Original Article

Impact of Metabolic Syndrome on Brachial-Ankle Pulse Wave Velocity in Japanese

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The aim of this study was to determine the effect of metabolic syndrome on brachial-ankle pulse wave velocity (baPWV) by using the new guidelines for diagnosis of this syndrome in Japan. We examined 525 men and women without a history of cardiovascular disease or cancer, and an ankle-brachial index < 0.9. The baPWV was measured using a device (Form PWV/ABI) that simultaneously monitored bilateral brachial and ankle pressure wave forms. Metabolic syndrome was defined as a waist circumference ≥ 85 (90) cm in men (women) and two or more of the following risk factors: hypertension, dyslipidemia, and glucose intolerance diagnosed by a 75 g oral glucose tolerance test. The baPWV showed a significant linear relationship with waist circumference, waist-to-hip ratio, body fat, systolic and diastolic blood pressure, triglycerides, fasting glucose, 2-h-postload glucose, fasting insulin, and glycosylated hemoglobin-A_{1c}, after adjusting for sex and age. These factors were also strongly related to fasting insulin levels. When subjects were classified into six groups based on waist circumference and the number of risk factors for metabolic syndrome (0, 1, and ≥2), we found that more risk factors clearly increased the odds ratios for an elevated baPWV in those subjects in the highest quartile of the baPWV distribution in multivariate logistic models. An increase in odds ratio was observed despite a normal waist circumference and may well have been due to increased fasting insulin and blood pressure levels. An increase in the number of risk factors for metabolic syndrome was highly correlated with an increased baPWV, probably due to insulin resistance. (*Hypertens Res* 2006; 29: 29–37)

***Key Words*: brachial-ankle pulse wave velocity, metabolic syndrome, insulin resistance, epidemiology**

Introduction

Pulse wave velocity (PWV) is an effective index of the arterial stiffness of large arteries, and is widely used for noninvasive assessment of atherosclerosis (*1*, *2*). It was documented that a PWV measurement predicted future cardiovascular events in hypertensive patients (*3*) and elderly individuals (*4*, *5*), and was of benefit for evaluating carotid arteriosclerosis (*6*). Indeed, PWV values have been closely related to cardiovascular risk factors such as age, blood pressure, diabetes (*7*–*10*), and abdominal aortic calcification (*11*). These findings imply that PWV is greatly influenced by the atherosclerotic process.

Recently, the concept of metabolic syndrome, as proposed by Reaven (*12*), has become important for disease prevention

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Table 1. Means±SD and Percentages of Investigated Variables in Men and Women with and without Metabolic Syndrome

	Both sexes		Men		Women	
	Metabolic syndrome		Metabolic syndrome		Metabolic syndrome	
	Present (n=58)	Absent (n=467)	Present (n=37)	Absent (n=149)	Present (n=21)	Absent (n=318)
Age (years)	61.5±10.0**	56.9±11.0	61.1±10.3*	56.4±12.2	62.2±9.8*	57.1±10.4
Body mass index (kg/m^2)	26.4±3.1***	23.0±3.0	25.9±2.1***	23.8±2.6	27.4±4.2***	22.7±3.1
Waist circumference (cm)	92.9±6.7***	79.3±9.3	90.9±4.6***	82.4±7.1	96.5±8.3***	77.8±9.9
Waist-to-hip ratio	0.95±0.05***	0.86±0.08	0.93±0.04***	0.88±0.06	0.98±0.04***	0.86±0.08
Body fat (%)	31.3±8.0*	29.2±7.5	26.0±2.4***	22.4±4.7	40.5±5.6***	32.3±6.3
Systolic blood pressure (mmHg)	125.5±15.4***	113.2±16.5	123.9±15.3**	114.6±16.1	128.3±15.6***	112.5±16.7
Diastolic blood pressure (mmHg)	77.6±8.7***	70.0±10.5	76.8±9.5*	72.1±11.1	79.0±7.2***	69.1±10.0
Total cholesterol (mmol/l)	5.16±0.79	5.34±0.84	5.09±0.77	5.08±0.85	5.28±0.82	5.46±0.82
Low-density lipoprotein cholesterol (mmol/l)	3.28±0.76	3.36±0.78	3.26±0.77	3.23±0.83	3.31±0.77	3.43±0.76
High-density lipoprotein cholesterol (mmol/l)	1.26±0.30***	1.50±0.34	1.16±0.24***	1.37±0.30	1.44±0.31	1.57±0.34
Triglycerides† (mmol/l)	1.37***	1.01	1.58***	1.16	1.08	0.95
Uric acid (μmol/l)	358.1±79.1***	296.2±76.1	386.0±80.9	358.7±75.5	308.7±49.4**	267.1±55.9
Fasting glucose† (mmol/l)	5.8***	5.3	6.0***	5.4	5.5	5.2
2-h-postload glucose† (mmol/l)	9.6***	6.7	9.3***	6.6	10.0***	6.8
Fasting insulin† (mmol/l)	42***	21	39***	22	48***	20
Glycosylated hemoglobin-A_{1c} (%)	5.26±0.84***	4.87±0.48	5.27±0.94**	4.82±0.53	5.23±0.64*	4.89±0.45
Hypertension‡ (%)	64.4***	20.3	52.6***	18.7	85.7***	21.1
Dyslipidemia‡ (%)	66.1	55.6	71.1*	52.0	57.1	57.2
Diabetes‡ (%)	25.4***	5.6	26.3**	8.0	23.8***	4.4
Left ventricular hypertrophy§ (%)	5.2	5.1	5.4	10.7	4.8	2.5
Current smoker (%)	24.6	15.2	33.3	35.6	9.5	5.7
Alcohol drinker (%)	36.2*	23.8	54.1	55.7	4.8	8.8
Regular exercise (%)	58.6	50.9	62.2	53.0	52.4	49.8
Brachial-ankle pulse wave velocity (cm/s)	1,587±305***	1,425±277	1,588±331*	1,468±293	1,584±261**	1,405±267

*p<0.05, **p<0.01, ***p<0.001 for differences *vs*. subjects without metabolic syndrome. †Geometric means. ‡Hypertension was defined as a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg or the current use of any antihypertensive medication. Dyslipidemia was defined as a total cholesterol level ≥5.69 mmol/l (220 mg/dl), a high-density lipoprotein cholesterol <1.03 mmol/l (40 mg/dl), a triglycerides level ≥1.68 mmol/l (150 mg/dl), or current use of any dyslipidemic agent. Diabetes was defined as a fasting serum glucose level ≥7.0 mmol/l (126 mg/dl), a 2-h-postload glucose level ≥11.1 mmol/l (200 mg/dl), or current use of any diabetes medication. §Defined as the Minnesota code 3-1 by the electrocardiogram.

related to atherosclerosis (*13*, *14*). Although the National Cholesterol Education Program's Adult Treatment Panel III (ATPIII) (*15*) or WHO (*16*) criteria have been commonly cited for the definition of metabolic syndrome, a new guideline for metabolic syndrome in Japanese was introduced in 2005. This guideline revised the earlier criteria such that abdominal obesity is now considered an underlying cause of metabolic syndrome, and it primarily requires an assessment of waist circumference based on the body composition of Japanese (*17*).

In the present study, we examined the association between metabolic syndrome and brachial-ankle PWV (baPWV) in the general Japanese population. Although a few previous studies have demonstrated an association between the two (*18*, *19*), it is important to re-examine this association based on the new guidelines for the diagnosis of metabolic syndrome in Japanese. Furthermore, since the 2-h-postload glucose value is considered to be more accurate for the detection of glucose intolerance than fasting glucose, a 75 g oral glucose tolerance test (OGTT) was performed.

Methods

Study Population

There were 542 residents aged 30–79 years in Asuka Village, Nara Prefecture, Japan, who participated in the Asuka Diabetes and Atherosclerosis Prevention Program from 2003 to

Table 2. Pearson's Correlation Coefficients ($n=525$)

	baPWV	BMI	WC	WHR	BF	SBP	DBP	TCH	LDLC	HDLC	TG	UA	FBS	2-h-BS	FIRI	HbA_{1c}
baPWV	1.000															
BMI	0.094*	1.000														
WC	0.244***	0.743***	1.000													
WHR	0.329***	0.448***	0.851***	1.000												
BF	0.089*	0.562***	0.417***	0.289***	1.000											
SBP	0.613***	0.290***	0.297***	0.272***	0.182***	1.000										
DBP	0.502***	0.287***	0.296***	0.276***	0.116**	0.845***	1.000									
TCH	0.061	−0.013	0.012	0.028	0.214***	0.121**	0.078	1.000								
LDLC	0.071	0.103*	0.106*	0.082	0.225***	0.123**	0.074	0.875***	1.000							
HDLC	−0.113**	−0.350***	−0.351***	−0.246***	−0.013	−0.095*	−0.111*	0.257***	−0.083	1.000						
TG†	0.238***	0.288***	0.300***	0.249***	0.058	0.261***	0.311***	0.123**	0.110*	−0.525***	1.000					
UA	0.126**	0.352***	0.358***	0.237***	−0.163***	0.171***	0.243***	−0.063	−0.001	−0.289***	0.321***	1.000				
FBS†	0.247***	0.164***	0.180***	0.166***	−0.038	0.239***	0.227***	0.031	0.032	−0.150***	0.239***	0.107*	1.000			
2-h-BS†	0.229***	0.259***	0.260***	0.241***	0.203***	0.271***	0.231***	0.070	0.046	−0.082	0.224***	0.049	0.574***	1.000		
FIRI†	0.168***	0.556***	0.410***	0.273***	0.349***	0.322***	0.326***	0.042	0.122**	−0.331***	0.397***	0.298***	0.310***	0.251***	1.000	
HbA_{1c}	0.213***	0.134**	0.166***	0.167***	0.131**	0.193***	0.155***	0.123**	0.102*	−0.088*	0.240***	−0.036	0.677***	0.602***	0.176***	1.000

*$p<0.05$, **$p<0.01$, ***$p<0.001$. †Calculated after log-transformation. baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio; BF, body fat; SBP, systolic blood pressure; DBP, diastolic blood pressure; TCH, total cholesterol; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TG, triglycerides; UA, uric acid; FBS, fasting glucose; 2-h-BS, 2-h-postload glucose; FIRI, fasting insulin; HbA_{1c}, glycosylated hemoglobin-A_{1c}.

Table 3. Sex- and Age-Adjusted Means and Percentages (Unadjusted) by Quartile of Brachial-Ankle Pulse Wave Velocity

	Quartile of brachial-ankle pulse wave velocity					
	Q1 (low) (n=131)	Q2 (n=131)	Q3 (n=132)	Q4 (high) (n=131)	p value[¶]	p for trends[#]
Brachial-ankle pulse wave velocity (cm/s)	1,149	1,320	1,468	1,836	<0.001	
Sex (% male)	25.2	38.2	38.6	39.7	<0.001	
Age	48.6	54.8	60.3	65.7	<0.001	
Body mass index (kg/m^2)	22.8	23.3	23.8	23.7	0.116	0.199
Waist circumference (cm)	78.6	80.2	82.2	82.1	0.026	0.033
Waist-to-hip ratio	0.85	0.87	0.88	0.89	0.006	0.002
Body fat (%)	27.9	28.8	30.3	30.5	0.007	0.008
Systolic blood pressure (mmHg)	99.5	109.3	116.7	132.5	<0.001	<0.001
Diastolic blood pressure (mmHg)	62.4	68.4	73.2	79.6	<0.001	<0.001
Total cholesterol (mmol/l)	5.25	5.38	5.37	5.29	>0.2	>0.2
Low-density lipoprotein-cholesterol (mmol/l)	3.25	3.41	3.42	3.33	>0.2	>0.2
High-density lipoprotein cholesterol (mmol/l)	1.54	1.48	1.44	1.45	0.138	0.060
Triglycerides[†] (mmol/l)	0.83	1.07	1.13	1.20	<0.001	<0.001
Uric acid (μmol/l)	289.2	306.6	310.4	306.9	0.082	>0.2
Fasting glucose[†] (mmol/l)	5.2	5.3	5.4	5.5	0.001	0.005
2-h-postload glucose[†] (mmol/l)	6.5	6.9	7.2	7.5	0.007	0.056
Fasting insulin[†] (mmol/l)	17	21	26	28	<0.001	<0.001
Glycosylated hemoglobin-A_{1c} (%)	4.81	4.87	4.92	5.03	0.053	0.021
Hypertension[‡] (%)	3.8	12.1	28.0	56.8	<0.001	<0.001
Dyslipidemia[‡] (%)	41.2	58.3	62.9	64.4	0.144	0.024
Diabetes[‡] (%)	3.1	7.6	5.3	15.2	0.063	0.047
Left ventricular hypertrophy[§] (%)	2.3	3.8	2.3	12.9	0.079	>0.2
Current smoker (%)	17.6	17.6	15.9	14.4	>0.2	>0.2
Alcohol drinker (%)	22.1	27.3	22.7	28.8	>0.2	>0.2
Regular exercise (%)	47.3	45.8	53.0	61.4	>0.2	>0.2
Metabolic syndrome (%)	4.6	7.6	13.6	18.3	0.002	0.033

[†, ‡, §]The same as indicated in Table 1. [¶]Calculated by analysis of covariance (continuous) or the Mantel-Haenszel method (dichotomous) adjusted for sex and age. [#]Calculated by the regression model (continuous) or the Mantel-Haenszel correlation statistics (dichotomous) using continuous brachial-ankle pulse wave velocity values or scores of its quartile adjusted for sex and age.

2004. Asuka Village is located in a rural community of the Kinki area, and the 2000 census reported that the percentage of the population aged ≥65 years was 23.9%, and 12.4% of households were agriculturally based.

Of the 542 residents, we selected 525 for this analysis after exclusion of those who had a history of myocardial infarction, angina, stroke, or cancer; who did not give informed consent; or who did not have an ankle-brachial index <0.9.

This study was approved by the Ethical Review Committee of Nara Medical University (No. 88). Written informed consent was obtained from all participants under the privacy policy of this approval.

Measurements

Overnight fasting blood samples were drawn from an antecubital vein into vacuum tubes containing a serum separator gel (for glucose and blood chemistries). The serum tube was centrifuged immediately at 3,000 × g for 15 min, and the separated serum was quickly frozen in a box with dry ice. The frozen samples were sent to the Osaka Medical Center for Health Science and Promotion, where all blood measurements were performed.

Enzymatic methods were used to measure serum total cholesterol (TCH) and triglycerides (TG) levels. Both low-density lipoprotein cholesterol (LDLC) and high-density lipoprotein cholesterol (HDLC) were measured by using the direct homogeneous method (Daiichi Pure Chemicals, Tokyo, Japan). This laboratory is a member of the US National Cholesterol Reference Method Laboratory Network (CRMLN). Lipid measurements have been standardized by the CDC-NHLBI Lipid Standardization Program provided by the Centers for Disease Control and Prevention (Atlanta, USA) (*20*). Uric acid (UA) was assayed by enzymatic methods (Kyowa Medex, Tokyo, Japan). Serum glucose was measured by the hexokinase method (Sysmex, Kobe, Japan). Glycosylated hemoglobin-A_{1c} (HbA_{1c}) was measured by latex agglutination immunoassay (Kyowa Medex). These serum assays were per-

Table 4. Multivariate Adjusted Odds Ratios for an Elevated Brachial-Ankle Pulse Wave Velocity in Subjects in the Highest Quartile of Brachial-Ankle Pulse Wave Velocity

	Waist circumference					
	<85 (90) cm in men (women)			≥85 (90) cm in men (women)		
	Number of risk factors†			Number of risk factors†		
	0	1	≥2	0	1	≥2‡
Number	188	119	79	29	52	58
Sex (% male)	22.3	31.1	28.8	62.1	57.7	64.4
Age (years)	52.9	59.8	61.2	55.3	58.7	61.5
Sex- and age-adjusted means						
Brachial-ankle pulse wave velocity (cm/s)	1,351	1,472	1,575	1,372	1,466	1,518
Waist circumference (cm)	75.0	77.2	79.3	91.9	92.7	92.3
Systolic blood pressure (mmHg)	105.3	115.4	126.2	111.7	118.1	124.8
Fasting insulin§ (mmol/l)	16	22	29	25	30	44
2-h-postload glucose§ (mmol/l)	5.8	7.3	8.6	6.0	7.1	9.5
Model 1¶						
Odds ratio	1.00	3.71***	9.53***	2.30	3.30*	5.08***
95% confidence interval		1.77–7.75	4.40–20.6	0.68–7.73	1.31–8.31	2.16–11.9
Model 2¶						
Odds ratio	1.00	3.99***	10.6***	2.20	3.58**	5.96***
95% confidence interval		1.85–8.59	4.77–23.6	0.63–7.71	1.41–9.08	2.46–14.4

*$p<0.05$, **$p<0.01$, ***$p<0.001$. †Indicated as hypertension, dyslipidemia, and glucose intolerance, *i.e.*, a blood pressure level ≥130/85 mmHg; a high-density lipoprotein cholesterol level <1.03 mmol/l (40 mg/dl) or a triglycerides level ≥1.68 mmol/l (150 mg/dl); a fasting glucose level ≥6.1 mmol/l (110 mg/dl) or a 2-h-postload glucose level ≥11.1 mmol/l (200 mg/dl). Subjects taking medications for each component were included as having risk factors. ‡Defined as metabolic syndrome. §Geometric means. ¶Model 1: adjusted for sex and age; Model 2: adjusted for model 1 plus left ventricular hypertrophy, current smoker, alcohol drinker and regular exercise.

formed by an automatic analyzer (AU2700; Olympus, Tokyo, Japan). Insulin was measured by using the electrochemiluminescence method in ECLusys (Roche Diagnostics, Tokyo, Japan). Intra-assay coefficients of variation (CV) were less than 3% for all assays in this laboratory.

Blood pressure was measured twice in the sitting position after a rest of at least 5 min using an automatic sphygmomanometer (BP-103iII; Colin Medical Technology, Komaki, Japan). The mean of the two measurements was used for analysis. Hypertension was defined as a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood pressure (DBP) ≥90 mmHg or the current use of any antihypertensive medication. All participants received an OGTT after a 10-h fast. Three subjects were excluded from the test because of current diabetes medications. We used the American Diabetes Association criteria (*21*) to identify persons who had normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes by fasting and 2-h-postload glucose levels. Physicians measured the circumferences of the waist (umbilical level) and hips (pubis level) to calculate the waist-to-hip ratio (WHR). The body mass index (BMI, kg/m^2) was computed from the participants' weights and heights. Total body fat was measured by using a body fat calculator (BC-118; Tanita, Tokyo, Japan) based on leg-to-leg bioelectrical impedance analysis (BIA). Interviewers also assessed smoking status, alcohol consumption, and exercise habits.

Prevalent diabetes mellitus was defined as a fasting serum glucose level ≥7.0 mmol/l (126 mg/dl), a 2-h-postload glucose level ≥11.1 mmol/l (200 mg/dl), or the current use of any diabetes medication. Dyslipidemia was defined as a TCH level ≥5.69 mmol/l (220 mg/dl), an HDLC level <1.03 mmol/l (40 mg/dl), a TG level ≥1.68 mmol/l (150 mg/dl), or the current use of any dyslipidemic agent. The electrocardiogram was coded using the Minnesota code (*22*), in which left ventricular hypertrophy (LVH) is defined as a code of 3–1.

Brachial-Ankle Pulse Wave Velocity (baPWV)

The baPWV was assessed by using a Form PWV/ABI device (Colin Medical Technology, Komaki, Japan). Subjects were examined in the supine position after a rest of at least 5 min. The cuffs were wrapped on both sides of the brachium and ankle, and contained a plethysmographic sensor that determined the wave form data, including blood pressure measurements by the oscillometric method. The baPWV was calculated as distance/time (cm/s). The time delay between the arrival of the pulse wave at the brachium and ankle was automatically obtained by gating the pulse wave to the peak of the R wave of the electrocardiogram. The distance was estimated from a subject's height as $L = L_a - L_b$ (L_a: the path length from the heart to the ankle, L_b: the path length from the heart to the brachium) and adjusted for average Japanese

body composition. Then, we used the mean of the right and left baPWV values for analysis. The reproducibility of baPWV measurement has been validated previously (*23*). In our study, when the baPWV was measured twice in each individual by the same method at an interval of 10 months, the reliability was similar to that reported previously (Pearson's $r=0.83$, $n=70$).

Metabolic Syndrome

Metabolic syndrome was defined as a waist circumference level ≥85 cm in men and ≥90 cm in women and two or more of the following three risk factors: hypertension (a blood pressure level ≥130/85 mmHg), dyslipidemia (an HDLC level <1.03 mmol/l [40 mg/dl] or a TG level ≥1.68 mmol/l [150 mg/dl]), and glucose intolerance (a fasting glucose level ≥6.1 mmol/l [110 mg/dl] or a 2-h-postload glucose level ≥11.1 mmol/l [200 mg/dl]) (*17*). Subjects taking medications for any of the three components were also considered to have the corresponding risk factor. Although subjects who were treated for a low HDLC concentration or hypertriglyceridemia should have been recognized for the definition of dyslipidemia, we did not identify them correctly. Instead, we classified subjects who were taking any hyperlipidemic agent into the dyslipidemia category.

Data Analysis

Because of skewed distributions, TG, fasting glucose, 2-h-postload glucose, and fasting insulin values were transformed to logarithms for calculations. Sex- and age-adjusted means in the different quartiles of baPWV were calculated using analysis of covariance. To test for linear associations, we calculated the *p* value for trends using continuous baPWV values, adjusted for sex and age. Also, the Mantel-Haenszel correlation statistics stratified by sex and age groups were used to examine linear relationships between rates and scores of baPWV quartiles. Logistic models were used to calculate multivariate-adjusted odds ratios for the highest quartile of baPWV in those subjects who had 1 or ≥2 risk factors and a normal waist circumference; and who had 0, 1, or ≥2 risk factors and a high waist circumference. Subjects with a waist circumference <85 (90) cm in men (women) and 0 risk factors served as the reference group for the calculation of odds ratios. The odds ratios were adjusted for sex and age in model 1. LVH, current smoking status (yes, no), alcohol drinker (yes, no), and regular exercise (yes, no) were added by using dummy variables in model 2. We used SAS software, version 8.2 (SAS Institute, Inc., Cary, USA), for all analyses.

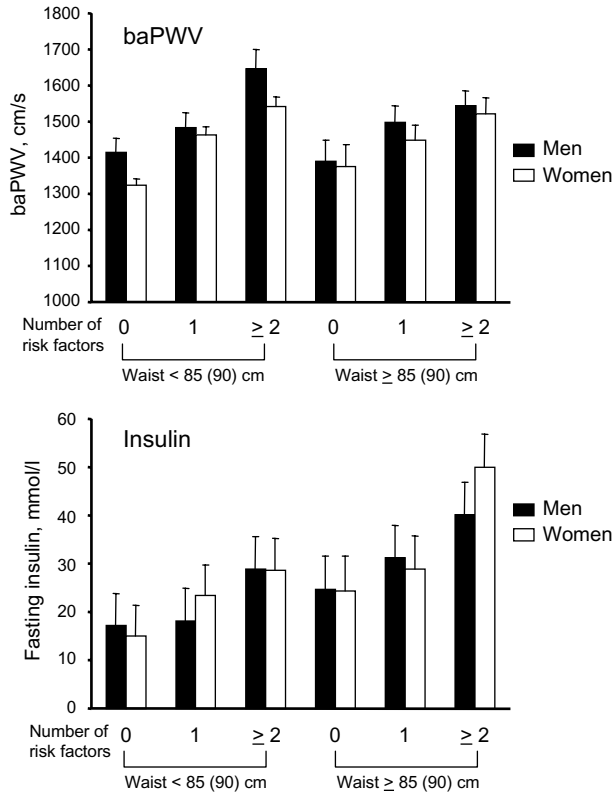

Fig. 1. *Sex-specified age-adjusted means of brachial-ankle pulse wave velocity (baPWV) and fasting insulin stratified by waist circumference and the number of risk factors for metabolic syndrome (hypertension, dyslipidemia, and glucose intolerance). The definition of metabolic syndrome for Japanese primarily requires a waist circumference of ≥85 cm in men and ≥90 cm in women. Error bars indicate the SEM.*

Results

Among our subjects, 37 (19.9%) men and 21 (6.2%) women were diagnosed with metabolic syndrome. Their risk profiles are listed in Table 1. Significant differences in BMI, waist circumference, WHR, body fat, SBP, DBP, HDLC, TG, UA, fasting glucose, 2-h-postload glucose, fasting insulin, and HbA_{1c} were found between the subjects with and without metabolic syndrome. Significantly higher percentages of hypertension, dyslipidemia, and diabetes were also found in the subjects with metabolic syndrome. LVH was most frequent in women with metabolic syndrome. The percentages of current smokers, alcohol drinkers, and regular exercisers were not different among the different groups. The baPWV values of subjects with and without metabolic syndrome were 1,587 cm/s and 1,425 cm/s, respectively. The baPWV was significantly higher in both male and female subjects with metabolic syndrome.

The baPWV was strongly correlated with SBP and DBP, and moderately with waist circumference, WHR, HDLC, TG, UA, fasting glucose, 2-h-postload glucose, fasting insulin, and HbA_{1c} (Table 2). The waist circumference, WHR, HDLC, TG, UA, fasting glucose, 2-h-postload glucose, and HbA_{1c} values were also correlated with fasting insulin levels and each other, with the majority of correlation coefficients being

>0.20.

When the data were stratified based on baPWV quartiles, significant differences were identified in waist circumference, WHR, body fat, SBP, DBP, TG, fasting glucose, 2-h-postload glucose, fasting insulin, hypertension, and metabolic syndrome (Table 3). Furthermore, there were significant linear trends between baPWV and waist circumference, WHR, body fat, SBP, DBP, TG, fasting glucose, fasting insulin, HbA_{1c}, hypertension, dyslipidemia, diabetes, and metabolic syndrome. TCH and LDLC levels were not different among the baPWV quartiles, and their associations with BMI, HDLC, and UA were weak. Subjects with hypertension made up 56.8% of patients in the highest baPWV quartile. The prevalence of diabetes and LVH was slightly greater in the upper baPWV quartiles.

Subjects were classified into six groups based on waist circumference and the number of risk factors. The sex- and age-adjusted means of baPWV, waist circumference, SBP, fasting insulin, and 2-h-postload glucose increased with the number of risk factors and waist circumference (Table 4). Using the subjects with a waist circumference <85 (90) cm in men (women) and 0 risk factors as a reference group (odds ratio, 1.00), the sex- and age-adjusted odds ratio for an elevated baPWV in subjects with metabolic syndrome was 5.08 (95% confidence interval, 2.16–11.9) in model 1. Similar to the mean baPWV, the odds ratios were elevated with an increase in the number of risk factors and waist circumference. After adjustment for health practices and LVH (model 2), the significant associations were unchanged. The sex-specific effects of metabolic categories on baPWV and fasting insulin levels were similar (Fig. 1). There were no interactions of sex with the associations among baPWV, fasting insulin levels and the accumulation of risk factors.

Discussion

The prevalence of metabolic syndrome was 19.9% for men and 6.2% for women in the present study. The new definition of metabolic syndrome for Japanese primarily requires a waist circumference ≥ 85 cm in men and ≥ 90 cm in women and requires two or more risk factors of hypertension, dyslipidemia, and glucose intolerance. These cutoff points of the waist circumference are believed to correspond to a visceral fat area of 100 cm^2 at the umbilical level (*24*). Although glucose intolerance can be defined from fasting glucose values alone, we believe that OGTT should be used as the gold standard for the diagnosis of impaired glucose tolerance. Had we not used the 2-h-postload value, the prevalence of metabolic syndrome would have been underestimated by 14.0% in men and 1.8% in women.

We found that baPWV was clearly associated with fasting insulin levels and insulin-related factors, leading to reduced insulin sensitivity. Despite a normal waist circumference, the aggregation of risk factors was associated with an elevated baPWV and insulin levels in both sexes. Unexpectedly, subjects with a normal waist circumference plus two or more risk factors had an increased odds ratio for an elevated baPWV, similar to the odds ratio in metabolic syndrome. This may imply that aggregation of metabolic components, especially hypertension (*6*), contributes to atherosclerosis in Japanese, despite a normal waist circumference, as hypertension was strongly associated with the incidence of stroke or ischemic heart disease in previous Japanese cohorts (*25*).

The value for the homeostasis model assessment of insulin resistance (HOMA-IR) is used as an index of insulin sensitivity (*26*). However, since the correlation coefficient between the HOMA-IR and insulin was 0.99 in the present study, the fasting insulin level was a reasonable estimate of the HOMA-IR index.

In present study, we determined the effect of metabolic syndrome on baPWV by using an updated definition of metabolic syndrome for Japanese. Although there have been a few similar studies in Japan (*18*, *19*), they did not assess waist circumference, which was an initial requirement in the updated diagnosis. Nonetheless, significant associations between PWV, insulin sensitivity, and glucose intolerance have been reported in previous studies despite various definitions of metabolic syndrome (*18*, *19*, *27–29*). A recent study also demonstrated that metabolic syndrome was strongly associated with subclinical atherosclerosis and aortic stiffness, using both the National Cholesterol Education Program and WHO definitions in the French population (*29*). The effects of metabolic syndrome on PWV and several risk factors in that study were somewhat consistent with our findings. The ATP III documented 6 components of metabolic syndrome related to cardiovascular diseases: abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance, a proinflammatory state, and a prothrombotic state (*15*). Therefore, elevated baPWV in the setting of metabolic syndrome is potentially mediated by the cumulative effects of these risk factors, considering that there is also a significant association between high-sensitivity C-reactive protein (hs-CRP) levels and baPWV among Japanese (*30*, *31*).

There is no doubt that LDLC directly participates in atherogenesis and is a great risk factor for cardiovascular events; however, we did not find an association between LDLC and baPWV in the present study, which is consistent with earlier studies (*27*, *30*). This was probably due to the weak association of LDLC with fasting insulin and blood pressure in the present study. Nonetheless, given the significant relationships of apolipoprotein B, which is a reasonable index of the number of LDL particles, and LDL particle size with central adiposity and insulin resistance (*32–34*), these specific measurements will help us understand the relationship between LDLC and baPWV in future investigations.

Although our study population was relatively small, a detailed assessment was performed using the revised definition of metabolic syndrome along with an OGTT. However, several limitations should be considered. First, because of the small number of participants, we did not present sex-specific

data. The prevalence of metabolic syndrome was different between men and women, but we did not find any interaction of sex with the relationship between metabolic disorders and baPWV, which is similar to the findings of other studies. Second, because of the inclusion criteria of our study, severe diabetics were not included, such as type 1 diabetics or individuals with the complications of diabetes. This may have caused a slight selection bias in our findings, which may weaken the association of diabetes-related factors with baPWV. Third, the degree to which the prevalence of metabolic syndrome determined in the present study is generalizable to other populations remains uncertain. Although similar rates have been reported (*19*), large populations will be needed to confirm the prevalence in Japan.

In conclusion, baPWV, representing arterial stiffness, was closely associated with the number of risk factors for metabolic syndrome, and this association was attributed to the effects of insulin resistance. Among the general Japanese population with a low coronary heart disease mortality rate (*35*), the atherosclerotic process might be strongly influenced by the action of insulin.

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