Clinica Chimica Acta 495 (2019) 94–99

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Relationships between alcohol intake and cardiovascular risk factors in middle-aged men with hypo-HDL cholesterolemia

Ichiro Wakabayashi

Department of Environmental and Preventive Medicine, Hyogo College of Medicine, Mukogawa-cho 1-1, Nishinomiya, Hyogo 663-8501, Japan

ARTICLE INFO

Keywords:
Alcohol
Cardiovascular disease
Hypo-HDL cholesterolemia
LDL cholesterol
Triglycerides

ABSTRACT

Background: Light-to-moderate alcohol drinking reduces the risk of ischemic heart disease, and this effect of alcohol is mainly explained by alcohol-induced elevation of HDL cholesterol. Hypo-HDL cholesterolemia is a potent risk factor for cardiovascular disease. The aim of this study was to clarify how alcohol relates to cardiovascular risk factors in men with hypo-HDL-cholesterolemia.

Methods: The subjects were middle-aged men with hypo-HDL cholesterolemia (< 40 mg/dl), and they were divided into four groups by daily alcohol consumption (non-; light, < 22 g ethanol/day; moderate, ≥22 g ethanol and < 44 g ethanol/day; heavy drinkers, ≥44 g ethanol/day). Each risk factor was compared among the groups after adjustment for age and histories of smoking and regular exercise.

Results: Systolic and diastolic blood pressure levels, log-transformed lipid accumulation product and log-transformed cardio-metabolic index were significantly higher in moderate and heavy drinkers than in nondrinkers. Log-transformed triglycerides and triglycerides-to-HDL cholesterol ratio were significantly higher in light, moderate and heavy drinkers than in nondrinkers and tended to be higher with an increase of alcohol intake. LDL cholesterol and LDL cholesterol-to-HDL cholesterol ratio were significantly lower in light, moderate and heavy drinkers than in nondrinkers and tended to be lower with an increase of alcohol intake. The above trends for the relationships of alcohol drinking with the cardiovascular risk factors were also found in multivariate logistic regression analysis.

Conclusions: In men with hypo-HDL cholesterolemia, alcohol drinking shows positive associations with blood pressure and triglycerides and an inverse association with LDL cholesterol.

1. Introduction

Light-to-moderate alcohol drinking is known to reduce the risk of cardiovascular disease, especially ischemic heart disease [1]. On the other hand, excessive drinking causes an increased risk of hemorrhagic types of stroke such as cerebral hemorrhage and subarachnoid hemorrhage [2]. The beneficial effect of alcohol on cardiovascular disease is mainly explained by alcohol-induced elevation of blood HDL cholesterol level [3,4], while its harmful effect is thought to be due to excessive drinking-induced hypertension [5,6] and hyper-triglyceridemia [7,8]. Thus, alcohol shows diverse effects on cardiovascular health depending on the degree of alcohol consumption.

Hypo-HDL cholesterolemia is a potent risk factor for atherosclerotic disease, especially ischemic heart disease. In a large US population of patients hospitalized with coronary artery disease, 54.6% of the patients showed low HDL cholesterolemia (< 40 mg/dl) [9]. Since alcohol has a potent HDL cholesterol-elevating action [3,4], drinkers with hypo-HDL cholesterolemia are thought to be insensitive to alcohol, at least regarding its effect on HDL cholesterol. However, it is unknown how other cardiovascular risk factors are influenced by alcohol in persons with hypo-HDL cholesterolemia. It would be interesting to determine whether habitual alcohol drinking, especially light-to-moderate drinking, has beneficial effects on cardiovascular health in persons with hypo-HDL cholesterolemia, as in a general population.

Lipid-related indices including the ratio of LDL cholesterol to HDL cholesterol (LDL-C/HDL-C ratio) [10], ratio of triglycerides to HDL cholesterol (TG/HDL-C ratio) [11,12], atherogenic index of plasma (AIP) [13], lipid accumulation product (LAP) [14] and cardio-metabolic index (CMI) [15] are useful for evaluating cardiovascular risk. HDL cholesterol is included in the components of LDL-C/HDL-C ratio, TG/HDL-C ratio, AIP, and CMI. Therefore, these indices must be higher in persons with hypo-HDL cholesterolemia than in persons with normo-HDL cholesterolemia. Alcohol is expected to affect not only HDL cholesterol but also other components of the lipid-related indices. However, it remains to be clarified how the lipid-related indices are modified by habitual alcohol drinking in persons with hypo-HDL cholesterolemia.

E-mail address: wakabaya@hyo-med.ac.jp.

https://doi.org/10.1016/j.cca.2019.04.006
Received 7 February 2019; Received in revised form 23 March 2019; Accepted 3 April 2019
Available online 04 April 2019

The purpose of this study was therefore to determine whether and how habitual alcohol intake is related to cardiovascular risk in men with hypo-HDL cholesterolemia. Relationships of alcohol intake with various cardiovascular risk factors, including lipid-related indices, were investigated by using multivariate analysis of covariance and logistic regression analysis.

2. Methods

2.1. Subjects

A cross-sectional study was performed using a local population-based database. The subjects in the original database of health checkups included 33,273 men, aged from 35 to 60 years, who had received periodic health checkup examinations at their workplaces in Yamagata Prefecture in Japan. The original database used in this study was a collection of the results of annual health checkup examinations performed from April 2005 to March 2006 for workers in a district of Japan. Subjects who were receiving treatment for any illness were requested to state the names of the diseases in a questionnaire at the health checkup.

In a questionnaire at the health checkup, each subject was required to identify any conditions for which he was receiving treatment. The questionnaire also surveyed the subjects' histories of alcohol consumption, cigarette smoking and habitual exercise. The subjects were divided into four groups based on average daily cigarette consumption (nonsmokers; light smokers, 20 or less cigarettes per day; heavy smokers, > 20 and < 41 cigarettes per day; very heavy smokers, 41 or more cigarettes per day). The frequency of habitual alcohol drinking was assessed using the following questionnaire item: “How frequently do you drink alcohol?”. The frequency of weekly alcohol drinking was categorized as “every day” (regular drinkers), “sometimes” (occasional drinkers) and “never” (nondrinkers). Only regular drinkers who answered “every day” were used as drinkers for analysis in this study since it was difficult to know the correct average alcohol consumption of occasional drinkers who answered “sometimes”. Subjects who exercised almost every day for 30 min or longer per day were defined as those with a habit of regular exercise.

From overall subjects in the original database, subjects showing hypo-HDL cholesterolemia (n = 3453) were selected. Hypo-HDL cholesterolemia was defined as an HDL cholesterol level of < 40 mg/dl [16]. The prevalence of hypo-HDL cholesterolemia in the overall subjects was 10.4%. Opportunistic drinkers (36.5%) were excluded, and then persons receiving medication therapy for dyslipidemia (5.8%), hypertension (13.5%) and/or diabetes (5.5%) (totally 19.7% of the nondrinker and regular drinker subjects) were excluded. Finally, 1760 men were enrolled as subjects for analysis in this study (Fig. 1). This study was approved by the Ethics Committee of Hyogo College of Medicine (No. 3003).

2.1.1. Classification of drinker groups

The average alcohol consumption of each subject per week was reported on questionnaires. Frequency of habitual alcohol drinking was asked in the questionnaire as “How frequently do you drink alcohol?”. Frequency of weekly alcohol drinking was categorized as “every day” (regular drinkers), “sometimes” (occasional drinkers) and “never” (nondrinkers). Only regular drinkers who answered “every day” were used as drinkers for analysis and were compared with nondrinkers in this study. Usual weekly alcohol consumption was recorded in terms of the equivalent number of “go”, a traditional Japanese unit of amount of sake (rice wine). The amounts of other alcoholic beverages, including beer, wine, whisky and shochu (traditional Japanese distilled spirit), were converted and expressed as units of “go”. One “go” contains about 22 g of ethanol, and average daily alcohol intake (grams of ethanol per day) was calculated. From the viewpoint of prevention of hypertension, it is generally accepted that alcohol intake should be reduced to < 20–30 g ethanol per day [17]. One “go” is within the above range of alcohol consumption recommended for prevention of hypertension. Thus, 22 g of ethanol per day was used as a cutoff for light drinkers. The subjects were divided into four groups according to ethanol consumption per day (nondrinkers; light drinkers: < 22 g of ethanol per day; moderate drinkers: ≥22 and < 44 g of ethanol per day; heavy drinkers: ≥44 g ethanol per day).

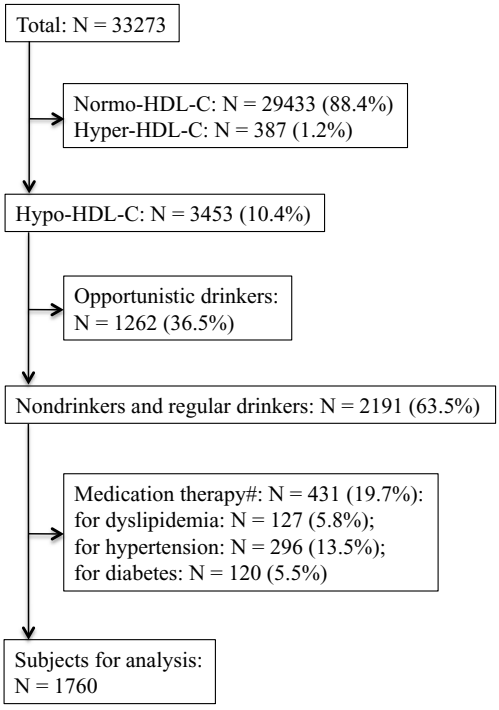

Fig. 1. Subjects of this study. Opportunistic drinkers and subjects receiving medication therapy for dyslipidemia, hypertension and/or diabetes were excluded from the subjects for analysis in this study. #, Medication therapy for dyslipidemia, hypertension and/or diabetes.

2.1.2. Measurements

Height and body weight were measured with the subjects wearing light clothes without a jacket or coat at the health checkup. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the navel level according to the recommendation of the definition of the Japanese Committee for the Diagnostic Criteria of Metabolic Syndrome [18]. The cut-off value of waist-to-height ratio used was 0.5 [19]. Blood pressure was measured by trained nurses, who were part of the local health-checkup company, with a mercury sphygmomanometer once on the day of the health checkup after each subject had rested quietly for at least 5 min in a sitting position. Korotkoff phase V was used to define diastolic pressure. Hypertension was defined as systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg.

Fasted blood was sampled from each subject in the morning, and serum triglyceride, HDL cholesterol and LDL cholesterol levels were measured by enzymatic methods using commercial kits, pureauto S TG-N, cholestest N-HDL and cholestest LDL (Sekisui Medical Co., Ltd., Tokyo, Japan), respectively. The coefficients of variation for the reproducibility of measurement were ≤3% for triglycerides, ≤5% for HDL cholesterol and ≤5% for LDL cholesterol. Triglyceride and HDL cholesterol levels were shown both in units of mg/dl and mmol/L. The cut-off values used for high triglycerides and high LDL cholesterol were 150 and 140 mg/dl, respectively, and the cut-off values used for high TG/HDL-C ratio and high LDL-C/HDL-C ratio were 3.75 and 3.5, respectively. AIP was determined by using levels of triglycerides (TG) and HDL cholesterol [13], and LAP was determined by using triglyceride

level and waist circumference (WC) [14]. CMI was calculated as the product of waist-to-height ratio and TG/HDL-C ratio [15]. The equations of AIP, LAP and CMI are as follows:

$$AIP = Log[TG\ (mmol/L)/HDL\text{–}C\ (mmol/L)]$$

$$LAP = TG\ (mmol/L) \times [WC\ (cm) - 65]$$

$$CMI = [TG\ (mg/dl)/HDL\text{–}C\ (mg/dl)] \times [WC\ (cm)/height\ (cm)]$$

The cut-off values of high LAP and high CMI were defined as 37.2 and 1.748, respectively, which have been reported to discriminate diabetes best in men [20,21]. Hemoglobin A1c was measured by the NGSP (National Glycohemoglobin Standardization Program)-approved technique using the latex cohesion method with a commercial kit (Determiner HbA1c, Kyowa Medex, Tokyo, Japan). The coefficient of variation for reproducibility of hemoglobin A1c measurement was ≤5%. Since the standards of hemoglobin A1c used for measurement are different in the NGSP method and JDS (the Japan Diabetes Society) method, hemoglobin A1c values were calibrated by using a formula proposed by JDS [22]: hemoglobin A1c (NGSP) (%) = 1.02 x hemoglobin A1c (JDS) (%) + 0.25%. Subjects with diabetes were defined as those showing hemoglobin A1c levels of ≥6.5%, according to the criteria for diagnosis of diabetes by the American Diabetes Association [23].

2.2. Statistical analysis

Statistical analyses were performed using a computer software program (SPSS version 22.0 J for Windows, IBM, Chicago IL, USA). Categorical variables were compared between each group pair using the chi-square test for independence. For continuous variables, means of each variable were compared among the alcohol intake groups by using analysis of variance (ANOVA) followed by the Scheffé's F-test as a post-hoc test in univariate analysis and by using analysis of covariance (ANCOVA) followed by the Student's *t*-test after Bonferroni correction in multivariate analysis. Since triglycerides, TG/HDL-C ratio, LAP and CMI did not show a normal distribution, they were compared non-parametrically by using the Kruskal-Wallis test followed by the Steel-Dwass test as a post-hoc test in univariate analysis or were used after log-transformation in multivariate analysis. Subjects showing waist circumference of 65 cm or smaller ($n = 3$) were excluded from subjects in analysis using ANCOVA for LAP because their values for log-transformation were zero or less than zero, and thus log-transformed LAP could not be calculated. In logistic regression analysis, odds ratios of each drinker group vs. the nondrinker group for each risk factor (high waist-to-height ratio, hypertension, hypertriglyceridemia, hyper-LDL-cholesterolemia, high LDL-C/HDL-C ratio, high TG/HDL-C ratio, high LAP, high CMI or diabetes) were estimated. Age and habits of smoking and regular exercise were adjusted in ANCOVA and logistic regression analysis. In addition, BMI was added to the explanatory variables in analysis for the risk factors not including waist circumference. All *p* values are 2-sided and values of $p < .05$ were considered to indicate statistical significance.

3. Results

3.1. Characteristics of subjects

Table 1 shows characteristics of subjects classified by alcohol intake. The percentage of smokers was high in overall subjects (72.7%), and there was no significant difference in the percentages of smokers in the four groups of alcohol intake. Waist circumferences and waist-to-height ratios in light, moderate and heavy drinkers were not significantly different from those in nondrinkers. Systolic and diastolic blood pressure levels were significantly higher in moderate and heavy drinkers than in nondrinkers. Triglycerides, TG/HDL-C ratio and AIP were higher in light, moderate and heavy drinkers than in nondrinkers and tended to be higher with an increase of alcohol intake. LDL cholesterol level and LDL-C/HDL-C ratio were significantly lower in light, moderate and heavy drinkers than in nondrinkers and tended to be lower with an increase of alcohol intake. LAP and CMI were significantly higher in moderate and heavy drinkers than in nondrinkers. HDL cholesterol and hemoglobin A1c were slightly but significantly higher and lower, respectively, in moderate drinkers than in nondrinkers, while these variables in light and heavy drinkers were not significantly different from those in nondrinkers.

Table 1
Characteristics of overall subjects and non-, light, moderate and heavy drinker groups in men with hypo-HDL cholesterolemia.

Variable	Overall	Nondrinkers	Light drinkers	Moderate drinkers	Heavy drinkers
Number	1760	974	153	429	204
Age (years)	47.3 ± 7.5	46.7 ± 7.7	46.6 ± 7.5	48.4 ± 7.0**	48.1 ± 7.0
Smokers (%)	72.7	72.7	71.2	72.0	75.0
Regular exercise (%)	7.6	6.4	8.5	8.9	9.8
Body mass index (kg/m^2)	25.3 ± 3.5	25.6 ± 3.8*	24.7 ± 2.6	25.1 ± 2.9	25.0 ± 3.2
Waist circumference (cm)	88.2 ± 8.7	88.5 ± 9.5	86.8 ± 6.5	88.0 ± 7.4	88.3 ± 8.3
Waist-to-height ratio	0.519 ± 0.049	0.522 ± 0.054	0.512 ± 0.037	0.517 ± 0.043	0.516 ± 0.045
Systolic blood pressure (mm Hg)	129.8 ± 16.7	128.0 ± 17.0	128.6 ± 15.6	132.6 ± 15.9**	133.9 ± 15.7**
Diastolic blood pressure (mm Hg)	79.2 ± 12.0	77.8 ± 12.2	78.9 ± 11.5	81.0 ± 11.5**	82.1 ± 11.1**
Triglycerides (mg/dl)	227 (151, 339)	204 (135, 294)	229 (158, 330)*	253 (168, 405)**	315 (194, 509)**
Triglycerides (mmol/L)	2.56 (1.70, 3.83)	2.30 (1.52, 3.32)	2.58 (1.78, 3.72)**	2.86 (1.90, 4.57)**	3.56 (2.19, 5.74)**
LDL-C (mg/dl)	116.6 ± 33.6	125.5 ± 30.7	112.3 ± 30.0**	107.3 ± 33.1**	97.1 ± 36.0**
HDL-C (mg/dl)	35.3 ± 3.4	35.1 ± 3.4	35.7 ± 2.9	35.8 ± 3.2*	35.2 ± 4.0
HDL-C (mmol/L)	0.913 ± 0.088	0.908 ± 0.089	0.923 ± 0.075	0.925 ± 0.083*	0.910 ± 0.103
LDL-C/HDL-C ratio	3.32 ± 0.96	3.60 ± 0.89	3.15 ± 0.82**	3.01 ± 0.92**	2.76 ± 1.02**
TG/HDL-C ratio	6.33 (4.19, 9.83)	5.74 (3.77, 8.58)	6.16 (4.32, 9.85)	7.18 (4.57, 11.31)**	8.77 (5.65, 13.98)**
AIP	0.455 ± 0.292	0.397 ± 0.263	0.462 ± 0.275	0.514 ± 0.297**	0.605 ± 0.348**
LAP	58.0 (34.1, 96.7)	52.0 (29.9, 84.4)	54.5 (33.2, 92.4)	69.1 (41.0, 106.1)**	80.8 (44.6, 133.0)**
CMI	3.31 (2.12, 5.23)	3.03 (1.90, 4.55)	3.19 (2.18, 5.15)	3.76 (2.38, 6.05)**	4.51 (2.87, 7.33)**
Hemoglobin A1c (%)	5.56 ± 0.77	5.61 ± 0.80	5.48 ± 0.73	5.47 ± 0.63*	5.54 ± 0.87

Shown are numbers, means with standard deviations, and medians with 25 and 75 percentile values of each variable. TG, triglycerides; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; AIP, atherogenic index of plasma; LAP, lipid accumulation product; CMI, cardio-metabolic index. Asterisks denote significant differences from nondrinkers

* $p < .05$.

** $p < .01$.

Table 2
Comparison of the mean levels of each risk factor in non-, light, moderate and heavy drinkers.

Risk factor	Nondrinkers	Light drinkers	Moderate drinkers	Heavy drinkers
Waist circumference (cm)	88.4 ± 0.3	86.7 ± 0.7	88.2 ± 0.4	88.4 ± 0.6
Waist-to-height ratio	0.522 ± 0.002	0.512 ± 0.004	0.517 ± 0.002	0.516 ± 0.003
Systolic blood pressure (mm Hg)	127.7 ± 0.5	129.7 ± 1.2	132.5 ± 0.7**	134.4 ± 1.1**
Diastolic blood pressure (mm Hg)	77.5 ± 0.3	79.7 ± 0.9	81.1 ± 0.5**	82.6 ± 0.8**
Log(triglycerides[mg/dl])	2.30 ± 0.01	2.39 ± 0.02**	2.43 ± 0.01**	2.51 ± 0.02**
Log(triglycerides[mmol/L])	0.349 ± 0.009	0.438 ± 0.022**	0.481 ± 0.013**	0.560 ± 0.019**
LDL cholesterol (mg/dl)	124.8 ± 1.0	114.2 ± 2.5**	108.1 ± 1.5**	97.2 ± 2.2**
HDL cholesterol (mg/dl)	35.1 ± 0.1	35.6 ± 0.3	35.7 ± 0.1**	35.3 ± 0.2
HDL cholesterol (mmol/L)	0.908 ± 0.003	0.921 ± 0.007	0.924 ± 0.004**	0.912 ± 0.006
LDL-C/HDL-C ratio	3.58 ± 0.03	3.21 ± 0.07**	3.30 ± 0.04**	2.76 ± 0.06**
Log(TG/HDL-C ratio)	0.754 ± 0.009	0.835 ± 0.023**	0.877 ± 0.014**	0.963 ± 0.020**
AIP	0.393 ± 0.009	0.475 ± 0.023**	0.517 ± 0.014**	0.604 ± 0.020**
Log(LAP)	1.68 ± 0.01	1.75 ± 0.03	1.82 ± 0.02**	1.89 ± 0.03**
Log(CMI)	0.472 ± 0.009	0.535 ± 0.024	0.587 ± 0.014**	0.671 ± 0.021**
Hemoglobin A1c (%)	5.60 ± 0.02	5.53 ± 0.06	5.47 ± 0.04*	5.53 ± 0.05

Shown are means with standard errors of each variable after adjustment for age and histories of smoking and regular exercise in ANCOVA. BMI was also added as an explanatory variable in the analysis for risk factors except for waist-to-height ratio, LAP and CMI. TG, triglycerides; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; Log(TG/HDL-C ratio), Log(TG[mg/dl]/HDL-C[mg/dl] ratio); AIP, atherogenic index of plasma; LAP, lipid accumulation product; CMI, cardio-metabolic index. Asterisks denote significant differences from nondrinkers

* $p < .05$.

** $p < .01$.

3.2. Comparison of the mean levels of each cardiovascular risk factor in the groups classified by alcohol intake

Mean levels of each cardiovascular risk factor were compared by multivariate analysis of covariance (Table 2). Waist circumferences and waist-to-height ratios in light, moderate and heavy drinkers were not significantly different from those in nondrinkers. Systolic and diastolic blood pressure levels were significantly higher in moderate and heavy drinkers than in nondrinkers and tended to be higher with an increase of alcohol intake. Log-transformed triglycerides, log-transformed TG/HDL-C ratio and AIP were significantly higher in light, moderate and heavy drinkers than in nondrinkers and tended to be higher with an increase of alcohol intake. LDL cholesterol and LDL-C/HDL-C ratio were significantly lower in light, moderate and heavy drinkers than in nondrinkers and tended to be lower with an increase of alcohol intake. LAP and CMI were significantly higher in moderate and heavy drinkers than in nondrinkers and tended to be higher with an increase of alcohol intake. HDL cholesterol and hemoglobin A1c were slightly but significantly higher and lower, respectively, in moderate drinkers than in nondrinkers, but these variables in light and heavy drinkers were not significantly different from those in nondrinkers. The results for triglycerides and HDL cholesterol in a unit of mmol/L were similar to the results for triglycerides and HDL cholesterol in a unit of mg/dl.

3.3. Comparison of the prevalences of each cardiovascular risk factor in the groups classified by alcohol intake

Table 3 shows the prevalences of each risk factor in non-, light, moderate and heavy drinkers and in overall subjects. The prevalences of hypertension, hyper-triglyceridemia, high TG/HDL-C ratio, high LAP and high CMI were significantly higher in moderate and heavy drinkers than in nondrinkers. The prevalences of hyper-LDL cholesterolemia and high LDL-C/HDL-C ratio were significantly lower in light, moderate and heavy drinkers than in nondrinkers. The prevalences of high waist-to-height ratio and diabetes were not significantly different in the three drinker groups and the nondrinker group.

3.4. Odds ratios for each risk factor of light, moderate and heavy drinkers vs. nondrinkers

Table 4 shows results of multivariate logistic regression analysis for relationships of different degrees of alcohol intake with each cardiovascular risk factor. Odds ratios of moderate and heavy drinkers vs. nondrinkers for hypertension, high LAP and high CMI were significantly higher than the reference level of 1.00. Odds ratios of light, moderate and heavy drinkers vs. nondrinkers for hyper-triglyceridemia and high TG/HDL-C ratio were significantly higher than the reference

Table 3
Comparison of the prevalences of each risk factor in light, moderate and heavy drinkers vs. nondrinkers.

Risk factor	Overall	Nondrinkers	Light drinkers	Moderate drinkers	Heavy drinkers
High waist-to-height ratio	65.2	65.2	57.5	67.1	66.7
Hypertension	30.3	26.1	26.1	37.5**	38.2**
Hyper-triglyceridemia	75.5	70.3	76.5	81.6**	86.3**
Hyper-LDL cholesterolemia	23.4	30.8	13.1**	15.6**	12.3**
High LDL-C/HDL-C ratio	41.1	53.3	28.1**	28.2**	20.1**
High TG/HDL-C ratio	79.7	75.2	81.0	85.1**	88.7**
High LAP	71.7	65.9	71.2	78.6**	85.3**
High CMI	83.1	79.4	84.3	87.4**	91.2**
Diabetes	5.6	6.3	2.6	4.4	6.9

Prevalence of each risk factor is shown. Asterisks denote significant differences from nondrinkers.

** $p < .01$.

Table 4
Odds ratios for each risk factor of light, moderate and heavy drinkers vs. nondrinkers.

Risk factor	Nondrinkers	Light drinkers	Moderate drinkers	Heavy drinkers
High waist-to-height ratio	1.00	0.72 (0.51–1.02)	1.06 (0.83–1.35)	1.06 (0.77–1.46)
Hypertension	1.00	1.24 (0.83–1.87)	1.91 (1.47–2.48)**	2.05 (1.46–2.88)**
Hyper-triglyceridemia	1.00	1.59 (1.06–2.39)*	1.97 (1.48–2.63)**	2.77 (1.80–4.27)**
Hyper-LDL cholesterolemia	1.00	0.37 (0.23–0.61)**	0.44 (0.33–0.60)**	0.31 (0.12–0.49)**
High LDL-C/HDL-C ratio	1.00	0.38 (0.26–0.56)**	0.35 (0.27–0.45)**	0.20 (0.14–0.29)**
High TG/HDL-C ratio	1.00	1.64 (1.06–2.54)*	1.99 (1.46–2.71)**	2.73 (1.71–4.36)**
High LAP	1.00	1.29 (0.89–1.88)	1.92 (1.47–2.51)**	2.95 (1.96–4.46)**
High CMI	1.00	1.42 (0.90–2.26)	1.79 (1.29–2.48)**	2.56 (1.53–4.26)**
Diabetes	1.00	0.55 (0.19–1.55)	0.77 (0.45–1.33)	1.19 (0.64–2.23)

Shown are odds ratios for each risk factor of each drinker group vs. the nondrinker group estimated after adjustment for age and histories of smoking and regular exercise. BMI was also added as an explanatory variable in the logistic regression analysis for risk factors except for high waist-to-height ratio, high LAP and high CMI. Asterisks denote significant differences from the reference level of 1.00.

* $p < .05$.

** $p < .01$.

level and tended to be higher with an increase of alcohol intake. Odds ratios of light, moderate and heavy drinkers vs. nondrinkers for hyper-LDL cholesterolemia and high LDL-C/HDL-C ratio were significantly lower than the reference level. Odds ratios for high waist-to-height ratio and diabetes of any drinker groups vs. the nondrinker group were not significantly different from the reference level.

4. Discussion

In this study, the associations between habitual alcohol intake and cardiovascular risk factors were, for the first time, demonstrated in persons with hypo-HDL cholesterolemia. There were dose-dependent positive associations of alcohol intake with blood pressure and triglycerides, while a dose-dependent inverse association was found between alcohol intake and LDL cholesterol. Since a J-shaped association between alcohol intake and triglycerides has been shown in a general population [8], light drinking is suggested to have opposite effects on triglycerides in men with and men without hypo-HDL cholesterolemia.

Regarding the mechanisms for alcohol-induced hyper-triglyceridemia, alcohol inhibits lipoprotein lipase activity, resulting in postprandial hyper-triglyceridemia, and increases synthesis of large VLDL particles in the liver [7]. However, the reason for the decrease in triglyceride levels caused by habitual low alcohol consumption in a general population remains to be clarified. It is also not known why the association between light drinking and triglyceride levels was different in men with and men without hypo-HDL cholesterolemia. Triglyceride levels are usually reciprocally related to HDL cholesterol levels [24]. In fact, as shown in Tables 1 and 3, the median triglyceride level was much higher than its cutoff value (227 mg/dl vs. 150 mg/dl) and three fourths of the subjects showed high triglyceride levels (≥ 150 mg/dl) in the subjects of the present study. Thus, alteration in metabolism of triglycerides in persons with hypo-HDL cholesterolemia might be related to the above difference in the association between light drinking and triglyceride levels.

In the present study, there were linear positive associations of alcohol intake with TG/HDL-C ratio, AIP, LAP and CMI, which reflect triglyceride levels. Since no apparent associations of alcohol intake with HDL cholesterol, waist circumference and waist-to-height ratio were found in the present study, the differences in the lipid-related indices in drinkers and nondrinkers were attributable to theirdifference in triglycerides. The associations between alcohol and the lipid-related indices found in this study are also different from previously reported findings in a general population: TG-HDL-C ratio, LAP and CMI were lower in light drinkers than in nondrinkers in a general population [25–27]. The above differences in the relations of alcohol with the lipid-related indices can be mainly explained by the aforementioned difference in the relation of alcohol with triglycerides in men with and men without hypo-HDL cholesterolemia: triglycerides were higher in light drinkers than in nondrinkers in men with hypo-HDL cholesterolemia, while triglycerides were lower in light drinkers than in nondrinkers in a general population [8].

Drinkers who show hypo-HDL cholesterolemia are thought to be less sensitive to the HDL cholesterol-elevating effect of alcohol than drinkers without hypo-HDL cholesterolemia. Moreover, the present study demonstrated that in men with hypo-HDL cholesterolemia, triglycerides and related indices such as TG/HDL-C ratio, AIP, LAP and CMI were higher in light drinkers than in nondrinkers. Thus, the results suggest that the beneficial (HDL cholesterol-lowering) and harmful (triglycerides-elevating) effects of alcohol on cardiovascular risk are smaller and greater, respectively, in men with hypo-HDL cholesterolemia than in men with normo-HDL cholesterolemia. Therefore, even light drinking, which is believed to be generally beneficial for cardiovascular health, should be avoided in men with hypo-HDL cholesterolemia.

There are limitations of this study. Although the number of subjects in the original database was large, the prevalence of hypo-HDL choelsterolemia was low (10.4%), and after further exclusion of opportunistic drinkers and subjects receiving medication therapy for dyslipidemia, hypertension and diabetes, the number of subjects for analysis was not large enough for more detailed analysis using stratified subgroups of subjects, e.g., nonsmokers and smokers. Polymorphism of genes for alcohol-metabolizing enzymes, especially aldehyde dehydrogense 2, is known to determine the sensitivity to alcohol in Asians [28,29]. The subjects of this study were men with hypo-HDL cholesterolemia and might thus be less sensitive to alcohol than men with normo- or hyper-HDL cholesterolemia since alcohol has a potent HDL cholesterol-elevating action. However, no information on the above polymorphism was included in the database used in this study. Consuming a light-to-moderate amount of red wine has been shown to be more beneficial for cardiovascular health than beer or a spirit, and this beneficial effect of red wine is mainly explained by the antioxidant action of compounds such as polyphenols contained in red wine [30]. It would be interesting to elucidate in future studies whether the antioxidant action of red wine on LDL is similar in persons with normo-HDL cholesterolemia and persons with hypo-HDL cholesterolemia. On the other hand, the blood pressure-elevating action of alcohol has been shown to be independent of the type of alcoholic beverage [31]. It was also shown that there was no clear relationship between type of alcoholic beverage and triglyceride level [32]. The association between alcohol drinking and metabolic syndrome was also reported to be independent of the type of beverage consumed [33]. Thus, the difference in alcoholic beverages may not affect the associations of alcohol intake with blood pressure and triglyceride levels in men with hypo-HDL cholesterolemia, although information on the type of alcoholic beverage was not available in the present study. Finally, since the design of this study is cross-sectional, further prospective studies are needed to clarify causality of the relation of alcohol to cardiovascular risk in hypo-HDL cholesterolemic men.

In conclusion, in men with hypo-HDL cholesterolemia, alcohol intake shows dose-dependent positive associations with blood pressure and triglycerides and shows a dose-dependent inverse association with LDL cholesterol, resulting in lower LDL-C/HDL-C ratio and higher TG/HDL-C ratio, AIP, LAP and CMI in drinkers than in nondrinkers. The detrimental effect of habitual alcohol intake on cardiovascular health may be stronger in persons with hypo-HDL cholesterolemia than in persons with normo-HDL cholesterolemia.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research (No. 17H02184) from the Japan Society for the Promotion of Science.

References

[1] G. Corrao, L. Rubbiati, V. Bagnardi, A. Zambon, K. Poikolainen, Alcohol and coronary heart disease: a meta-analysis, Addiction 95 (2000) 1505–1523.
[2] K. Reynolds, B. Lewis, J.D. Nolen, G.L. Kinney, B. Sathya, J. He, Alcohol consumption and risk of stroke: a meta-analysis, JAMA 289 (2003) 579–588.
[3] D.P. Agarwal, Cardioprotective effects of light-moderate consumption of alcohol: a review of putative mechanisms, Alcohol Alcohol. 37 (2002) 409–415.
[4] E.B. Rimm, P. Williams, K. Fosher, M. Criqui, M.J. Stampfer, Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors, BMJ 319 (1999) 1523–1528.
[5] A.L. Klatsky, Alcohol and cardiovascular disease—more than one paradox to consider. Alcohol and hypertension: does it matter? Yes, J. Cardiovasc. Risk 10 (2003) 21–24.
[6] B. Taylor, H.M. Irving, D. Baliunas, M. Roerecke, J. Patra, S. Mohapatra, J. Rehm, Alcohol and hypertension: gender differences in dose-response relationships determined through systematic review and meta-analysis, Addiction 104 (2009) 1981–1990.
[7] A. Van de Wiel, The effect of alcohol on postprandial and fasting triglycerides, Int. J. Vasc. Med. 862504 (2012), https://doi.org/10.1155/2012/862504.
[8] B. Klop, A.T. do Rego, M.C. Cabezas, Alcohol and plasma triglycerides, Curr. Opin. Lipidol. 24 (2013) 321–326.
[9] A. Sachdeva, C.P. Cannon, P.C. Deedwania, K.A. LaBresh, S.C. Smith Jr., D. Dai, A. Hernandez, G.C. Fonarow, Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines, Am. Heart J. 157 (2009) 111–117.
[10] W.B. Kannel, Lipids, diabetes, and coronary heart disease: insights from the Framingham Study, Am. Heart J. 110 (1985) 1100–1107.
[11] J. Jeppesen, H.O. Hein, P. Suadicani, F. Gyntelberg, Relation of high TG-low HDL cholesterol and LDL cholesterol to the incidence of ischemic heart disease. An 8-year follow-up in the Copenhagen Male Study, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 1114–1120.
[12] J.M. Gaziano, C.H. Hennekens, C.J. O'Donnell, J.L. Breslow, J.E. Buring, Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction, Circulation 96 (1997) 2520–2525.
[13] V. Soška, J. Jarkovský, B. Ravčuková, L. Tichý, L. Fajkusová, T. Freiberger, The logarithm of the triglyceride/HDL-cholesterol ratio is related to the history of cardiovascular disease in patients with familial hypercholesterolemia, Clin. Biochem. 45 (2012) 96–100.
[14] H.S. Kahn, The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison, BMC Cardiovasc. Disord. 5 (2005) 26, , https://doi.org/10.1186/1471-2261-5-26.
[15] I. Wakabayashi, Y. Sotoda, S. Hirooka, H. Orita, Association between cardiometabolic index and atherosclerotic progression in patients with peripheral arterial disease, Clin. Chim. Acta 446 (2015) 231–236.
[16] K.G. Alberti, R.H. Eckel, S.M. Grundy, et al., International diabetes federation task force on epidemiology and prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity, Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity, Circulation 120 (2009) 1640–1645.
[17] G. Mancia, R. Fagard, K. Narkiewicz, et al., ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), Eur. Heart J. 34 (2013) 2159–2219.
[18] Anonymous, Metabolic syndrome-definition and diagnostic criteria in Japan, J. Jpn. Soc. Int. Med. 94 (2005) 794–809 (in Japanese).
[19] S.D. Hsieh, T. Muto, Metabolic syndrome in Japanese men and women with special reference to the anthropometric criteria for the assessment of obesity: proposal to use the waist-to-height ratio, Prev. Med. 42 (2006) 135–139.
[20] I. Wakabayashi, T. Daimon, A strong association between lipid accumulation product and diabetes mellitus in Japanese women and men, J. Atheroscler. Thromb. 21 (2014) 282–288.
[21] I. Wakabayashi, T. Daimon, The "cardiometabolic index" as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus, Clin. Chim. Acta 438 (2015) 274–278.
[22] A. Kashiwagi, M. Kasuga, E. Araki, et al., Committee on the Standardization of Diabetes Mellitus-Related Laboratory Testing of Japan Diabetes Society, International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values, J. Diabetes Investig. 3 (2012) 39–40.
[23] Anonymous; American Diabetes Association, Diagnosis and classification of diabetes mellitus, Diabetes Care 33 (Suppl. 1) (2010) S62–S69.
[24] M.C. Mahaney, J. Blangero, A.G. Comuzzie, J.L. VandeBerg, M.P. Stern, J.W. MacCluer, Plasma HDL cholesterol, triglycerides, and adiposity. A quantitative genetic test of the conjoint trait hypothesis in the San Antonio Family Heart Study, Circulation 92 (1995) 3240–3248.
[25] I. Wakabayashi, Inverse association between triglycerides-to-HDL-cholesterol ratio and alcohol drinking in middle-aged Japanese men, J. Stud. Alcohol Drugs 73 (2012) 998–1004.
[26] I. Wakabayashi, Relationship between alcohol intake and lipid accumulation product in middle-aged men, Alcohol Alcohol. 48 (2013) 535–542.
[27] I. Wakabayashi, A U-shaped relationship between alcohol consumption and cardiometabolic index in middle-aged men, Lipids Health Dis. 15 (2016) 50, , https://doi.org/10.1186/s12944-016-0217-4.
[28] Y. Mizoi, Y. Tatsuno, J. Adachi, M. Kogame, T. Fukunaga, S. Fujiwara, S. Hishida, I. Ijiri, Alcohol sensitivity related to polymorphism of alcohol-metabolizing enzymes in Japanese, Pharmacol. Biochem. Behav. 18 (Suppl. 1) (1983) 127–133.
[29] R.F. Suddendorf, Research on alcohol metabolism among Asians and its implications for understanding causes of alcoholism, Public Health Rep. 104 (1989) 615–620.
[30] L.H. Opie, S. Lecour, The red wine hypothesis: from concepts to protective signalling molecules, Eur. Heart J. 28 (2007) 1683–1693.
[31] A.L. Klatsky, Alcohol-associated hypertension: when one drinks makes a difference, Hypertension 44 (2004) 805–806.
[32] G. Chiva-Blanch, S. Arranz, R.M. Lamuela-Raventos, R. Estruch, Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: evidences from human studies, Alcohol Alcohol. 48 (2013) 270–277.
[33] L. Djoussé, D.K. Arnett, J.H. Eckfeldt, M.A. Province, M.R. Singer, R.C. Ellison, Alcohol consumption and metabolic syndrome: does the type of beverage matter? Obes. Res. 12 (2004) 1375–1385.