Relation of Drinking Alcohol to Atherosclerotic Risk in Type 2 Diabetes

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OBJECTIVE — The effects of drinking alcohol on atherosclerotic risks were investigated in 194 type 2 diabetic patients to determine whether drinking alcohol influences risk of atherosclerosis in diabetic subjects.

RESEARCH DESIGN AND METHODS — The subjects were divided by the degree of their average weekly alcohol consumption into three groups: nondrinkers, light drinkers (ethanol consumption <210 g/week), and heavy drinkers (ethanol consumption ≥210 g/week). The degree of atherosclerotic progression was evaluated using aortic pulse wave velocity (a-PWV), and possible atherosclerotic risks were evaluated using known atherosclerotic risk factors.

RESULTS — a-PWV was significantly lower in light drinkers than in nondrinkers and heavy drinkers, but there was no significant difference in a-PWV between nondrinkers and heavy drinkers. Systolic blood pressure, HDL cholesterol, and triglyceride levels were significantly higher in heavy drinkers than in nondrinkers and light drinkers, whereas there was no significant difference in these levels between nondrinkers and light drinkers. The mean levels of BMI and blood HbA_{1c}, uric acid, and fibrinogen were not different between the three groups. There were significant positive correlations of a-PWV with age and systolic blood pressure and weak but significant negative correlations of a-PWV with alcohol consumption and HDL cholesterol level.

CONCLUSIONS — Light drinking, but not heavy drinking, has preventive effects on atherosclerosis in type 2 diabetic subjects. The known beneficial effects of drinking alcohol on blood lipids and fibrinogen may not be involved in the preventive effect of light drinking on atherosclerosis in diabetic subjects.

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V ascular diseases are major complications in diabetic patients and often influence their prognosis. Diabetic angiopathies are divided into two categories, macroangiopathies and microangiopathies, and the former consists of atherosclerotic lesions. Approximately 30% of deaths in diabetic patients in Japan are caused by ischemic heart disease and stroke (1). It is well known that the incidence of atherosclerotic diseases, especially coronary heart disease, is lower in light-to-moderate drinkers than in non-drinkers (2), whereas the incidence of stroke increases in heavy drinkers (3). The beneficial effects of alcohol are believed to be mainly due to effects on lipid metabolism (4) and blood coagulation-fibrinolysis balance (5,6), whereas the harmful effects of heavy drinking are mainly due to the action of alcohol on blood pressure (7,8). Therefore, it is of interest to know whether drinking affects progression of atherosclerosis in diabetic subjects.

Drinking alcohol induces an acute increase in insulin resistance (9,10). On the other hand, recent prospective studies have shown that light-to-moderate drinking reduces incidence of type 2 diabetes and that alcohol decreases insulin resistance (11,12). Moreover, previous studies have shown that habitual drinking does not affect glucose tolerance in patients with type 1 and type 2 diabetes (13,14). However, other than glucose tolerance, little is known about the relationship in diabetic patients between alcohol consumption and atherosclerotic risks. In the present study of subjects with type 2 diabetes, we investigated the effects of drinking on aortic pulse wave velocity (a-PWV), which reflects aortic stiffness and is increased with atherosclerotic progression (15,16), as well as well-known atherosclerotic risk factors to determine whether drinking should be restricted from the viewpoint of atherosclerotic progression in diabetic subjects.

RESEARCH DESIGN AND METHODS

Study subjects
The subjects were 194 Japanese patients (111 men and 83 women) who were recruited from outpatients of the Hospital of Hyogo College of Medicine and had been diagnosed as having type 2 diabetes based on the criteria of the American Diabetes Association (17).

Measurements
Blood samples were collected from each subject in the morning after fasting for at least 10 h. Serum triglyceride level was measured by the standard enzymatic method. Serum HDL cholesterol was assayed enzymatically in combination with an inhibition assay. Serum uric acid was measured by the uricase method. Plasma fibrinogen was measured by the thrombin-time method. HbA_{1c} was assayed using high-performance liquid chromatography with a cation exchange column. The normal reference limits of HbA_{1c} measured by this method are 4.3–5.8%.

After each subject had rested quietly in a sitting position, blood pressure of the right brachial artery was recorded using a mercury sphygmomanometer: Korot-

koff's fifth phase was used to define diastolic pressure.

a-PWV was determined using a pulse-wave velocimeter (model PWV-200; Fukuda Denshi, Tokyo, Japan) with each subject in the supine position. Carotid-femoral pulse wave velocity was assessed using this automatic device. One transducer was positioned at the base of the neck over the left common carotid artery, and another was positioned over the right femoral artery. An on-line pulse wave was then recorded, and a-PWV was automatically calculated as the ratio (meters per second) of the distance traveled by the pulse wave to the time delay between the rapid upstroke of the pulse waves recorded simultaneously in the carotid and femoral arteries.

Average alcohol consumption per week was reported on questionnaires in which subjects were instructed to indicate their customary drinking frequency (days per week) and the average amount (ml) of alcoholic beverages ingested on a typical occasion or during a typical day. Alcoholic beverages included beer, sake (rice wine), wine, and whiskey. Usual weekly alcohol consumption (grams per week) was then calculated. For analyses of effects of drinking on atherosclerotic risks, the subjects were divided into three groups according to mean ethanol consumption per week (nondrinkers, light drinkers [<210 g per week], and heavy drinkers [≥210 g per week]). The value of 30 g per day was used to separate heavy drinkers from light drinkers, because the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends ethanol consumption of <30 g per day to prevent cardiovascular diseases (18).

Smoking history was reported on questionnaires and evaluated by the Brinkman index, which is the product of the number of cigarettes consumed per day and duration (years) of smoking history.

Statistical analyses

The data are expressed as means ± SD or SE. Statistical analyses were performed using computer software (SPSS version 9.0J for Windows). The mean levels of each item in the groups were compared using ANOVA followed by Student's *t* test with Bonferroni correction for multiple comparisons. In simple and multiple regression analyses, simple (Pearson's) correlation coefficients and standardized partial regression coefficients were calculated, respectively, and their significances were examined using Student's *t* test after standardization. The data of HbA_{1c} were log-transformed for regression analysis. Because alcohol consumption and the Brinkman index did not show a normal distribution, their correlation with a-PWV was analyzed using Spearman's correlation coefficient by rank. *P* values <0.05 were defined as significant.

RESULTS

Profiles of the subjects

The mean HbA_{1c} level of the subjects was 8.25% [±2.02 (SD)], which is much higher than the upper limit of the normal range, and 92.8% of the subjects showed an abnormally high HbA_{1c} level. Because a-PWV and atherosclerotic risk factors are influenced by age and sex (19), comparison of the mean levels of each item among the groups of different degrees of alcohol consumption and quartiles of a-PWV was performed with adjustment for age and sex.

Effects of age on a-PWV

The mean a-PWV value of subjects aged <60 years was 8.49 ± 1.46 m/s (mean ± SD), and that of subjects aged ≥60 years was 10.96 ± 2.22 m/s. Suzuki et al. (20) reported that abnormally high values of a-PWV in Japanese subjects from the viewpoint of atherosclerosis were ≥8.0 m/s for persons aged <60 years and ≥9.0 m/s for persons aged ≥60 years. According to these criteria, 66.7% of the subjects in the present study aged <60 years and 80.8% of those aged ≥60 years had abnormally high values of a-PWV.

Effects of drinking on a-PWV

a-PWV was significantly lower in light drinkers than in nondrinkers and heavy drinkers. There was no significant difference in a-PWV between nondrinkers and heavy drinkers (Table 1). These tendencies were not altered when smoking history (Brinkman index) was also added to the items of adjustment in calculation of the mean a-PWV values (mean ± SE) [nondrinkers, 10.22 ± 0.23 m/s; light drinkers, 9.47 ± 0.28 m/s (*P* < 0.05 and *P* < 0.01 compared with nondrinkers and heavy drinkers, respectively); heavy drinkers, 10.31 ± 0.27 m/s]. The mean

alcohol consumption tended to be higher in the first and fourth quartiles of a-PWV than in the other quartiles (Fig. 1*A*).

Effects of drinking on blood pressure

Systolic blood pressure was significantly higher in heavy drinkers than in nondrinkers and light drinkers, whereas there was no difference in systolic blood pressures between nondrinkers and light drinkers (Table 1). The mean diastolic blood pressure was higher in heavy drinkers than in nondrinkers and light drinkers, but the differences were not significant (Table 1).

Effects of drinking on serum lipid levels

Both HDL cholesterol and triglyceride levels were significantly higher in heavy drinkers than in nondrinkers and light drinkers, but these levels were not different between nondrinkers and light drinkers (Table 1).

Effects of drinking on other atherosclerotic risk factors

The mean levels of BMI, HbA_{1c}, and uric acid were not significantly different among nondrinkers, light drinkers, and heavy drinkers (Table 1). In heavy drinkers, age and Brinkman index were significantly lower and higher, respectively, than in nondrinkers and light drinkers, whereas there were no significant differences in age and Brinkman index between nondrinkers and light drinkers (Table 1).

Relation of atherosclerotic risk factors to a-PWV

Simple regression analysis showed that a-PWV was significantly correlated positively with age, systolic blood pressure, and blood fibrinogen level and negatively with alcohol consumption and HDL cholesterol level (Table 2). However, these correlations, except for the correlation with age, were weak. In multiple regression analysis, blood HbA_{1c} and serum uric acid levels showed weak but significant positive correlations with a-PWV, whereas the correlation coefficients between a-PWV on one hand and HDL cholesterol and blood fibrinogen on the other hand were not statistically significant (Table 2).

Figure 1*B–D* shows a comparison of the levels of the atherosclerotic risk factors affected by drinking among four quartile groups of a-PWV. The mean level

Table 1—*Effects of drinking on atherosclerotic risks in diabetic subjects*

Characteristics	Nondrinkers	Light drinkers	Heavy drinkers
n	83	48	63
Age (years)	65.7 ± 1.1	66.2 ± 1.5	$58.1 \pm 1.4*$
Alcohol consumption (g/week)	0	94.3 ± 7.3†	$643.4 \pm 86.2*$
Brinkman index	439.9 ± 83.1	398.4 ± 98.9	$904.4 \pm 94.1*$
BMI (kg/m^2)	23.2 ± 0.4	23.5 ± 0.5	23.3 ± 0.5
Systolic blood pressure (mmHg)	131.6 ± 2.0	131.7 ± 2.4	$138.6 \pm 2.2*$
Diastolic blood pressure (mmHg)	75.0 ± 1.3	76.4 ± 1.5	78.6 ± 1.4
a-PWV (m/s)	10.21 ± 0.23	9.43 ± 0.27†	10.42 ± 0.26
HbA$_{1c}$ (%)	8.43 ± 0.25	8.07 ± 0.30	8.16 ± 0.29
Triglycerides (mg/dl)	132.0 ± 11.1	114.8 ± 13.2	$170.1 \pm 12.6*$
HDL cholesterol (mg/dl)	51.4 ± 2.0	49.9 ± 2.4	$58.8 \pm 2.3*$
Uric acid (mg/dl)	5.00 ± 0.16	4.86 ± 0.19	5.24 ± 0.18
Fibrinogen (mg/dl)	281.1 ± 7.1	290.8 ± 8.5	286.5 ± 8.1

Data are means $\pm$ SE. The subjects were divided by the degree of their average weekly alcohol consumption into three groups: nondrinkers, light drinkers (ethanol consumption of <210 g/week), and heavy drinkers (alcohol consumption of ≥210 g/week). The mean values of each item (except age and alcohol consumption) were calculated with adjustment for age and sex and compared among the groups of different degrees of alcohol consumption. *Significantly different from the values of nondrinkers and light drinkers ($P < 0.05$); †significantly different from the values of nondrinkers and heavy drinkers ($P < 0.05$).

of the Brinkman index in the fourth quartile of a-PWV was higher than those in the other three quartiles, although these differences were not significant (Fig. 1*B*). The mean levels of systolic blood pressure in the third and fourth quartiles were significantly higher than that in the first quartile (Fig. 1*C*). The mean fibrinogen level in the fourth quartile of a-PWV was significantly higher than those in the other three quartiles (Fig. 1*D*).

CONCLUSIONS— There was no difference in HbA$_{1c}$ levels between nondrinkers, light drinkers, and heavy drinkers in the diabetic subjects. This agrees with findings in previous studies that habitual drinking does not affect glucose tolerance in diabetic subjects (13,14). a-PWV, a popular functional marker for assessment of atherosclerotic progression, is known to be greater in patients with diabetes (19) and even in those with a family history of type 2 diabetes (21). The mean a-PWV values of diabetic subjects in the present study were much higher than the normal range of a-PWV values in Japanese subjects. A recent study has demonstrated a significant correlation between a-PWV and the intima-media thickness of the carotid artery in patients with type 2 diabetes (22), indicating that functional changes evaluated by a-PWV in the arterial walls are associated with their structural changes in diabetic subjects.

In the present study, the mean a-PWV

value in light drinkers was found to be significantly lower than that in nondrinkers, whereas the values in nondrinkers and heavy drinkers were not different. Moreover, the levels of alcohol consumption in the first and fourth quartiles of a-PWV tended to be higher than those in the other quartiles. Therefore, a U-shaped relationship may exist between alcohol consumption and a-PWV. These results suggest that light drinking, but not heavy drinking, has preventive effects on progression of atherosclerosis in diabetic subjects. Therefore, our data support the hypothesis that the general concept that light-to-moderate drinking prevents atherosclerosis (2) can also be applied to diabetic subjects. However, further studies are needed to prove this hypothesis. In a recent study using Japanese-Americans living in Seattle, the rate of high a-PWV was significantly lower in drinkers than in nondrinkers (23). Although the degree of alcohol consumption in the drinkers was not evaluated in that study, alcohol consumption of the Japanese-American subjects living in Seattle was found to be much lower than that of general Americans in the U.S. and Japanese in Japan (23), suggesting that light-to-moderate drinking lowers a-PWV. The present study showed the possibility of a beneficial action of habitual light drinking of alcohol on prevention of atherosclerotic progression evaluated by a-PWV also in type 2 diabetic subjects.

To clarify the mechanisms underlying

the preventive action of light drinking of alcohol on atherosclerosis in diabetic subjects, we investigated the effects of drinking on known atherosclerotic risk factors. Serum HDL cholesterol, which is a negative risk factor for atherosclerosis, was higher in the group of heavy drinkers than in the other two groups but was not different in nondrinkers and light drinkers. On the other hand, systolic blood pressure and serum triglyceride level, both of which are positive risk factors for atherosclerosis, were also higher in the group of heavy drinkers than in the other two groups but were not different between the nondrinkers and light drinkers. Therefore, changes in serum lipid levels are not involved in the beneficial effects of light drinking of alcohol on prevention of atherosclerotic progression in diabetic subjects. This is in contrast with the effects of drinking on atherosclerosis in nondiabetic persons, because HDL cholesterol levels in general subjects are known to be higher in light drinkers than in nondrinkers, and this HDL cholesterol–elevating effect of alcohol is believed to be mainly involved in the beneficial action of light-to-moderate drinking (4).

Alcohol is known to affect coagulation-fibrinolysis balance: in drinkers, blood fibrinogen and plasminogen activator levels are known to be lower and higher, respectively (5,6), and platelet function is known to be depressed by alcohol in vitro (24). In diabetic subjects, increased blood coagulation activity is a
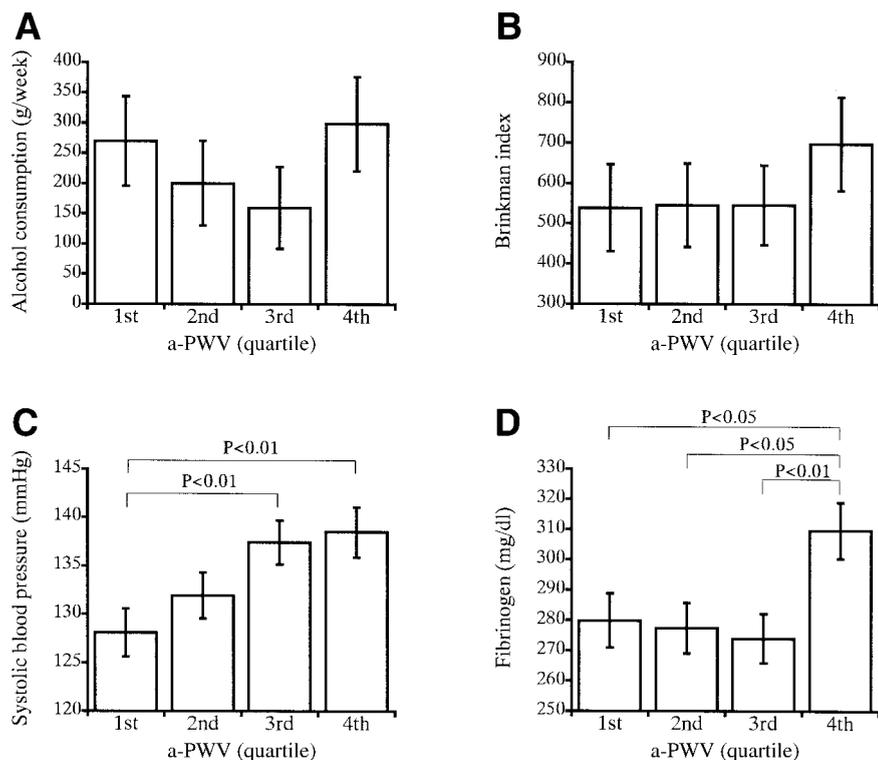
Figure 1—*Comparison of alcohol consumption* (A)*, Brinkman index* (B)*, systolic blood pressure* (C)*, and plasma fibrinogen level* (D) *among the four quartile groups of a-PWV. The values of a-PWV were arranged in ascending order, and the subjects were then divided into four groups of approximately equal sizes. Mean levels of each item (alcohol consumption, Brinkman index, systolic blood pressure, and plasma fibrinogen) after adjustment for age and sex were compared among the quartiles for a-PWV. Bars indicate SE.*

despite the fact that HDL cholesterol was higher in heavy drinkers than in nondrinkers and light drinkers. Therefore, there is no beneficial effect of heavy drinking on prevention of atherosclerosis in diabetic subjects, despite the beneficial effect of drinking on the HDL cholesterol level. One possible explanation for this is that the adverse effects on blood pressure and serum triglyceride level caused by heavy drinking (Table 1), which promote progression of atherosclerosis, might be greater than the beneficial action of heavy drinking on the HDL cholesterol level. Regarding the influences of smoking on a-PWV, adjustment for the Brinkman index resulted in a decrease in the mean a-PWV value in the heavy drinkers (from 10.42 to 10.31) and resulted in slight increases in the mean a-PWV value in the nondrinkers (from 10.21 to 10.22) and the light drinkers (from 9.43 to 9.47). These diverse effects of adjustment for the Brinkman index on mean a-PWV values may reflect the finding that heavy drinkers smoke more than twice the number of cigarettes than nondrinkers or light drinkers (Table 1). Cigarette smoking accelerates progression of atherosclerosis and has been reported to be associated with increasing a-PWV (22,31). Therefore, the influence of smoking on a-PWV may be much greater in the group of

major cause of proneness to atherosclerotic cardiovascular diseases (25). Therefore, one possible explanation for the aforementioned beneficial effect of light drinking in diabetic subjects is that alcohol also affects the coagulation-fibrinolysis balance in diabetic subjects as in nondiabetic persons, although there have been few studies on effects of alcohol on this balance in diabetic subjects. In the present study, blood fibrinogen levels were found to be slightly correlated with a-PWV, and the mean fibrinogen level in the highest quartile of a-PWV was significantly higher than those in the other three quartiles. However, there were no differences in mean blood fibrinogen levels between nondrinkers, light drinkers, and heavy drinkers. Therefore, changes in blood fibrinogen levels may not be involved in the effect of light drinking on a-PWV. Further studies on the effects of drinking on other factors of blood coagulation and fibrinolysis, such as plasminogen activator and platelet function, are needed to clarify the mechanism underly-

ing the beneficial action of light drinking of alcohol on atherosclerotic progression in diabetic subjects.

Hyperinsulinemia is known to be a cardiovascular risk factor, and type 2 diabetes is associated with hyperinsulinemia (26). Hyperinsulinemia induces proliferation of vascular smooth muscle, and this is suggested to be an early process of atherosclerosis (27). Moreover, hyperinsulinemia is associated with medial hypertrophy of myocardial arterioles (28). An inverse relationship between alcohol consumption and insulin concentrations has been reported in people with type 2 diabetes (29) as well as in nondiabetic people (30). Therefore, there is a possibility that drinking alcohol decreases the risk of cardiovascular disease by reducing hyperinsulinemia, although blood insulin levels were not evaluated in the present study.

On the other hand, the mean a-PWV value in heavy drinkers was significantly higher than that in light drinkers but was not different from that in nondrinkers,

Table 2—Correlations of atherosclerotic risk factors with a-PWV

Characteristics	Simple regression	Multiple regression
Age	0.60†	—
Alcohol consumption	−0.15*	—
Brinkman index	0.06	—
Systolic blood pressure	0.28†	0.15*
HbA$_{1c}$	0.02	0.12*
Triglycerides	−0.09	0.03
HDL cholesterol	−0.14*	−0.10
Uric acid	0.05	0.13*
Fibrinogen	0.15*	0.10

Data are correlation coefficients between each item and a-PWV by univariate and multivariate analyses. In multivariate analysis, age and sex were added to the variables. In univariate and multivariate analyses, simple (Pearson's) correlation coefficients and standardized partial regression coefficients were calculated, respectively. Because alcohol consumption and the Brinkman index did not show a normal distribution, their correlation with a-PWV was analyzed using Spearman's correlation coefficient by rank. *$P < 0.05$; †$P < 0.01$.

heavy drinkers than in the other two groups. In heavy drinkers, a greater number of cigarettes smoked as well as higher systolic blood pressure and serum triglyceride level may be involved in cancellation of the beneficial effects of alcohol drinking on atherosclerotic progression, resulting in no difference in a-PWV between nondrinkers and heavy drinkers. Another possible explanation is that an unknown beneficial action for prevention of atherosclerosis, as shown in light drinkers, does not appear in heavy drinkers.

In the simple or multiple regression analyses of the present cross-sectional study, a-PWV was correlated strongly with age but only weakly with alcohol consumption, systolic blood pressure, HbA_{1c}, HDL cholesterol, uric acid, and fibrinogen. The reason for these weak associations of a-PWV with known atherosclerotic risk factors might be the heterogeneous nature of subjects used in the present study. Moreover, the ages of the present subjects (mean age 63.4 years) were relatively high, and most of them already had some degree of atherosclerotic progression. In fact, the percentage of subjects with abnormally high values of a-PWV was very high (75.8% in all ages). Therefore, studies using younger subjects and subjects who are more homogeneous with regard to age, sex, and drug-controlled condition of diabetes and other risk factors, in addition to prospective studies, are needed to confirm the present findings.

The conclusions obtained from the present study are summarized as follows: *1*) light drinking but not heavy drinking of alcohol decreases a-PWV in type 2 diabetic subjects, and *2*) changes in serum HDL cholesterol and plasma fibrinogen levels are not involved in this beneficial effect of light drinking of alcohol. The mechanism underlying the proposed preventive action of alcohol drinking on atherosclerotic progression in diabetic subjects still remains to be clarified.

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