Original Article

The Effects of Changes in the Metabolic Syndrome Detection Status on Arterial Stiffening: A Prospective Study

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We conducted a prospective study to examine the effects of alterations of the metabolic syndrome detection status on the rate of progression of arterial stiffness, which is recognized as a marker of arterial damage and an indicator of cardiovascular risk. Brachial-ankle pulse wave velocity as an index of arterial stiffening was recorded twice over a 3-year period in 2,080 Japanese men (age, 42±9 years). At the start of the prospective study, pulse wave velocity was higher in the subjects with metabolic syndrome (*n*=125) than in those without metabolic syndrome (*n*=1,955) even after adjusting for mean blood pressure. The annual rate of increase of the pulse wave velocity was higher in the group with persistent metabolic syndrome (27±51 cm/s/year, *n*=71) than in the group with regression of metabolic syndrome (6±39 cm/s/year, *n*=54) or the group in which metabolic syndrome was absent (13±37 cm/s/year, *n*=1,843; *p*<0.05) after adjustment for changes in blood pressure. In conclusion, the changes in the metabolic syndrome detection status of the subjects during the study period affected the annual rate of progression of arterial stiffening, and persistent metabolic syndrome during the study period was associated with acceleration of arterial stiffening in middle-aged Japanese men. On the other hand, resolution of metabolic syndrome may be associated with attenuation of the progression of arterial damage. Therefore, the increased cardiovascular risk associated with the presence of metabolic syndrome may be at least partly mediated by acceleration of the progression of arterial stiffening. (*Hypertens Res* 2006; 29: 673–678)

***Key Words*: arterial stiffness, metabolic syndrome, follow-up study**

Introduction

Arterial stiffness is a marker of arterial damage (*1*–*3*) and its increase has been shown to be associated with an increased risk of cardiovascular events (*4*, *5*). Recently, attention has been paid to the metabolic syndrome (MetS) as a potent atherogenic state, and the presence of this syndrome has been reported to be associated with poor cardiovascular outcomes (*6*, *7*). Raised blood pressure and raised fasting plasma glucose are components of MetS, and our previous prospective study demonstrated that presence of raised blood pressure and raised plasma glucose may synergistically lead to progression of arterial stiffness (*8*). However, no prospective studies have confirmed that the presence of MetS is associated with accelerated progression of arterial stiffening.

In this prospective cohort study, we examined the effects of changes in the MetS (defined by the modified Japanese

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Expert Committee on the Diagnosis and Classification of Metabolic Syndrome: body mass index [BMI]≥25.0 kg/m^2 (*9*)) status of the subjects between two examinations conducted at an interval of 3 years. The subjects were classified into four groups based on the changes in their MetS status between the two examinations, as follows: persistent MetS, defined as detection of MetS at both the first and the second examinations; newly detected MetS, defined as detection of MetS only at the second examination; regression of MetS, defined as detection of MetS only at the first examination; and absence of MetS, defined as no detection of MetS at either the first or the second examination. We then compared the rate of progression of arterial stiffening among groups.

Methods

Design and Subjects

This prospective study was performed on male employees of a single large construction company, all of whom were required to undergo a routine annual health checkup. For this study, in addition to the routine tests, brachial-ankle pulse wave velocity (PWV) measurements were also conducted on two occasions, that is, at the beginning and at the end of the 3-year study period. The details of this prospective study protocol are described elsewhere (*8*, *10*), and this protocol was initiated in the year 2000. The routine annual health checkup included evaluation of the atherosclerotic risk factors (BMI, serum levels of triglycerides [TG], high density lipoprotein cholesterol [HDL] and total cholesterol [TC], fasting plasma glucose, and blood pressure). Subjects with positive atherosclerotic risk factors (BMI≥25 kg/m^2, TG≥150 mg/dl, HDL<40 mg/dl, fasting plasma glucose >125 mg/dl, blood pressure ≥140/90 mmHg, and TC≥240 mg/dl) were treated in accordance with the guidelines of the Japanese societies of atherosclerosis (*11*), diabetes mellitus (*12*), and hypertension (*13*). Subjects with the above-mentioned abnormalities were advised to visit the Health Care Center of their construction company as a first step, and the details of the management plan were described elsewhere (*8*, *10*).

Subjects meeting any of the following criteria were considered to be ineligible for the study (*8*, *10*, *14*, *15*): an ankle/brachial systolic blood pressure index (ABI) of less than 0.95; atrial fibrillation; or undergoing regular hemodialysis. In addition, subjects who were receiving medication for hypertension, dyslipidemia, diabetes mellitus, heart disease and/or stroke were also excluded from this study. Verbal informed consent was obtained from all of the participants prior to their participation in this study. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University.

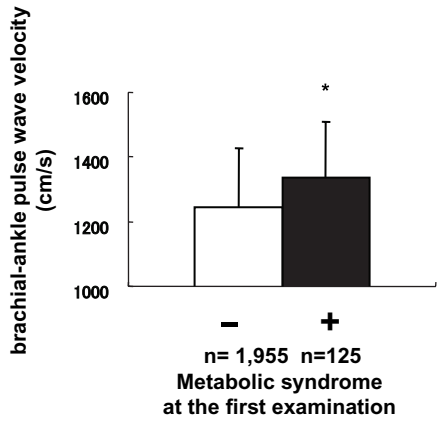

Fig. 1. *Brachial-ankle pulse wave velocity at the first examination in subjects with and without metabolic syndrome defined at the first examination. –, subjects without metabolic syndrome defined at the first examination; +, subjects with metabolic syndrome defined at the first examination.* *p*< 0.05* vs. *subjects without metabolic syndrome (assessed by general linear model multivariate analysis adjusted for mean blood pressure).*

Measurements

Pulse Wave Velocity

The brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI; Colin Co., Ltd., Komaki, Japan), in accordance with a previously described methodology (*8*, *10*, *14*, *15*). The measurement was conducted after the subject had rested for at least 5 min in the supine position, in an air-conditioned room (24–26°C) earmarked exclusively for this purpose. The interobserver and intraobserver coefficients of variation for the measurement have been reported to be 8.4% and 10.0%, respectively (*15*).

Laboratory Measurements

The TG, HDL, TC, fasting plasma glucose, and serum creatinine levels were measured using enzymatic methods (Falco Biosystems Co., Ltd., Tokyo, Japan). The interassay coefficients of variation for the laboratory measurements were as follows: TG, 1.5%; HDL, 1.9%; TC, 0.4%; blood sugar, 0.8%; serum creatinine, 0.5%. All the blood samples were obtained in the morning after the patients had fasted overnight.

Definitions

We adopted the modified version of the Japanese Expert Committee Guidelines on the Diagnosis and Classification of Metabolic Syndrome (*9*) for the clinical recognition of MetS in this study, namely, BMI≥25.0 kg/m^2 (waist circumference records were not available for this study) and two or more of following three risk factors: raised blood pressure (blood

Table 1. Clinical Characteristics of the Subjects Classified According to the Changes in the Metabolic Syndrome Status during the Study Period

	Group category							
	Absence of MetS		Regression of MetS		New detection of MetS		Persistence of MetS	
	1st	2nd	1st	2nd	1st	2nd	1st	2nd
Number of subjects	1,843		54		112		71	
Age (years)	41±9		43±8		43±8		43±8	
BMI (kg/m^2)	23.0±2.5	23.3±2.6*	27.1±2.1†	26.7±2.7*,†	26.8±2.2†	27.7±2.1*,†	28.0±2.3†,§	28.4±2.3*,†,‡
Smoking (%)	741 (40.3)	644 (35.1)	24 (44.4)	21 (38.8)	58 (51.8)	44 (39.3)	29 (40.9)	27 (38.0)
SBP (mmHg)	122±13	123±13*	135±11†	128±11*,†	130±12†	137±10*,†,‡	137±13†,§	139±13*,†,‡
DBP (mmHg)	75±10	75±10	86±9†	80±10*,†	81±9†,‡	85±9*,†,‡	88±9†,§	87±10†,‡
HR (bpm)	64±10	66±9*	67±10	68±10	68±10†	69±11†	69±10†	71±11*,†
TC (mg/dl)	193±31	200±32*	207±36†	213±40	209±32†	217±33*,†	221±40†	227±39*,†
HDL (mg/dl)	56±11	58±13	46±8†	51±8†	50±11†,‡	49±10†	45±9†	47±11†
TG (mg/dl)	110±78	115±75*	203±76†	171±109*,†	158±89†,‡	217±99*,†,‡	264±204†,§	266±150†,‡,§
FPG (mg/dl)	92±11	91±12	98±14†	97±21	95±17	97±12*,†	102±16†,§	107±22*,†,‡,§
baPWV (cm/s)	1,240±180	1,279±180*	1,296±145	1,314±136	1,321±186†	1,382±179*,†	1,368±182†	1,449±257*,†

Absence of MetS, defined as absence of the metabolic syndrome at both the first and the second examination; Regression of MetS, defined as detection of the metabolic syndrome at the first examination but not at the second examination; New detection of MetS, defined as detection of the metabolic syndrome at the second examination but not at the first examination; Persistence of MetS, defined as detection of the metabolic syndrome at both the first and the second examination; 1st, the first examination; 2nd, the second examination; BMI, body mass index; SBP, systolic blood pressure obtained in an office setting; DBP, diastolic blood pressure obtained in an office setting; HR, heart rate; TC, serum total cholesterol; HDL, serum high density lipoprotein cholesterol; TG, serum triglycerides; FPG, fasting plasma glucose; baPWV, brachial-ankle pulse wave velocity. *$p<0.05$ *vs*. that at the first examination; $^{\dagger}p<0.01$ *vs*. that in the group with Absence of MetS; $^{\ddagger}p<0.05$ *vs*. that in the group with Regression of MetS; $^{\S}p<0.05$ *vs*. that in the group with New detection of MetS (assessed by one-way analysis of variance or the χ^2 test).

pressure ≥130/85 mmHg), dyslipidemia (HDL<40 mg/dl and/or TG≥150 mg/dl), and raised plasma glucose (fasting plasma glucose ≥110 mg/dl). Blood pressure was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer. To adjust the brachial-ankle PWV for the blood pressure, the heart rate and the mean arterial pressure simultaneously obtained during measurement of the brachial-ankle PWV were used; the blood pressure was recorded simultaneously from the right arm and the left arm using an oscillometric method, and the blood pressure variables were calculated as the means of the variables measured for the right arm and the left arm values. Then, the mean arterial pressure was calculated as diastolic pressure plus (pulse pressure × 1/3) as a continuous variable.

Statistical Analysis

Data were expressed as the means±SD. The differences in variables between the first and the second examinations in each group were assessed by the paired *t*-test. For the assessment of the differences in the status of each variable among the groups, a one-way analysis of variance with Scheffe's adjustment was applied for continuous variables and the χ^2 test was applied for categorical variables.

The difference of brachial-ankle PWV between the subjects with and without MetS at the first examination was assessed by a general linear model (GLM) multivariate analysis adjusted for mean blood pressure. The differences of the annual rate of increase of the brachial-ankle PWV {(the value at the second examination − the value at the first examination)/3 (years)} were compared across the four MetS statuses by a GLM multivariate analysis with post hoc multiple comparison with Bonferroni's adjustment to control for covariates that have been reported to affect PWV in previous reports continuous variables (values at the first examination of age, BMI, brachial-ankle PWV, mean arterial pressure and heart rate recorded during measurement of the brachial-ankle PWV, TC, TG, HDL, fasting plasma glucose, and serum creatinine, and changes in the BMI, mean arterial pressure and heart rate recorded during measurement of the brachial-ankle PWV, TC, TG, HDL, fasting plasma glucose, and serum creatinine during the study period), and categorical variables (smoking status and alcohol intake at the first examination and the change in the smoking status and alcohol intake during the study period).

For the persistence of each component of MetS (BMI≥25.0 kg/m^2, raised blood pressure, dyslipidemia, and raised plasma glucose), the same GLM analysis was conducted to determine the component with the most persistent effect on the annual rate of increase of the brachial-ankle PWV. All analyses were conducted using SPSS software for Windows, version 11.0J

(SPSS, Chicago, USA). A p value of <0.05 was considered to denote statistical significance.

Results

As previously reported (*8*), during the 3-year period from May 2000 to December 2004, brachial-ankle PWV measurements and other demographic and laboratory examinations were successfully conducted on two occasions in a total of 2,389 Japanese male subjects. The subjects ranged in age from 29 to 76 years. At the first examination, 4 subjects had an ABI of less than 0.95, 5 subjects had atrial fibrillation, 4 subjects were undergoing regular hemodialysis, and 194 were under medication for hypertension, dyslipidemia, diabetes mellitus, heart disease or stroke, and were excluded from the analysis. During the study period (spanning the first and second examinations), 3 subjects were newly diagnosed as having atrial fibrillation and 99 subjects were started on medication for one/more of the above-mentioned diseases. Finally, 2,080 subjects could be successfully included in the present analysis.

At the first examination, 125 subjects were categorized as having MetS. Brachial-ankle PWV at the first examination was higher in subjects with MetS than in those without MetS even after adjusting for mean blood pressure (Fig. 1). Table 1 shows the clinical characteristics of the four groups of patients classified based on the changes in the MetS detection status between the first and second examinations. The measured brachial-ankle PWV values were significantly higher at the second examination in the groups with persistent or newly detected MetS than in the group in which MetS was absent; however, no significant increase of this parameter was observed in the group with regression of MetS. The annual rate of increase of the brachial-ankle PWV was higher in the group with persistent MetS than in the group in which MetS was absent or the group with regression of MetS (Fig. 2). In addition, this value was lower in the group with regression of MetS than in the other three groups (Fig. 2).

Table 2 shows the results of a GLM analysis to determine which component of MetS (BMI≥25.0 kg/m^2, raised blood pressure, dyslipidemia, or raised plasma glucose) had the most persistent effect on the annual rate of increase of the brachial-ankle PWV. The raised blood pressure and raised plasma glucose, but not BMI≥25.0 kg/m^2 or dyslipidemia, had significantly persistent effects on the annual rate of increase of the brachial-ankle PWV.

Discussion

The present study was the first to examine the effects of changes in the MetS status on the rate of increase of the brachial-ankle PWV during a 3-year study period. While recent studies have demonstrated that the rate of increase of the PWV increased as the number of components of MetS present in the subjects increased, they did not examine the effects of changes of the MetS status over time (persistence, new detection, regression, or absence of MetS) on the rate of increase of the PWV (*16–18*). The present study demonstrated that changes in the MetS status of the subjects during the study period significantly influenced the rate of increase of the brachial-ankle PWV; that is, persistent MetS during the study period was associated with accelerated progression of arterial stiffening even after adjustment for changes in the mean arterial pressure. Although increased distension of the arterial wall caused by increased blood pressure is considered to be one of the major determinants of increased arterial stiffness (*19*, *20*), it would appear that this accelerated progression of arterial stiffening may be driven, at least in part, by pressure-independent mechanisms. Thus, the presence of MetS may progress arterial damage.

While the brachial-ankle PWV reflects the stiffness of not only the central, but also the peripheral, arterial components (*14*, *15*), it has been shown to bear a close correlation with the aortic PWV (*15*), which is a known marker of cardiovascular risk (*1–3*). On the other hand, increased peripheral arterial stiffness has also been shown to be associated with increased cardiovascular risk (*21*). Furthermore, we demonstrated in a recent study that the brachial-ankle PWV may be a predictor of future cardiovascular events in subjects with acute coronary syndromes (*22*). Therefore, evolutional changes in the detection status of MetS may influence the risk of cardiovas-

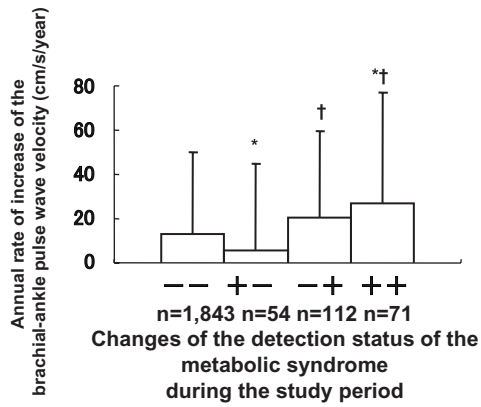

Fig. 2. *Annual rate of increase of the brachial-ankle pulse wave velocity in the four groups classified according to the changes in the metabolic syndrome status during the study period. − −, metabolic syndrome not detected at either examination; + −, metabolic syndrome detected only at the first examination; − +, metabolic syndrome detected only at the second examination; + +, metabolic syndrome detected at both the first and the second examination.* *p $<$ *0.05* vs. *that in the group in which metabolic syndrome was not detected at either examination;* †p $<$ *0.05* vs. *that in the group in which metabolic syndrome was detected only at the first examination (assessed by a general linear model analysis with post hoc multiple comparison with Bonferroni's adjustment).*

Table 2. The Results of a General Linear Model Multivariate Analysis to Find the Significant Component of Metabolic Syndrome That Its Persistence Affects on the Annual Rate of Increase of the Brachial-Ankle Pulse Wave Velocity

Variable	B (95% confidence interval)	*F*-value	*p*-value
Body mass index ≥25 kg/m^2	1.7 (−2.3–5.7)	0.7	n.s.
Raised blood pressure	3.5 (0.2–7.3)	3.3	<0.05
Raised plasma glucose	16.9 (6.1–27.7)	9.4	<0.01
Dyslipidemia	1.8 (−2.8–6.4)	0.6	n.s.

r^2=0.20.

cular events at least partly through their association with the rate of progression of arterial stiffening.

Lifestyle modifications are considered to be the first-line of therapy for MetS (*23*). In this study protocol, since the criteria for providing guidance for lifestyle modifications were different from the criteria defining MetS, we could not evaluate the compliance of the subjects in relation to lifestyle modifications. Furthermore, we could not rule out the possibility of some of the subjects using alternative therapies, besides following the guidance on therapeutic lifestyle modifications, to improve their atherogenic abnormalities. Nonetheless, the present study demonstrated that the progression of arterial stiffening was slower in the group showing regression of MetS than in the other three groups. Therefore, early intervention by non-pharmacological approaches for MetS may be effective for attenuating the progression of arterial damage in these subjects.

Among the components of MetS, the present study demonstrated that the persistence of raised blood pressure and the persistence of raised plasma glucose play a role in accelerating the progression of arterial stiffness. Recent studies have suggested that the formation of advanced glycation end products is an important pathway in the development of arterial stiffness (*24*, *25*). Not only abnormal glucose metabolisms but also hypertension affects the metabolism of advanced glycation end products (*25*, *26*). Therefore, a further study is needed to clarify the underlying mechanisms of the progression of structural arterial stiffening related to MetS.

It must be pointed out, however, that the present study has some limitations, as follows. 1) Central, rather than peripheral, arterial stiffness is thought to have a major role in the increased cardiovascular risk related to increased arterial stiffness (*3–5*, *19*, *20*). Therefore, further studies are needed to confirm the present results using a more robust marker of central arterial stiffness than the brachial-ankle PWV, such as the carotid-femoral PWV or augmentation index (*3–5*, *19*, *20*). 2) The subjects of this study were restricted to Japanese men, and further studies including women are needed to confirm the findings. 3) In the definition of MetS for our study, we used the BMI instead of the waist circumference. Several studies have suggested that central obesity has a key role in the elevated cardiovascular risk associated with MetS (*27*, *28*), and the BMI is not a robust marker of central obesity. A recent study suggested that subcutaneous trunk fat is an independent determinant of arterial stiffness (*29*). Therefore, the significance of central obesity as a determinant of the rate of progression of arterial stiffening should be evaluated in future studies.

In conclusion, the changes in the MetS detection status of the subjects during the study period affected the annual rate of progression of arterial stiffening, and persistent MetS during the study period was associated with acceleration of arterial stiffening in middle-aged Japanese men. Pressure-independent mechanisms were also surmised to contribute, at least in part, to this acceleration of arterial stiffening. On the other hand, resolution of MetS may be associated with attenuation of the progression of arterial damage. Therefore, the increased cardiovascular risk associated with the presence of MetS may be mediated, at least in part, by acceleration of the progression of arterial stiffening. The next logical step in this context may be to evaluate whether the changes in the rate of progression of arterial stiffening caused by the changes in the MetS status of the subjects show any correlations with the cardiovascular outcomes in cases of MetS.

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