

# The impact of visceral adipose tissue and high-molecular weight adiponectin on cardio-ankle vascular index in asymptomatic Japanese subjects

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## Abstract

Few studies addressed the relation of visceral adiposity and high-molecular weight (HMW) adiponectin to arterial stiffness. We investigated the impact of visceral adipose tissue (VAT) and HMW adiponectin on cardio-ankle vascular index (CAVI) in asymptomatic Japanese subjects. We studied 487 consecutive subjects (271 men and 216 women) who underwent general health examination between October 2005 and May 2008. The abdominal, visceral, and subcutaneous adipose tissue areas were determined by low-dose x-ray computed tomography. Serum levels of total and HMW adiponectin were measured using the enzyme-linked immunosorbent assay system based on a monoclonal antibody to humans. Cardio-ankle vascular index was positively correlated with VAT area and negatively correlated with HMW adiponectin levels. We also found the positive association of the number of metabolic syndrome components with CAVI in both sexes. A stepwise multiple regression analysis revealed that age, VAT area, serum HMW adiponectin levels, and homeostasis model assessment of insulin resistance were independent determinants of CAVI. Receiver operating characteristic analyses demonstrated that the predictive value of the VAT area for the extent of CAVI (mild: <25th percentile vs severe: >75th percentile) exceeded that of total or HMW adiponectin levels in both sexes. In conclusion, increased CAVI is associated with both amounts of VAT measured by computed tomography and serum HMW adiponectin levels in asymptomatic Japanese subjects. Receiver operating characteristic analysis indicates that the VAT area is a lot better predictor of arterial stiffness than adiponectin levels.

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## 1. Introduction

Visceral adipose tissue (VAT) is now generally considered to play an important role in the metabolic syndrome (MetS) and the development of atherosclerosis [1,2]. The adipose tissue is a remarkable endocrine organ that is a source of several adipokines [3]. Although most adipokines appear to promote cardiovascular disease (CVD), adiponectin is thought to possess antiatherogenic and anti-inflammatory effects and may be protective against CVD development [4]. Recent studies have demonstrated that high-molecular

weight (HMW) adiponectin is the major active form of this protein associated with insulin sensitivity and protective activities on the vasculature [5,6]. Clinical studies have also reported that HMW adiponectin is more associated with MetS and coronary heart disease than total adiponectin [7,8], suggesting that HMW adiponectin rather than total adiponectin may exert antiatherosclerotic properties that would prevent the development of atherosclerosis.

It has been demonstrated that aortic pulse wave velocity (PWV), which reflects arterial stiffness, is a marker of CVD risk [9]. Recently, the cardio-ankle vascular index (CAVI) has been developed for the quantitative evaluation of vascular wall stiffness in the aorta, femoral arteries, and tibial artery by measuring PWV and blood pressure (BP) [10]. Indeed, CAVI has been reported to be correlated with

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other CVD risk markers, such as intima-media thickness (IMT) and coronary atherosclerosis, thus reflecting the degree of atherosclerotic change in general populations and patients with high CVD risk [11,12].

Previous studies have reported that visceral adiposity is associated with PWV in patients with type 2 diabetes mellitus [13] or that total adiponectin is inversely related to PWV in patients with essential hypertension [14]. However, there are little data assessing the relationship of visceral adiposity, total adiponectin levels, and HMW adiponectin levels to arterial stiffness in apparently healthy subjects without any medication. Furthermore, it is not known which of these adiposity-related measurements is more closely related to arterial stiffness. The purpose of this study was to evaluate the impact of VAT measured by computed tomography (CT) and total and HMW adiponectin levels on CAVI in asymptomatic Japanese subjects.

## 2. Methods

### 2.1. Subjects

The study population consisted of 487 Japanese individuals (271 men, 216 women) who underwent general health examination between October 2005 and May 2008 at Grand Tower Medical Court Life Care Clinic. Subjects who were diagnosed as having CVD and received any medication were excluded. We measured abdominal VAT areas by low-dose x-ray CT, the serum total and HMW adiponectin levels, and the CAVI in all subjects. This study was approved by the Medical Ethics Committee of the Grand Tower Medical Court Life Care Clinic. All subjects provided written informed consent before their inclusions in the study.

### 2.2. Anthropometric measurement and laboratory methods

After an overnight fast, blood samples were obtained; and BP was measured in the sitting position with the right arm. Height (in meters) and body weight (in kilograms) were used to calculate the body mass index (BMI). The waist circumference (WC) was measured at a level of umbilicus in the late exhalation phase while standing. Measurements of the abdominal VAT and subcutaneous adipose tissue (SAT) areas were undertaken using low-dose x-ray CT with a Hitachi Robusto (Hitachi Medical, Tokyo, Japan). Serum lipid profile was determined by an enzymatic method (total cholesterol and triglycerides) or a direct method (low-density lipoprotein [LDL] cholesterol and high-density lipoprotein [HDL] cholesterol) with a Hitachi 7080 analyzer. The fasting plasma glucose (FPG) levels were measured using the hexokinase method. Serum insulin levels were measured using a chemiluminescent enzyme immunoassay. Insulin resistance was evaluated by the homeostasis model assessment (HOMA-IR), calculated as fasting insulin (in microunits per milliliter)  $\times$  FPG (in

millimoles per liter)/22.5. Hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) was determined by turbidimetric immunoassay. Serum concentrations of high-sensitivity C-reactive protein (hsCRP) were determined by latex turbidimetric immunoassay. Serum levels of total and HMW adiponectin were measured using the enzyme-linked immunosorbent assay system (Sekisui Medical, Tokyo, Japan) based on a monoclonal antibody to humans [15]. For total adiponectin, the intraassay coefficient of variation (CV) was 4.5% and the interassay CV was 3.0%. For HMW adiponectin, the intraassay CV was 7.7% and the interassay CV was 9.1%. *Metabolic syndrome* was defined by the Japanese criteria as a WC level of at least 85 cm in men and at least 90 cm in women and 2 or more of the following 3 risk factors: hypertension (a BP level  $\geq$ 130/85 mm Hg), dyslipidemia (an HDL cholesterol level  $\leq$ 40 mg/dL or a triglycerides level  $\geq$ 150 mg/dL), and glucose intolerance (an FPG level  $\geq$ 110 mg/dL) [16]. Metabolic syndrome score (MS) means the number of components of the MetS.

### 2.3. Measurement of CAVI

Cardio-ankle vascular index was recorded using a VaseraVS-1000 vascular screening system (Fukuda Denshi, Tokyo, Japan) by the methods as previously described [10]. Briefly, cuffs were applied to bilateral upper arms and ankles, electrocardiogram leads were attached to both wrists, and a phonocardiogram was placed at the right sternum border in the second intercostal space. The subjects were placed in the supine position for at least 10 minutes, and then measurements were performed automatically. Cardio-ankle vascular index was calculated by the following formula:  $CAVI = a[(2\rho/\Delta P) \times \ln(Ps/Pd)PWV^2] + b$ , where Ps is systolic BP, Pd is diastolic BP,  $\Delta P$  is Ps – Pd,  $\rho$  is blood density, and  $a$  and  $b$  are constants to match aortic PWV. The equation was derived from Bramwell-Hill's equation and the stiffness parameter  $\beta$ . The obtained data were analyzed using VSS-10 software (Fukuda Denshi), and the values of right and left CAVI were calculated. Averages of the right and left CAVI were used in the analysis. The average CV of CAVI has been reported to be 3.8% [10]. The ankle brachial index (ABI) was also calculated as the highest ankle systolic pressure divided by the highest brachial systolic pressure on both sides, and the lower ABI from right and left measurements was used in subsequent statistical analysis.

### 2.4. Statistical analysis

Categorical variables were presented as number of patients (percentage), and continuous variables were expressed as means  $\pm$  SD or medians (interquartile range). Differences between men and women in the clinical variables were evaluated using Student  $t$  test or the Mann-Whitney  $U$  test. The mean CAVI values were stratified by the number of components of MetS using analysis of variance. The correlation coefficient was estimated by

Pearson correlation. As triglycerides, fasting insulin, HOMA-IR, total and HMW adiponectin levels, and hsCRP were not normally distributed, logarithmic transformation was performed for the analysis. We performed stepwise multiple regression analysis to evaluate the independent determinants of CAVI in all subjects using age, sex, BMI, WC, systolic and diastolic BP, triglycerides, HDL cholesterol, LDL cholesterol, FPG, fasting insulin, HOMA-IR, HbA<sub>1c</sub>, prevalence of MetS, VAT area, SAT area, total adiponectin levels, HMW adiponectin levels, and hsCRP as covariates. A receiver operating characteristics (ROC) analysis was used to compare the predictive power of the VAT area, total adiponectin levels, and HMW adiponectin levels in the prediction of the extent of CAVI. Prediction of CAVI extent was based on discrimination between subjects with mild (CAVI <25th percentile) and severe (CAVI >75th percentile) values of CAVI. Statistical comparisons of the area under ROC curves were performed using a computer program (ROCKIT; Charles E Metz, University of Chicago). Statistical analyses were performed using the JMP 5.0.1 statistical software (SAS Institute, Cary, NC). A *P* value less than .05 was considered statistically significant.

### 3. Results

#### 3.1. Patient characteristics

The study subjects consisted of 271 men (mean age, 46 years; range, 23–73 years) and 216 women (mean age, 47 years; range, 25–70 years). The clinical and biochemical

Table 1  
Clinical and biochemical characteristics of the study subjects

	Men (n = 271)	Women (n = 216)	<i>P</i>
Age (y)	46.3 ± 10.5	46.6 ± 10.8	NS
BMI (kg/m <sup>2</sup> )	24.6 ± 3.9	21.0 ± 3.1	<.01
WC (cm)	87.0 ± 10.6	76.7 ± 8.9	<.01
SBP (mm Hg)	125.9 ± 15.5	116.3 ± 14.1	<.01
DBP (mm Hg)	79.0 ± 10.5	72.0 ± 9.2	<.01
Total cholesterol (mg/dL)	208.4 ± 34.2	207.7 ± 38.7	NS
Triglycerides (mg/dL)	120.0 (80.0–189.0)	66.0 (48.0–93.0)	<.01
HDL cholesterol (mg/dL)	55.6 ± 13.9	70.2 ± 16.7	<.01
LDL cholesterol (mg/dL)	124.7 ± 32.4	118.2 ± 32.8	<.05
FPG (mg/dL)	109.3 ± 23.7	94.6 ± 17.3	<.01
Fasting insulin (μU/mL)	6.8 (4.6–10.8)	4.7 (3.5–6.8)	<.01
HOMA-IR	1.75 (1.11–2.90)	1.07 (0.79–1.57)	<.01
HbA <sub>1c</sub> (%)	5.38 ± 0.81	5.12 ± 0.60	<.01
MetS (n, %)	81 (29.9)	15 (6.9)	<.01
VAT area (cm <sup>2</sup> )	99.3 ± 54.0	38.7 ± 31.2	<.01
SAT area (cm <sup>2</sup> )	139.6 ± 73.8	143.6 ± 69.6	NS
Total adiponectin (μg/mL)	4.2 (3.1–5.4)	7.6 (5.8–10.0)	<.01
HMW adiponectin (μg/mL)	1.5 (0.8–2.2)	3.8 (2.4–5.3)	<.01
hsCRP (mg/L)	0.68 (0.37–1.36)	0.33 (0.19–0.68)	<.01
CAVI	7.49 ± 1.03	7.21 ± 0.95	<.01
ABI	1.15 ± 0.1	1.10 ± 0.1	NS

Data are expressed as number of subjects (percentage), means ± SD, or medians (interquartile range). SBP indicates systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

Table 2

Correlation between CAVI and clinical variables in men and women

Clinical variables	Men (n = 271)		Women (n = 216)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
Age (y)	0.474	<.0001	0.568	<.0001
BMI (kg/m <sup>2</sup> )	0.048	.42	−0.08	.23
WC (cm)	0.046	.44	0.071	.29
SBP (mm Hg)	0.183	.0025	0.185	.0064
DBP (mm Hg)	0.121	.046	0.184	.0067
Total cholesterol (mg/dL)	−0.038	.53	0.164	.015
Triglycerides (mg/dL) <sup>a</sup>	0.0756	.21	0.25	.0002
HDL cholesterol (mg/dL)	−0.034	.57	−0.115	.091
LDL cholesterol (mg/dL)	−0.049	.41	0.186	.0061
FPG (mg/dL)	0.232	.0001	0.236	.0005
Fasting insulin (μU/mL) <sup>a</sup>	0.211	.0007	0.238	.0005
HOMA-IR <sup>a</sup>	0.260	<.0001	0.284	<.0001
HbA <sub>1c</sub> (%)	0.232	.0001	0.282	<.0001
VAT area (cm <sup>2</sup> )	0.366	<.0001	0.383	<.0001
SAT area (cm <sup>2</sup> )	0.15	.013	0.154	.023
Total adiponectin (μg/mL) <sup>a</sup>	−0.113	.061	−0.09	.18
HMW adiponectin (μg/mL) <sup>a</sup>	−0.254	.0001	−0.214	.0021
hsCRP (mg/L) <sup>a</sup>	0.173	.0041	0.112	.1
ABI	0.122	.06	0.091	.2

Abbreviations are the same as in Table 1.

<sup>a</sup> Log-transformed values.

characteristics of the study subjects are shown in Table 1. Body mass index, WC, systolic and diastolic BP, triglycerides, LDL cholesterol, FPG, fasting insulin, HOMA-IR, HbA<sub>1c</sub>, prevalence of MetS, hsCRP, and CAVI were significantly higher in men than in women. The VAT area was also significantly larger in men than in women. High-density lipoprotein cholesterol and the serum total and HMW adiponectin levels were significantly lower in men than in women.

#### 3.2. Correlation between CAVI and clinical variables

Table 2 shows the result of simple linear regression analysis between CAVI and clinical variables. Cardio-ankle vascular index was positively correlated with age, systolic and diastolic BP, FPG levels, fasting insulin, HOMA-IR, HbA<sub>1c</sub> levels, VAT area, and SAT area and negatively correlated with HMW adiponectin levels in both sexes. Cardio-ankle vascular index was positively correlated with hsCRP in men and with total cholesterol, triglycerides, and LDL cholesterol in women. Fig. 1 shows the comparison of CAVI values according to the MS in men and women. In both sexes, CAVI increased linearly as the MS increased; average CAVI values for those with MS of 0, 1, 2, or at least 3 were 7.13, 7.27, 7.53, and 7.92 in men (*P* for trend < .0001) and 7.05, 7.32, 7.62, and 8.18 in women (*P* for trend < .0001), respectively. In addition, subjects with MetS had a significantly higher CAVI than those without in men ([mean ± SD] 7.91 ± 1.0 vs 7.31 ± 0.98, *P* < .001) and women (8.18 ± 1.54 vs 7.15 ± 0.82, *P* < .001). Table 3 describes the result of stepwise multiple regression analysis in all subjects. Age, VAT area, HMW adiponectin levels,

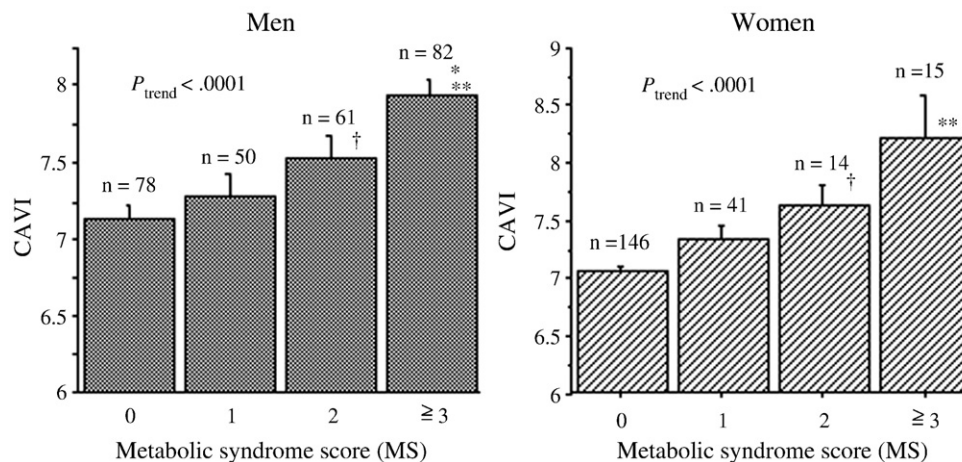


Fig. 1. Comparison of CAVI values according to the MS in men and women. MS means the number of components of the MetS including WC, BP, triglycerides or HDL cholesterol, and FPG. †*P* less than .05 vs MS = 0 group, \**P* less than .05 vs MS = 2 group, \*\**P* less than .01 vs MS = 0 or MS = 1 group in men, †*P* less than .05 vs MS = 0 group, \*\**P* less than .01 vs MS = 0 or MS = 1 group in women.

and HOMA-IR were found to be independent determinants of CAVI (adjusted  $R^2 = 0.38$ ,  $P < .0001$ ).

### 3.3. Predictive values of the VAT area, total adiponectin levels, and HMW adiponectin levels for the extent of CAVI

Receiver operating characteristic analyses were performed to quantify the power of the VAT area, total adiponectin levels, and HMW adiponectin levels for the prediction of CAVI extent (Fig. 2). Analyses were performed in subjects representing the upper ( $n = 66$ , CAVI  $>8.05$  in men;  $n = 52$ , CAVI  $>7.70$  in women) and lower quartile ( $n = 67$ , CAVI  $<6.80$  in men;  $n = 50$ , CAVI  $<6.60$  in women) of CAVI. The area under the curve for the VAT area was significantly larger than that for HMW adiponectin levels in men (VAT area: 0.763 [95% confidence interval {CI}, 0.676–0.836] vs HMW adiponectin levels: 0.653 [95% CI, 0.556–0.741],  $P = .05$ ) and women (VAT area: 0.762 [95% CI, 0.670–0.837] vs HMW adiponectin levels: 0.627 [95% CI, 0.524–0.720],  $P = .02$ ). The area under the curve for HMW adiponectin levels was also significantly larger than that for total adiponectin levels in men (HMW adiponectin levels: 0.653 [95% CI, 0.556–0.741] vs total adiponectin levels: 0.583 [95% CI, 0.485–0.677],  $P = .03$ ) and women (HMW adiponectin

levels: 0.627 [95% CI 0.524–0.720] vs total adiponectin levels: 0.538 [95% CI, 0.436–0.638],  $P = .01$ ).

## 4. Discussion

In the present study, we first evaluated the association of the VAT area, total adiponectin levels, and HMW adiponectin levels with CAVI as a marker of arterial stiffness in a group of subjects without previous manifestation of CVD. We found a positive association of MetS components and VAT area with CAVI. We also found an inverse relation between HMW adiponectin levels and CAVI. A stepwise multiple regression analysis revealed that age, VAT area, HMW adiponectin levels, and HOMA-IR were independent predictors for increase of CAVI. On ROC analysis, VAT area demonstrated superior discrimination for the extent of CAVI compared with total and HMW adiponectin levels in both sexes.

We showed that CAVI is higher in subjects with MetS than in those without and increased linearly as the components of MetS increased, which is consistent with prior result that MetS is independently associated with arterial stiffness [17]. Previous studies also reported that the VAT area is significantly associated with arterial stiffness in older adults [18], middle-aged women [19], and patients with type 2 diabetes mellitus [13]. With respect to total adiponectin and arterial stiffness, there is a significant relationship in hypertensive patients [14] and nondiabetic subjects [20]. However, there has been no information regarding the effect of VAT and HMW adiponectin levels on arterial stiffness in asymptomatic subjects. We found that both the VAT area and HMW adiponectin levels remained as independent determinants of CAVI in multivariable analysis even after adjustment for MetS or other indices of adiposity measurement such as BMI, SAT, and WC. These results indicate that the measurement of the VAT area and HMW

Table 3  
Stepwise multiple regression analysis between CAVI and clinical variables

Independent variables	Standardized $\beta$	Standard error	<i>t</i>	<i>P</i>
Age	1.47	0.12	12.4	<.0001
VAT area	0.46	0.18	2.62	.0092
HMW adiponectin <sup>a</sup>	−0.54	0.26	−2.10	.036
HOMA-IR <sup>a</sup>	1.52	0.76	2.00	.046
$R^2$	0.40			
Adjusted $R^2$	0.38			

Abbreviations are the same as in Table 1.

<sup>a</sup> Log-transformed values.

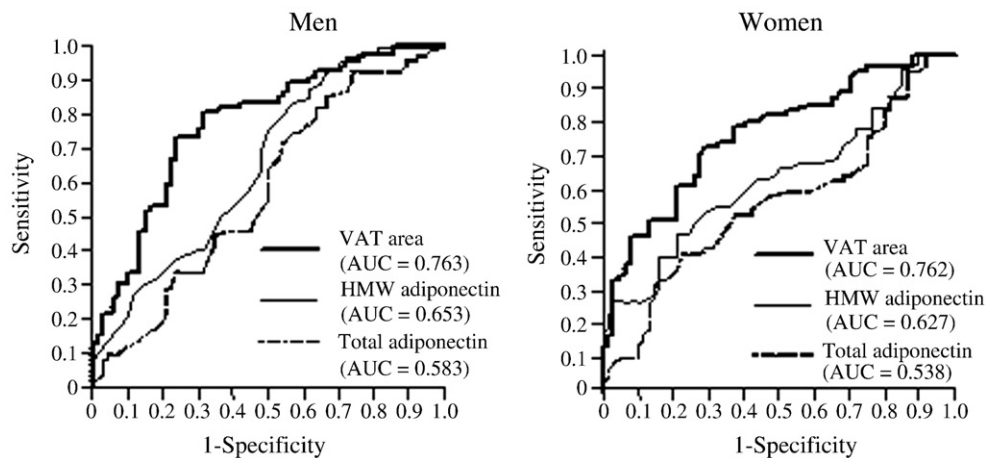


Fig. 2. Receiver operating characteristic curves of the VAT area, total adiponectin levels, and HMW adiponectin levels and predictive values for the extent of CAVI in men and women.

adiponectin levels in conjunction with CAVI may help identify subjects needing more aggressive risk modification in clinical practice.

The mechanisms of linking VAT and adiponectin to arterial stiffness are not entirely understood. In the present study, we demonstrated that HOMA-IR as a marker of insulin resistance was an independent predictor of CAVI, which implies one of the plausible mechanisms of increased arterial stiffness. Arner [21] has suggested that the flux of lipid from the visceral fat to the liver via portal circulation might account for hepatic insulin resistance. Adiponectin was also reported to modulate insulin sensitivity by stimulating glucose utilization and fatty acid oxidation via the phosphorylation and activation of adenosine monophosphate-activated protein kinase in both muscle and liver cells [22]. Clinical study also suggests that HMW adiponectin is a more useful marker to evaluate insulin resistance and MetS than total adiponectin [7]. Insulin resistance is reported to be associated with decreased endothelium-dependent vasodilation [23] and increased arterial stiffness [24]. These results indicated that decreased HMW adiponectin levels concomitant with the accumulation of visceral fat could potentially be involved with the acceleration of the increased arterial stiffness via insulin resistance.

From ROC analysis, we can clearly see that the VAT area was a lot better predictor of arterial stiffness than adiponectin levels. The accumulation of VAT is considered to be causally linked to atherosclerosis as a result of the dysregulation of various kinds of adipokines production and chronic intravascular inflammation [3]. Our findings suggested that other factors than adiponectin, such as inflammatory factors, other proteins secreted by adipose tissue, or insulin or glucose levels may also be important in the pathophysiologic mechanisms by which abdominal adiposity leads to arterial stiffness. In addition, HMW adiponectin was more associated with arterial stiffness than total adiponectin. One

possible explanation of this result may be the higher affinity of HMW adiponectin to collagen in the vascular wall compared with low-molecular weight or middle-molecular weight forms, thus possibly exerting better repair on injured vessels [25]. In addition, a recent study revealed that only HMW adiponectin selectively suppressed endothelial cell apoptosis, whereas neither the low-molecular weight nor the middle-molecular weight form had this effect [6]. Clinical data also confirmed that HMW to total adiponectin ratio was an independent determinant for PWV and CAVI in hemodialysis patients [26].

In the present study that represents arterial stiffness by CAVI, neither BP nor sex remained as independent predictors of CAVI in stepwise multiple regression analysis. Whereas BP is a major determinant of PWV, CAVI is designed to be adjusted for BP based on the stiffness parameter  $\beta$  and is hypothesized to measure arterial stiffness independent of BP. It has been reported that CAVI has a lower correlation with BP than PWV [10] or that the significant risk factors of high CAVI were age and HbA<sub>1c</sub>, whereas systolic BP was not relevant [27], which is consistent with our results in that BP did not contribute to CAVI. In addition, there was no significant sex interaction in our analyses. For instance, menopause is reported to augment the age-related increase in arterial stiffness [28]. However, our study subjects are relatively young and the proportion of postmenopausal women is low, which may be one of the reasons that CAVI was not affected by sex in a multivariable model.

This study had some limitations. First, because this is a cross-sectional study, causality cannot be established. However, it has been already reported that arterial stiffness defined by stiffness parameter  $\beta$  is partly improved by interventions to insulin resistance such as the insulin sensitizer pioglitazone and aerobic exercise in type 2 diabetes mellitus [29,30]. Our findings in the present study are almost in keeping with these previous observations,

suggesting that intervention therapy such as diet and exercise may reduce total and abdominal fat and that these changes in body composition mediate improvements in insulin sensitivity and may improve endothelial vasodilator function. Prospective randomized controlled trials are needed to confirm this issue. Second, as data were exclusively collected from asymptomatic Japanese subjects, it is uncertain whether our findings can be generalized to other ethnic groups or patients with CVD or diabetes. Third, although adiponectin is not the only cytokine that is being secreted by the fat tissue, we could not evaluate the relationship between CAVI and other adiposity-related factors such as leptin, monocyte chemoattractant protein 1, and biochemical markers of endothelial dysfunction, which may not allow us to exclude the potential effects of these influences on arterial stiffness. Fourth, in contrast to CAVI, neither the VAT area nor HMW adiponectin shows a significant relationship with the ABI in the present study (data not shown). This is probably due to only a small proportion (0.5%) of subjects with a low ABI (<0.9). Further studies in the general population are warranted to confirm an association among the 3 variables. Finally, we could not validate the use of VAT and adiponectin as screening tool for other indexes of CVD, such as IMT, flow-mediated vasodilation, or clinical atherosclerosis. However, it was recently reported that CAVI was more associated with the severity of atherosclerosis determined by coronary angiography than IMT and plaque score [31]. Thus, CAVI may provide a more sensitive predictor of CVD risk.

## 5. Conclusions

Cardio-ankle vascular index as a marker of arterial stiffness is significantly associated with both amounts of VAT measured by CT and serum HMW adiponectin levels in asymptomatic Japanese subjects. On ROC analysis, the VAT area demonstrated superior discrimination for the extent of CAVI compared with total and HMW adiponectin levels in both sexes.

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