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Association of visceral adiposity with hypertension, dyslipidemia, and type 2 diabetes: a cross-sectional study among Japanese men and women

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Objective: Cross-sectional evaluations were used to assess the association of visceral adiposity, measured by computed tomography (CT), with the prevalence of hypertension, dyslipidemia, and type 2 diabetes in Japanese people.
Methods: The visceral fat area (VFA) of each Japanese participant (n = 2,445, mean age 56.7 years) was measured at the umbilicus level using abdominal CT. Participants were divided into low, moderate, and high tertile VFA groups. Multivariate logistic regression analyses were used to examine the association between tertile groups and the diagnosis of hypertension, dyslipidemia, or type 2 diabetes. Multiple linear regression analysis was used to examine the relationship between VFA and systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c).
Results: Multivariate logistic regression analyses showed that the high VFA group had a significantly higher odds ratio (OR) compared with the low VFA group with respect to hypertension (OR: 4.37, 95% confidence interval; 3.28-5.80 for men; 5.92, 4.09-8.58 for women), dyslipidemia (5.78, 4.08-8.18 for men; 6.76, 4.07-11.24 for women), and type 2 diabetes (3.55, 2.38-5.27 for men; 8.85, 4.12-19.00 for women). Multiple linear regression analyses showed that VFA was significantly associated with SBP, DBP, TG, HDL-C, FPG, and HbA1c.
Conclusion: VFA was significantly associated with hypertension, dyslipidemia, and type 2 diabetes in the Japanese participants of this study.

Key words: visceral adiposity, hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome

Introduction

Obesity is often complicated by arteriosclerotic diseases, such as ischemic heart disease and stroke, as well as their risk factors, including hypertension, dyslipidemia, and type 2 diabetes.[1,2] Recent reports described that the incidence of cardiovascular diseases is high even in nonobese individuals with a body mass index (BMI) within the normal range who have an accumulation of visceral fat and visceral adiposity.[3,4] It has been reported that visceral adiposity is a better index for developments of cardiovascular diseases compared with other indexes such as regional or generalized obesity.[3,5,6]

Furthermore, several reports described that visceral adiposity, as determined directly by computed tomography (CT), was associated with hypertension, dyslipidemia, and type 2 diabetes. Hayashi et al.[7] reported that visceral adiposity was positively associated with the prevalence of hypertension among Japanese Americans by multiple logistic regression analysis and that the association was independent of fasting plasma insulin, even though the expanded visceral fat promotes insulin resistance. Boyko et al.[5] showed that greater visceral adiposity preceded the development of type 2 diabetes in Japanese Americans. Anjana et al.[8] reported that visceral fat had a strong positive association with type 2 diabetes in the case control study among Asian Indians. Taniguchi et al.[9] showed that visceral fat was positively correlated with triglyceride (TG) levels in nonobese type 2 diabetes Japanese patients.

Of late, the metabolic syndrome has become a major

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public health concern among many Japanese people. Studies on Japanese populations living in Japan have reported that visceral adiposity was associated with hypertension, type 2 diabetes, and dyslipidemia in the metabolic syndrome.[10,11] However, Oka et al.[12] described that previous studies for the relationships between visceral fat area (VFA) and hypertension, dyslipidemia, and type 2 diabetes with sufficiently large sample populations had mainly been confined to Caucasians or Japanese Americans, and there were not many studies for Japanese. Oka et al.'s study[12] was a relatively large sample size, but some previous studies were small sample sizes. We secured a data set with sufficiently large sample size including the VFA determined by CT, blood pressure, and laboratory data for blood samples from the participants who were receiving periodical medical check-ups. It is still worthwhile to evaluate the association between the VFA determined by CT and hypertension, dyslipidemia, or type 2 diabetes in large sample Japanese populations. Furthermore, Ito et al.[13] pointed out the importance of involvement of lifestyle-related factors for examination of the causes of obesity. For the relationships between VFA and hypertension, type 2 diabetes, or dyslipidemia, it is necessary to adjust lifestyle factors, such as exercise, smoking, and drinking. Our data set also contained the data for lifestyle factors, such as exercise, smoking, and drinking. Therefore, it was possible to examine the relationships between VFA and hypertension, type 2 diabetes, or dyslipidemia with the adjustment of lifestyle factors. It is of interest to confirm whether or not lifestyle factors affect the values of blood pressure and laboratory data.

In the present study, we aimed to evaluate the relationship between VFA determined by CT and hypertension, dyslipidemia, and type 2 diabetes in a large Japanese population, adjusted by age and lifestyle factors (exercise, drinking, and smoking). In addition, the effects of lifestyle factors on blood pressure and laboratory data were also evaluated.

Methods

Participants

The participants consisted of 1,479 men and 966 women, who were receiving periodical medical check-ups in a medical check-up center located in the Chubu region of Japan. The protocol for the present study was approved by the Kitasato University Ethics Committee. Written informed consent was obtained from all participants. All evaluations were performed at this center.

Measurement methods

Abdominal VFA was determined by CT (Aquilion 16; Toshiba Medical Systems Corp., Ohtawara) at the level of the umbilicus followed by the method described in previous studies.[14,15] Abdominal cross-sectional images was traced using a trackball; the total cross-sectional area with a CT number from -200 to 1,000 Hounsfield units (HU) was determined using automatic calculation of portions using the method of Grauer et al.[16] Then, areas with a CT number from -200 to -10 HU were determined as adipose tissues. The total areas of adipose tissues were calculated automatically by using Virtual Place WS-series software; AZE, Tokyo.

For all participants, height, body weight, and blood pressure were measured. Height and body weight were measured, respectively, at increments of 0.1 cm and 0.1 kg at the conditions that subjects lightly dressed and their shoes were removed. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured twice consecutively on the upper arm using an automated sphygmomanometer (H-55; Terumo Corp., Tokyo) in a seated resting position. The mean values of two determined values of SBP or DBP were calculated respectively.

Blood samples were taken after fasting for 8 hours or longer after their prior meal. Blood samples were used for determining high-density lipoprotein cholesterol (HDL-c), TG, fasting plasma glucose (FPG), and hemoglobin A1c (HbA1c). For this study, HDL-c was determined using enzymatic method, TG was determined using enzymatic colorimetric method, FPG was determined using the glucose oxidase immobilized oxygen electrode maximum reaction acceleration method, and HbA1c was determined using the enzyme immunoassay method by using automatic Toshiba Clinical Analyzer TBA-120FR (Toshiba Medical Systems Corp.).

Diagnostic criteria for cardiovascular disease risk factors

Hypertension was defined as having a SBP ≥ 140 mmHg, having a DBP ≥ 90 mmHg based on the Japanese Society of Hypertension,[17] or taking antihypertensive medications. Dyslipidemia was defined as having a TG ≥ 150 mg/dl, having a HDL-c < 40 mg/dl based on Japan Atherosclerosis Society[18], or taking antidyslipidemic medications. Type 2 diabetes was defined as having an FPG ≥ 126 mg/dl, having an HbA1c ≥ 5.8% based on American Diabetes Association 1997 criteria,[19] or taking medications for diabetes.

Lifestyle factors

Participants filled out a self-administered questionnaire. The questionnaire included age and lifestyle factors, such as exercise habits (two-level variables: exercise more than three times a week/exercise less than twice a week or not at all), drinking habits (two-level variables: current drinking/quit or never drank), and smoking habits (two-level variables: current smoking/quit or never smoked).

Statistical analyses

All statistical analyses were performed separately for men and women. Participants were divided into tertiles based on VFA (low tertile: 3.2-63.9 cm^2 in men and 4.1-47.8 cm^2 in women, moderate tertile: 64.2-109.8 cm^2 and 48.1-97.7 cm^2, and high tertile: 110.2-285.3 cm^2 and 97.8-269.9 cm^2). The mean values of SBP, DBP, TG, HDL-c, FPG, HbA1c, and VFA were compared by ANOVA following the Dunnet test. The mean values in the group low tertile used as references. Exercise habits, drinking habits, and smoking habits were counted for the number of participants for each group and calculated as percentages. The percentages among the groups were compared by the χ^2 test. The association between VFA categories and hypertension, dyslipidemia, or type 2 diabetes were examined by multivariable logistic regression analyses with adjustment of age, drinking habits, smoking habist, and exercise habits. Multivariable linear regression analysis was used to assess the associations of VFA, age, exercise habits, drinking habits, or smoking habits as independent variables and SBP, DBP, TG, HDL-c, FPG, or HbA1c as dependent variables. In the multivariable linear regression analyses, the people who took medications for hypertension, dyslipidemia, or type 2 diabetes were excluded.

In all analyses, the level of significance was $P < 0.05$. Statistical analyses were performed using SPSS for Windows ver. 17.0 J (Japan IBM, Tokyo).

Table 1. Age, blood pressures, laboratory data of the participants according to visceral fat area (VFA) tertiles

				P value	
	Low VFA tertile	Moderate VFA tertile	High VFA tertile	Moderate vs. Low tertile	High vs. Low tertile
Men					
n	492	493	494		
Age (years)	55.9 ± 11.5	57.0 ± 11.2	57.8 ± 10.9	<0.001	<0.001
Systolic blood pressure (mmHg)	115.5 ± 18.7	124.7 ± 19.2	130.6 ± 17.5	<0.001	<0.001
Diastolic blood pressure (mmHg)	73.3 ± 12.2	79.2 ± 12.1	83.9 ± 11.7	<0.001	<0.001
Triglycerides (mg/dl)	81.9 ± 39.9	122.5 ± 72.9	146.7 ± 80.2	<0.001	<0.001
HDL cholesterol (mg/dl)	60.8 ± 13.5	52.3 ± 12.7	48.0 ± 10.8	<0.001	<0.001
Fasting plasma glucose (mg/dl)	97.8 ± 18.6	104.5 ± 20.8	112.4 ± 27.6	<0.001	<0.001
Hemoglobin A1c (%)	5.1 ± 0.5	5.3 ± 0.8	5.5 ± 0.9	<0.001	<0.001
Women					
n	322	322	322		
Age (years)	57.0 ± 11.3	56.3 ± 11.0	56.2 ± 10.6	<0.001	<0.001
Systolic blood pressure (mmHg)	112.6 ± 17.6	121.5 ± 17.	130.5 ± 18.8	<0.001	<0.001
Diastolic blood pressure (mmHg)	71.9 ± 11.7	77.2 ± 11.8	85.7 ± 12.5	<0.001	<0.001
Triglycerides (mg/dl)	76.3 ± 47.4	116.8 ± 76.2	163.5 ± 106.9	<0.001	<0.001
HDL cholesterol (mg/dl)	63.0 ± 14.5	52.3 ± 12.1	49.0 ± 11.6	<0.001	<0.001
Fasting plasma glucose (mg/dl)	94.2 ± 12.4	102.4 ± 25.8	109.5 ± 26.9	<0.001	<0.001
Hemoglobin A1c (%)	4.9 ± 0.4	5.2 ± 0.8	5.4 ± 0.9	<0.001	<0.001

Data are expressed as mean ± standard deviation.

HDL, high-density lipoprotein.

In men, Low VFA tertile is VFA 3.2-63.9 cm^2, Moderate VFA tertile is 64.2-109.8 cm^2, and High VFA tertile is 110.2-285.3 cm^2. In women, Low VFA tertile is VFA 4.1-47.8 cm^2, Moderate VFA tertile is 48.1-97.7 cm^2, and High VFA tertile is 97.8-269.9 cm^2.

P values were calculated by the Dunnet test as a post-hoc test.

Results

The participants were 2,445 (1,479 men and 966 women). The mean age and SD were 56.9 ± 11.2 years for men and 56.5 ± 11.0 years for women. The mean values ± SD of VFA in the tertile groups were as follows; 36.2 ± 16.1 for low, 87.8 ± 13.2 for moderate, and 149.2 ± 34.1 for high VFA tertile for men, 25.5 ± 11.1 for low, 71.8 ± 14.4 for moderate, and 137.0 ± 31.3 for high VFA tertile for women. The mean values of age, SBP, DBP, TG, HDL-c, FPG, and HbA1c in the groups were demonstrated in Table 1. For ages, the mean values in moderate and high tertile groups were significantly higher for men and lower for women than that in the low tertile groups. The mean values of SBP, DBP, TG, FPG and HbA1c in the moderate and high VFA groups were significantly higher than those in the low VFA group for groups men and women. The mean values of HDL-c in the moderate and high VFA were significantly lower than that of the low tertile group for men and women.

Of all participants, we found hypertension in 591 men (40.0%) and 323 women (33.4%), dyslipidemia in 385 men (26.0%) and 190 women (19.7%), and type 2 diabetes in 222 men (15.0%) and 94 women (9.7%). Exercise, drinking and smoking habits and the prevalence of hypertension, dyslipidemia and type 2 diabetes according to VFA tertiles were demonstrated in Table 2. There were significant differences among the groups for drinking habit and prevalences of hypertension, dyslipidemia and type 2 diabetes. The percentages of those indexes were highest in the high VFA tertile group, followed by the moderate tertile group.

Table 2. The prevalence of hypertension, dyslipidemia, and type 2 diabetes and exercise, drinking and smoking habits according to visceral fat area (VFA) tertiles

	Low VFA tertile n (%)	Moderate VFA tertile n (%)	High VFA tertile n (%)	P value
Men				
n	492	493	494	
Hypertension	108 (22.0)	207 (42.0)	276 (55.9)	<0.001
Dyslipidemia	55 (11.2)	142 (28.8)	188 (38.1)	<0.001
Type 2 diabetes	39 (7.9)	668 (13.4)	117 (23.7)	<0.001
Exercise habits	131 (26.6)	153 (31.0)	135 (27.3)	0.256
Drinking habits	259 (52.6)	306 (62.1)	376 (76.1)	<0.001
Smoking habits	86 (17.5)	107 (21.7)	117 (23.7)	0.050
Women				
n	322	322	322	
Hypertension	56 (17.4)	93 (28.9)	174 (54.0)	<0.001
Dyslipidemia	21 (6.5)	70 (21.7)	99 (30.7)	<0.001
Type 2 diabetes	8 (2.5)	9 (9.0)	57 (17.7)	<0.001
Exercise habits	69 (21.4)	78 (24.2)	71 (22.0)	0.672
Drinking habits	173 (53.7)	196 (60.9)	229 (71.1)	<0.001
Smoking habits	81 (25.2)	95 (29.5)	107 (33.2)	0.079

Data are the number (percentages) of participants. Each disease includes subjects taking each medication.

P values were calculated by the χ^2 test.

Hypertension was defined as having a SBP ≥ 140 mmHg, having a DBP ≥ 90 mmHg based on the Japanese Society of Hypertension, or taking antihypertensive medications. Dyslipidemia was defined as having a TG ≥ 150 mg/dl, having a HDL-c < 40 mg/dl based on the Japan Atherosclerosis Society, or taking antidyslipidemic medications. Type 2 diabetes was defined as having an FPG 126 mg/dl, having an HbA1c ≥ 5.8% based on the American Diabetes Association 1997 criteria, or taking medications for diabetes.

Exercise habits: the participants who exercised more than three times a week/ exercise less than twice a week or nothing; drinking habits: the participants who currently drink or quit or never drank; smoking habits: the participants who currently smokes or quit or never smoked.

Table 3. Multivariate logistic regression analysis for prevalence of hypertension, dyslipidemia, and type 2 diabetes in relation to VFA

VFA	Hypertension		Dyslipidemia		Type 2 diabetes	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Men						
Low VFA tertile	1.00		1.00		1.00	
Moderate VFA tertile	2.56 (1.93-3.39)	<0.001	3.47 (2.45-4.90)	<0.001	1.75 (1.15-2.67)	<0.01
High VFA tertile	4.37 (3.28-5.80)	<0.001	5.78 (4.08-8.18)	<0.001	3.55 (2.38-5.27)	<0.001
Women						
Low VFA tertile	1.00		1.00		1.00	
Moderate VFA tertile	1.97 (1.35-2.87)	<0.001	4.04 (2.41-6.79)	<0.001	3.92 (1.76-8.73)	<0.01
High VFA tertile	5.92 (4.09-8.58)	<0.001	6.76 (4.07-11.24)	<0.001	8.85 (4.12-19.00)	<0.001

VFA, visceral fat area; OR, odds ratio; CI, confidence interval. Adjusted by age, drinking habits, smoking habits, and exercise habits. Each disease includes taking each medication. In men, the Low VFA tertile is VFA 3.2-63.9 cm^2, Moderate VFA tertile is 64.2-109.8 cm^2, and High VFA tertile is 110.2-285.3 cm^2. In women, Low VFA tertile is VFA 4.1-47.8 cm^2, Moderate VFA tertile is 48.1-97.7 cm^2, and High VFA tertile is 97.8-269.9 cm^2. Hypertension includes SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Dyslipidemia includes TG ≥ 150 mg/dl or HDL-c < 40 mg/dl. Type 2 diabetes includes FPG ≥ 126 mg/dl or HbA1c ≥ 5.8%.

Table 4. Multiple linear regression analysis of metabolic risk factors with VFA and lifestyle factors

	SBP		DBP		TG		HDL-c		FPG		HbA1c	
	β	P value	β	P value	β	P value	β	P value	β	P value	β	P value
Men												
n	1,101				1,245				1,349			
VFA	0.360	<0.001	0.382	<0.001	0.385	<0.001	-0.411	<0.001	0.329	<0.001	0.279	<0.001
Age	0.012	0.679	-0.008	0.779	-0.076	<0.01	-0.043	0.094	-0.034	0.191	-0.021	0.425
Exercise habits	0.027	0.347	-0.008	0.771	-0.016	0.524	-0.005	0.845	0.059	<0.05	0.061	<0.05
Drinking habits	0.040	0.157	0.090	<0.01	-0.007	0.785	0.107	<0.001	0.059	<0.05	-0.076	<0.01
Smoking habits	-0.099	<0.01	-0.043	0.124	0.160	<0.001	-0.121	<0.001	0.023	0.382	0.006	0.82
Model R^2	0.138	<0.001	0.162	<0.001	0.179	<0.001	0.181	<0.001	0.120	<0.001	0.074	<0.001
Women												
n	799				916				867			
VFA	0.374	<0.001	0.438	<0.001	0.404	<0.001	-0.425	<0.001	0.32	<0.001	0.328	<0.001
Age	-0.050	0.132	-0.031	0.323	-0.031	0.300	0.003	0.912	0.017	0.586	0.016	0.612
Exercise habits	0.050	0.13	-0.010	0.763	-0.034	0.260	0.066	0.066	0.053	0.09	0.045	0.154
Drinking habits	0.023	0.496	0.091	<0.01	0.085	<0.01	0.122	<0.001	0.048	0.136	-0.072	<0.05
Smoking habits	-0.067	<0.05	-0.087	<0.01	0.152	<0.001	-0.129	<0.001	0.012	0.709	0.002	0.951
Model R^2	0.143	<0.001	0.207	<0.001	0.218	<0.001	0.200	<0.001	0.112	<0.001	0.101	<0.001

VFA, visceral fat area; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; HDL-c, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c.
Subjects who took medication for hypertension, dyslipidemia, and type 2 diabetes were excluded from analyses.

Table 3 showed that the results of multivariable logistic regression analyses. After adjusting for age, exercise habits, smoking habits, and drinking habits, the moderate and high VFA groups showed significantly higher odds ratios for hypertension, dyslipidemia, and type 2 diabetes compared with the low VFA group. The odds ratios of hypertension, dyslipidemia, and type 2 diabetes were the highest in the high VFA group.

Results from the multiple linear regression analysis between VFA, age, exercise habits, drinking habits, or smoking habits as independent variables and the metabolic variables, such as SBP, DBP, TG, HDL-c, FPG, or HbA1c as dependent variables are shown in Table 4. VFA was significantly associated with all metabolic variables in men and women. Age was negatively correlated with TG for men. Drinking habits were significantly associated with DBP, HDL-c, FPG, and HbA1c in men, DBP, TG, HDL-c, and HbA1c in women. Smoking habits were positively associated with TG in both men and women, while smoking habits negatively associated with SBP and HDL-c for men and SBP, DBP, and HDL-c for women. Exercise habits were correlated with FPG and HbA1c for men but not for women.

Discussion

We aimed to evaluate whether or not greater visceral adiposity was associated with a higher prevalence of hypertension, dyslipidemia, and type 2 diabetes in Japanese populations with a relatively large sample size. Our data set consisted of 1,479 men and 996 women. In the analyses stratified by VFA tertiles, we had sufficient participants with hypertension, dyslipidemia, and type 2 diabetes in each VFA tertile group. The prevalences of hypertension, dyslipidemia, and type 2 diabetes were highest in the high VFA tertile followed by those in the moderate VFA tertile. Also, we got enough numbers of participants who have certain exercise, drinking, and smoking habits in each VFA group. In addition, the high and moderate VFA groups had significantly higher mean values of blood pressures and all laboratory data than those in the low VFA group. Then, we evaluated the relationships between VFA and hypertension, dyslipidemia, or type 2 diabetes using multiple logistic regression analysis and multiple linear regression analysis.

For the comparisons of ages among the VFA groups, male high and moderate VFA groups had significantly higher mean values than that in the low VFA group. However, female high and moderate VFA groups had significantly lower mean values than that in the low VFA group. For men, the percentage of BMI ≥ 25 was the highest in the ages of 40-49 followed by the ages of 50-59 years old in Japan.[20] That was the lowest in the ages of 20-29 years old. For women, the percentages of BMI ≥ 25 were increased with age and those of BMI < 18.5 decreased with age. Generally speaking, VFA is closely related to obesity. High mean value of age in male high VFA group and low mean value of age in female high VFA group women were in accordance with the statistics of obesity in Japan. The differences in mean values of age among the VFA tertile group were not so large. TG levels, which were closely related to VFA, were negatively correlated with age in men in the multiple regression analyses. It may be better to consider that the effects of aging on VFA or lipid metabolism are not so great.

In the present study, greater VFA was positively associated with a higher prevalence of hypertension, dyslipidemia, and type 2 diabetes in men and women in the multiple logistic regression analysis. With increasing VFA determined by CT, SBP, DBP, TG, FPG, and HbA1c showed higher levels, and HDL-c showed lower levels in the multiple linear regression analysis.

There have been several reports that examined the relationships between VFA determined by CT and blood pressure.[3,7,12,21,22] Fox et al.[21] reported that VFA significantly correlated with SBP and DBP for both men and women by multiple linear regression analyses among Americans (n = 3,001). Boyko et al.[3] examined the association between VFA and SBP or DBP by multiple regression analyses among the Nisei (second generation Japanese Americans) (n = 290) and the Sansei (third generation) (n = 230). VFA significantly correlated with DBP for the second generation and tended to be correlated with DBP for the third generation. VFA tended to be correlated with SBP for the second generation and significantly correlated with the third generation. The same group evaluated the relationship between VFA and hypertension among the Japanese American populations consisted of the second and the third generation Japanese Americans by multiple logistic regression analyses.[7] The participants were divided into the tertile groups by VFAs at the umbilicus level, and the adjusted odds ratio of hypertension by the VFAs were significant. For Japanese, Kanai et al.[22] reported that the significant positive correlation between VFA and SBP or DBP in 67 obese women. Oka et al.[12] examined the relationships between VFA and SBP or DBP by multiple regression analyses among Japanese (n = 1,119 men, n = 854 women). VFA positively correlated with SBP or DBP for both men and

women. Our results showed positive relationships between VFA and hypertension by both multiple regression analyses and multiple logistic analyses were in accordance with the results in the previous studies. To show significant relationships between VFA and hypertension adjusted by other factors, a large sample size is important.

For dyslipidemia, in the study by Fox et al.[21] it was demonstrated that VFA was significant positive correlation with the log value of TG and the significant negative correlation with HDL-c for men and women in the multiple linear regression analyses among 3,001 Americans. VFA also had a significant positive correlation with TG, even in Japanese nonobese men in a previous study (simple correlation coefficient = 0.389).[23] In their study, the correlation coefficient between the VFA and HDL-c was -0.277; however, it did not reach a significant level. Our results, in which VFA was positively related to TG and negatively related to HDL-c, were basically in accordance with these results. The large sample was also considered to more adequately show the significant relationships of VFA and HDL-c.

For type 2 diabetes, there were studies showing the relationships between VFA and type 2 diabetes. Fox et al.[21] also demonstrated that VFA significantly correlated with type 2 diabetes which was defined as FPG ≥ 126 mg/dl or treatment with either insulin or hypoglycemic agents among Americans. Boyko et al.[5] showed that a positive association was observed between diabetes incidence and VFA by multiple logistic analyses after 10 years observation among the second generation of Japanese Americans. In a case-control study, VFA was a significant variable for type 2 diabetes in Asian Indians in Chennai, Southern India.[8] For Japanese, Fujikawa et al.[10] reported that the group who had more risk factors for the metabolic syndrome had higher mean values of VFAs and higher mean values of FPGs. The mean values of FPGs in the group that had 3 risk factors of the metabolic syndrome were 137.2 mg/dl for men and 119.9 mg/dl for women. In the present study, we confirmed that VFA is significantly associated with type 2 diabetes in Japanese men and women. It is in accordance with the results in the previous studies.

There were many hypotheses for the mechanisms that increased VFA causes that increased blood pressures, TG levels, and FPGs. For hypertension, the activation of the sympathetic nervous system, which associated with the initiation and maintenance of hypertension, links with adipose tissue and leptin has been identified as a key component of this linking.[24] The adipose tissue is a remarkable endoctrine organ which is a source of adiponectin and proinflammatory cytokines, such as tumor necrosis factor α (TNFα) and interleukin-6 (IL-6), which could contribute to impair the hepatic lipoprotein mechanism leading to the increase in the TG in the serum.[25] These cytokines and adiponectin could also contribute to the development of insulin resistance. Gene expression studies on adipose tissue demonstrated that TNFα is produced by adipose-tissue resident macrophages, leptin is produced by adipocytes, and IL-6 is produced by both cells. The alterations in cytokines might induce insulin resistance and play a major role in the pathogenesis of endothelial dysfunction and subsequent atherosclerosis.[25,26]

In the present study, we also examined whether or not lifestyle factors, such as exercise, drinking, and smoking habits were related with VFA and metabolic risk factors. The male and female high VFA groups had higher percentages of drinking habits. In the multiple linear regression analysis, drinking habits were correlated with DBP, HDL-c, HbA1c (negative correlation) for both men and women, as were FPG for men and TG for women. Smoking habits were correlated with SBP (negative), TG, and HDL-c (negative) for men and women, and DBP for women. Exercise habits were correlated with FPG and HbA1c for men. Alcohol consumption increases in serum TG.[27] Several mechanisms were suggested for this increase in TG by alcohol. For example, the increase in metabolism of alcohol increases the synthesis of fatty acids.[28] Ethanol inhibits the degradation of fatty acids or the increase in the synthesis of TG.[27] There have been many reports that drinkers had higher mean values of blood pressures compared with non-drinkers.[29] Ethanol consumption increases in HDL-c.[28] For diabetes, although it has not been conclusive, Fujikawa and Ito[30] report that drinking inhibited the onset of type 2 diabetes. Our results for drinking were generally in accordance with previous studies. In the present study, drinking habits were not related to TG in men by multiple regression analyses. Independent of drinking habits on TG in men may be difficult to be detected, since VFA was closely related to TG. An epidemiological study by Minami[31] considering smoking and blood pressure demonstrated that the mean values of SBP and/or DBP in smokers were significantly lower compared with those in non-smokers. For the smoking and lipid metabolism, there was a report that smoking is independently related with the low adiponectin in the blood after adjustment for age, BMI, drinking, and exercise.[32] The lower levels of adiponectin cause the increase in free fatty acids, which may contribute to the synthesis of low-density lipoprotein enriched TG. In a previous study for smoking and serum HDL-c, the

percentages of subjects with HDL-c < 40 mg/dl were the highest among smokers compared with ex-smokers and non-smokers.[33] The positive correlation between exercise and FPG or HbA1c observed in this study is difficult to explain. The male subjects who had higher FPG or HbA1c might start exercising. Since there were many correlations between lifestyle factors and metabolic risk factors in our results, it is suggested that lifestyle modifications were important to prevent cardiovascular diseases as well as reducing VFA.

Several limitations of this study warrant mention. First, the cross-sectional design used in this study was unable to examine the causality and temporal sequence between VFA and metabolic risk factors. Secondly, participants were limited to those attending only one medical check-up center, which may have resulted in a selection bias.

In conclusion, these results confirmed that VFA is significantly associated with hypertension, dyslipidemia, and type 2 diabetes in Japanese men and women after adjustment of lifestyle factors. The data of our study population with a large sample size was useful for getting clear results, which may prove useful for Japanese for future studies.

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