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ORIGINAL ARTICLE

Metabolic syndrome is a significant and independent risk factor for increased arterial stiffness in Japanese subjects

Hiroki Satoh[1,2], Reiko Kishi[2] and Hiroyuki Tsutsui[1]

Metabolic syndrome (MetS) has been recognized as a risk factor for cardiovascular disease; however, the impact of MetS on arterial stiffness has not been fully established in the general Japanese population. We analyzed the relationship between MetS and the severity of arterial stiffness using brachial-ankle pulse wave velocity (baPWV) in 2744 male and 358 female subjects aged 38–62 years, adjusted for conventional risk factors and C-reactive protein. The prevalence rates of MetS identified by Japanese criteria were 22.7% (n=624) and 7.8% (n=28) in male and female subjects, respectively. The subjects with MetS had significantly greater mean values of baPWV than those without MetS among both male and female subjects (1444 ± 209 *vs.* 1294 ± 165 cm/s in male subjects, $P<0.001$; 1379 ± 151 *vs.* 1220 ± 171 cm/s in female subjects, $P<0.001$). After adjustment for atherosclerotic variables such as age, smoking habits, total cholesterol and C-reactive protein, the odds ratio (OR) of MetS for increased baPWV was 3.65 in male subjects (95% confidence interval (CI): 2.99–4.47, $P<0.001$) and 8.02 in female subjects (95% CI: 3.18–20.25 $P<0.001$). In conclusion, MetS was identified as a significant and independent risk factor for increased arterial stiffness in both the male and female general population in Japan.
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Keywords: arterial stiffness; Japanese population; metabolic syndrome; pulse wave velocity

INTRODUCTION

Metabolic syndrome (MetS) is an accumulation of risk factors such as visceral obesity, hypertension, dyslipidemia and glucose intolerance,[1] and has been closely associated with increased risk of cardiovascular disease,[2–4] diabetes mellitus[5] and mortality.[6–8] MetS is defined according to the diagnostic criteria set forth by the National Cholesterol Education Program Adults Treatment Panel III (NCEP-ATPIII)[9] and the International Diabetes Federation (IDF).[10] In Japan, MetS is diagnosed by criteria proposed for the Japanese population in 2005.[11]

Arterial stiffness has been identified as an independent risk factor for cardiovascular disease and subsequent mortality.[12–15] The brachial–ankle pulse wave velocity (baPWV) obtained by a non-invasive automatic device is an indicator of arterial stiffness.[16,17] Several studies have indicated that MetS defined by the NCEP-ATPIII and IDF criteria is closely associated with increased arterial stiffness.[18–21] The impact of MetS defined by Japanese criteria on arterial stiffness, however, has not been fully examined in the general population in Japan. Moreover, previous studies have not examined the effects of MetS on arterial stiffness after adjustment for other atherogenic risk factors such as age, smoking, total cholesterol and C-reactive protein (CRP).

The aim of this study was to investigate the relationship between MetS and arterial stiffness measured by baPWV in the general Japanese population.

METHODS

Study subjects

The study subjects included 3144 Japanese subjects employed by two companies in Hokkaido, aged 38–62 years old, who had an annual health checkup during the period from April 2007 to March 2008. A total of 42 subjects (37 male and 5 female subjects) were excluded from the analysis because of the following reasons: prior coronary heart disease or stroke (n=28, 24 male and 4 female subjects), peripheral artery disease (n=9, 8 male subjects and 1 female subject), hemodialysis (n=2, 2 male subjects), and atrial fibrillation (n=3, 3 male subjects). Thus, a total of 3102 subjects remained in the present analysis. The two companies having study subjects approved the study protocol and informed consent was obtained from all participants.

Data collection

Body weight, height and waist circumference were measured in the morning in the fasting state. Body mass index was calculated as body weight (kilograms) divided by height (meters) squared. Smoking habits, alcohol intake and exercise

[1]Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan and [2]Department of Public Health, Hokkaido University Graduate School of Medicine, Sapporo, Japan
Correspondence: Dr H Satoh, Department of Cardiovascular Medicine, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan.
E-mail: h-satoh@imb.me-h.ne.jp
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habits were evaluated by interviews. Subjects who had never smoked and ex-smokers were classified as 'nonsmokers'. Subjects were divided into two groups by the frequency of exercise; <1 time per week or $\geqslant 1$ time per week. Blood pressure was measured by a trained nurse using a standard mercury sphygmomanometer with the study subjects in the sitting position and after at least 5 min of rest. Blood samples were obtained from the antecubital vein in the morning after an overnight fast, and the serum was separated. After precipitation by heparin manganese, total cholesterol and high-density lipoprotein (HDL)-cholesterol were measured by the phosphotungstate method. Triglycerides were measured enzymatically. Fasting plasma glucose was enzymatically determined by the hexokinase method. CRP was measured by nephelometry with a latex particle-enhanced immunoassay.

We used the definition and diagnostic criteria of MetS in Japan;[11] subjects with waist circumference $\geqslant 85$ cm in male and $\geqslant 90$ cm in female subjects with at least two of the other three criteria, including systolic blood pressure $\geqslant 130$ mm Hg and/or diastolic blood pressure $\geqslant 85$ mm Hg, triglycerides

Table 1 Baseline characteristics of male subjects

	MetS (n=*624*)	*No MetS* (n=*2120*)	P-*value*
Age (years)	52.6 ± 6.1	51.2 ± 6.6	<0.001
Body mass index (kg m^{-2})	25.6 ± 2.7	23.1 ± 2.7	<0.001
Waist circumference (cm)	92 ± 6	85 ± 7	<0.001
Systolic blood pressure (mm Hg)	139 ± 14	123 ± 14	<0.001
Diastolic blood pressure (mm Hg)	87 ± 9	77 ± 10	<0.001
Total cholesterol (mg per 100 ml)	209 ± 36	201 ± 30	<0.001
Triglyceride (mg per 100 ml)	176 (137–245)	105 (75–141)	<0.001
HDL-cholesterol (mg per 100 ml)	54 ± 13	62 ± 16	<0.001
Fasting plasma glucose (mg per 100 ml)	114 ± 28	97 ± 16	<0.001
Heart rate (b.p.m.)	68 ± 11	63 ± 9	<0.001
CRP (mg per 100 ml)	0.08 (0.05–0.13)	0.06 (0.04–0.10)	<0.001
Current smoking (%)	44.1	47.2	0.17
Alcohol intake (%)	74.7	69.8	<0.05
Frequency of exercise			
⩾1/week (%)	27.6	28.0	0.82
Medical history			
Hypertension (%)	32.1	8.4	<0.001
Diabetes mellitus (%)	9.6	1.8	<0.001
Hyperlipidemia (%)	12.8	4.5	<0.001

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; MetS, metabolic syndrome.
Variables are presented as mean ± s.d., median (interquartile range) for skewed variables, or percentage.

Table 2 Baseline characteristics of female subjects

	MetS (n=*28*)	*No MetS* (n=*330*)	P-*value*
Age (years)	51.2 ± 5.0	50.1 ± 7.4	0.50
Body mass index (kg m^{-2})	28.3 ± 4.0	21.6 ± 3.1	<0.001
Waist circumference (cm)	99 ± 7	83 ± 9	<0.001
Systolic blood pressure (mm Hg)	138 ± 11	118 ± 17	<0.001
Diastolic blood pressure (mm Hg)	84 ± 7	72 ± 11	<0.001
Total cholesterol (mg per 100 ml)	210 ± 37	206 ± 33	0.54
Triglyceride (mg per 100 ml)	167 (105–281)	74 (58–99)	<0.001
HDL-cholesterol (mg per 100 ml)	63 ± 16	75 ± 17	<0.01
Fasting plasma glucose (mg per 100 ml)	117 ± 32	93 ± 18	<0.01
Heart rate (b.p.m.)	69 ± 11	64 ± 9	<0.01
CRP (mg per 100 ml)	0.09 (0.05–0.21)	0.04 (0.04–0.07)	<0.01
Current smoking (%)	28.0	28.5	0.96
Alcohol intake (%)	56.0	40.9	0.14
Frequency of exercise			
⩾1/week (%)	8.0	24.2	0.06
Medical history			
Hypertension (%)	40.0	5.2	<0.001
Diabetes mellitus (%)	16.0	1.5	<0.001
Hyperlipidemia (%)	6.2	5.5	0.34

Abbreviations: CRP, C-reactive protein; HDL, high-density lipoprotein; MetS, metabolic syndrome.
Variables are presented as mean ± s.d., median (interquatile range) for skewed variables, or percentage.

$\geqslant$150 mg per 100 ml and/or HDL-cholesterol $<$40 mg per 100 ml, and fasting plasma glucose $\geqslant$110 mg per 100 ml.

Arterial stiffness was assessed using baPWV measured by a volume-plethysmographic apparatus (Form PWV/ABI; Colin, Komaki, Japan).[22] baPWV was recorded after at least 5 min of rest. This device was able to measure the phonocardiogram, electrocardiogram, volume pulse form and arterial blood pressure at left and right brachia and ankles, and time intervals between the wave front of the right brachium and that of both ankles were calculated. Ankle/brachial pressure is the ratio of ankle to brachial systolic blood pressure, and right and left ankle/brachial pressures were measured simultaneously. We used the mean of right and left baPWV values in the analysis.

Statistical analysis

All analyses were performed separately for male and female subjects. The clinical and biochemical data of the study subjects are expressed as mean ± s.d., as median (and interquartile range) for variables with a skewed distribution, and as a percentage. The differences in variables between the two groups were examined by Student's unpaired *t*-test for approximately normally distributed variables; by the Wilcoxon rank-sum test for triglycerides and CRP; and by the χ^2-test for smoking habits, alcohol intake, exercise habits and medical history. Multiple logistic regression analysis was performed to investigate the relationship between MetS and arterial stiffness with adjustment for other variables such as age, smoking habits, total cholesterol, and CRP.

A *P*-value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using SPSS software version 11.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline characteristics of the male and female study subjects are shown in Tables 1 and 2, respectively. The prevalence of MetS was 22.7% in male subjects and was 7.8% in female subjects. Male subjects with MetS had significantly higher age, body mass index, systolic and diastolic blood pressure, total cholesterol, triglycerides, fasting plasma glucose, heart rate and CRP, along with lower HDL-cholesterol values. The prevalence of alcohol intake, hypertension, diabetes mellitus and hyperlipidemia was higher in male subjects with MetS than in those without MetS. Female subjects with MetS had significantly greater body mass index, systolic and diastolic blood pressure, triglycerides, fasting plasma glucose, heart rate and CRP, along with lower HDL-cholesterol values. The prevalence of hypertension and diabetes mellitus was higher in female subjects with MetS than in those without MetS.

Figure 1 shows the mean values of baPWV in male and female subjects with or without MetS. Male and female subjects with MetS had significantly higher mean values of baPWV than subjects without MetS (male subjects; 1444 ± 209 *vs.* 1294 ± 165 cm/s, female subjects; 1379 ± 151 *vs.* 1220 ± 171 cm/s).

Baseline characteristics of the study subjects according to low and high baPWV values are shown in Table 3. High baPWV was designated as more than 1429 and 1308 cm/s in male and female subjects, respectively, which was the cutoff value between the third and fourth quartiles. The prevalence of MetS was significantly higher in subjects with a high baPWV than in those with a low baPWV among both male and female subjects (42.3 *vs.* 16.2% in male subjects, $P<0.001$; 18.9 *vs.* 3.0% in female subjects, $P<0.001$). Male subjects with a high baPWV had significantly greater age, smoking and CRP values than those with low baPWV. Female subjects with high baPWV had significantly greater age than those with low baPWV.

Multiple logistic regression analysis was performed to examine the relationship between high baPWV and dependent variables in Table 4. After adjustment for age, smoking habits, total cholesterol, CRP and heart rate, the odds ratio (OR) of MetS for high baPWV values was 3.65 in male subjects (95% confidence interval (CI): 2.99–4.47, $P<0.001$) and 8.02 in female subjects (95% CI: 3.18–20.25 $P<0.001$).

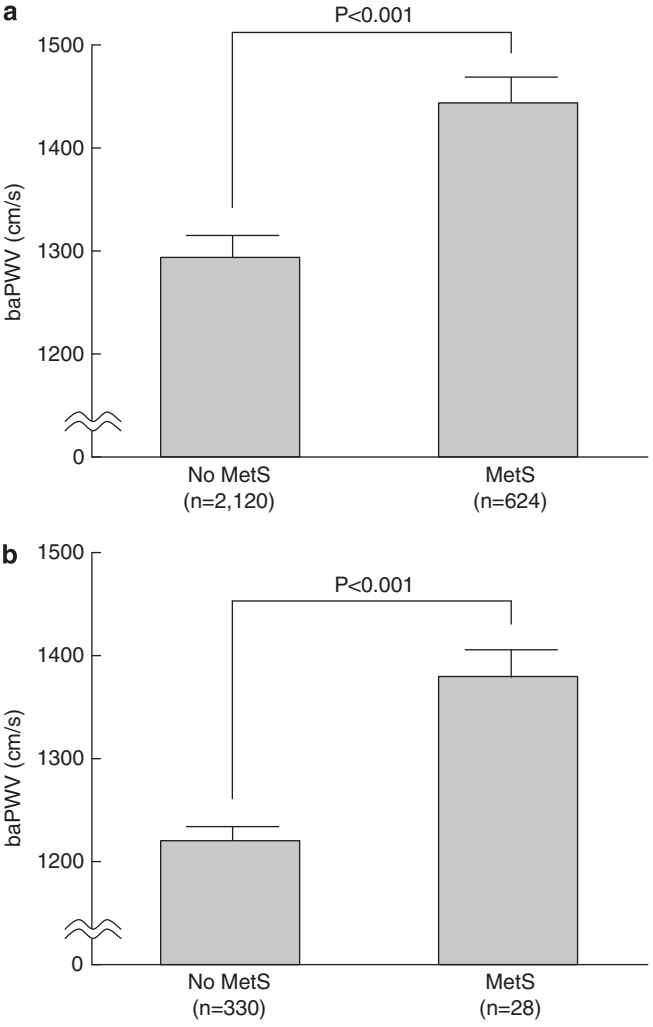

Figure 1 Brachial–ankle pulse wave velocity (baPWV) in male (**a**) and female (**b**) subjects with and without metabolic syndrome (MetS). baPWV, brachial–ankle pulse wave velocity; MetS, metabolic syndrome.

DISCUSSION

This study shows that MetS is associated with increased arterial stiffness in the general Japanese population, independent of other atherogenic risk factors.

The prevalence of MetS subjects defined by Japanese criteria in this study was 21.0%; 22.7% in male subjects and 7.8% in female subjects. Thus, the prevalence rate was about 3-fold higher in male subjects than in female subjects. The prevalence rate of MetS in this study was similar to that found in the latest National Health and Nutrition survey in 2004.[23] In that survey, the incidence of MetS in male and female subjects was reported to be 23.0 and 8.9%, respectively.

The previous studies have reported that MetS is closely associated with increased arterial stiffness[18–21] Schillaci *et al.*[20] found that MetS, according to the NCEP-ATP III criteria, was associated with arterial stiffness measured by carotid–femoral PWV. Li *et al.*[19] found that baPWV values increased with increasing components of MetS as defined by the NCEP-ATP III criteria. Sipilä *et al.*[21] showed a similar relationship between MetS and arterial stiffness using the IDF criteria. Conventional risk factors such as age, smoking, total cholesterol and CRP are closely associated with arterial stiffness;[24–27] however, these

Table 3 Baseline characteristics of male and female subjects according to baPWV

	High baPWV	*Low baPWV*	P-*value*
Male			
n	775	2327	
MetS (%)	42.3	16.2	<0.001
Age (years)	54.4 ± 5.1	50.6 ± 6.6	<0.001
Total cholesterol (mg per 100 ml)	203 ± 31	203 ± 32	0.92
Current smoking (%)	48.8	39.7	<0.001
CRP (mg per 100 ml)	0.07 (0.05–0.13)	0.06 (0.04–0.10)	<0.001
Female			
n	92	266	
MetS (%)	18.9	3.0	<0.001
Age (years)	53.0 ± 4.4	49.3 ± 7.8	<0.001
Total cholesterol (mg per 100 ml)	207 ± 33	206 ± 33	0.83
Current smoking (%)	27.8	28.7	0.87
CRP (mg per 100 ml)	0.04 (0.04–0.10)	0.05 (0.04–0.07)	0.31

Abbreviations: baPWV, brachial–ankle pulse wave velocity; CRP, C-reactive protein; MetS, metabolic syndrome.
High baPWV was designated as greater than 1429 cm s^{-1} and 1308 cm s^{-1} in male and female subjects, respectively.
Variables are presented as mean ± s.d., median (interquartile range) for skewed variables, or percentage.

Table 4 Multiple logistic regression analysis with the relationship between high baPWV and risk variables

Variables	*OR*	*95% CI*	P-*value*
Male			
MetS	3.65	2.99–4.47	<0.001
Age	1.11	1.09–1.13	<0.001
Total cholesterol	0.98	0.95–1.01	0.21
Smoking	1.26	1.04–1.52	0.02
CRP	2.09	1.43–3.07	<0.001
Female			
MetS	8.02	3.18–20.25	<0.001
Age	1.12	1.06–1.18	<0.001
Total cholesterol	0.95	0.87–1.03	0.20
Smoking	1.02	0.58–1.81	0.95
CRP	1.77	0.60–5.29	0.30

Abbreviations: baPWV, brachial–ankle pulse wave velocity; CI, confidence interval; CRP, C-reactive protein; MetS, metabolic syndrome; OR, odds ratio.

studies could not exclude the influence of these atherogenic conventional risk factors. In this study, Japanese subjects with MetS had greater baPWV values than those without MetS, and importantly, MetS was a significant risk for increased arterial stiffness in both genders, even after adjustment for other risk factors such as age, smoking habits, CRP and total cholesterol.

The baPWV is a non-invasive index of arterial stiffness.[22] Increased arterial stiffness is one of the pathological states of vascular damage and has been closely associated with the development of cardiovascular diseases. Nagano *et al*.[28] showed that age and blood pressure were major determinants of baPWV values, and other risk factors such as diabetes mellitus, dyslipidemia, smoking and high CRP were also associated with increased baPWV.[29] In this study, risk factors such as age and CRP, which are not involved as risk components in the MetS definition, were also associated with increased arterial stiffness.

MetS has been established as an endocrine and inflammatory disorder related to insulin resistance.[30] Nakanishi *et al*.[31] showed that insulin resistance was closely associated with the risk of increased arterial stiffness. These results indicate that hyperinsulinemia may be involved in the increased arterial stiffness in MetS found in this study. Hyperinsulinemia has been shown to promote the synthesis of collagen, stimulate hyperplasia and hypertrophy of vascular smooth cells[32] and cause endothelial dysfunction by interfering with the generation of vasodilatory and vasoconstrictive substances such as nitric oxide and endothelin-1.[33]

There are several limitations that should be acknowledged in this study. First, medications such as anti-hypertensive drugs and lipid-lowering agents were not examined in our study subjects. Second, baPWV is an indirect marker of increased arterial stiffness or decreased arterial compliance, and we did not examine structural changes of the arterial wall using ultrasound technology.

In conclusion, this study has identified MetS as a significant and independent risk factor for increased arterial stiffness in both male and female subjects. As such, MetS should be recognized to have a crucial impact on public health in the general Japanese population.

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