Original Article

Relationship between Arterial Stiffness and the Risk of Coronary Artery Disease in Subjects with and without Metabolic Syndrome

Yutaka KOJI[1)], Hirofumi TOMIYAMA[1)], Jiko YAMADA[1)], Minoru YAMBE[1)], Kohki MOTOBE[1)], Kazuki SHIINA[1)], and Akira YAMASHINA[1)]

We examined the influence of metabolic syndrome (MetS) on the relationship between arterial stiffness and the risk of coronary artery disease (CAD). In 396 subjects (age, 63±11 years) who underwent coronary angiography, multiple linear regression analysis demonstrated that the brachial-ankle pulse wave velocity (PWV), but not the presence of MetS, was a significant determinant of the number of diseased coronary arteries (β=0.10, p<0.05), even though both the brachial-ankle PWV and the number of diseased coronary arteries were higher in subjects with MetS (n=100) than in those without MetS (n=296). However, in subjects with MetS, multiple linear regression analysis demonstrated that the brachial-ankle PWV was not a significant determinant of the number of diseased coronary arteries. The brachial-ankle PWV values were classified into tertile ranges in subjects with and without MetS. The number of diseased coronary arteries increased significantly with an increase in the tertile number of the brachial-ankle PWV in the subjects without MetS (tertile 1=1.00±0.86, tertile 2=1.29±1.01, and tertile 3=1.45±1.05), but not in those with MetS. In conclusion, the results of this study suggest that arterial stiffness is a marker of the risk of CAD in subjects without MetS, whereas in subjects with MetS, the syndrome may directly produce clinically significant atherosclerotic stenosis of the coronary arteries independent of its significant promotion of the development of coronary atherosclerosis *via* an increase of arterial stiffness. (*Hypertens Res* 2007; 30: 243–247)

***Key Words*: metabolic syndrome, arterial stiffness, coronary artery disease**

Introduction

Arterial stiffness is a marker of the risk of future cardiovascular events (*1*, *2*). Several mechanisms may underlie this association, such as aggravation of atherosclerotic vascular damage, unfavorable influence on the cardiac workload, and direct atherogenic effects due to the increased arterial stiffness (*3*–*5*). Therefore, some studies have suggested that arterial stiffness is a marker of the risk of coronary artery disease (CAD) (*6*–*8*). On the other hand, metabolic syndrome (MetS) has also come to be recognized as a potent atherogenic state and as a major risk factor for CAD (*9*, *10*). While cross-sectional studies have demonstrated an increase in the arterial stiffness in subjects with MetS (*11*, *12*), the influence of MetS on the significance of arterial stiffness as a risk marker of CAD has not yet been fully elucidated.

This cross-sectional study was conducted to examine the influence of the presence of MetS, defined according to the modified Japanese Definition of Metabolic Syndrome (*13*), on the relationship between the pulse wave velocity (PWV), a marker of arterial stiffness, and the risk of CAD.

From the [1)]Second Department of Internal Medicine, Tokyo Medical University, Tokyo, Japan.

Address for Reprints: Hirofumi Tomiyama, M.D., Second Department of Internal Medicine, Tokyo Medical University, 6–7–1 Nishi-Shinjuku, Shinjuku-ku, Tokyo 160–0023, Japan. E-mail: tomiyama@tokyo-med.ac.jp

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Methods

Subjects

Three hundred ninety-six patients who underwent coronary angiography at the Tokyo Medical University Hospital between January 2002 and September 2005 for the evaluation, follow-up or treatment of coronary artery disease were enrolled in the present study. None of them had any of the following factors known to influence the PWV: current hemodialysis, an ankle-brachial pressure index of less than 0.95, atrial fibrillation, valvular heart disease, a low left ventricular ejection fraction of <40%, or a permanent pacemaker. Written informed consent was obtained from all the subjects prior to their participation in this study. The study protocol was approved by the ethical committee of Tokyo Medical University.

Definition of Metabolic Syndrome

We used the modified version of the criteria of the Committee for Establishing the Definition of Metabolic Syndrome in Japan for the diagnosis of MetS in this study (*13*), namely, body mass index ≥25 (waist circumference measurements were not available in this study) with at least two of the other four criteria (high-density lipoprotein cholesterol <40 mg/dl, triglycerides ≥150 mg/dl, blood pressure ≥130/85 mmHg, fasting blood glucose ≥110 mg/dl).

Brachial-Ankle PWV Measurements

After the subject had rested in a supine position for at least 5 min, the brachial-ankle PWV was measured using a volume-plethymographic apparatus (FORM/ABI; Colin Co. Ltd, Komaki, Japan) while the subject was in the same position. The complete methodology has been described elsewhere (*11*, *14*). Briefly, electrocardiographic electrodes were placed on both wrists, and a microphone for the phonocardiogram was attached on the left chest. Electrocardiograms and phonocardiograms were recorded to provide timing markers for the device. Occlusion cuffs, which were connected to both the plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles while the subjects lay in the supine position. The brachial and post-tibial arterial pressures were measured by the oscillometric sensor. All the recordings were performed while the patients were on their regular medication.

Coronary Angiography

After hospitalization, coronary angiography was performed in all the subjects using the standard Judkin's or Sone's technique. The results of the coronary angiographies were analyzed using a quantitative coronary angiographic technique (Cathcor, Siemens, Munich, Germany); the definition of diseased coronary arteries is described elsewhere (*15*). The severity of the CAD was defined in terms of the number of diseased arteries showing >50% narrowing, as 0-, 1-, 2-, or 3-vessel disease. In addition, when the left main coronary artery showed a >50% stenosis, the patient was defined as having 2-vessel disease. All the coronary angiograms were visually assessed by two experienced angiographers.

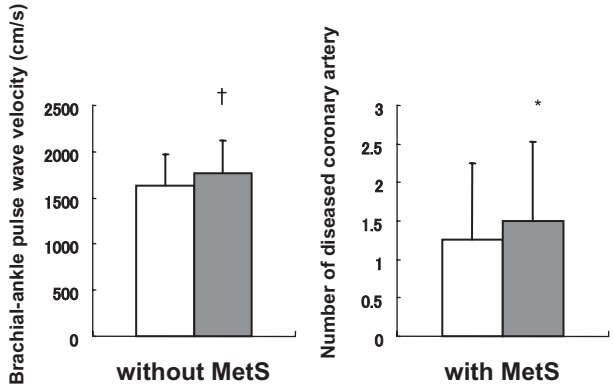

Fig. 1. *Brachial-ankle pulse wave velocity and the number of diseased coronary arteries in the subjects with and without metabolic syndrome. The gray bar represents the subjects with metabolic syndrome and the open bar represents those without metabolic syndrome. Without MetS, subjects without metabolic syndrome; with MetS, subjects with metabolic syndrome.* *$p<0.05$ vs. *the subjects without metabolic syndrome;* †$p<0.01$ vs. *the subjects without metabolic syndrome.*

Laboratory Measurements

On the morning of the coronary angiography, a fasting blood sample was collected prior to the cardiac catheterization. The blood samples were analyzed for the following parameters using standard techniques: total cholesterol, high-density lipoprotein cholesterol, low-density cholesterol, triglycerides, glucose, and uric acid.

Statistical Analysis

All the data were expressed as the mean±SD, including in figures and tables. The differences in each variable between any two study groups (groups with and without CAD or groups with and without MetS) were evaluated using Welch's *t*-test for continuous variables and the χ^2 test for categorical variables. The relationship of the number of diseased coronary arteries with other clinical variables was assessed by multiple linear regression analysis. The brachial-ankle PWV values were classified into tertile ranges. Under a general linear model, the differences in the number of diseased arteries among the groups with the brachial-ankle PWV values in the

Table 1. Clinical Characteristics in the Group with and without Coronary Artery Disease in the Subjects with and without Metabolic Syndrome

Parameter	Without MetS (n=296)		With MetS (n=100)	
	CAD (–) (n=77)	CAD (+) (n=219)	CAD (–) (n=20)	CAD (+) (n=80)
Age	59±13	66±10*	61±11	61±11†
Male/female	49/28	182/37*	13/7	61/19
Smoker (n (%))	28 (36)	57 (26)*	5 (25)	29 (36)*
BMI	23±3	23±3	27±2†	28±3†
SBP (mmHg)	129±18	124±17*	144±20†	140±17†
DBP (mmHg)	76±12	72±10	83±10†	80±10†
TC (mg/dl)	197±31	184±40	202±38	205±33†
HDL (mg/dl)	58±16	53±16	50±20†	47±20†
TG (mg/dl)	130±77	132±67	210±100†	195±81†
FPG (mg/dl)	106±12	112±18	116±22†	127±29†
Number and percentage (%) of patients				
Hypertension	43 (56)	145 (66)*	17 (85)	67 (84)
Dyslipidemia	31 (40)	150 (68)*	17 (85)	67 (84)*
Diabetes mellitus	12 (16)	47 (21)*	9 (45)	37 (46)*,†

Without MetS, subjects without metabolic syndrome; with MetS, subjects with metabolic syndrome; CAD (–), the group without coronary artery disease; CAD (+), the group with coronary artery disease; smoker, active smoking; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein; TG, triglycerides; FPG, fasting plasma glucose. *$p<0.05$ *vs*. subjects without coronary artery disease; †$p<0.05$ *vs*. the subjects without metabolic syndrome.

various tertile ranges were assessed in the subjects with and without MetS by analysis of covariance after adjustment for age, gender, smoking status, and hypercholesterolemia (total cholesterol>220 mg/dl or patient receiving lipid-lowering medication) as the covariates. All the analyses were conducted using the SPSS software for Windows, version 11.0J (SPSS, Chicago, USA). p values of <0.05 were considered to be statistically significant.

Results

Among all the subjects enrolled in this study (n=396), 100 (25.2%) satisfied the criteria for the diagnosis of MetS, and 299 (75.5%) were diagnosed as having CAD. The brachial-ankle PWV and number of diseased coronary arteries were higher in the subjects with MetS than in those without MetS (Fig. 1). However, multiple linear regression analysis revealed that the brachial-ankle PWV, but not the presence of MetS, was a significant determinant of the number of diseased coronary arteries in the entire study population, even after adjustment for age, gender, smoking status, and hypercholesterolemia (r^2=0.17, β=0.10, t=1.73, $p<0.05$). Similarly, in the subjects without MetS, multiple linear regression analysis revealed that the brachial-ankle PWV was a significant determinant of the number of diseased coronary arteries, even after adjustment for the same factors as above (r^2=0.20, β=0.14, t=2.34, $p<0.05$). In contrast, in the subjects with MetS, multiple linear regression analysis revealed that the brachial-ankle PWV was no longer a significant determinant of the number of diseased coronary arteries (r^2=0.04, β=−0.01, t=−0.10, n.s.). Table 1 shows the clinical characteristics of the subjects with and without CAD in the subject groups with and without MetS. The blood pressure and plasma levels of total cholesterol, triglycerides and fasting plasma glucose were higher, and the plasma level of high-density lipoprotein cholesterol was lower in the subjects with MetS than in those without MetS. While the brachial-ankle PWV values were comparable between the groups with and without CAD in the subjects with MetS, in the subjects without MetS, the brachial-ankle PWV values were higher in the group with CAD than in that without CAD (Fig. 2).

The tertile ranges of the brachial-ankle PWV in the patients without and with MetS were as follows: subjects without MetS, 958 to 1,465, 1,466 to 1,739, and 1,740 to 3,124 cm/s; subjects with MetS, 1,028 to 1,533, 1,534 to 1,833, and 1,884 to 2,699 cm/s. In the subjects without MetS, but not in those with MetS, the number of diseased coronary arteries increased with an increase in the tertile number of the brachial-ankle PWV; the number of diseased coronary arteries was significantly increased in the patients with brachial ankle PWV values in the highest tertile range as compared with those in the patients with brachial-ankle PWV values in the lowest tertile range (Fig. 3).

Discussion

MetS is a major risk factor for CAD, independent of conventional risk factors (*10*), and increase in arterial stiffness has also been demonstrated in subjects with MetS (*11*, *12*). Several studies have demonstrated the existence of a relationship

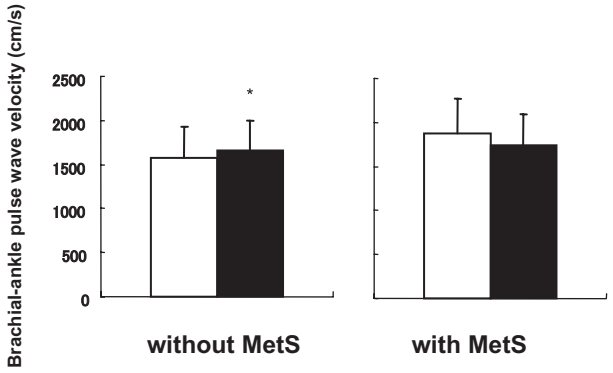

Fig. 2. *Brachial-ankle pulse wave velocity in the patients with and without coronary artery disease in the groups with and without metabolic syndrome. The closed bar represents the group with coronary artery disease and the open bar represents the group without coronary artery disease. Without MetS, subjects without metabolic syndrome; with MetS, subjects with metabolic syndrome.* *p$<$*0.05* vs. *the group without coronary artery disease.*

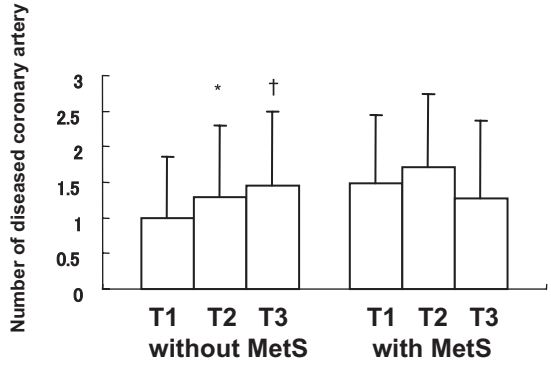

Fig. 3. *The number of diseased coronary arteries in the groups with the three tertile ranges of the brachial-ankle pulse wave velocity in the subjects with and without metabolic syndrome. T1, the first tertile of brachial-ankle pulse wave velocity; T2, the second tertile of brachial-ankle pulse wave velocity; T3, the third tertile of brachial-ankle pulse wave velocity; without MetS, subjects without metabolic syndrome; with MetS, subjects with metabolic syndrome.* *p$<$*0.05* vs. *tertile 1;* †p$<$*0.01* vs. *tertile 1.*

between arterial stiffness and the risk of CAD (*6–8*, *16*). Pulse pressure, PWV and augmentation index (AI) are used as markers of arterial stiffness in the clinical setting. Pulse pressure has been reported as a predictor of future CAD events (*16*), and PWV and AI have been shown to be related to the extent of coronary atherosclerosis (*6*, *8*). McLeod *et al*. hypothesized that these relationships reflect two concepts: 1) The presence of common etiologic factors between aortic and coronary atherosclerosis; and 2) The fact that increased central arterial stiffness promotes the development of coronary atherosclerosis (*6*). Furthermore, these relationships were significant even after adjustment for conventional atherosclerotic risk factors (*6–8*). However, it still remains unclear whether MetS promotes the development of coronary atherosclerosis by increasing the arterial stiffness or independently promotes the development of coronary atherosclerosis and increase in arterial stiffness. The present study was the first to examine the influence of the presence of MetS on the relationship between arterial stiffness and the risk of CAD.

In the present study population, the brachial-ankle PWV and the number of diseased coronary arteries were higher in subjects with MetS than in those without MetS. Therefore, it is possible that this increased arterial stiffness is related to the increased risk of CAD in MetS. Multiple linear regression analysis demonstrated that the brachial-ankle PWV, rather than the presence of MetS, was a significant determinant of the number of diseased coronary arteries in the entire study population even after adjustment for age, gender, smoking status, and hypercholesterolemia. However, a general linear model analysis revealed that the number of diseased coronary arteries increased significantly with an increase in the tertile number of the brachial-ankle PWV in subjects without MetS, but not in those with MetS. Therefore, we speculated that, while MetS may promote both the development of coronary atherosclerosis and the increase in the arterial stiffness, it may directly produce clinically significant atherosclerotic stenosis of the coronary arteries, independent of its promoting the development of coronary atherosclerosis by increasing the arterial stiffness.

The present study has two major limitations. 1) While several studies have suggested that central obesity has a key role in the elevated cardiovascular risk associated with MetS (*12*, *17*), the waist circumference, which is a robust marker of central obesity (*12*), was not measured in this study. Therefore, this study might only be considered as a preliminary study; 2) Central, rather than peripheral, arterial stiffness is thought to play a major role in the development of coronary atherosclerosis related to increased arterial stiffness (*3–5*, *18*, *19*). Therefore, the present results should be confirmed using a more robust marker of central arterial stiffness, such as the carotid-femoral PWV or AI (*3–5*, *18*, *19*).

In conclusion, the results of this study suggested that arterial stiffness is a marker of the risk of CAD in subjects without MetS, but in patients with MetS, the syndrome may directly produce clinically significant atherosclerotic stenosis of the coronary arteries independent of its promoting the development of coronary atherosclerosis by increasing the arterial stiffness. Further studies are required to examine the pathophysiological relationship of arterial stiffening with the development of coronary atherosclerosis and the prognosis of CAD in cases with MetS.

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