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Relationships of Obesity-Related Indices and Metabolic Syndrome with Subclinical Atherosclerosis in Middle-Aged Untreated Japanese Workers

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Aim: Obesity is a social problem due to the prevalence of the Western lifestyle. In particular, visceral fat accumulation, which is a main component of metabolic syndrome, is closely associated with the progression of atherosclerosis. This study aimed to investigate the relationships of obesity-related indices and metabolic syndrome with subclinical atherosclerosis in middle-aged untreated workers.

Methods: Employees undergoing their periodic health check-up but without previous cardiovascular events or cardiovascular medications were enrolled in this study (n=7,750). Body mass index (BMI), percent body fat, waist circumference, and visceral fat area were evaluated as obesity-related indices. Assessment of visceral fat area was performed by computed tomography (CT). Subclinical atherosclerosis was assessed by measuring arterial stiffness using cardio-ankle vascular index (CAVI) and by ultrasound examination of carotid intima-media thickness (IMT).

Results: Obesity-related indices were significantly correlated with each other and were positively associated with carotid IMT but negatively associated with CAVI in multivariate regression analysis. In a logistic regression analysis including CAVI and carotid IMT simultaneously, CAVI was negatively associated, but carotid IMT was positively associated, with obesity defined by each obesity-related index. In contrast, both CAVI and carotid IMT were positively associated with the presence of metabolic syndrome based on visceral fat accumulation.

Conclusions: Obesity-related indices were negatively associated with CAVI and positively associated with carotid IMT in middle-aged untreated workers, while both CAVI and carotid IMT were worsened in the presence of metabolic syndrome.

Key words: Obesity, Metabolic syndrome, Atherosclerosis, Cardio-ankle vascular index, Carotid intima-media thickness

1. Introduction

Overweight and obesity are becoming a global health care problem with the increasing prevalence of the Western lifestyle, not only in industrialized countries but also in developing countries[1-3]. Body mass index (BMI) is simply calculated by anthropometric measurements of body weight and body height and is conveniently and widely used for the diagnosis of obesity[1-3]. The World Health Organization (WHO) defines the conditions of being overweight and obesity based on a BMI ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively, and

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recently at least 2.8 billion people worldwide were estimated to be overweight or obese[1-3].

Obesity has been shown to be associated with cardiovascular disease and all-cause death[4-6]. Increasing visceral adipose tissue and fat, rather than subcutaneous fat, are associated with insulin resistance and vascular inflammation, leading to the development of multiple metabolic disorders[7-10]. The overlapping or combination of metabolic disruptions, including visceral fat accumulation, lipid metabolism disorder, elevated blood pressure, and impaired fasting glucose constitute metabolic syndrome, which is considered to be a high-risk condition for future cardiovascular events[11-14]. Hence, visceral fat accumulation evaluated by computed tomography (CT) could be a reliable risk factor for atherosclerotic cardiovascular disease. Alternatively, the anthropometric measurement of waist circumference is just as simple as calculating BMI and gives us additional information regarding the approximate abdominal fat content without CT equipment[8, 11].

Although obesity is generally accepted as a risk factor for the promotion of atherosclerosis, the relationship between obesity and arterial stiffness, which reflects the functional profile of early-stage arteriosclerosis, has not been consistent among the reports[15-20]. Particularly, the relationship between visceral fat accumulation and arterial stiffness has not to date been sufficiently investigated. We then hypothesized that the impact of visceral fat accumulation on subclinical atherosclerosis might be different from the impact of other obesity-related indices, such as BMI and percent body fat.

2. Aim

The aim of this present study was to investigate the relationship of obesity-related indices and metabolic syndrome with subclinical atherosclerosis in middle-aged untreated workers.

3. Methods

The present study enrolled individuals attending their periodic physical check-up and the study protocol was approved by the Ethics Committee of the Toyota Memorial Hospital. The study was performed in accordance with the principles of the Declaration of Helsinki.

3.1. Study Participants

In this study, a total of 15,764 individuals who visited the Health Support Center WELPO, the health care institute for employees of the Toyota Motor Corporation (Toyota, Japan) and their spouses, in 2008–2009 for a periodic health check-up were screened. All employees received annual medical examinations in accordance with the Industrial Safety and Health Law of Japan. All obtained data were supplied from medical examination records. Of the 15,764 people screened, 4,881 individuals were excluded due to blank questionnaires, non-workers (spouses), or uncertain workstyle. Then, 3,133 individuals taking medication were excluded to eliminate the effects of medications, and data from the remaining 7,750 untreated employees were finally used for the analysis.

Participants were instructed to fast overnight before the examination. The physical examination included body height, body weight, and percent body fat, measured using an automated BF-220 instrument equipped with a bioelectrical impedance analyzer system (Tanita, Tokyo, Japan). Waist circumference was measured at the level of the umbilicus in a standing position while

Table 1. Characteristics of all the study participants.

Variable	Total participants (n=7,750)
Age (years)	45.3 ± 8.1
Male gender, n (%)	7135 (92.1)
Current smoking, n (%)	3035 (39.2)
Systolic BP (mmHg)	118 ± 14
Diastolic BP (mmHg)	75 ± 9
Creatinine (mg/dL)	0.80 ± 0.13
HDL-C (mg/dL)	60 ± 16
LDL-C (mg/dL)	119 ± 28
Triglyceride (mg/dL)	114 ± 75
FBG (mg/dL)	94 ± 13
HbA1c (%)	5.6 ± 0.5
Obesity-related indices	
Body mass index (kg/m^2)	22.8 ± 3.0
Percent body fat (%)	21.6 ± 5.3
Waist circumference (cm)	81.5 ± 8.2
Visceral fat area (cm^2)	59.7 ± 37.3
Diagnosis of metabolic syndrome	
Based on abdominal obesity, n (%)	411 (5.3)
Based on visceral fat accumulation, n (%)	277 (3.6)
Examination for subclinical atherosclerosis	
CAVI	7.3 ± 0.8
Carotid IMT (mm)	0.55 ± 0.11

Data are presented as the mean ± standard deviation or as n (%).
BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; CAVI, cardio-ankle vascular index; IMT, intima-media thickness.
Metabolic syndrome based on abdominal obesity was diagnosed by a waist circumference ≥ 85 cm for men and ≥ 90 cm for women. Metabolic syndrome based on visceral fat accumulation was diagnosed by a visceral fat area ≥ 100 cm^2 using computed tomography.

Table 2. Results of univariate regression analysis showing relationships among obesity-related indices, cardio-ankle vascular index, and carotid intima-media thickness in all participants (n=7,750).

Variable	BMI		PBF		WC		VFA		CAVI		Carotid IMT	
	r	P value	r	P value	r	P value	r	P value	r	P value	r	P value
BMI	–	–	0.757	<0.0001	0.884	<0.0001	0.666	<0.0001	−0.186	<0.0001	0.170	<0.0001
PBF	0.757	<0.0001	–	–	0.723	<0.0001	0.588	<0.0001	−0.154	<0.0001	0.069	<0.0001
WC	0.884	<0.0001	0.723	<0.0001	–	–	0.757	<0.0001	−0.064	<0.0001	0.199	<0.0001
VFA	0.666	<0.0001	0.588	<0.0001	0.757	<0.0001	–	–	0.082	<0.0001	0.220	<0.0001

BMI, body mass index; PBF, percent body fat; WC, waist circumference; VFA, visceral fat area; CAVI, cardio-ankle vascular index; IMT, intima-media thickness.

breathing normally (and at the end of expiration while breathing gently). Systolic and diastolic blood pressures (BP) were measured using a validated oscillometric technique in a seated position. Blood samples were taken from the antecubital vein in the morning for laboratory measurements. For assessment of arterial stiffness, the cardio-ankle vascular index (CAVI) was measured. Then, ultrasound examination and CT imaging were performed for measurement of carotid intima-media thickness (IMT) and visceral fat area (VFA). Participants with a systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg were defined as having hypertension[21]. Participants with high-density lipoprotein cholesterol (HDL-C) levels <40 mg/dL, low-density lipoprotein cholesterol (LDL-C) levels ≥140 mg/dL, or triglycerides ≥150 mg/dL were defined as having dyslipidemia[22]. Participants presenting with a fasting blood glucose (FBG) level ≥126 mg/dL were defined as having diabetes[23]. Participants with a BMI ≥ 25 kg/m^2, percent body fat ≥25% for men and ≥30% for women, waist circumference ≥85 cm for men and ≥90 cm for women, and VFA ≥ 100 cm^2 for both men and women were defined as having general obesity, body fat obesity, abdominal obesity, and visceral fat obesity, respectively[11, 12, 24-26]. Metabolic syndrome was defined based on either abdominal obesity or visceral fat obesity and two or more of the following three criteria: (1) triglyceride ≥150 mg/dL and/or HDL-C < 40 mg/dL; (2) systolic BP ≥130 mmHg and/or diastolic BP ≥85 mmHg; and (3) FBG ≥110 mg/dL[11].

3.2. Biochemical Analyses

Biochemical tests, which were inclusive of determination of total cholesterol; LDL-C; HDL-C; triglycerides; creatinine; and FBG, were performed using standard laboratory assays as previously described[27]. Concentrations of glycated hemoglobin A1c (HbA1c) were measured by high-performance liquid chromatography and expressed according to the National Glycohemoglobin Standardization Program[28].

3.3. Assessment of Arterial Stiffness

Assessment of arterial stiffness was performed by CAVI using a Vasera VS-1000 automatic system (Fukuda Denshi, Tokyo, Japan), as previously described[29]. CAVI was recorded after resting in the supine position. Electrocardiogram electrodes and a microphone were placed on both wrists and on the sternum to detect heart sounds. Cuffs were wrapped around both upper arms and both ankles. Cardio-ankle pulse wave velocity was calculated by dividing the distance from the aortic valve to the ankle artery with the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same waves were transmitted to the ankle, and the time difference between the second heart sound on the phonocardiogram and that on the notch of the brachial pulse wave. CAVI is calculated by the stiffness parameter β in the following equation: $CAVI = a[2\rho/Pp \times [\ln Ps/Pd]\ PWV^2] + b$ (where a, b = constants; ρ = blood density; Pp = pulse pressure; Ps = systolic pressure; Pd = diastolic pressure; and PWV = cardio-ankle pulse wave velocity). Theoretically, CAVI is not affected by BP. The mean CAVI of each side was used for the analysis.

3.4. Assessment of Carotid Artery IMT and Plaque Presence

Assessment of carotid artery IMT was performed by ultrasound using an Aplio 500 device (Cannon Medical Systems, Otawara, Japan), as previously described[27]. All estimations of carotid IMT and plaque were performed by well-trained clinical laboratory technicians who were blinded to other clinical information. Common carotid artery IMT and the presence of plaque were evaluated by the manual method using a 7.5 MHz frequency probe. All participants were examined in the supine position. IMT was measured in the far wall at ~20 mm from the carotid bifurcation using recorded images of the carotid artery. The mean common carotid artery IMT of each side was used for the analysis.

Table 3. Results of multiple regression analysis showing the association of cardio-ankle vascular index and/or each obesity-related index with carotid mean intima-media thickness in all participants (n=7,750)

a) Analysis using either CAVI or each obesity-related index as an independent variable

Variable	Carotid mean intima-media thickness			
	Model 1		Model 2	
	Coefficient (β)	P value	Coefficient (β)	P value
CAVI	0.022	0.065	0.013	0.265
Body mass index	0.173	<0.0001	0.140	<0.0001
Percent body fat	0.123	<0.0001	0.075	<0.0001
Waist circumference	0.159	<0.0001	0.124	<0.0001
Visceral fat area	0.128	<0.0001	0.085	<0.0001

CAVI, cardio-ankle vascular index.
Model 1 was adjusted for age, gender, and smoking status.
Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine, plus those for Model 1.

b) Analysis using both CAVI and each obesity-related index as independent variables

Variable	Carotid mean intima-media thickness			
	Model 1		Model 2	
	Coefficient (β)	P value	Coefficient (β)	P value
CAVI	0.074	<0.0001	0.058	<0.0001
Body mass index	0.188	<0.0001	0.155	<0.0001
CAVI	0.037	<0.01	0.023	0.056
Percent body fat	0.126	<0.0001	0.077	<0.0001
CAVI	0.052	<0.0001	0.038	<0.01
Waist circumference	0.166	<0.0001	0.131	<0.0001
CAVI	0.030	<0.05	0.019	0.104
Visceral fat area	0.130	<0.0001	0.089	<0.0001

CAVI, cardio-ankle vascular index.
Model 1 was adjusted for age, gender, and smoking status.
Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine, plus those for Model 1.

3.5. Assessment of VFA

Assessment of VFA was performed by CT imaging using an Aquillion system (Cannon Medical Systems), as previously described[27]. The umbilicus was assessed for areas of visceral and subcutaneous fat in accordance with the guidelines for obesity treatment set by the Japan Society for the Study of Obesity. Modified measurement levels were adopted in cases of apparently low umbilical body type. Image analysis software SlimVision V4.0 (Cybernet Systems, Tokyo, Japan) was used at an attenuation range of -70 to -160 Hounsfield units to quantify abdominal areas of adipose tissue. The VFA was defined as intra-abdominal fat bound by the parietal peritoneum or transversalis fascia.

3.6. Statistical Analysis

Data were analyzed using SPSS Statistics 19 (IBM Corp., Chicago, IL, USA). Dichotomous variables (gender and smoking status) were assigned a value of 0 (female and non-smoking) or one (male and smoking). Data with a normal distribution are expressed as mean ± standard deviation (SD). Comparative analyses of continuous variables were performed using t-tests. Univariate and multivariate regression analyses were performed as appropriate. Logistic regression analyses were performed to determine the independent variables. A two-tailed $P<0.05$ value was considered significant.

Table 4. Results of logistic regression with the endpoint of carotid atherosclerosis (intima-media thickness ≥ 1.1mm) in all participants (n=7,750)

a) Analysis using either CAVI or each obesity-related index as an independent variable

Variable	Carotid atherosclerosis (IMT ≥ 1.1 mm)					
	Model 1			Model 2		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
CAVI	1.214	1.105−1.128	<0.0001	1.170	1.059−1.293	<0.01
Body mass index	1.029	1.004−1.054	<0.05	0.993	0.966−1.021	0.611
Percent body fat	1.020	1.006−1.034	<0.01	0.999	0.983−1.015	0.918
Waist circumference	1.023	1.014−1.031	0.060	0.995	0.985−1.006	0.370
Visceral fat area	1.003	1.001−1.004	<0.01	1.001	0.998−1.002	0.988

CAVI , cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval.
IMT ≥ 1.1 mm indicates having carotid atherosclerosis.
Model 1 was adjusted for age, gender, and smoking status.
Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine, plus those for Model 1.

b) Analysis using both CAVI and each obesity-related index as independent variables

Variable	Carotid atherosclerosis (IMT ≥ 1.1 mm)					
	Model 1			Model 2		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
CAVI	1.247	1.129−1.377	<0.0001	1.173	1.059−1.300	<0.01
Body mass index	1.039	1.014−1.065	<0.01	1.003	0.975−1.032	0.825
CAVI	1.222	1.108−1.347	<0.0001	1.171	1.059−1.294	<0.01
Percent body fat	1.021	1.007−1.035	<0.01	1.001	0.985−1.017	0.887
CAVI	1.227	1.112−1.353	<0.0001	1.166	1.054−1.290	<0.01
Waist circumference	1.010	1.001−1.019	<0.05	0.998	0.987−1.008	0.634
CAVI	1.214	1.101−1.338	<0.001	1.170	1.059−1.293	<0.001
Visceral fat area	1.003	1.001−1.004	<0.01	1.001	0.998−1.002	0.917

CAVI , cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval.
IMT ≥ 1.1 mm indicates having carotid atherosclerosis.
Model 1 was adjusted for age, gender, and smoking status.
Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine, plus those for Model 1.

4. Results

Of the 7,750 individuals enrolled in the study, the majority (92.1%) were men (**Table 1**). The number of participants (percentage of total) who met the diagnostic criteria of metabolic syndrome based on waist circumference (85 cm for men or 90 cm for women) was 411 (5.3%), while 277 participants (3.6%) were diagnosed with true metabolic syndrome based on visceral fat obesity defined by a VFA ≥ 100 cm^2.

The obesity-related indices were significantly correlated with each other (**Table 2**). Among them, the highest correlation coefficient was observed between BMI and waist circumference while the lowest correlation coefficient was observed between percent body fat and VFA. Each obesity-related index was positively correlated with mean carotid IMT in univariate regression analysis (**Table 2**). On the other hand, VFA was positively correlated with CAVI while the other obesity-related indices were negatively correlated with CAVI (**Table 2**). To investigate whether CAVI and/or each obesity-related index predicts atherosclerosis, we conducted multiple regression analysis taking carotid IMT as an dependent variable (**Table 3**) and logistic regression analysis with the endpoint of carotid atherosclerosis (carotid IMT greater than 1.1 mm[30]) (**Table 4**). These additional analyses showed that the CAVI was partially associated with the carotid IMT in the multi-

Table 5. Results of logistic regression analysis with the endpoint of "obesity" based on each obesity-related criterion (n=7,750).

Variable	General obesity		Body fat obesity		Abdominal obesity		Visceral fat obesity	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Model 1								
CAVI, per 1.0	0.501 (0.456−0.550)	<0.0001	0.783 (0.718−0.852)	<0.0001	0.637 (0.589−0.690)	<0.0001	0.853 (0.773−0.942)	<0.0001
Carotid IMT, per 0.1 mm	1.408 (1.396−1.569)	<0.0001	1.304 (1.233−1.379)	<0.0001	1.408 (1.377−1.482)	<0.0001	1.302 (1.222−1.387)	<0.0001
Model 2								
CAVI, per 1.0	0.442 (0.399−0.489)	<0.0001	0.751 (0.686−0.824)	<0.0001	0.579 (0.532−0.631)	<0.0001	0.782 (0.703−0.870)	<0.0001
Carotid IMT, per 0.1 mm	1.327 (1.246−1.414)	<0.0001	1.163 (1.095−1.236)	<0.0001	1.285 (1.216−1.359)	<0.0001	1.170 (1.093−1.252)	<0.0001

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval.
General obesity was diagnosed by a body mass index ≥ 25 kg/m^2. Body fat obesity was diagnosed by a percent body fat ≥ 25% for men or ≥ 30% for women. Abdominal obesity was diagnosed by a waist circumference ≥ 85 cm for men or ≥ 90 cm for women. Visceral fat obesity was diagnosed by a visceral fat area ≥ 100 cm^2.
Model 1 was adjusted for age, gender, and smoking status.
Model 2 was further adjusted for systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglyceride, fasting blood glucose, and creatinine, plus those for Model 1.
The cardio-ankle vascular index and intima-media thickness were simultaneously included as independent variables in both models.

ple regression analysis and was independently associated with carotid atherosclerosis in the logistic regression analysis.

On the other hand, logistic regression analyses with the endpoint of "obesity" for each obesity-related index showed that CAVI was negatively associated with the obesity criteria where IMT was positively associated with the obesity criteria (**Table 5**). In contrast, logistic regression analysis with the endpoint of metabolic syndrome, based on either waist circumference or VFA, revealed that both CAVI and IMT were positively associated with the presence of metabolic syndrome (**Table 6**).

5. Discussion

The main findings of the present study are that: (i) the evaluated obesity-related indices, including BMI, percent body fat, waist circumference, and VFA, were significantly correlated with each other; (ii) all of the obesity-related indices were positively associated with IMT but negatively associated with CAVI in multivariate regression analysis; (iii) CAVI was negatively associated, but IMT was positively associated, with obesity in logistic regression analysis where both CAVI and IMT were simultaneously included; and (iv) logistic regression analysis with the endpoint of metabolic syndrome revealed that both CAVI and IMT were positively associated with the presence of metabolic syndrome, however the odds ratio for IMT was greater than for CAVI when the metabolic syndrome was based on visceral fat obesity. The observed inconsistencies between the relationships of obesity-related indices with regard to CAVI and to IMT in middle-aged untreated workers may suggest that the progression of atherosclerosis might be underestimated when evaluated only by a single measurement of CAVI in the early stages of atherosclerosis.

General obesity and abdominal obesity are easily diagnosed by the measurement of BMI and waist circumference, respectively. Several investigators have suggested that the definition of obesity using BMI should be different in Asian people compared to Caucasian people, since the proportion of bone and muscle mass and distributions of body fluid are different in Asian and Caucasian people[24, 25]. Actually, the Japanese guidelines for obesity adopt BMI ≥ 25 kg/m^2 as the definition of obesity[24]. Thus, BMI should be carefully employed when comparing individuals with apparently different body types. However, it is often difficult to distinguish excess body fat using BMI, since weight gain could be derived not only from body fat but also from bone or muscle[31, 32]. The measurement of percent body fat, defined as the proportion of body fat mass to body weight, can be easily measured with a bioelectrical impedance analyzer by an automated appa-

Table 6. Results of logistic regression analysis with the endpoint of metabolic syndrome in all participants (n=7,750).

Variable	Based on abdominal obesity		Based on visceral fat obesity	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Model 1				
CAVI, per 1.0	1.339 (1.197−1.499)	<0.0001	1.188 (1.003−1.406)	<0.05
Carotid IMT, per 0.1 mm	1.309 (1.217−1.409)	<0.0001	1.439 (1.292−1.602)	<0.0001
Model 2				
CAVI, per 1.0	1.338 (1.196−1.497)	<0.0001	1.191 (1.006−1.409)	<0.05
Carotid IMT, per 0.1 mm	1.311 (1.218−1.411)	<0.0001	1.485 (1.288−1.598)	<0.0001

CAVI, cardio-ankle vascular index; IMT, intima-media thickness; CI, confidence interval.
Endpoint of analysis fulfilled the criteria of metabolic syndrome, which is a combination of either abdominal obesity (waist circumference ≥ 85 cm for men and ≥ 90 cm for women) or visceral fat obesity (visceral fat area ≥ 100 cm^2) and two other risk factors from lipid metabolism disorder (triglyceride ≥ 150 mg/dL and/or high-density lipoprotein cholesterol < 40 mg/dL), high blood pressure (systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg), or high fasting blood glucose (fasting blood glucose ≥ 110 mg/dL).
Model 1 was adjusted for age, gender, and smoking status.
Model 2 was further adjusted for creatinine, plus those for Model 1.

ratus, could be a useful tool for distinguishing body fat from other body compositions, such as bone and muscle, but it has not to date been sufficiently validated and, thus, is often used in combination with BMI[33-37]. Moreover, percent body fat is totally calculated without the separation of subcutaneous and visceral fat content. On the other hand, VFA highlights a different aspect of obesity from BMI or percent body fat, and anthropometric measurement of waist circumference is an alternative method to identify visceral fat-related abdominal obesity[7-10].

There have been some previous studies that have reported a positive relationship between CAVI and VFA, but the number of enrolled individuals was less than 500[38-40]. Thus, a further study with a large number of people was needed to ascertain the conclusion. Hence, in the present study, we investigated the association between CAVI and obesity-related indices, including waist circumference and VFA, and demonstrated that both abdominal obesity and visceral fat obesity, as well as general obesity, had similar impacts on CAVI in middle-aged participants. Strikingly, VFA, as well as the other obesity-related indices evaluated in the present study, was positively associated with the progression of carotid IMT but negatively associated with CAVI. CAVI is a functional index calculated from physiological parameters and is pathologically characterized by decreased arterial elasticity following the loss of elastic fiber content, while carotid IMT represents morphological changes due to pathological thickening in the vascular wall[41-44]. Although the detail of the mechanisms are not clearly understood, a negative association between CAVI and BMI has also been reported previously in children and young adults[17, 18]. In these previous studies, the negative association was considered as a physiological adaptation to the hyperemic state of obesity and a transient response in this period[17, 18]. The present study showed in a multiple regression analysis that CAVI was partially associated with carotid IMT and showed in a logistic regression analysis that CAVI was independently associated with carotid atherosclerosis. CAVI itself might not be a significant predictor for IMT, but the adjustment for obesity-related indices made CAVI a significant predictor for IMT. This implies that obesity has an unfavorable influence on CAVI measurements as an index of atherosclerosis, which is compatible with the negative association between obesity and CAVI observed in the present study. Consequently, both CAVI and each obesity-related index have a significant impact on the carotid IMT.

Since obesity and adiposity are basic concepts of metabolic syndrome, we investigated the association between the presence of metabolic syndrome and CAVI or carotid IMT. Although literature regarding the relationship between CAVI and metabolic syndrome has been previously published, VFA had not been evaluated by CT imaging in these previous reports[40, 45, 46]. The Japanese guidelines recommend that people who fulfill the criteria of metabolic syndrome based on waist circumference should be measured for visceral fat accumulation by CT imaging, and people with a VFA ≥ 100 cm^2 are diagnosed as having true metabolic syndrome[11]. In previous studies, based on visceral fat accumulation by CT imaging both CAVI and IMT were not simultaneously assessed in relation to metabolic syndrome[45-49]. The present study revealed that both CAVI and carotid IMT had a positive association with metabolic syndrome defined by a VFA ≥ 100 cm^2. Nagayama *et al.* in their study reported a negative rela-

tionship between CAVI and BMI in healthy individuals with a mean age of 47.1 years[50]. Other investigators have also reported a similar inverse relationship between CAVI and BMI in 2,354 adults ranging in age from 35 to 74 years, with a mean age of 61.4 years[51]. These previous reports support the findings obtained in the present study. On the other hand, the study by Nagayama *et al*. also observed that: (1) CAVI positively correlates with VFA at baseline; (2) changes in CAVI and VFA are positively correlated with each other after a weight-loss diet; and (3) the change in VFA is a significant independent predictor for change in CAVI in patients with metabolic syndrome[40]. These findings support the concept that the impact of obesity on CAVI is different in healthy individuals compared to patients with metabolic syndrome. The present results are compatible with this concept, because most of our study participants did not have metabolic syndrome. Metabolic syndrome is an overlapping of metabolic disruptions and, therefore, vascular inflammation is stronger and cardiovascular risk is higher than in cases of simple visceral fat obesity[7-10]. This may be the reason why metabolic syndrome promotes arterial stiffness rather than simple visceral fat accumulation. These findings reinforce the notion that subclinical atherosclerosis in metabolic syndrome is morphologically promoted from the early stage and is followed by slow functional progression, and that, in order not to miss the slow progression of functional atherosclerosis, subclinical atherosclerosis should be periodically assessed, not only in individuals with metabolic syndrome, but also in obese individuals who present modest values for CAVI. Although the usefulness of CAVI for detecting arterial stiffness and cardiovascular events has been established[46, 52, 53], assessment of subclinical atherosclerosis using CAVI alone should be carefully interpreted when evaluated only at one timepoint without periodic measurements.

The present study has several limitations and the findings should thus be interpreted with caution. Firstly, this was a cross-sectional study and the background of the participants enrolled in the study was heterogeneous. Secondly, no causal relationships were investigated in this study. Further investigations with a longitudinal design are necessary for definite conclusions to be drawn. Thirdly, the majority of the enrolled participants were men and the proportion of women was quite low. Although the multivariate analyses were adjusted for gender, the results obtained might only be applicable to men.

6. Conclusions

Obesity-related indices were correlated with each other and had significant associations with the examination of subclinical atherosclerosis in middle-aged untreated workers. Inconsistencies were observed between visceral fat accumulation and early-stage atherosclerosis with CAVI preserved but carotid IMT increased, while both carotid IMT and CAVI were worsened with the development of metabolic syndrome.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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