0.1$) because of smaller numbers. The associations were largely unaffected by adjustments for blood pressure, lipids, smoking, BMI, and medication. The magnitude of the difference was generally higher in a subgroup that was free of IHD at baseline. We conclude that the pattern of drinking associates with the progression of carotid atherosclerosis independently of the total level of alcohol consumption and risk factors. (***Arterioscler Thromb Vasc Biol.* 1999;19:3001-3006.**)

Key Words: alcohol ■ atherosclerosis ■ cardiovascular ■ epidemiology

Many epidemiological studies have suggested a U-shaped association between alcohol consumption and cardiovascular disease morbidity and mortality. Although light or moderate drinking seems to relate to reduced risk, the probability of coronary heart disease and cardiovascular mortality increases with heavier consumption and with abstention.[1-4] The mechanisms of the alcohol effects have remained controversial, and in particular, the pathways for the risk-increasing effects of heavy consumption are not well known.

Advances in ultrasonographic assessment of carotid arteries have provided opportunities to noninvasively study the pathophysiological processes that underlie the development of cardiovascular disease.[5,6] Although carotid atherosclerosis is only an indirect marker of coronary disease, it has been shown to predict the incidence of myocardial infarction.[7] Results from studies looking at the association between alcohol and atherosclerotic disease have been somewhat incongruent. The cross-sectional observations in the ARIC study[8] did not show significant association between current alcohol intake and carotid atherosclerosis. Conversely, the ultrasound findings in a subsample of the Bruneck Study[9] suggested that the relationship between alcohol use and carotid atherosclerosis may indeed be U-shaped, and the adverse and beneficial effects of alcohol in cardiovascular diseases may in part mediate the atherogenic processes.

Most etiological studies have used total consumption or assumed average intake of alcohol per unit of time as a measure of alcohol use. Drinking habits, however, can vary greatly between individuals and are sometimes very irregular. Individuals with the same average consumption may differ widely, with some having episodic heavy exposure, whereas others show fairly equal consumption from day to day. Few studies have attempted to examine the differential effects of these patterns.[10,11]

The present study is, to the best of our knowledge, the first to examine prospectively the association between heavy acute drinking style and the progression of carotid atherosclerosis. We examined the relationship in a nonselected population sample of middle-aged men, adjusting for the total average level of alcohol use and various covariates, using 3 indicators of the atherosclerotic process as outcome measures.

Methods

Subjects

As described in detail elsewhere,[12,13] the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) was designed to investigate previously unestablished risk factors for ischemic heart disease

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(IHD) and carotid atherosclerosis in a population-based sample of middle-aged Finnish men.

Of the 3235 eligible noninstitutionalized men 42, 48, 54, or 60 years old who resided in the town of Kuopio or its surrounding rural communities, a total of 2682 (82.9%) participated in the study. Baseline examinations were conducted between March 1984 and December 1989. At baseline, the subjects were recruited in 2 waves. The first group comprised 1166 men 54 years old, and the second comprised an age-stratified sample of 1516 men 42, 48, 54, or 60 years old. Ultrasonographic assessment of carotid atherosclerosis at baseline was conducted between February 1987 and December 1989 on the second wave of participants. There were no systematic differences between the 2 waves of recruitment other than the different age distribution. A 4-year follow-up examination was conducted between March 1991 and December 1993 on those men who had undergone ultrasonographic examination at baseline. The ultrasound recordings and other information were obtained from a total of 1022 men.

The study protocol was approved by the Research Ethics Committee of the University of Kuopio, and all participants gave a written informed consent to participate in KIHD.

Evaluation of Carotid Atherosclerosis Progression

Atherosclerosis progression was assessed with high-resolution B-mode ultrasonographic examination of a 1.0- to 1.5-cm section of the left and right common carotid artery (CCA) below the carotid bulb. Images were focused on the posterior (far) wall with the subject in the supine position. At baseline, ultrasonographic scanning was conducted with the ATL UM4 duplex ultrasound system with a 10-MHz sector transducer (Advanced Technology Laboratories). The Biosound Phase 2 equipped with a 10-MHz annular array probe was used at the 4-year follow-up examinations. Wedge phantom studies of this system, calibrated against an RMI 414B tissue phantom, have demonstrated measurement precision of ±0.03 mm.[14,15] Both the baseline and the 4-year follow-up scannings were recorded by a videocassette recorder. Video frames of the B-mode scanning were digitized, and the intima-media thickness (IMT) was assessed by a physician (R.S.) with Prosound software, which incorporates an edge-detection algorithm specifically designed for use with ultrasound scanning and allows automatic detection, tracking, and recording of the lumen/intima and media/adventitia interfaces.[16] On average, 100 estimates of the distance between these interfaces were recorded over the 1.0- to 1.5-cm section of each CCA. The IMT of the posterior wall was measured as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line, as explained earlier in detail.[14] Measurements of the near wall were not conducted because of greater measurement variability.[17]

The present study used 3 measures of IMT. First, we used the maximum IMT, defined as the average of the maximum IMT in the right and left CCA. Second, we used the plaque height, defined as the difference between the maximum and minimum IMT recordings averaged over the right and left CCA. As a third measure, we used the mean IMT, defined as the mean of the ≈100 IMT readings from each CCA. These measures were conceptualized to represent potentially different aspects of atherosclerosis progression. Maximum IMT was thought to provide an assessment of how deeply intima-media thickening intruded into the lumen in this segment of the CCA. The measurement of plaque height was conceptualized to be sensitive to the roughness of the arterial wall by representing the range of IMT. Mean IMT was seen as an overall measure of the process of atherosclerosis. Progression of carotid atherosclerosis was calculated as the arithmetic difference between the baseline and 4-year follow-up values for each of the 3 measures.

Evaluation of Alcohol Use and Drinking Pattern

Alcohol consumption was assessed with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory.[18,19] Usual frequency of intake and usual dose per sitting (in glasses or bottles) were queried separately for each beverage type (beer, strong beer, wine, fortified wine, spirits) with a structured response form. Thus, we were able to assess both total alcohol use and the timing or pattern of drinking (usual number of drinks per session). The measure of average weekly use of all alcoholic beverages was computed on the basis of the known alcohol content of each type of drink. For example, a ⅓-L (12-oz) bottle or can of regular beer in Finland contains ≈12 g ethanol. Strong beer has ≈14 g, which is also the ethanol content in 1 shot of vodka. Men were classified as abstinent if they had not consumed any alcohol during the past 12 months, and they were excluded from the analyses.

Covariates

Lipoproteins were separated from unfrozen plasma within 3 days of sampling. HDL and LDL fractions were separated from fresh plasma by both ultracentrifugation and precipitation. The cholesterol content of all lipoprotein fractions was measured enzymatically (CHOD-PAP cholesterol method, Boehringer Mannheim) on the day after the last spin. Serum apolipoprotein B (apoB) was determined with an immunoturbidimetric method (KONE Corp) using an antiserum (Orion).[20] Blood pressure was measured with a random-zero sphygmomanometer with the subject both supine and sitting, after a 5-minute rest in each position. Three systolic and diastolic pressures were taken and averaged. We used the average systolic pressure in these analyses. Body mass index was calculated as the subject's weight divided by the square of his height in meters (kg/m^2). Smoking was assessed by a questionnaire and classified for this analysis as "never smoked," "former smoker," and "current smoker" (measured in pack-years). Treatment for hypertension or hyperlipidemia was assessed by a review of medications.

Statistical Methods

The association between binge drinking and the progression of IMT was assessed by estimating the mean change in each measure of IMT (maximum thickness, mean thickness, and plaque height) for different levels of usual drinking dose of both beer and spirits. Analyses of drinking pattern were performed separately for the beer and spirit drinkers, with adjustment for the total consumption of any alcohol from all categories, including wine. In addition, we analyzed the relationship between drinking pattern and IMT progression in a group that was free of IHD at baseline. Statistical analyses were conducted by the GLM procedure in SAS version 6.09 on a Sun Sparc Station II (SAS User's Guide). This procedure allows least-squares mean values of the IMT to be estimated and contrasted for each level of drinking pattern while simultaneously controlling for age; baseline IMT; average weekly consumption of beer, wine, and spirits; cholesterol-lowering medication; the zoom depth of the ultrasound scan; and indicator variables for the individual technicians who conducted the scans.[14] In addition to these covariates, in a second stage of models, we included systolic blood pressure, apoB, HDL_2, smoking, BMI, and antihypertension medication to the linear multivariate models in further analyses.

Results

There were 768 men (74.8%) who reported consuming beer at least occasionally, and 874 men (85.2%) who similarly reported using spirits (Table 1). Among beer drinkers, the usual dose was <3 bottles for 526 men (68.5%), 3 to 5 bottles for 218 men (28.4%), and ≥6 bottles for 24 men (3.1%). Among those who reported consuming spirits, usual doses were in general higher, reflecting the Scandinavian and Eastern European traditions in drinking. A total of 672 men (76.9%) had a usual dose of six 4-cL drinks or less, for 81 men (9.3%) a usual dose was 7 to 12 drinks, and for 121 men (13.8%) it was >12. Table 1 shows means (SD) or prevalences (%) for baseline IMT thickness and covariates across the drinking pattern categories.

Binge Drinking and Progression of Maximum IMT

Table 2 presents the estimated mean change in the maximum thickness of IMT by usual drinking dose, with adjustment for age; baseline IMT measure; total average consumption of

TABLE 1. Means (SD) or Prevalence (%) of Covariates Across Beer and Spirit Drinking Categories in KIHD Participants

	Usual Beer Dose, Bottles			Usual Spirits Dose, 4-cL Portions		
	≤2 (n=526)	3–5 (n=218)	≥6 (n=24)	≤6 (n=672)	7–12 (n=81)	>12 (n=121)
Beer, g/wk	14.2 (20.7)	62.7 (75.9)	148.6 (134.2)	21.0 (42.6)	46.9 (66.0)	47.9 (84.6)
Wine, g/wk	7.0 (19.2)	21.3 (52.6)	16.1 (32.3)	7.5 (18.7)	16.8 (36.6)	23.7 (66.0)
Spirits, g/wk	37.5 (66.9)	79.7 (111.0)	85.3 (129.4)	28.1 (43.9)	112.5 (155.6)	142.5 (160.6)
Total alcohol use, g/wk	58.7 (78.7)	163.8 (173.5)	250.1 (198.6)	56.6 (75.0)	176.3 (209.1)	214.0 (200.7)
Age, y	51.5 (6.5)	49.1 (6.6)	47.0 (6.5)	51.4 (6.6)	49.6 (6.9)	50.9 (6.9)
Baseline maximum IMT, mm	0.96 (0.24)	0.92 (0.22)	0.94 (0.19)	0.95 (0.24)	0.93 (0.20)	0.94 (0.19)
Baseline plaque height, mm	0.39 (0.17)	0.36 (0.16)	0.35 (0.12)	0.39 (0.18)	0.35 (0.13)	0.37 (0.14)
Baseline mean IMT, mm	0.77 (0.17)	0.74 (0.17)	0.76 (0.15)	0.76 (0.18)	0.76 (0.17)	0.77 (0.13)
ApoB, mg/L	1014.4 (214.9)	1036 (255.4)	1025 (256.7)	1012.5 (224.3)	1031.8 (261.8)	1042.6 (211.2)
HDL_2, mmol/L	0.88 (0.27)	0.88 (0.32)	0.85 (0.29)	0.87 (0.28)	0.89 (0.29)	0.85 (0.27)
BMI, kg/m^2	26.5 (3.2)	26.9 (3.7)	27.1 (2.9)	26.4 (3.1)	28.0 (3.7)	27.9 (4.2)
Systolic blood pressure, mm Hg	131.2 (15.0)	134.0 (15.4)	136.2 (21.3)	131.3 (15.2)	136.0 (17.8)	134.0 (18.1)
Smoking, %						
Never	28.0	13.8	8.3	26.6	18.5	7.4
Former	38.8	35.3	37.5	40.4	40.8	33.9
Current lowest tertile	12.9	15.6	8.3	11.8	12.3	14.9
Current medium tertile	10.8	20.2	29.2	11.8	11.1	24.0
Current highest tertile	9.5	15.1	16.7	9.4	17.3	19.8
Treatment for, %						
Hypertension	13.0	13.4	12.5	13.6	16.1	15.8
Hyperlipidemia	1.1	0	0	0.9	1.2	0

beer, wine, and spirits; zoom depth; and sonographer (model 1). Additional adjustments were conducted in model 2 for systolic blood pressure, HDL_2, apoB, smoking, body mass index, cholesterol-lowering medication, and antihypertension medication. The 4-year maximum progression adjusted for age, baseline IMT, total alcohol use, zoom depth, and sonographer was 0.35 mm for those who usually consumed ≥6 beers, 0.26 mm for those who drank 3 to 5 beers, and 0.27 mm for those whose usual dose was <3 bottles (Table 2). Men with a usual beer dose of ≥6 bottles had 26% more atherosclerosis progression in 4 years than those who drank <3 bottles at time ($P<0.1$). The estimated difference in progression attenuated only little (22% more progression in men with heavier doses) after further adjustments for covariates in model 2 (Table 2).

TABLE 2. Mean 4-Year Change in the Maximum IMT in Middle-Aged Finnish Men by Drinking Pattern

		Mean Change in Maximum IMT, mm	
	n	Model 1*	Model 2†
Usual beer dose, bottles			
≤2	526	0.27	0.27
3–5	218	0.26	0.25
≥6	24	0.35‡	0.33
Usual spirits dose, 4-cL portions			
≤6	672	0.26	0.26
7–12	81	0.26	0.25
>12	121	0.32§	0.31§

*Adjusted for age; total beer, wine, and spirits consumption; baseline IMT; zoom depth; and sonographer.

†Model 1+adjustments for systolic blood pressure, apoB, HDL_2, smoking, BMI, and cholesterol-lowering and antihypertensive medication.

‡Marginally different ($P<0.10$) from the lowest-consumption group.

§Significantly different ($P<0.05$) from the lowest-consumption group.

A similar relationship was observed with the spirit drinking pattern. In model 1, there was a 23% difference in the maximum IMT progression (0.32 mm in the highest drinking category versus 0.27 mm in the lowest) ($P<0.05$). Adjustments for other covariates did not remarkably change the magnitude of the difference (19%, $P<0.05$) (Table 2).

Binge Drinking and Change in Mean IMT

The results for progression of mean IMT were very similar to those for maximum IMT progression (Table 3). The mean IMT change in 4 years adjusted for age, baseline IMT, and total alcohol use was 0.18 mm for the highest beer dose category and 0.11 mm for the 2 lower groups (64% higher progression, $P<0.05$). Adjustment for other covariates in model 2 somewhat attenuated the relationship. The estimated progression was 0.17 mm in the highest, 0.11 mm in the middle, and 0.12 mm in the lowest category (42% difference in progression between those who drank ≥6 beers and those who drank <3 beers at a time, $P<0.1$) (Table 3). Among spirit drinkers, the estimated mean IMT change was 0.11 mm for the 2 lower dose categories and 0.13 mm for those in the highest category. Addition of other covariates in model 2 increased the estimated difference between the highest and the lowest categories (Table 3).

TABLE 3. Four-Year Progression of Mean IMT in Middle-Aged Finnish Men by Drinking Pattern

	n	Change in Mean IMT, mm	
		Model 1*	Model 2†
Usual beer dose, bottles			
≤2	526	0.11	0.12
3–5	218	0.11	0.11
≥6	24	0.18§	0.17†
Usual spirits dose, 4-cL portions			
≤6	672	0.11	0.11
7–12	81	0.11	0.10
>12	121	0.13	0.17

*Adjusted for age; total beer, wine, and spirits consumption; baseline IMT; zoom depth; and sonographer.

†Model 1+adjustments for systolic blood pressure, apoB, HDL_2, smoking, BMI, and cholesterol-lowering and antihypertensive medication.

‡Marginally different ($P<0.10$) from the lowest-consumption group.

§Significantly different ($P<0.05$) from the lowest-consumption group.

TABLE 4. Mean 4-Year Change in Plaque Height in Middle-Aged Finnish Men by Drinking Pattern

	n	Mean Change in Plaque Height, mm	
		Model 1*	Model 2†
Usual beer dose, bottles			
≤2	526	0.28	0.28
3–5	218	0.26	0.26
≥6	24	0.31	0.30
Usual spirits dose, 4-cL portions			
≤6	672	0.26	0.26
7–12	81	0.26	0.26
>12	121	0.32‡	0.32‡

*Adjusted for age; total beer, wine, and spirits consumption; baseline IMT; zoom depth; and sonographer.

†Model 1+adjustments for systolic blood pressure, apoB, HDL_2, smoking, BMI, and cholesterol-lowering and antihypertensive medication.

‡Significantly different ($P<0.05$) from the lowest-consumption group.

Binge Drinking and Plaque Height

A consistent pattern of findings emerged when plaque height was used as an outcome (Table 4). The 4-year progression of plaque height adjusted for age, baseline IMT, total alcohol use, zoom depth, and sonographer was greatest for those who used the highest amount of beer or spirits in 1 session. Within categories of beer drinking, the progression of plaque height was 0.31 mm for those with the highest doses, 0.26 mm for those in the middle category, and 0.28 for those in the lowest category (12% difference between highest and lowest). Adjustments for covariates in model 2 did not greatly alter the estimates. For spirit categories, the differences in plaque height progression were clearer: 0.32 mm in the highest-dose group and 0.26 mm in both lower-dose groups (a difference of 23%, $P<0.05$). These differences across spirit dose categories remained the same after all adjustments in model 2 (Table 4).

Binge Drinking and IMT Progression in Men in a Healthy Subgroup

Table 5 shows the relationship between beer and spirit drinking patterns and progression of maximum IMT, mean IMT, and plaque height in a subgroup that included those men who were free of IHD at baseline (n=615 in beer drinkers and n=682 in spirit drinkers). The observed relationship was similar to the previous analyses, but generally the magnitude of differences was larger than in the total sample. Men without prevalent IHD at baseline who usually consumed ≥6 bottles of beer per sitting had 38% higher maximum IMT progression ($P<0.05$), 82% higher mean IMT progression ($P<0.05$), and 15% higher plaque height progression than the men who had a usual dose of ≤2 beers. Adjustment for risk factors did not greatly affect the magnitude of the differences. Among spirit drinkers, men in the highest-usual-dose group had 20% higher maximum IMT progression ($P<0.05$), 9% higher mean IMT progression, and 19% higher plaque height progression ($P<0.05$) than the lowest-dose group. Further risk factor adjustments had only a slight effect on the estimated differences (Table 5).

Discussion

The results of our study show that men with a heavy acute style of alcohol consumption had significantly greater 4-year progression of carotid atherosclerosis than men with a more evenly distributed drinking pattern. The positive relationship between heavy doses per sitting and carotid atherosclerosis progression was observed for use of both beer and spirits, after adjustment for the total average level of alcohol use.

The magnitude of these relationships was largely unaffected by adjustment for baseline atherosclerosis, known risk factors, and medications. The findings were consistent across different measures of atherosclerosis progression, with heavy acute drinking showing the same associations with progression of maximum IMT, mean IMT, and plaque height. The observed relationships remained, and appeared to be even stronger, in the analysis of the subgroup that was initially free of the diagnosis or signs of prevalent IHD.

It has been suggested that the relationship between alcohol use and atherosclerotic vascular disease follows the U-shaped pattern seen in studies of alcohol and cardiovascular morbidity and mortality,[9] but this has not been firmly established. Even less is known of the possible effects of different drinking styles on atherosclerosis progression. This study is the first in a large population-based sample to show a relationship between pattern of alcohol drinking and progression of atherosclerosis in carotid arteries. Heavy acute loads of alcohol seem to relate to enhanced progression of carotid atherosclerosis, independent of the total average level of alcohol consumption.

It is plausible that the metabolic and physiological stress that occurs in the body during and after heavy drinking[21–23] may facilitate atherosclerotic changes, but the actual mediating process is not clear. Increased shear stress and flow turbulence may raise the potential for endothelial lesions. Laboratory studies[24,25] have shown that large intakes of alcohol associate with increased LDL oxidation. It has also been shown that high titers of antibodies against oxidized LDL associate with accelerated progression of atherosclerosis.[26] The formation of acetaldehyde, which appears to be a particularly potent toxin,[27,28] has direct deleterious effects in

TABLE 5. The 4-Year Progression of Maximum IMT, Mean IMT, and Plaque Height in Beer Drinkers (n=615) and Spirit Drinkers (n=682) Who Were Free of Prevalent IHD at Baseline by Drinking Pattern

		Change in Maximum IMT, mm		Change in Mean IMT, mm		Change in Plaque Height, mm	
	n	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
Usual beer dose, bottles							
≤2	423	0.26	0.26	0.11	0.12	0.27	0.27
3–5	174	0.25	0.24	0.10	0.10	0.26	0.25
≥6	18	0.36†	0.34*	0.20†	0.19†	0.31	0.30
Usual spirits dose, 4-cL portions							
≤6	525	0.25	0.25	0.11	0.11	0.26	0.26
7–12	66	0.25	0.25	0.11	0.11	0.25	0.25
>12	91	0.30†	0.29*	0.12	0.11	0.31†	0.30†

Note: Model 1 adjusts for age; total beer, wine, and spirits consumption; baseline IMT; zoom depth; and sonographer. Model 2: Model 1+adjustments for systolic blood pressure, apoB, HDL_2, smoking, BMI, and cholesterol-lowering and antihypertensive medication.

*Marginally different ($P<0.10$) from the lowest-consumption group.

†Significantly different ($P<0.05$) from the lowest-consumption group.

the heart muscle cells. This may also be true inside vessels, because acetaldehyde adducts are likely to contribute to ethanol-related oxidative stress.[29] Thus, although moderate amounts of alcohol may have some health benefits, larger intakes of alcohol in 1 session seem to counteract them.

A few issues should be considered before we draw conclusions from these results. First, the assessment of drinking habits was based on a questionnaire and thus subject to underreporting or other misclassification. There is no reason to believe, however, that the possible reporting bias would be systematically differential across various drinking groups. In that case, misclassification would at most dilute the observed associations toward null.

Second, despite the wide array of adjustments, the possibility exists that the reported associations may be due to some yet unmeasured factors, eg, in diet, or to residual confounding.

Third, although the pathophysiological importance of each of the 3 atherosclerosis measures is not completely clear, these 3 progression measures that we used showed similar and consistent associations with binge drinking. Thus, it is reasonable to assume that this type of drinking style is related to the progression of overall atherosclerotic burden, to the development of focal lesions that protrude into the lumen, and to the increase in the surface roughness of the CCA.

Finally, because the magnitude of the relationship was even stronger in a healthy subgroup, it is suggested that a heavy acute drinking pattern may affect the atherosclerotic buildup even at the earlier, nonsymptomatic phase of the disease.

In summary, the evidence from our study indicates that drinking style, and not only the total amount of alcohol consumed, may have an impact on the development of atherosclerotic disease and especially its progression. Our findings also underline the methodological importance of correct representation of dose in exposure studies. In addition to the average exposure to a behavioral risk factor like alcohol drinking, it is important to consider the height and frequency of peak exposures.[30]

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