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Original Article

Heavy Alcohol Consumption is Associated with Impaired Endothelial Function:

The Circulatory Risk in Communities Study (CIRCS)

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***Aim*: Previous studies have reported that moderate alcohol consumption is protective against cardiovascular disease, but heavy alcohol consumption increases its risk. Endothelial dysfunction is hypothesized to contribute to the development of atherosclerosis and cardiovascular disease. However, few population-based studies have examined a potential effect of alcohol consumption on endothelial function.**

***Methods*: This study included 404 men aged 30–79 years who were recruited from residents in 2 communities under the Circulatory Risk in Communities Study in 2013 and 2014. We asked the individuals about the frequency and volume of alcohol beverages and converted the data into grams of ethanol per day. Endothelial function was assessed by brachial artery flow-mediated dilation (FMD) measurements during reactive hyperemia. We performed cross-sectional analysis of alcohol consumption and %FMD by logistic regression analysis, adjusting for age, baseline brachial artery diameter, body mass index, systolic blood pressure, low-density lipoprotein cholesterol, HbA1c, smoking, antihypertensive medication use, and community.**

***Results*: Individuals who drank ≥ 46 g/day ethanol had a lower age-adjusted mean %FMD than non-drinkers ($p<0.01$). Compared with non-drinkers, the age-adjusted odds ratios (ORs) (95% confidence interval) of low %FMD (<5.3%) for former, light (<23.0 g/day ethanol), moderate (23.0–45.9 g/day ethanol), and heavy (≥ 46.0 g/day ethanol) drinkers were 1.61 (0.67–3.89), 0.84 (0.43–1.66), 1.09 (0.52–2.25), and 2.99 (1.56–5.70), respectively. The corresponding multivariable-adjusted ORs were 1.76 (0.69–4.50), 0.86 (0.42–1.76), 0.98 (0.45–2.12), and 2.39 (1.15–4.95), respectively.**

***Conclusions*: Heavy alcohol consumption may be an independent risk factor of endothelial dysfunction in Japanese men.**

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Key words: Alcohol consumption, Endothelial function, Japanese men, Cross-sectional study

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Introduction

Endothelial dysfunction is hypothesized to contribute to the development of atherosclerosis and cardiovascular disease[1, 2]. Measurement of flow-mediated dilation (FMD) reflects nitric oxide (NO) production from endothelial cells. Increasing evidence has indicated that endothelial function as assessed by FMD may serve as an independent predictor of cardiovascu-

lar events[1-3].

Alcohol consumption has beneficial, as well as harmful, effects on atherosclerosis[4, 5]. Light-to-moderate alcohol consumption generally reduces the risk of cardiovascular disease, particularly ischemic stroke, as well as coronary heart disease[6-8]. In contrast, heavy alcohol consumption increases the risk of cardiovascular disease, particularly stroke[6-8].

In the United States, the Northern Manhattan Study (NOMAS) reported that moderate alcohol consumption was associated with better FMD in 884 multiethnic population samples[9]. In Japan, a study of 108 men with coronary artery disease reported that FMD was higher in drinkers than in non-drinkers, and alcohol consumption may be one of the factors that favorably affect FMD[10]. However, this finding was obtained from a case-series study of highly selected samples. The effect of alcohol consumption on endothelial function has not been investigated in a general Japanese population.

The objective of this study was to investigate the association between alcohol consumption and endothelial function in a general population-based sample of Japanese men.

Methods

Study Population Sample

We conducted FMD measurements in 2 communities of the Circulatory Risk in Communities Study (CIRCS) in a southwestern urban suburb (Yao City, Osaka Prefecture) and a northeastern rural community (Ikawa Town, Akita Prefecture). CIRCS is a dynamic community cohort study of Japanese covering 5 communities in Japan, including Yao City and Ikawa Town[11]. We recruited 410 men aged ≥ 30 years from participants of the annual cardiovascular risk surveys one by one. When the FMD measurement booth was full with participants, the applicants were asked to be examined in the next year. The subjects included 251 men from the district of Yao (recruitment rate among the cardiovascular survey participants of men, 19.7%) and 159 men from Ikawa (26.8%). We excluded 6 subjects aged ≥ 80 years to reduce the effect of age on endothelial dysfunction. A total of 404 men aged 30–79 years were enrolled in this study. We recruited only men for this study because the proportion of alcohol drinkers was low in women.

The study protocol was approved by the Medical Ethics Committee of Osaka University. Informed consent was obtained from the community representatives to conduct an epidemiological study based on the guidelines of the Council for International Organizations of Medical Science[12].

Assessment of FMD

FMD was determined using high-resolution ultrasonography and a forearm occlusive cuff by 3 well-trained observers. Smoking and exercise were refrained approximately ≥ 2 h before the measurement. Participants were not required to fast before the measurements. High-resolution ultrasound with a 10-MHz linear array transducer (UNEX Co. Ltd., Nagoya, Japan) was used to record longitudinal images of the right brachial artery at baseline and continuously from 30 s before to at least 2 min after cuff deflation. Computer-assisted analysis software (UNEX Co. Ltd., Nagoya, Japan) was used to determine the diameter of the brachial artery semi-automatically as previously described[13]. The baseline longitudinal image of the artery was acquired for 30 s, and then the blood pressure cuff was inflated to 50 mmHg above systolic pressure for 5 min. FMD was expressed as the percent change from baseline as follows: %FMD = (brachial artery diameter at hyperemia − brachial artery diameter at baseline)/brachial artery diameter at baseline × 100. The determination of endothelial function was performed in accordance with published guidelines[14]. A previous study reported that intra-class correlation coefficient was 0.84–0.99 for the intra-observer reproducibility and 0.82–0.87 for the inter-observer reliability[15].

Measurement of Alcohol Intake and Confounding Variables

Trained interviewers obtained information of the usual weekly intake of alcohol in units of "gō," a traditional Japanese unit of volume equal to 180 mL of sake (Japanese rice wine), which contains 23 g of ethanol. One gō is equal to 1 bottle (633 mL) of beer, 2 single shots (75 mL) of whisky, or 2 glasses (180 mL) of wine. We then converted alcohol intake of gō into grams of ethanol per day. Persons who reported consuming ≥ 0.3 gō per week were considered as current drinkers. Former drinkers were defined as abstainers for the previous 3 months or longer. Information on smoking status, antihypertensive agents use, and medical history of stroke and coronary heart disease was also asked by trained interviewers. Persons who smoked ≥ 1 cigarette per day were defined as current smokers. Height in stocking feet and weight in light clothing were measured, and body mass index (BMI) was calculated as weight divided by height (kg/m^2). Systolic and diastolic blood pressures were measured by trained physicians using a standard mercury sphygmomanometer on the right arm of the seated participant after a rest period of at least 5 min. Hypertension

Table 1. Cardiovascular risk factors in 404 Japanese men

Total number	404
Age, years	54.8 ± 10.8
Current drinkers, %	72
Alcohol consumption, g/day of ethanol	24.5 ± 28.8
%Flow-mediated dilation	6.7 ± 3.2
Baseline brachial artery diameter, mm	4.4 ± 0.6
Body mass index, kg/m^2	24.3 ± 3.3
Systolic blood pressure, mmHg	126.9 ± 15.7
Diastolic blood pressure, mmHg	81.6 ± 10.4
Hypertension, %	49
Antihypertensive medication use, %	27
Total cholesterol, mmol/L	5.2 ± 0.9
LDL-cholesterol, mmol/L	3.1 ± 0.8
HDL-cholesterol, mmol/L	1.5 ± 0.4
Triglycerides, mmol/L	1.5 ± 1.2
Lipid lowering medication use, %	10
Glucose, mmol/L	5.6 ± 1.1
HbA1c, %	5.7 ± 0.8
Medication use for diabetes mellitus, %	6
Current smokers, %	30
History of stroke, %	1.2
History of coronary heart disease, %	2

Values are mean ± standard deviation and proportions.
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Serum total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and glucose were measured using enzymatic methods by an automatic analyzer (AU2700, Olympus Co., Tokyo, Japan in 2013 and TBA-2000FR, Toshiba Co., Tokyo, Japan in 2014) at the Osaka Center for Cancer and Cardiovascular Diseases Prevention, an international member of the US National Cholesterol Reference Method Laboratory Network. HbA1c was measured using latex agglutination method (AU2700, Olympus Co., Tokyo, Japan) in 2013 and high performance liquid chromatography method (HLC-723 G8, Tosoh Co., Yamaguchi, Japan) in 2014.

Statistical Analysis

Characteristics of the study participants are presented as mean ± standard deviation (SD) or proportions (%). Age-adjusted mean values and proportions of baseline characteristics according to categories of drinking status (never, former, and ethanol intakes of < 23.0, 23.0–45.9, and ≥ 46.0 g/day) were calculated using analysis of covariance. For the analysis of alcohol consumption and %FMD, we divided the study population into tertiles of %FMD on the basis of their distribution of %FMD. Logistic regression analysis was used to estimate the odds ratio (OR) of the lowest %FMD tertile according to the categories of ethanol intake. Potential confounding variables were selected from the results of analysis of covariance: age (years), baseline brachial artery diameter (mm), BMI (kg/m^2), systolic blood pressure (mmHg), LDL cholesterol levels (mmol/L), HbA1c (%), smoking (never, former, current < 20, and ≥ 20 cigarette per day), antihypertensive medication use (yes), and community (Yao and Ikawa) based on previous findings of the risk factors for FMD and atherosclerosis[13, 16-19].

All statistical analyses were performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA). All probability values for statistical tests were two-tailed, and values of $p < 0.05$ were considered statistically significant.

Results

Table 1 shows mean values ± SD and proportions of selected cardiovascular risk factors among 404 Japanese men. The proportion of current drinkers was 72%, and the mean alcohol consumption was 24.5 ± 28.8 g/day. The mean value of %FMD was 6.7% ±

Table 2. Age-adjusted mean values and proportions of baseline characteristics according to alcohol consumption category

	Never	Former	Alcohol consumption, ethanol g/day		
			Light < 23.0	Moderate 23.0-45.9	Heavy ≥ 46.0
No. of subjects	81	33	114	74	102
Age, years	52.8	59.2*	54.5	55.9	54.5
%Flow mediated dilation, %	7.16	6.42	7.49	6.72	5.72**
Baseline brachial artery diameter, mm	4.34	4.21	4.27	4.39	4.61**
Body mass index, kg/m^2	24.8	24.6	24.2	24.2	23.9
Systolic blood pressure, mmHg	123.4	123.8	124.5	128.5	132.2***
Diastolic blood pressure, mmHg	80.6	80.5	80.3	82.7	83.4
Hypertension, %	37.9	43.8	39.8	58.3*	61.1**
Antihypertensive medication use, %	21.1	33.7	25.8	31.0	27.8
Total cholesterol, mmol/L	5.34	5.06	5.26	5.35	5.13
LDL-cholesterol, mmol/L	3.44	3.25	3.23	3.13*	2.79***
HDL-cholesterol, mmol/L	1.32	1.27	1.41	1.56***	1.64***
Triglycerides, mmol/L	1.47	1.53	1.47	1.58	1.62
Lipid lowering medication use, %	8.48	12.8	10.7	4.82	12.9
Glucose, mmol/L	5.77	5.35	5.42	5.61	5.74
HbA1c, %	5.93	5.61	5.65*	5.74	5.60*
Medication use for diabetes mellitus, %	10.7	4.18	5.39	7.64	4.04
Former smokers, %	47.3	47.9	53.7	47.7	55.1
Current smokers, %	27.1	24.0	23.5	35.8	38.1
Current smokers of 1-19 cigarettes per day, %	10.9	6.5	10.5	10.9	9.8
Current smokers of ≥ 20 cigarettes per day, %	16.2	17.5	13.0	24.9	28.3

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with never drinkers (Dunnett's test).
HDL indicates high-density lipoprotein; LDL, low-density lipoprotein.

Table 3. Mean values (SE) of %FMD according to alcohol consumption category

	Never	Former	Alcohol consumption, g/day of ethanol		
			Light < 23.0	Moderate 23.0–45.9	Heavy ≥ 46.0
No. of subjects	81	33	114	74	102
Age-adjusted mean	7.16 (0.34)	6.42 (0.54)	7.49 (0.29)	6.72 (0.36)	5.72 (0.31)**
Age- and community-adjusted mean	7.09 (0.33)	6.14 (0.52)	7.31 (0.28)	6.73 (0.34)	6.06 (0.30)*
Multivariable-adjusted mean	6.98 (0.34)	6.25 (0.52)	7.25 (0.28)	6.76 (0.34)	6.16 (0.31)

Multivariable variables included age, baseline brachial artery diameter, body mass index, systolic blood pressure, LDL-cholesterol, HbA1c, ex-smoking, smoking < 20 cigarettes per day, smoking ≥ 20 cigarettes per day, antihypertensive medication use, and community.
*$p<0.05$, **$p<0.01$ compared with the never group (Dunnett's test).

3.2% (median, 6.3%).

Table 2 shows the age-adjusted mean values and proportions of baseline characteristics according to alcohol consumption category. Men with ≥ 46.0 g/day of ethanol consumption showed the lower mean value of %FMD, larger mean of baseline brachial artery diameter, higher mean of systolic blood pressure, higher proportion of hypertension, higher mean of HDL cholesterol, lower mean of LDL cholesterol, and lower mean of HbA1c than never-drinking men.

Table 3 shows the age-adjusted and multivariable-adjusted mean values (standard errors) of %FMD according to alcohol consumption category. Men with ≥ 46.0 g/day of ethanol consumption showed significantly lower mean values of %FMD ($p=0.007$) than never-drinking men. This association did not change after adjustment for age, community, and other confounding factors. The significance levels of these con-

Table 4. ORs (95% CIs) for low %FMD (<5.3%) by alcohol consumption category

	Never	Former	Alcohol consumption, g/day of ethanol		
			Light <23.0	Moderate 23.0–45.9	Heavy ≥ 46.0
No. of subjects	81	33	114	74	102
%FMD <5.3, no.	20	13	26	21	51
Age-adjusted OR (95% CI)	1.00	1.61 (0.67-3.89)	0.84 (0.43-1.66)	1.09 (0.52-2.25)	2.99 (1.56-5.70)***
Age- and community-adjusted OR (95% CI)	1.00	1.48 (0.61-3.58)	0.82 (0.41-1.62)	1.03 (0.49-2.14)	2.74 (1.42-5.27)**
Multivariable-adjusted OR (95% CI)	1.00	1.76 (0.69-4.50)	0.86 (0.42-1.76)	0.98 (0.45-2.12)	2.39 (1.15-4.95)*

*$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with never drinkers.
Multivariable variables included age, baseline brachial artery diameter, body mass index, systolic blood pressure, LDL-cholesterol, HbA1c, ex-smoking, smoking <20 cigarettes per day, smoking ≥ 20 cigarettes per day, antihypertensive medication use, and community.

founding factors were $p=0.004$ for age, $p<0.0001$ for baseline brachial artery diameter, $p=0.50$ for BMI, $p=0.65$ for systolic blood pressure, $p=0.80$ for LDL cholesterol, $p=0.95$ for HbA1c, $p=0.96$ for former smoking, $p=0.35$ for current <20 cigarette per day, $p=0.55$ for ≥ 20 cigarette per day, $p=0.22$ for antihypertension medication use, and $p<0.0001$ for community. Light drinkers tended to show higher mean values of %FMD than never drinkers, but this was not significant.

Table 4 shows ORs for low %FMD (<5.3%) by alcohol consumption category. Heavy drinkers had a higher prevalence of low %FMD than never drinkers. Compared with never drinkers, age-adjusted ORs [95% confidence interval (CI)] of the low %FMD category for former, light (<23.0 g/day ethanol), moderate (23.0–45.9 g/day ethanol), and heavy (≥ 46.0 g/day ethanol) drinkers were 1.61 (0.67–3.89), 0.84 (0.43–1.66), 1.09 (0.52–2.25), and 2.99 (1.56–5.70), respectively. After further adjustment for baseline brachial artery diameter, BMI, systolic blood pressure, LDL cholesterol, HbA1c, smoking (never, former, current <20, and ≥ 20 cigarette per day), antihypertensive medication use, and community, the corresponding multivariable-adjusted ORs were 1.76 (0.69–4.50), 0.86 (0.42–1.76), 0.98 (0.45–2.12), and 2.39 (1.15–4.95), respectively. Light alcohol drinkers (<23.0 g/day ethanol) tended to show a lower prevalence of low %FMD than never drinkers, but this association was weak and not significant. On the other hand, heavy alcohol drinkers (≥ 46.0 g/day ethanol) showed a significant high proportion of low %FMD compared with never drinkers ($p=0.0009$). This association did not appreciably change after excluding participants on antihypertensive medication or those with a history of cardiovascular disease (data not shown). Heavy alcohol drinkers (≥ 46.0 g/day ethanol) showed lower multivariable-adjusted mean value of %FMD ($p=0.038$) and higher proportion of low %FMD than light drinkers; multivariable-adjusted OR (95% CI) = 2.79 (1.44–5.42) (not shown in table).

Discussion

In this study of a general population sample of 404 Japanese men, we found that ≥ 46.0 g/day of ethanol consumption was associated with a lower mean value of %FMD and a higher proportion of low %FMD compared with never drinkers. In contrast, light drinking may have had a beneficial effect on endothelial function, although this association was not significant.

In a study of 108 male Japanese patients with coronary artery disease[10], mean FMD was higher in light-to-moderate drinkers than in non-current drinkers. In this previous study, mean %FMD for non-drinkers, for those consuming 1–20 g alcohol per day, 21–50 g alcohol per day, and ≥ 51 g alcohol per day was 2.3%, 4.0%, 3.8%, and 3.0% respectively, whereas the corresponding values were 7.0%, 7.6%, 6.8%, and 5.7% in our study. Although mean %FMD values were different, both the studies showed that %FMD tended to be lower in heavy drinkers than in light or moderate drinkers. NOMAS of 884 general population samples of American men and women reported that persons who drank >1 drink/month to 2 drinks/day were more likely to have FMD above the median[9]. We also analyzed ORs for the high FMD category (>5.5%) to compare our results with those of NOMAS, considering 2 drinks as 1 "gō" (23 g/day ethanol). The unadjusted ORs (95% CI) for high %FMD for ≤ 2 drinks/day and >2 drinks/day compared with never drinkers were 1.02 (0.60–1.73) and 0.58 (0.35–0.95) in our study, whereas they were 1.69 (1.17–2.44) and 1.56 (0.96–2.54), respectively, in

NOMAS. No harmful effect on FMD was observed for those who drank >2 drinks/day in NOMAS, probably because the amount of ethanol intake among heavy drinkers may have been lower than that of our Japanese >2 drinks/day drinkers (mean ethanol intake=53.9 g/day). However, NOMAS did not specify the mean ethanol intake among heavy drinkers. The proportion of >2 drinks/day drinkers in NOMAS was much lower than that in our study (13% versus 38% in Japanese), and 57% of them were women[9]. To the best of our knowledge, this is the first study to show a significant association between heavy alcohol consumption and reduced %FMD.

Previous cohort studies showed a J-shaped relation of alcohol consumption with the risk of ischemic stroke in Japanese men[7, 8]. In addition, endothelial function is hypothesized to be an independent predictor or an important marker of cardiovascular events[1-3]. Because endothelial function reflects the early stages of atherosclerosis, our study suggests that heavy alcohol drinking contributes to the pathogenesis of atherosclerosis by lowering endothelial function and may increase the risk of cardiovascular disease.

Several cross-sectional and longitudinal studies have shown that alcohol consumption is associated with elevated blood pressure as well as a higher prevalence and incidence of hypertension[20-22]. Possible mechanisms of alcohol-induced hypertension include effects of alcohol on cardiac function, acetaldehyde, blood vessels, endothelium, sympathetic activity, noradrenaline metabolism, the renin–angiotensin system, plasma vasopressin, plasma cortisol, adrenocorticotropic hormone, and calcium metabolism[23-25]. In our study, heavy drinkers had higher systolic blood pressure than never drinkers (**Table 2**). However, the association between heavy alcohol consumption and a low mean value of %FMD or a high proportion of low %FMD did not substantially change after adjustment for systolic blood pressure. This finding suggests that endothelial dysfunction in heavy drinkers was probably because of a large amount of alcohol *per se*.

The mechanism of a negative effect on endothelial function can be explained by the direct actions of a large amount of alcohol itself. A previous *in vivo* study suggested that high concentrations of ethanol (100 mM and 150 mM) significantly reduced the synthesis of vasodilators, such as NO[26]. Chronic alcohol consumption interferes with NO production or release from endothelial cells[27, 28]. According to a study using rats, alcohol decreases NO because of inhibition of endothelial NO synthase activity and causes inflammatory/oxidative injury to the endothelium[27].

A Framingham study showed that high blood pressure or antihypertensive medication use (reflecting hypertension) had an influence on FMD[29]. However, in that study habitual smoking did not show any significant association with %FMD. Our study indicated that systolic blood pressure and antihypertensive medication use were not significantly associated with %FMD in the multivariable analysis: 0.91 (95% CI: 0.66–1.25) per 20 mmHg increment of systolic blood pressure and 1.00 (95% CI: 0.57–1.76) for antihypertensive medication use. The lack of significant associations in our study was probably because of the small number of subjects and the lower mean age compared with the Framingham heart study.

The limitations of our study need to be discussed. First, fasting was not required. We estimated the time intervals since the last meal from blood collection data of annual cardiovascular risk surveys. Because FMD measurements were conducted approximately 1 h after blood collection, the time intervals since the last meal were mostly ≥ 6 h [0 to <1 h (0%), 1 to <2 h (1.7%), 2 to <3 h (1.7%), 3 to <6 h (12.9%), and ≥ 6 h (83.7%)]. Therefore, we speculate that the effect of meals is relatively low.

Second, we did not examine the differential effect of alcoholic beverage types on the associations of alcohol consumption with %FMD. Several experimental studies have reported that FMD improves after ingestion of red wine, suggesting its additional antioxidation effect[30, 31]. However, a previous study from CIRCS demonstrated that a small number of the population consumed wine (<1%) in Yao and Ikawa[32]. Therefore, we believe that the positive effect of red wine consumption on the association of alcohol intake with endothelial function was probably minor in this study.

Conclusion

In conclusion, heavy alcohol consumption is associated with a low mean value of %FMD and a high proportion of low %FMD compared with never drinkers in the general population of Japanese men. Therefore, heavy alcohol consumption may be an independent risk factor of endothelial dysfunction. Follow-up studies are needed to clarify the effect of habitual alcohol intake on the incidence of endothelial dysfunction to confirm the causality.

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Conflict of Interest

None declared.

Appendix

The CIRCS is a collaborative study managed by the Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka University, University of Tsukuba, and Ehime University. The CIRCS investigators who contributed to this study are as follows: Masahiko Kiyama, Takeo Okada, Isao Muraki, Mina Hayama-Terada, Takeshi Sawai, Shinichi Sato, and Yuji Shimizu, Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka; Hiroyasu Iso, Akihiko Kitamura, Hironori Imano, and Renzhe Cui, Osaka University, Suita; Tomoko Sankai and Kazumasa Yamagishi, University of Tsukuba, Tsukuba; Isao Koyama and Masakazu Nakamura, National Cerebral and Cardiovascular Center, Suita; Mitsumasa Umesawa and Masanori Nagao, Dokkyo Medical University, Mibu; Tetsuya Ohira, Fukushima Medical University, Fukushima; Isao Saito and Shinichi Hitsumoto, Ehime University, Tōon, Takeshi Tanigawa, Ai Ikeda, and Koutatsu Maruyama, Jyuntendo University, Tokyo, Japan.

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