Original Article

Alcohol Drinking Status is Associated with Serum High Molecular Weight Adiponectin in Community-Dwelling Japanese Men

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Aim: Serum high molecular weight (HMW) adiponectin improves insulin sensitivity, and a decreased level of serum HMW adiponectin has been reported as a risk factor for the development of diabetes and coronary heart disease. This association may be further confounded by the alcohol drinking status, which is involved in the development of liver dysfunction. The aim of this study was to determine whether the alcohol drinking status is associated with serum HMW adiponectin levels in community-dwelling Japanese men.

Methods: A cross-sectional study was carried out in 2002. Study participants without a clinical history of diabetes (747 men aged 60 ± 14 (mean $\pm$ standard deviation) (range, 20–89) years) were randomly recruited from a single community at the time of their annual health examination. They were classified into never drinkers, light drinkers (<1 unit/day), moderate drinkers (1–1.9 units/day), and heavy drinkers (≥ 2 units/day). We examined the effects of alcohol consumption on serum HMW adiponectin.

Results: Overall, mean serum HMW adiponectin levels were significantly lower in the group with higher alcohol consumption, and there were inter-group differences in the alcohol drinking status. Moreover, age-adjusted mean serum HMW adiponectin levels were significantly lower in the group with higher alcohol consumption. Multiple linear regression analysis showed that the alcohol drinking status was significantly and independently associated with serum adiponectin as well as age, smoking status, TG, HDL-C, LDL-C, serum ALT, and HOMA-IR. Multivariate-adjusted mean serum HMW adiponectin levels were also significantly lower in the group with higher alcohol consumption.

Conclusion: The alcohol drinking status is negatively associated with serum HMW adiponectin levels in Japanese community-dwelling men.

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Key words; HMW adiponectin, Alcohol drinking, Confounding factor, Insulin resistance, Men

Introduction

Serum adiponectin, which is a protein secreted specifically by adipose tissue, improves insulin sensi-

tivity¹⁾, and plays significant roles in the development of various lifestyle-related diseases, such as obesity, hypertension, hyperlipidemia, type 2 diabetes mellitus, and metabolic syndrome, leading to the development of heart and vascular diseases^{2,3)}. Adiponectin is a 247-amino acid protein containing four differentiable domains that regulate the metabolism of lipids and glucose. A large number of studies have demonstrated that adiponectin exhibits anti-inflammatory, antidiabetic, antimetabolic and antiatherogenic properties⁴⁾. Moreover, Waki *et al.*⁵⁾ recently demonstrated that

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adiponectin forms multimers and is present in the serum as a trimer, hexamer, or as a high molecular weight (HMW) form. The HMW form is the most active form of this protein and has better predictive power for the development of insulin resistance and metabolic syndrome than the plasma total adiponectin level⁵⁻⁸.

The alcohol drinking status is a major lifestyle factor that increases morbidity and mortality as it is associated with conditions such as liver disease (i.e., alcoholic fatty liver and chronic hepatitis) and several types of cancer (i.e., pharyngeal cancer and esophageal cancer). Moderate alcohol consumption has also been known to affect adipocytokines and is able to decrease⁹, or increase adiponectin levels¹⁰⁻¹⁴. Moreover, a few studies have shown that moderate alcohol consumption did not affect adiponectin levels¹⁵⁻¹⁷. This association may be further confounded by the alcohol drinking status, which is related to the development of both insulin sensitivity and alcoholic fatty liver. There is a great deal of controversy surrounding this relationship, and relevant literature on the relationship between the influence of alcohol intake and serum HMW adiponectin is sparse¹⁰⁻¹⁷. To our knowledge, few studies have demonstrated a relationship between alcohol consumption and serum HMW adiponectin in the Japanese population¹⁴⁻¹⁷.

We hypothesized that serum HMW adiponectin is associated with the alcohol drinking status regardless of age and body weight. We therefore evaluated whether the alcohol drinking status is associated with serum HMW adiponectin levels, using cross-sectional data on community-dwelling Japanese men.

Materials and Methods

Subjects

Participants were recruited at the time of their annual health examination in a rural town with a total population of 11,136 (as of April 2002), located in Ehime prefecture, Japan, in 2002. Among the 9,133 adults (4,395 men) aged 19 to 90 years in this population, a random sample of 3,164 subjects (34.6%) was recruited. Information on medical history, present conditions, and drugs was obtained by interview. The prevalence of regular alcohol drinkers among women was 5.5%, therefore, women were excluded. Subjects with a clinical history of diabetes were also excluded from the study. The final study sample consisted of 747 eligible men. All procedures were approved by the Ethics Committee of Ehime University School of Medicine.

Evaluation of Risk Factors

Information on demographic characteristics and risk factors was collected using clinical files. Body mass index was calculated by dividing weight (in kilograms) by the square of the height (in meters). We measured blood pressure in the right upper arm of participants in the sedentary position using an automatic oscillometric blood pressure recorder (BP-103i; Colin, Aichi, Japan) after they had rested for at least 5 min. Total cholesterol (T-C), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), fasting blood glucose (FBG), uric acid, immuno-reactive insulin (IRI), serum alanine aminotransferase (ALT), and HMW adiponectin (FUJIREBIO, Tokyo, Japan) were measured during fasting. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula¹⁸. Participants with TG levels ≥ 400 mg/dL were excluded. Homeostasis of minimal assessment of insulin resistance (HOMA-IR) was calculated from FBG and IRI levels using the following formula: $\text{FBG (mg/dL)} \times \text{IRI (mU/mL)} / 405$ ¹⁹. Other characteristics, e.g., smoking and alcohol habits, and medication were investigated by individual interviews using a structured questionnaire. Smoking status was defined as the number of cigarette packs per day multiplied by the number of years smoked (pack $\cdot$ year), and daily alcohol consumption was measured using the Japanese liquor unit, in which a unit corresponds to 22.9 g ethanol. The participants were classified into never drinkers, light drinkers (< 1 unit/day), moderate drinkers (1–1.9 units/day), and heavy drinkers (≥ 2 unit/day).

Statistical Analysis

Statistical analyses were performed using SPSS 17.0J (PASW Statistics 17.0; Statistical Package for Social Science Japan, Inc., Tokyo, Japan). All values are expressed as the mean $\pm$ standard deviation (SD), unless otherwise specified. Data for TG, FBG, HOMA-IR, serum ALT, and HMW adiponectin were skewed and log-transformed for analysis. Differences based on drinking status (never-drinkers, light drinkers, moderate drinkers, and heavy drinkers) were analyzed by the Kruskal Wallis test or chi-square (χ^2) test. Pearson's correlation coefficients were calculated in order to characterize the relationships between various characteristics as these factors are supposed to be highly inter-correlated⁸. Multiple linear regression analysis was used to evaluate the contribution of each confounding factor for serum HMW adiponectin^{8, 20-23}. ANCOVA was performed using a general linear model approach to determine the association between confounding factors and serum HMW adiponectin. In these analyses, serum HMW adiponectin was the

Table 1. Characteristics of various confounding factors of subjects categorized by alcohol drinking status

Alcohol consumption [†]	Never	Light	Moderate	Heavy	
Characteristics	<i>n</i> = 100	< 1 unit/day <i>n</i> = 218	1–1.9 units/day <i>n</i> = 259	≥ 2 units/day <i>n</i> = 170	<i>p</i> -value [*]
Age (years)	65 ± 14	58 ± 15	61 ± 13	58 ± 12	< 0.001
Body mass index [‡] (kg/m ²)	23.2 ± 3.3	23.5 ± 3.1	23.4 ± 2.8	23.9 ± 3.0	0.237
Smoking status (never/past/light/heavy (%))	38.0/30.0/13.0/19.0	45.4/16.1/19.3/19.3	46.7/27.4/11.2/14.7	30.6/23.5/16.5/29.4	< 0.001
Systolic blood pressure (mmHg)	137 ± 24	135 ± 20	139 ± 19	143 ± 18	0.001
Diastolic blood pressure (mmHg)	81 ± 13	82 ± 11	84 ± 11	87 ± 10	< 0.001
Antihypertensive medication (%)	32.0	20.6	25.9	21.8	0.124
Triglycerides (mg/dL)	92 (71–130)	99 (73–141)	91 (68–124)	112 (78–122)	0.001
HDL cholesterol (mg/dL)	55 ± 12	55 ± 13	61 ± 15	63 ± 16	< 0.001
LDL cholesterol (mg/dL)	127 ± 26	115 ± 33	107 ± 29	102 ± 32	< 0.001
Antilipidemic medication (%)	6.0	3.2	3.1	2.4	0.430
Fasting blood glucose (mg/dL)	94 (88–100)	93 (88–99)	94 (89–101)	97 (90–104)	0.003
Uric acid (mg/dL)	5.3 ± 1.2	5.9 ± 1.3	6.1 ± 1.4	6.3 ± 1.4	< 0.001
Serum alanine aminotransferase (mg/dL)	19 (15–25)	20 (14–26)	20 (16–29)	24 (18–33)	< 0.001
HOMA-IR [§]	1.02 (0.85–1.26)	1.07 (0.88–1.26)	1.02 (0.82–1.22)	1.03 (0.78–1.26)	0.293

HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, Homeostasis of minimal assessment of insulin resistance. Data presented are the mean ± standard deviation. Data for triglycerides, fasting blood glucose, serum alanine aminotransferase, and HOMA-IR were skewed, and are presented as the median (interquartile range). [†]Alcohol consumption was measured using a Japanese liquor unit, in which 1 unit corresponds to 22.9 g ethanol. [‡]Body mass index was calculated using weight in kilograms divided by the square of the height in meters. [§]HOMA-IR was calculated using the following formula; fasting blood glucose (mg/dL) × immuno-reactive insulin (mU/mL)/405. Data for triglycerides, serum alanine aminotransferase, HOMA-IR, and serum HMW adiponectin were skewed, and log-transformed for analysis. **p*-value: Kruskal Wallis test or χ^2 test.

dependent variable, the four categories of alcohol drinking status were fixed factors, and significant confounding factors in multiple linear regression analysis were added as covariates. A value of $p < 0.05$ was considered significant.

Results

Table 1 shows the characteristics of each subject's background factors categorized according to alcohol drinking status. The subjects comprised 747 men aged 60 ± 14 (range, 20–89) years, 100 (13.4%), who were defined as never-drinkers, 218 (29.2%) light drinkers, 259 (34.7%) moderate drinkers, and 170 (22.8%) heavy drinkers. The prevalence of heavy smoking, SBP, DBP, HDL-C, FBG, uric acid, and serum ALT was higher, but age and LDL-C were lower in heavy drinkers than in never- and light drinkers. There were no inter-group differences regarding BMI, the prevalence of antihypertensive and antilipidemic medication, and HOMA-IR.

Table 2 shows mean log serum HMW adiponectin of the subjects categorized by alcohol drinking status. Mean log serum HMW adiponectin levels were significantly lower in the group with higher alcohol consumption, and there were inter-group differences

in the alcohol drinking status. Moreover, as serum HMW adiponectin levels have been demonstrated to increase with aging and decrease progressively with increasing BMI⁸⁾, we adjusted for age or age and BMI. Age-adjusted, and age and BMI-adjusted mean serum HMW adiponectin levels were also significantly lower in the group with higher alcohol consumption.

Table 3 shows the results of the correlation coefficient matrix with *p*-values. It was shown that levels of serum HMW adiponectin were inversely associated with BMI, alcohol drinking status, smoking status, DBP, TG, LDL-C, FBG, uric acid, serum ALT, and HOMA-IR, while directly associated with age, antihypertensive medication, and HDL-C. In addition, BMI and HOMA-IR, or SBP and DBP were highly inter-correlated.

To further investigate whether the alcohol drinking status can be a confounding factor of serum HMW adiponectin independently of other known risk factors, stepwise multiple linear regression analyses for serum HMW adiponectin were performed with five models (**Table 4**). They revealed that the alcohol drinking status was significantly and independently associated with serum HMW adiponectin as well as age, BMI, smoking status, TG, HDL-C, LDL-C, FBG, serum ALT, and HOMA-IR.

Table 2. Mean log serum HMW adiponectin (95% CI) of subjects categorized by alcohol drinking status

Alcohol consumption [†]	Never	Light	Moderate	Heavy	
Characteristics	<i>n</i> = 100	< 1 unit/day <i>n</i> = 218	1–1.9 units/day <i>n</i> = 259	≥ 2 units/day <i>n</i> = 170	<i>p</i> -value*
Serum HMW adiponectin (μg/mL)	0.64 (0.58–0.69)	0.53 (0.49–0.57)	0.55 (0.52–0.59)	0.45 (0.40–0.49)	< 0.001
Age-adjusted	0.60 (0.55–0.65)	0.54 (0.51–0.58)	0.54 (0.51–0.57)	0.46 (0.42–0.50)	< 0.001
Serum HMW adiponectin (μg/mL)					
Age and BMI-adjusted	0.59 (0.54–0.64)	0.54 (0.51–0.57)	0.54 (0.51–0.57)	0.47 (0.43–0.51)	0.001
Serum HMW adiponectin (μg/mL)					

HMW, high molecular weight; BMI, body mass index. Data presented are the log-transformed mean (95% confidence interval) values. [†]Alcohol consumption was measured using a Japanese liquor unit, in which 1 unit corresponds to 22.9 g ethanol. Data for serum HMW adiponectin were skewed, and log-transformed for analysis.

Fig. 1 shows the mean log serum HMW adiponectin levels after adjustments for significant confounding factors in **Table 4**. Mean serum HMW adiponectin levels were significantly lower in the group with higher alcohol consumption.

Discussion

To examine the possible contribution of alcohol drinking status to decreasing serum HMW adiponectin levels in community-dwelling men, we studied the relationship between the alcohol drinking status, potential confounders, and the serum HMW adiponectin level. Multiple linear regression analysis of serum HMW adiponectin revealed that the alcohol drinking status was significantly associated with serum HMW adiponectin levels as well as age, smoking status, TG, HDL-C, LDL-C, serum ALT and HOMA-IR, and decreased HMW adiponectin. The present study also showed a dose-dependent relationship between alcohol consumption and serum HMW adiponectin

levels in Japanese community-dwelling men.

In this study, the relationship between serum HMW adiponectin levels and confounding factors was consistent with previous studies in that serum adiponectin was significantly associated with age, smoking status, TG, HDL-C, LDL-C, ALT, and HOMA-IR²⁰. In our previous study, we demonstrated the relationship between serum HMW adiponectin and smoking status, and alcohol consumption was also a significant confounding factor for serum HMW adiponectin after multiple adjustments in that study²⁴; however, there are few reports on the associations between alcohol consumption and plasma adiponectin levels in Japanese men^{15–17}. Thus, we re-assessed whether alcohol consumption affected serum HMW adiponectin levels in the present study, and found that alcohol consumption was dose-dependently associated with decreased serum HMW adiponectin.

These studies vary greatly in design, the number of participants, sex, and the heterogeneity of alcohol consumption (i.e., beverage type, gram/day, pattern of

Table 3. Pearson's correlation coefficients matrix validation of subjects

Characteristics	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1 Age	r														
	p-value														
2 Body mass index [†] (kg/m ²)	-0.110 0.003	1													
3 Alcohol consumption [‡]	0.091 0.012	0.056 0.124	1												
4 Smoking status (never/past/light/heavy (%))	-0.237 <0.001	-0.057 0.119	0.069 0.058	1											
5 Systolic blood pressure (mmHg)	0.350 <0.001	0.206 <0.001	0.112 0.002	-0.193 <0.001	1										
6 Diastolic blood pressure (mmHg)	0.108 0.003	0.279 <0.001	0.189 <0.001	-0.119 0.001	0.745 <0.001	1									
7 Antihypertensive medication (%)	0.338 <0.001	0.139 <0.001	-0.038 0.747	-0.209 <0.001	0.392 <0.001	0.290 <0.001	1								
8 Triglycerides (mg/dL)	-0.208 <0.001	0.332 <0.001	0.072 0.048	0.115 0.002	0.018 0.622	0.157 <0.001	-0.047 0.203	1							
9 HDL cholesterol (mg/dL)	0 0.994	-0.312 <0.001	0.226 <0.001	-0.094 0.011	0.045 0.219	0.023 0.527	0.048 0.190	-0.408 <0.001	1						
10 LDL cholesterol (mg/dL)	0.102 0.005	0.195 <0.001	-0.248 <0.001	-0.071 0.052	0.044 0.232	0.048 0.186	0.047 0.197	0.113 0.002	-0.126 0.001	1					
11 Antilipidemic medication (%)	0.051 0.167	0.080 0.029	-0.051 0.161	-0.071 0.052	-0.041 0.265	0 0.990	0.051 0.163	0.085 0.020	-0.012 0.736	0.096 0.009	1				
12 Fasting blood glucose (mg/dL)	0.100 0.006	0.272 <0.001	0.129 <0.001	-0.160 <0.001	0.297 <0.001	0.277 <0.001	0.181 <0.001	0.142 <0.001	-0.015 0.689	0.101 0.006	0.033 0.373	1			
13 Uric acid (mg/dL)	-0.210 <0.001	0.237 <0.001	0.207 <0.001	0.064 0.078	0.033 0.366	0.102 0.005	0.029 0.425	0.233 <0.001	-0.080 0.030	0.008 0.832	0.028 0.438	0.108 0.003	1		
14 Serum alanine aminotransferase (mg/dL)	-0.245 <0.001	0.389 <0.001	0.161 <0.001	0.034 0.347	0.050 0.174	0.191 <0.001	0.011 0.766	0.316 <0.001	-0.023 0.523	0.067 0.067	0.053 0.146	0.161 <0.001	0.191 <0.001	1	
15 HOMA-IR [§]	-0.158 <0.001	0.568 <0.001	-0.035 0.345	-0.069 0.061	0.147 <0.001	0.207 <0.001	0.129 <0.001	0.384 <0.001	-0.314 <0.001	0.206 <0.001	0.069 0.060	0.478 <0.001	0.240 <0.001	0.307 <0.001	1
16 serum HMW adiponectin	0.396 <0.001	-0.297 <0.001	-0.165 <0.001	-0.153 <0.001	0.035 0.340	-0.112 0.002	0.121 0.001	-0.365 <0.001	0.206 <0.001	-0.075 0.040	-0.054 0.140	-0.141 <0.001	-0.245 <0.001	-0.295 <0.001	-0.337 <0.001

HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, Homeostasis of minimal assessment of insulin resistance; HMW, high molecular weight. [†] Body mass index was calculated using weight in kilograms divided by the square of the height in meters. [‡] Alcohol consumption was measured using a Japanese liquor unit, in which 1 unit corresponds to 22.9 g ethanol (never-drinkers, light drinkers (<1 unit/day), moderate drinkers (1–1.9 units/day), heavy drinkers (≥2 units/day)). [§] HOMA-IR was calculated using the following formula; fasting blood glucose (mg/dL) × immuno-reactive insulin (mU/mL)/405. Data for triglycerides, serum alanine aminotransferase, and HOMA-IR were skewed, and log-transformed for analysis. r, Pearson's correlation coefficient.

alcohol use) within the study population (Table 5). It is likely that the variability shown in the outcomes of these studies are the result of these differences, and the relationship between alcohol consumption and adiponectin is controversial. A recent randomized, controlled, crossover trial including some healthy subjects revealed that brief moderate alcohol intake did not lead to a decrease but to an increase in adiponectin

levels²⁵⁻²⁸). Also, in case-controlled analyses, moderate alcohol consumption contributed to increased adiponectin concentrations³⁰⁻³²). In a cross-sectional study of 532 men without a history of cardiovascular disease and living in the United States, Pischon *et al.*¹²) showed that moderate alcohol consumption was independently associated with higher plasma adiponectin levels but plasma adiponectin tended to be slightly lower

Table 4. Association between various confounding factors and serum HMW adiponectin assessed by multiple linear regression analysis

Characteristics	Model 1 β (<i>p</i> -value)	Model 2 β (<i>p</i> -value)	Model 3 β (<i>p</i> -value)	Model 4 β (<i>p</i> -value)	Model 5 β (<i>p</i> -value)
Age (years)	0.338 (<0.001)	0.335 (<0.001)	0.332 (<0.001)	0.315 (<0.001)	0.299 (<0.001)
Body mass index [†] (kg/m ²)	-0.258 (<0.001)	-0.242 (<0.001)	-0.128 (<0.001)	-0.079 (0.040)	
Alcohol consumption [‡]	-0.114 (<0.001)	-0.097 (0.003)	-0.148 (<0.001)	-0.121 (<0.001)	-0.135 (<0.001)
Smoking status (never/past/light/heavy (%))	-0.080 (0.016)	-0.081 (0.015)	-0.055 (0.093)	-0.062 (0.055)	-0.065 (0.046)
Diastolic blood pressure (mmHg)		-0.985 (0.016)	-0.071 (0.041)	-0.052 (0.130)	-0.059 (0.086)
Antihypertensive medication (%)		0.046 (0.201)	0.024 (0.497)	0.035 (0.306)	0.040 (0.241)
Triglycerides (mg/dL)			-0.163 (<0.001)	-0.130 (<0.001)	-0.117 (0.002)
HDL cholesterol (mg/dL)			0.116 (0.002)	0.131 (<0.001)	0.125 (0.001)
LDL cholesterol (mg/dL)			-0.084 (0.011)	-0.075 (0.022)	-0.072 (0.027)
Antilipidemic medication (%)			-0.050 (0.110)	-0.048 (0.125)	-0.048 (0.119)
Fasting blood glucose (mg/dL)				-0.089 (0.007)	-0.048 (0.195)
Uric acid (mg/dL)				-0.059 (0.074)	-0.054 (0.099)
Serum alanine aminotransferase (mg/dL)				-0.078 (0.028)	-0.082 (0.017)
HOMA-IR [§]					-0.128 (0.002)
χ^2	0.242 (<0.001)	0.248 (<0.001)	0.306 (<0.001)	0.321 (<0.001)	0.326 (<0.001)

HMW, high molecular weight; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, Homeostasis of minimal assessment of insulin resistance. [†] Body mass index was calculated using weight in kilograms divided by the square of the height in meters. [‡] Alcohol consumption was measured using a Japanese liquor unit, in which 1 unit corresponds to 22.9 g ethanol (never drinkers, light drinkers (<1 unit/day), moderate drinkers (1–1.9 units/day), heavy drinkers (≥ 2 units/day)). [§] HOMA-IR was calculated using the following formula; fasting blood glucose (mg/dL) $\times$ immuno-reactive insulin (mU/mL)/405. Data for serum HMW adiponectin, triglycerides, serum alanine aminotransferase, and HOMA-IR were skewed, and log-transformed for analysis. β , standard coefficient.

Fig. 1. Multivariate-adjusted mean log serum HMW adiponectin of the subjects categorized by alcohol drinking status. HMW, high molecular weight. Data presented are the log-transformed mean (95% confidence interval) values. [‡]Alcohol consumption was measured using a Japanese liquor unit, in which 1 unit corresponds to 22.9 g ethanol (never-drinkers, light drinkers (<1 unit/day), moderate drinkers (1–1.9 units/day), heavy-drinkers (≥ 2 units/day)). Data for serum HMW adiponectin, triglycerides, and HOMA-IR are skewed and log-transformed for analysis. Multivariate-adjusted for significantly confounding factors of model 5 in multiple linear regression analysis of Table 4.

Table 5. Review of previous studies and the present study examining the association between adiponectin and alcohol consumption

Author, Year (Reference)	Participants	Study type	Adiponectin form	Type and amount of alcoholic beverage	Adjusted	Effect
Avogaro <i>et al.</i> 2003 (29)	22 volunteers	Case-control	Total form	Red wine Moderate consumption	None	No
Sierksma <i>et al.</i> 2004 (25)	23 men (52 ± 5 years)	Randomized, controlled, crossover	Total form	whisky 40 g ethanol/day (17 days)	None	Positive
Thamer <i>et al.</i> 2004 (10)	299 men 586 women	Cross-sectional population	Total form	No description 0–7 days/week	Percentage body fat	Positive
Shai <i>et al.</i> 2004 (11)	726 type 2 diabetic patients (mean: 65–67 years)	Cross-sectional	Total form	Bottle, beer, wine, or spirits 0–70 g/day	Multivariate	Positive
Yokoyama <i>et al.</i> 2004 (15)	738 Japanese men (30–65 years)	Cross-sectional	Total form	No description < 200 g/week (<i>n</i> = 615) or not (<i>n</i> = 123)	Multivariate	No
Stejskal <i>et al.</i> 2005 (30)	Liver steatosis 47 moderate drinkers (54 ± 11 years) 28 non-drinkers (59 ± 10 years)	Case-control	Total form	No description > 40 g ethanol/day	Body mass index	Positive
Pischon <i>et al.</i> 2005 (12)	532 men (65 ± 0.4 years)	Cross-sectional	Total form	Bottle, beer, wine, or spirits 0–> 30 g/day	Multivariate	Positive –Negative
Tsukinoki <i>et al.</i> 2005 (16)	202 Japanese male workers	Cross-sectional	Total form	No description	Multivariate	No
Ogge <i>et al.</i> 2006 (13)	64-years Caucasian women 209 with type 2 diabetes, 205 with IGT, and 186 with NGT	Cohort	Total form	Beer, wine, or spirits 0–> 30 g/day	Multivariate	Positive
Beulens <i>et al.</i> 2006 (26)	34 men with waist circumference ≥ 94 cm (35–70 years)	Randomized, controlled, crossover	Total form	Red wine 40 g ethanol/day (4 weeks)	None	Positive
Kotani <i>et al.</i> 2007 (14)	311 Japanese women (mean: 54 years)	Cross-sectional population	Total form	Japanese liquor 0–3 go/day	Multivariate	Positive
Kotani <i>et al.</i> 2007 (17)	109 Japanese men (55 ± 14 years)	Cross-sectional population	Total form	Japanese liquor 0–3 go/day	Multivariate	No
Beulens <i>et al.</i> 2007 (27)	19 men (18–40 years)	Randomized, controlled, crossover	HMW form	Whisky 32 g ethanol/day (4 weeks)	None	Positive
Beulens <i>et al.</i> 2008 (31)	20 men (18–25 years)	Case-control	Total form	Beer 40 g ethanol/day (3 weeks)	None	Positive
Joosten <i>et al.</i> 2008 (28)	36 postmenopausal women	Randomized, controlled, crossover	HMW form	White wine 25 g ethanol/day (6 weeks)	None	Positive
Imhof <i>et al.</i> 2009 (32)	72 volunteers (22–56 years)	Randomized, controlled, crossover	Total form	Ethanol solution, red wine or beer 30 g ethanol/day for men (3 weeks) 20 g ethanol/day for women (3 weeks)	None	Sex-specific positive depend on type of beverage
Kawamoto <i>et al.</i> (current study)	724 Japanese men (20–89 years)	Cross-sectional population	HMW form	Japanese liquor 0–> 45 g ethanol/day	Multivariate	Negative

IGT, impaired glucose tolerance; NGT, normal glucose tolerance; HMW, high molecular weight.

in subjects who consumed > 15 g alcohol/day than in those who consumed 5.0–14.9 g/day. Shai *et al.*¹¹⁾ found in a cross-sectional study of 726 type 2 diabetic men that each additional alcoholic drink per day was

independently associated with increased plasma adiponectin as well as increased HDL-C and decreased soluble tumor necrosis factor receptor-2, fibrinogen and soluble vascular adhesion molecule-1. In a commu-

nity-based cross-sectional study of 311 Japanese women with normal lifestyles and taking no medications, moderate alcohol consumption had a significant, independent, and positive effect on serum adiponectin levels¹⁴), although this relationship did not occur in 109 Japanese healthy men¹⁷). In 202 Japanese male workers at an annual health check, Tsukinoki *et al.*¹⁶) also showed that alcohol drinking was not associated with plasma adiponectin levels, and Yokoyama *et al.*¹⁵) showed in a cross-sectional study of 738 men that limiting ethanol consumption to <200 g/week was related to high serum adiponectin levels, but this relationship disappeared after adjustments. Moreover, a recent experimental study employing mice demonstrated that chronic intake of high amounts of alcohol, which leads to alcoholic liver disease, may decrease adiponectin concentrations³³). You *et al.* show that the development of alcoholic fatty liver, in those who consume excess alcohol, is associated with reduced circulating adiponectin levels, decreased hepatic adiponectin receptor expression, impaired hepatic adiponectin signaling, and elevated serum ALT, which is a marker of liver injury⁹). In our study, serum HMW adiponectin levels were significantly and negatively associated with serum ALT.

Thus far, the mechanisms that lead to decreased adiponectinemia in alcohol consumers are not completely understood. The mechanisms that underlie alcohol-induced reduction of adiponectin expression might be due to elevated levels of tumor necrotizing factor- α , which suppress adiponectin in adipose tissue through a paracrine or endocrine mechanism³⁴), and alcohol may also act directly on adipocytes and suppress adiponectin secretion³³). Furthermore, decreased serum HMW adiponectin may be associated with other non-traditional confounding factors not examined in this study. Excessive ethanol consumption of more than 20 g of ethanol per day is associated with an increased prevalence of metabolic syndrome¹⁵), and the metabolic syndrome group was shown to have significantly lower adiponectin levels than the non-metabolic syndrome group³⁵). Furthermore, the HMW form is the most active form and has better predictive power for insulin resistance and metabolic syndrome than the plasma total adiponectin level⁶⁻⁸). Wine is more strongly associated with adiponectin levels than beer or spirits¹¹). In our study, alcoholic beverages were likely to be sake, beer, or white liquor. Different types of alcoholic beverages may therefore have an effect on adiponectin levels.

Some limitations of this study must be considered. First, the response rate of 35% was as low as observations mostly done in other conventional com-

munity studies in Japan; however, the relatively large sample size enabled the assessment of an extensive array of alcohol drinking status in relation to serum HMW adiponectin. Second, the cross-sectional study design is limited in its ability to eliminate causal relationships between alcohol drinking status and serum HMW adiponectin. Third, a single assessment of serum HMW adiponectin levels may be susceptible to short-term variation and this may introduce a misclassification bias. Fourth, this study was performed in men only because there are few female drinkers in Japan, and subjects with a clinical history of diabetes were excluded; however, the results were changed also in the included analysis (data not shown). Fifth, this study, as well as other studies, relies on a self-reported drinking status, which may result in error and bias. Finally, the demographics and referral sources may limit the generalization of the results.

In conclusion, the present study showed that the alcohol drinking status was associated with decreased serum HMW adiponectin in community-dwelling Japanese men independent of traditional confounding factors, such as age, BMI, smoking status, lipids, serum ALT and HOMA-IR. For community-dwelling men, prospective population-based studies are needed to investigate the mechanisms underlying this association.

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