Original Article

Clinical Impact of Metabolic Syndrome by Modified NCEP-ATPⅢ Criteria on Carotid Atherosclerosis in Japanese Adults

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Aim: The present study aimed to clarify the clinical impact of modified NCEP-ATPⅢ criteria for metabolic syndrome (MS) and Framingham Risk Score (FRS) on carotid atherosclerosis in 615 Japanese adults (319 men and 296 women) including 307 with type 2 diabetes.

Methods: Waist circumference was the only component from the original NCEP-ATPⅢ criteria based on Japanese criteria. The intima-medial thickness (IMT) and stiffness parameter β of the carotid artery were measured by ultrasound.

Results: Both IMT and stiffness parameter β were significantly increased with the number of coexisting components of MS, and higher in subjects with MS than in those without MS (all P s < 0.0001). In a logistic regression analysis with each component of MS as independent factors, hyperglycemia and hypertension had the highest odds ratio for progressors of IMT and stiffness parameter β , respectively. Univariate odds ratios of MS for both IMT and stiffness parameter β were comparable with that of an increase of 10% in 10-year coronary heart disease (CHD) risk by FRS (CHD risk/10%) but inferior to CHD risk by FRS $\geq 20\%$.

Conclusion: The modified NCEP-ATPⅢ criteria for MS revealed an additive predictive impact on carotid atherosclerosis but no superiority to FRS.

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Key words; Metabolic syndrome, Type 2 diabetes, Intima-media thickness (IMT), Stiffness parameter β

Introduction

Metabolic syndrome (MS) increases the risk for diabetes mellitus and cardiovascular disease (CVD)¹⁾, and thus increases the morbidity²⁾ and mortality^{3,4)} of such diseases. Insulin resistance and/or visceral fat accumulation are underlying mechanisms of MS, which consists of a cluster of metabolic abnormalities that includes glucose intolerance, hypertriglyceridemia, low high-density lipoprotein (HDL) cholesterolemia, hypertension, and abdominal obesity. Since criteria for MS were proposed by the World Health Organization (WHO)⁵⁾ and National Cholesterol Education Pro-

gram Adult Treatment Panel III (NCEP ATPⅢ)⁶⁾, their clinical validity has been investigated²⁻⁴⁾. However, the composition and clinical validity of the criteria are still under argument^{7,8)}. Two major issues need to be addressed: first, no definition of abdominal obesity useful across different ethnic groups has been established, and second, clustering effects of MS criteria for the prediction of CVD or atherosclerosis have yet to be clearly determined. Asians, who have a lower prevalence and degree of obesity than Caucasians, have a higher percentage of body fat and risk for cardiovascular disease even at the same BMI or waist circumference as Caucasians⁹⁻¹¹⁾. The uses of different criteria for abdominal obesity have resulted in differences in the frequency of MS in Korean, Japanese, and other Asian populations¹²⁻¹⁴⁾. In the IDF provisional criteria for MS, it is recommended that the definition of visceral obesity be determined based on ethnic-specific values of waist circumference^{15,16)}.

Several studies have clarified the impact of a di-

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agnosis of MS on early atherosclerosis determined by ultrasound and pulse wave velocity (PWV), as a surrogate marker of cardiovascular disease, such as intima-medial thickness (IMT)¹⁷⁻²¹⁾ and stiffness parameter β ¹⁸⁾ in Caucasians and PWV in Japanese²²⁾. However, the superiority of MS criteria over previous scoring systems such as Framingham Risk Score (FRS) for predicting CVD is also unclear, in view of these early atherosclerotic changes⁷⁾. The aim of the present study was therefore to clarify the clinical impact of components of MS by modified NCEP-ATPIII criteria in comparison with FRS on early atherosclerotic change in the carotid artery, IMT as a parameter of morphological change, and stiffness parameter β as a parameter of functional change of atherosclerosis in 615 Japanese including some with type 2 diabetes.

Subjects and Methods

Subjects

A total of 615 subjects, including 319 men and 296 women, ranging from 15 to 82 years, were recruited from among individuals visiting the Diabetes Center at Osaka City University Hospital or participating in a local health check program at the Osaka Municipal Health Promotion Center. All subjects underwent the same evaluation of atherosclerosis by ultrasound as described below between 1995 and 2005 and live in the Osaka area. Three hundred seven type 2 diabetic subjects were sequentially selected from those who participated in an educational or atherosclerosis check program between 1995 and 2005 and had essential data of waist circumference. The 307 type 2 diabetic subjects (188 men and 119 women) with a mean duration of diabetes of 10 ± 9 years, ranging from 0 to 41 years. Two hundred and thirteen (34.6%) and 110 (17.9%) of the subjects were being treated with oral hypoglycemic agents or insulin or anti-hypertensive regimens, respectively. One hundred twenty subjects were treated by sulfonylureas, 46 by α -glucosidase inhibitors, 18 by metformin, 3 by pioglitazone, and 80 by insulin therapy, respectively. Among these type 2 diabetic subjects, 49 subjects were received by various combination therapies of these drugs. The following subjects were excluded: those with type 1 diabetes, other types of diabetes, renal failure (serum creatinine ≥ 2.0 mg/dL), or morbid obesity (BMI > 40), and/or those being treated with lipid-modifying medications. Informed consent was obtained from all participants, and the study was approved by the local ethics committee.

Definition of Metabolic Syndrome and Framingham Risk Score

In the present study, we used the diagnostic criteria for MS proposed by NCEP-ATPIII in 2001⁶⁾ after modifying the component for obesity, waist circumference. Using the NCEP-ATPIII criteria, subjects with 3 or more abnormalities are defined as having metabolic syndrome (MS). In our study, the criterium for waist circumference was replaced by ≥ 85 cm for men and ≥ 90 cm for women, based on the recommendation by the Japan Society for the Study of Obesity. The cut-off levels for waist circumference correspond to 100 cm² of visceral fat area at the umbilicus level on CT in Japanese adults²³⁾. The 10-year coronary heart disease (CHD) risk was estimated by using FRS as previously reported²⁴⁾.

IMT and Stiffness Parameter β of Carotid Artery Determined by Ultrasound

The intima-medial thickness (IMT) and stiffness parameter β of the common carotid artery were measured by an ultrasonic phase-locked echo-tracking system, which was equipped with a high-resolution real-time 13 MHz linear scanner (ProSound SSD 6500, Aloka, Tokyo), as previously reported²⁵⁾. In brief, approximately 4 cm of the common carotid artery was examined. This region was scanned bilaterally in the longitudinal and transverse projections. The image was focused on the far wall of the artery. IMT was measured at the site of the most advanced atherosclerotic lesion which exhibited the greatest distance between the lumen-intimal interface and the media-adventitia interface of the far wall in both carotid arteries. The stiffness parameter β , an index of arterial wall stiffness, was calculated as $\ln(P_s/P_d) \times Dd/(Ds-Dd)$, where P_s and P_d are the systolic and diastolic blood pressures and D_s and D_d are the systolic and diastolic inner diameters of the artery, respectively. We used the greatest carotid IMT including plaques and stiffness parameter β as a marker of atherosclerotic change in the carotid arteries of the subject.

Physical and Laboratory Measurements

Blood pressure was determined by the conventional cuff method using a mercury sphygmomanometer after the subject had rested for at least 15 min. Blood was withdrawn after an overnight fast for analysis of serum concentrations of glucose, total cholesterol, triglyceride, HDL cholesterol, and HbA1c by standard laboratory methods.

Statistical Analysis

All values are means $\pm$ SD unless otherwise indi-

Table 1. Clinical characteristics of all subjects, subjects with metabolic syndrome, (MS), and subjects without MS (non-MS)

	All subjects	MS	Non-MS	<i>p</i>
N (Male/Female)	615 (319/296)	215 (141/74)	400 (178/222)	<0.0001
Age (years)	54 ± 13	57 ± 12	52 ± 13	<0.0001
Diabetes patients (%)	307 (49.9)	179 (83.3)	128 (32.0)	<0.0001
BMI (kg/m ²)	23.8 ± 4.1	26.2 ± 4.1	22.5 ± 3.4	<0.0001
Abdominal obesity (%)	196 (31.9)	153 (71.2)	43 (10.8)	<0.0001
Waist circumference (cm)	82 ± 12	91 ± 10	77 ± 10	<0.0001
Hypertension (%)	302 (49.1)	167 (77.7)	135 (33.8)	<0.0001
SBP (mmHg)	127 ± 20	135 ± 20	122 ± 18	<0.0001
DBP (mmHg)	75 ± 11	78 ± 12	73 ± 10	<0.0001
Hyperglycemia n (%)	314 (51.1)	184 (85.6)	130 (32.5)	<0.0001
FPG (mg/dL)	122 ± 41	139 ± 43	113 ± 37	<0.0001
HbA1c (%)	6.8 ± 2.4	8.1 ± 2.1	6.1 ± 2.2	<0.0001
Total cholesterol (mg/dL)	205 ± 39	206 ± 42	205 ± 38	0.8627
Hypertriglyceridemia (%)	144 (23.4)	97 (45.1)	47 (11.8)	<0.0001
Triglycerides (mg/dL)	126 ± 91	169 ± 124	102 ± 53	<0.0001
Low HDL cholesterol (%)	198 (32.2)	144 (67.0)	54 (13.5)	<0.0001
HDL-c (mg/dL)	54 ± 16	42 ± 9	60 ± 16	<0.0001
IMT (mm)	0.816 ± 0.422	0.992 ± 0.475	0.721 ± 0.356	<0.0001
stiffness parameter β	12.3 ± 5.9	14.2 ± 6.1	11.3 ± 5.6	<0.0001

All values are the mean ± SD or number and percentage in parentheses of subjects. The definitions of abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL cholesterol were described in the text. Abbreviations are as follows: BMI, body mass index; SBP and DBP, systolic and diastolic blood pressures; FPG, fasting plasma glucose; HDL-c, high-density lipoprotein cholesterol; IMT, intima-media thickness; MS, metabolic syndrome. *P* values tested with Student's *t*-test or chi-square test (MS vs. non-MS groups).

cated. Statistical analyses were performed using the StatView 5 system (SAS Institute, Cary, NC) for Windows. Student's *t*-tests were performed for comparisons between the MS and non-MS groups. The Kruskal-Wallis test with Sheffe's test was used to examine the effects of the overlapping of MS components on IMT and stiffness parameter β . Logistic regression models were also used to determine odds ratio with their 95% confidence interval (95%CI) for progressors of IMT and stiffness parameter β . We defined the subjects with a IMT of greater than 0.874 mm as IMT progressors or with a stiffness parameter β of greater than 15.7 as stiffness parameter β progressors. Each cut-off level of IMT or stiffness parameter β was derived from the mean +1SD in non-diabetic subjects, respectively. *P* values <0.05 were considered significant.

Results

Clinical Characteristics of Subjects

Table 1 shows the clinical characteristics of the subjects. The subjects with plasma glucose levels greater than 110 mg/dL (6.1 mmol/L) and/or using antidiabetic medications totaled 314 (51.1%). One hundred and forty-four (23.4%) subjects had a increased serum

triglyceride level, 198 (32.2%) had a low HDL cholesterol level, 302 (49.1%) had an increased systolic blood pressure and/or diastolic blood pressure, and/or were receiving anti-hypertensive medications, and 196 (31.9%) had abdominal obesity. Using our modified NCEP-ATPIII criteria, metabolic syndrome (MS) was identified in 35.0% of subjects, including 44.2% of men and 25.0% of women. Seventeen (2.8%) subjects had all the components, 260 (42.3%) subjects had at least 1 risk factor but not the full syndrome, and 140 (22.8%) subjects had no components of MS. There were significant differences between MS and non-MS subjects in age, BMI, waist circumference, systolic and diastolic blood pressure, fasting plasma glucose, HbA1c, triglyceride level, and HDL cholesterol level (**Table 1**).

Effects of the Criteria for MS on IMT and Stiffness Parameter β

Both IMT and stiffness parameter β were significantly higher in MS subjects than in non-MS subjects (**Table 1**). Even in the non-MS group, the subjects with 1 or 2 components had significantly higher IMT and stiffness parameter β than those without MS components (IMT, 0.813 ± 0.400 vs. 0.551 ± 0.147, respectively, *p* < 0.0001; stiffness parameter β , 12.5 ± 6.2 vs.

Fig. 1. Relationship between number of coexisting components of the modified NCEP-ATPIII criteria for metabolic syndrome (MS) and IMT.

IMT significantly increased with number of coexisting components (each case, $p < 0.0001$). Each bar represents the mean $\pm$ SD. Numbers in parentheses are numbers of subjects in each group. * $p < 0.0001$ vs. the group with no components of MS, by Kruskal-Wallis test.

Fig. 2. Relationship between number of coexisting components of the modified NCEP-ATPIII criteria for metabolic syndrome (MS) and stiffness parameter β .

Stiffness parameter β significantly increased with number of coexisting components (each case, $p < 0.0001$). Each bar represents the mean $\pm$ SD. Numbers in parentheses are numbers of subjects in each group. * $p < 0.0001$ vs. the group with no components of MS, by Kruskal-Wallis test.

Table 2. Multivariate odds ratios for progressors of IMT or stiffness parameter β of each component of metabolic syndrome

	IMT progressor (≥ 0.874 mm)	<i>p</i> value	stiffness parameter β progressor (≥ 15.7)	<i>p</i> value
Age (/year)	1.09 (1.07-1.12)	< 0.0001	1.11 (1.08-1.14)	< 0.0001
Abdominal obesity	1.67 (1.03-2.69)	0.036	1.30 (0.81-2.11)	0.281
Hypertension	2.00 (1.28-3.26)	0.003	2.26 (1.38-3.71)	0.001
Hyperglycemia	7.66 (4.53-12.95)	< 0.0001	1.56 (0.95-2.58)	0.081
Hypertriglyceridemia	0.67 (0.40-1.13)	0.132	1.10 (0.66-1.84)	0.720
Low HDL cholesterol	1.60 (1.00-2.55)	0.049	1.19 (0.75-1.92)	0.461
R^2	0.35	< 0.0001	0.23	< 0.0001

Data are odds ratios with 95% confidential intervals in parentheses. The presence of abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia, and low HDL cholesterol was defined as 1 and the absence, as 0. Age was entered as a continuous variable.

9.2 ± 3.5 , respectively, $p < 0.0001$). Furthermore, both IMT and stiffness parameter β significantly increased with the number of components of MS (**Fig. 1, 2**). **Table 2** shows multivariate odds ratios for progressors of IMT and stiffness parameter β of age and each component of MS. Age, abdominal obesity, hypertension, hyperglycemia, and a low HDL cholesterol level were found to be independent factors for IMT progressors, and only age and hypertension, for stiffness parameter β progressors. We investigated the univariate odds ratio for predicting progressors of IMT or stiffness parameter β using the criteria for MS and CHD risk by FRS. The odds ratio was represented as an increase of

10% (CHD risk/10%) or greater than 20% (CHD risk $\geq 20\%$) of CHD risk by FRS as a reference of less than 20%. Both for IMT and for stiffness parameter β progressors, the odds ratio of MS criteria was comparable with that of CHD risk by FRS (/10%) and lower than that of CHD risk by FRS $\geq 20\%$ (**Table 3**).

Discussion

Can the definition of MS for Caucasians be applied without change to Asians? Since Asians have greater body fat deposition at a lower BMI than Caucasians and a higher risk of CVD and diabetes at the same

Table 3. Univariate odds ratios for progressors of IMT or stiffness parameter β using metabolic syndrome (MS) and 10-year coronary heart disease risk (CHD) by Framingham Risk Score (FRS)

	MS	CHD risk by FRS	
		$\geq 20\%$	/10%
IMT progressor (≥ 0.874 mm)	4.23 (2.94-6.09)	9.99 (6.60-15.11)	3.27 (2.65-4.03)
stiffness parameter β progressor (≥ 15.7)	2.29 (1.55-3.39)	5.35 (3.54-8.09)	2.06 (1.76-2.41)

Data are odds ratios with 95% confidential intervals in parentheses. All p values were less than 0.0001. The odds ratio of the existence of MS or greater than 20% of 10-year CHD risk by FRS (CHD risk $\geq 20\%$) was represented as a reference of absence of MS or less than 20%, respectively. Furthermore, the odds ratio of an increase of 10% in 10-year CHD risk by FRS (CHD risk/10%) was also calculated.

level of obesity^{9, 10}), the original NCEP ATPIII definition could result in an underestimation of the risk for CVD in individual Asians^{13, 14}. In fact, the WHO Expert Consultation and IDF recommended that appropriate waist circumferences be used based on ethnic-specific data and considerations^{16, 26}. In Asians, the criterium for waist circumference was modified to 90 cm for men and 80 cm for women from the original NCEP ATPIII, leading to an increase in frequency of MS in both men and women^{13, 14}. Furthermore, Heng *et al.* demonstrated that subjects who satisfied the modified Asian criteria (waist circumference 90 cm for men and 80 cm for women) but not the NCEP ATPIII criteria, were also at increased risk for ischemic heart disease²⁷. Takeuchi *et al.* have shown that subjects with MS diagnosed with the Japanese criteria²⁸ (waist circumference of 85 cm for men and 90 cm for women) had a 2.2-fold greater risk of developing cardiac disease than subjects without MS²⁹. As a result, the frequency of MS in men among our subjects was found to be higher than in previous reports on Caucasians^{30, 31} and even those on Asians^{13, 14}. This may be largely due to the use of a lower cut-off for waist circumference in men than in other studies and the inclusion of a large number of type 2 diabetic subjects in our study.

A few cross-sectional studies have revealed the impact of MS on atherosclerosis evaluated by IMT and PWV as a surrogate marker of cardiovascular disease. Olijhoek *et al.* found that an increase in the number of components used to define metabolic syndrome was associated with an increase in mean IMT in patients with various manifestations of vascular disease³². Iglseder *et al.* found a stronger impact of MS for women than for men on carotid IMT in a cohort of 1588 middle-aged Austrians¹⁹. For a group of 5752 middle-aged Japanese men, Tomiyama *et al.* confirmed that an increase in the number of metabolic components was associated with an increase in pulse wave velocity²². To the best of our knowledge, only one study has investigated the impact of MS on both IMT and stiffness parameter β of the carotid artery in a Cauca-

sian cohort. Scuteri *et al.* found in a study of 471 Caucasian individuals that subjects with MS had increases in IMT and stiffness parameter β , and that MS was an independent determinant of both¹⁸.

The present study is the first to demonstrate the impact of MS and its components on IMT and stiffness parameter β of the carotid artery in Asian individuals. Both IMT and stiffness parameter β were worse in the subjects with MS than in those without MS. Furthermore, both IMT and stiffness parameter β increased significantly with the number of coexisting components of MS, revealing a clear additive effect of each component on carotid IMT and stiffness parameter β . However, as a joint statement from the ADA and EDA pointed out⁷, it is important whether MS criteria have additive or clustering effects, i. e., effects greater than the sum of effects of each component, or not. In view of the effect on carotid atherosclerosis, our modified MS criteria did not reveal any such clustering effect as shown in **Fig. 1** and **2**. This finding reveals no clear superiority of MS criteria as a 'syndrome', of clinical entity, to previous individual risk factors or scoring in terms of carotid atherosclerosis. A few studies have reported the impact of MS criteria and FRS^{33, 34}. Stern *et al.* found that MS predicted CVD with a sensitivity of 67.3% and a false-positive rate of 34.2%, while FRS had a significantly higher sensitivity, 81.4%, when the false-positive rate was held to 34.2%. Although the odds ratio of MS was 3.95 (95%CI: 2.80-5.58) in a univariate analysis for predicting CVD, it dropped sharply to 1.14 (95%CI: 0.76-1.71) and became statistically nonsignificant in a multivariate analysis incorporating FRS and MS³³. Wannamethee *et al.* also reported that FRS was a better predictor of CHD and stroke than MS³⁴. Our findings revealed that MS criteria were comparable with CHD risk by FRS (/10%), but inferior to CHD risk by FRS $\geq 20\%$. This may come from the scoring system using a continuous value for each variable adopted in FRS, while the criteria of MS consists of dichotomous components with a cutoff level. However, this difference yields conveni-

ence and simplicity in the setting of clinical and epidemiological screenings for predicting atherosclerosis.

There are a few limitations to our study. Our subjects included a large number of type 2 diabetic patients because this was a hospital-based study. This limitation is likely to contribute to the difference in clinical profiles of subjects with MS from that in Japanese previous report³⁵). Therefore, our findings cannot be directly applied to estimations of the impact of our modified MS criteria for general populations of Asian or Japanese individuals. The cut-off level of waist circumference based on the present Japanese criteria for obesity and/or visceral fat accumulation requires further examination in Japanese and Asian populations.

In conclusion, the present study demonstrated the clinical impact of components of MS by the modified NCEP-ATP III criteria for obesity adjusted for use in Japanese on atherosclerosis of the carotid artery, IMT, and stiffness parameter β . Our findings suggest that the modified criteria and the components of it specific for each ethnicity have an additive but not clustering impact on morphological and functional atherosclerotic alterations of the carotid artery. Further longitudinal studies are needed to examine whether MS criteria have clustering effects on the progression of carotid atherosclerosis and/or the occurrence of CVD events.

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