Original Article

Hypertension Is the Most Common Component of Metabolic Syndrome and the Greatest Contributor to Carotid Arteriosclerosis in Apparently Healthy Japanese Individuals

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The cluster of metabolic and hemodynamic risk factors known as metabolic syndrome is known to be a risk factor for ischemic cardiovascular diseases and stroke. By analyzing the cross-sectional data from 8,144 individuals (age 19–88 years) who underwent general health screening, we have investigated the prevalence of metabolic syndrome, as diagnosed by modified-National Cholesterol Education Program (NCEP) criteria corresponding to the following five categories: triglycerides ≥150 mg/dl; high density lipoprotein (HDL)-cholesterol <40 mg/dl in men or <50 mg/dl in women; fasting plasma glucose ≥110 mg/dl; systolic/diastolic blood pressure ≥130/85 mmHg; and body mass index >25 kg/m^2. We found that the prevalence of metabolic syndrome was 19% in men and 7% in women. After adjustment for age, metabolic syndrome was found to be significantly more prevalent in men than in women, with an odds ratio of 3.08 (95% confidence interval [CI] 2.62–3.61, *p*<0.0001). Among the five metabolic/hemodynamic risk factor components, hypertension was observed most frequently in individuals with metabolic syndrome, at 85% in men and 87% in women. In addition, multivariate logistic regression analysis adjusted for age, sex, serum total cholesterol levels, and smoking status showed that hypertension possessed the greatest odds ratio (1.43, 95% CI 1.27–1.60) for carotid plaque among the metabolic/hemodynamic risk factors. These data emphasize the importance of controlling blood pressure for reducing the risk of both metabolic syndrome and carotid arteriosclerosis in apparently healthy individuals. (*Hypertens Res* 2005; 28: 27–34)

***Key Words*: metabolic syndrome, carotid artery, atherosclerosis, risk factor, cross-sectional study**

Introduction

Much evidence indicates that increased insulin resistance may be associated with a cluster of metabolic and hemodynamic abnormalities that have potent atherogenic properties and that have been designated metabolic syndrome (MetS) (*1–4*). Epidemiological studies have shown that MetS is not a rare occurrence (*5*) and is a risk factor for cardiovascular diseases (*6*) and stroke (*7*). The diagnostic criteria of MetS by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP-III) (*1*) are based on specific cut-off points in the following five categories: systemic blood pressure, waist circumference, serum levels of triglycerides (TG) and high density lipoprotein (HDL) cholesterol (HDL-C), and fasting plasma glucose (FPG).

In the present study, by analyzing the cross-sectional data from individuals who underwent general health screening, we

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Table 1. Baseline Characteristics, Metabolic, and Vascular Profiles by Metabolic Syndrome Status

Variables	Whole (n=8,144)	MetS (−) (n=6,893)	MetS (+) (n=1,251)
Age (years)	56.6±10.5	56.6±10.7	56.7±9.4
Male	5,473 (67%)	4,415 (64%)	1,058 (85%)
Body mass index (kg/m^2)	23.3±3.0	22.7±2.7	26.4±2.8
Systolic blood pressure (mmHg)	126±20	123±19	141±18
Diastolic blood pressure (mmHg)	78±12	76±11	87±11
Serum lipid data			
Total cholesterol (mg/dl)	209±34	208±34	213±36
HDL-cholesterol (mg/dl)	59±17	62±17	47±12
Triglycerides (mg/dl)	130±107	112±71	233±186
Glucose metabolisms			
Fasting glucose (mg/dl)	98±21	95±16	115±32
Haemoglobin A_{1C} (%)	5.3±0.7	5.2±0.6	5.7±1.0
Fasting insulin (U/ml)*	6.8±4.6	6.2±3.8	10.5±6.5
HOMA-IR*	1.71±1.46	1.46±0.98	3.03±2.52
HOMA-β*	79±58	77±57	89±63
Carotid ultrasonography			
Carotid plaque	2,047 (25%)	1,642 (24%)	405 (32%)
Intima-media thickness (mm)	0.74±0.40	0.74±0.42	0.78±0.23
Smoking status			
Never	3,946 (48%)	3,568 (52%)	378 (30%)
Former	1,955 (24%)	1,589 (23%)	366 (29%)
Current	2,243 (28%)	1,736 (25%)	507 (41%)

MetS, metabolic syndrome; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β cell function. *These variables were available in 6,339 of whole individuals, 1,004 and 5,335 of individuals with and without MetS, respectively.

have investigated the prevalence of both MetS and each MetS risk factor component in apparently healthy Japanese subjects, and have assessed the properties of each MetS risk factor component as a risk factor for carotid plaque.

Methods

Criteria for MetS

Diagnosis of MetS was made according to ATP-III of the NCEP (*1*), with body mass index (BMI) used as a surrogate for waist circumference, as has been done in other previous studies, because waist circumference was not available in this study sample. The five thresholds used were: 1) TG levels ≥150 mg/dl, 2) HDL-C levels <40 mg/dl in men or <50 mg/dl in women, 3) FPG ≥110 mg/dl, 4) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or current use of anti-hypertensive medication, and 5) BMI >25 kg/m^2. This BMI cut-off point was chosen instead of previously used values, such as 30 kg/m^2 (*8*), due to the discrepancy in BMI between Caucasian and Japanese populations in terms of morbidity (*9*). These five parameters were designated as "MetS risk factor component(s)" in the current study, and MetS was diagnosed when three or more MetS risk factor components were present.

Study Subjects

The study was approved by The Ethical Committee of Mitsui Memorial Hospital. Between September 1994 and December 2003, 8,144 subjects underwent general health screening including carotid ultrasonography and measurement of other metabolic markers necessary to assess the presence or absence of MetS at the Center for Multiphasic Health Testing and Services, Mitsui Memorial Hospital. In Japan, regular health checkups for employees are legally mandated. Therefore, the majority of these subjects did not have serious health problems. In addition, all or most of the costs are usually paid by the company they belong to, or by the subjects themselves, rather than by the government. Those who reported current usage of anti-hypertensive and/or anti-diabetic medications were included in the current study. Of the 8,144 subjects, the data of basal insulin levels were available for 6,339 (78%), and homeostasis model assessment of insulin resistance (HOMA-IR) and β cell function (HOMA-β) values were calculated in these individuals according to the following formula: HOMA-IR = [fasting immunoreactive insulin (IRI; U/ml) FPG (mg/dl)]/405, and HOMA-β = 360 [IRI /

Table 2. HOMA-IR According to the Status of Metabolic Syndrome and Metabolic Syndrome Risk Factor Components

Variables	HOMA-IR	*p* vlaue
Number of MetS riks factors		
0	1.12±0.70	<0.0001
1	1.49±0.92	
2	1.94±1.21	
3	2.78±2.56	
4	3.45±2.21	
5	4.36±3.00	
Status of metabolic syndrome		
No	1.46±0.97	<0.0001
Yes	3.03±2.52	
Status of each MetS risk factor		
Hypertension		
No	1.34±0.89	<0.0001
Yes	1.96±1.49	
Increased FPG		
No	1.47±0.95	<0.0001
Yes	2.89±2.01	
Decreased HDL-cholesterol		
No	1.64±1.19	<0.0001
Yes	2.17±1.86	
Increased TG		
No	1.53±1.02	<0.0001
Yes	2.30±1.85	
Increased BMI		
No	1.47±1.01	<0.0001
Yes	2.37±1.72	

HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; FPG, fasting plasma glucose; HDL, high density lipoprotein; TG, triglyceride; BMI, body mass index.

(FPG − 63)] (*10*). HOMA has been previously validated and used in cross-sectional population studies (*11*) such as the current one.

Carotid artery status was studied using high resolution B-mode ultrasonography (Sonolayer SSA270A; Toshiba, Tokyo, Japan) equipped with a 7.5 MHz transducer (PLF-703ST; Toshiba). The carotid arteries were examined bilaterally at the levels of the common carotid, the bifurcation, and the internal carotid arteries from transverse and longitudinal orientations by trained sonographers. The intima-media thickness was measured using a computer-assisted method by experienced sonographers who were unaware of the subjects' clinical and laboratory findings. Plaque was defined as a clearly isolated focal thickening of the intima-media layer with a thickness of ≥1.3 mm at the common or internal carotid artery or the carotid bulb. Carotid wall thickening was said to occur when intima-media thickness, which was measured at the far wall of the distal 10 mm of the common carotid artery, was ≥1.0 mm (*12*).

Statistical Analysis

The data in this study were analyzed by the χ^2 test, the unpaired *t*-test, and a multivariate logistic regression analysis using computer software, Statistica ver. 5J and StatView ver. 5.0. A value of $p<0.05$ was taken to be statistically significant. Results are expressed as the mean±SD.

Results

Baseline Characteristics

The age of the subjects enrolled ranged from 19 to 88 years (men, 19–88 years; women, 22–87 years) with a mean age of 56.6±10.5 years (men, 56.7±10.6 years; women, 56.4±10.4 years) (Table 1). The mean overall prevalence of MetS and number of MetS risk factor components were 15.3% and 1.22±1.17, respectively. The mean age did not significantly differ between individuals with MetS and those without. Of the 8,144 subjects, carotid plaque was found in 2,047 (25%). In men and women, the mean number of MetS risk factor components was 1.44±1.19 and 0.79±1.01, respectively ($p<0.0001$), and the prevalence of MetS was 19% and 7%, respectively ($p<0.0001$). After adjustment for age, MetS was found to be significantly more prevalent in men than in women, with an odds ratio of 3.08 (95% confidence interval [CI] 2.62–3.61, $p<0.0001$). Table 2 shows the HOMA-IR according to the number of MetS risk factors, status of MetS, and presence or absence of each MetS risk factor component. HOMA-IR increased progressively with an increase in the number of MetS risk factor components. HOMA-IR was also found to be greater in individuals who had any one of the MetS risk factor components than in those who did not have that specific component.

Figure 1 shows the mean number of MetS risk factor components and the prevalence of MetS according to the gender and age. In women, the number of MetS risk factor components increased with age. In men, by contrast, the mean number of MetS risk factor components increased with age until 50–55 years and then decreased thereafter. In individuals with MetS, the most common component among MetS risk factor components was hypertension, which was present in 85% and 87% of men and women, respectively (Fig. 2).

Comparison of Carotid Arteriosclerosis Prevalence with the Presence or Absence of Each MetS Risk Factor Component

The prevalence of carotid plaque *vs.* the presence or absence of each MetS risk factor component is shown in Fig. 2A. Univariate analysis showed that for each MetS risk factor component, carotid plaque was more prevalent in its presence than in its absence. When hypertension was absent, the prevalence of carotid plaque was 19% (867/4,560); this value was significantly less ($p<0.0001$ by χ^2 test) than that in the sub-

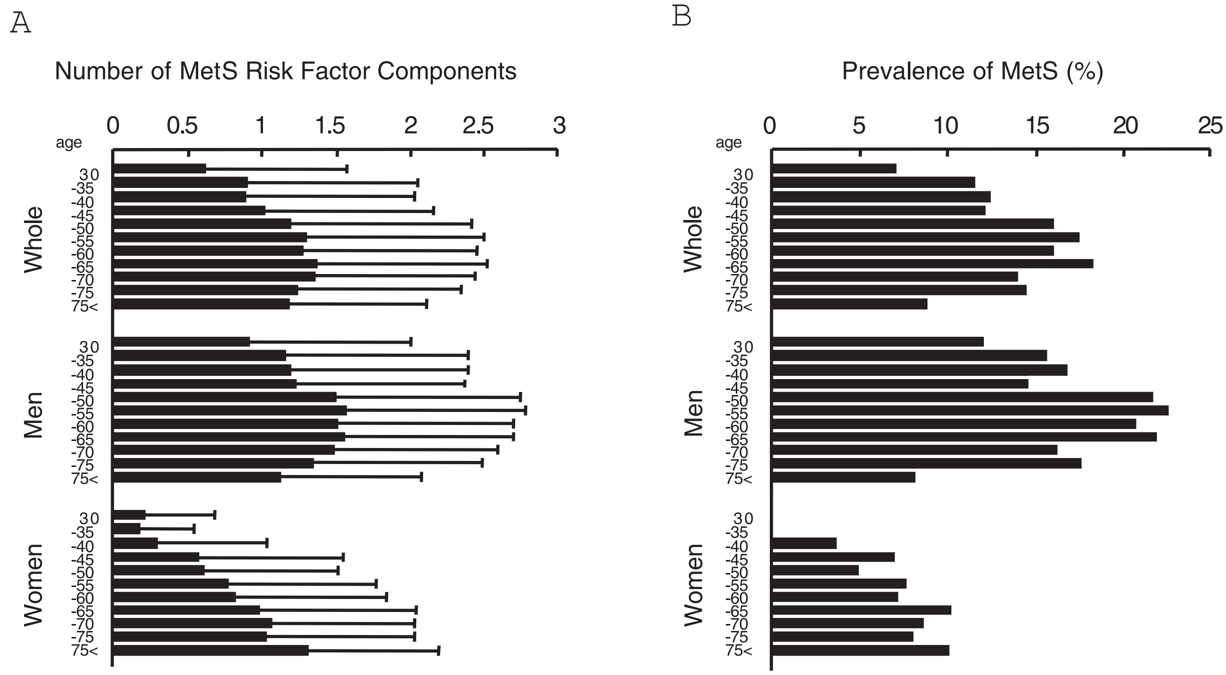

Fig. 1. *Number of metabolic syndrome (MetS) risk factor components (A) and prevalence of MetS (B) in the study population.*

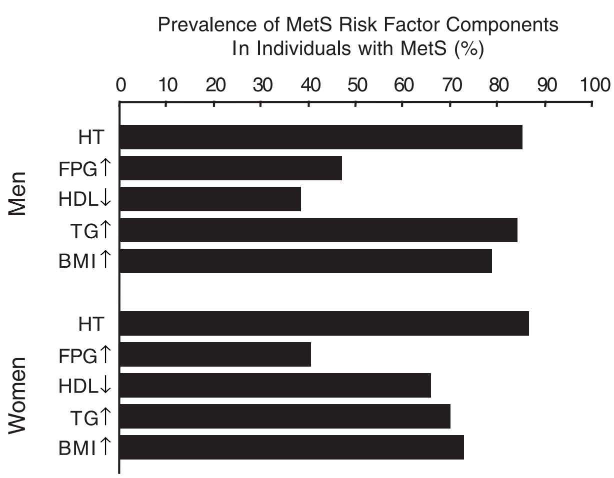

Fig. 2. *Prevalence of each metabolic syndrome (MetS) risk factor in individuals with MetS. Note that the prevalence of hypertension was greatest in both genders. HT indicates systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or current use of an anti-hypertensive medication; FPG↑, fasting plasma glucose ≥110 mg/dl or self-reported diabetes; HDL↓, HDL cholesterol <40 mg/dl in men or <50 mg/dl in women; TG↑, triglyceride level ≥150 mg/dl; BMI↑, BMI >25 kg/m^2.*

jects who did not have either increased FPG (24%; 1,663/7,060), decreased levels of HDL-C (25%; 1,760/7,092), increased levels of TG (24%; 1,430/5,998), or increased levels of BMI (25%; 1,475/6,006). Multivariate logistic regression analysis adjusted for age, sex, serum total cholesterol (TC) levels, and smoking status showed that hypertension, increased FPG, and increased TG were independent risk factors for carotid plaque, with odds ratios of 1.43 (95% CI 1.27–1.60), 1.22 (95% CI 1.05–1.42), and 1.16 (95% CI 1.02–1.33), respectively (Fig. 3).

We performed a similar multivariate analysis after dividing the study population according to their age (Fig. 4). The prevalences of carotid plaque in individuals aged ≤50 years (n=2,134), 50–60 years (n=3,128), and >60 years (n=2,882) were 7.4%, 19.6%, and 44%, respectively. In individuals aged ≤50 years old, only an increased level of FPG was found to be a significant independent risk factor for carotid plaque, with an odds ratio of 1.85 (95% CI 1.14–3.00) (Fig. 4A). By contrast, in individuals aged between 50 and 60 years, hypertension was found to be an independent risk factor for carotid plaque, with an odds ratio of 1.77 (95% CI 1.47–2.14), and an increased level of FPG just missed statistical significance (odds ratio 1.27, 95% CI 0.99–1.61, p=0.050) (Fig. 4B). In individuals aged >60 years old, among the tested MetS risk factor components, hypertension was again the only significant positive risk factor for carotid plaque, with an odds ratio of 1.31 (95% CI 1.13–1.53) (Fig. 4C). Interestingly, in the oldest population (>60 years), an increased level of BMI was found to be a negative risk factor for carotid plaque (odds ratio 0.81, 95% CI 0.67–0.96, p=0.053).

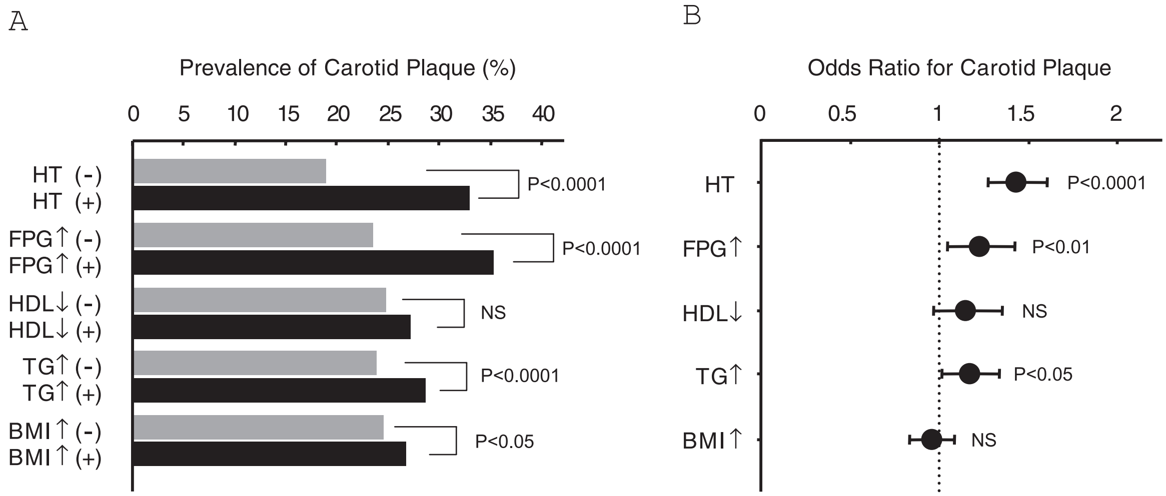

Fig. 3. *Univariate and multivariate analysis evaluating each metabolic syndrome (MetS) risk factor as a risk factor for carotid plaque. A: Univariate analysis. B: Multivariate analysis adjusted for all the variables shown, as well as age, sex, serum TC levels, and smoking status.*

Evaluation of MetS as a Risk Factor for Carotid Plaque in the Absence of Each MetS Risk Factor Component

We next assessed whether MetS was a risk factor for carotid plaque when any one of the MetS risk factor components was absent. Indeed, univariate (Fig. 5A) and multivariate (Fig. 5B) analyses showed that MetS was a risk factor for carotid plaque in the absence of any one of the MetS risk factor components.

Evaluation of MetS as a Risk Factor for Carotid Plaque after Adjustment for Each MetS Risk Factor Component

Then, we analyzed whether a cluster of at least three MetS risk factor components was independently associated with carotid plaque even after taking into account each individual component. After adjustment for age, sex, serum TC, and smoking status, MetS was found to be a significant risk factor for carotid plaque, with an odds ratio of 1.41 (95% CI 1.22–1.63, $p<0.0001$). When the parameters used to diagnose MetS (BMI, systolic blood pressure, serum levels of HDL-C and TG, and FPG) were added to this multivariate model, MetS was still found to be an independent risk factor for carotid plaque, with an odds ratio of 1.23 (95% CI 1.03–1.48, $p=0.023$).

Relationship between Severity of Hypertension and Risk for Carotid Plaque in Individuals with Hypertension

Finally, we assessed whether severity of hypertension had any link to the risk for carotid arteriosclerosis in individuals with MetS. For this purpose, only individuals who met the following three conditions were included in the analysis: 1) presence of MetS; 2) meeting the criteria of hypertension as a MetS risk factor component; and 3) not taking any anti-hypertensive drugs at the time of estimation. The severity of hypertension was defined according to the 1999 WHO/ISH guidelines as "high normal" or hypertension grades 1, 2, or 3 (*13*), which respectively corresponded to "high normal blood pressure," "mild hypertension," "moderate hypertension," and "severe hypertension" in the criteria of WHO/ISH and JSH 2000 (*14*). Prevalence of carotid plaque seemed to increase progressively with an increase in the severity of hypertension (Fig. 6A). Multivariate analysis adjusted for age, sex, BMI, TC, HDL-C, TG, and FBS showed that individuals in grade 3, but not in grade 1 or 2, had significantly greater risk for carotid plaque when "high normal" was used as reference.

Discussion

We have analyzed the data from 8,144 apparently healthy individuals (aged 19–88 years) and found that the average prevalence of MetS was 15% (19% in men and 7% in women). Among the five categories of MetS risk factor components, hypertension was the most prevalent factor in individuals with MetS. In addition, hypertension had the greatest odds ratio of 1.43 (95% CI 1.27–1.60) for carotid plaque among the MetS risk factor components.

There have been several previous reports describing the prevalence of MetS in populations of various race or ethnicity. For example, MetS has been reported to affect about 24% of US adults (aged 20–70 years and older) (*15*). On the basis of 11 prospective European cohort studies comprising more than 10,000 individuals (aged 30–89 years), the prevalence of

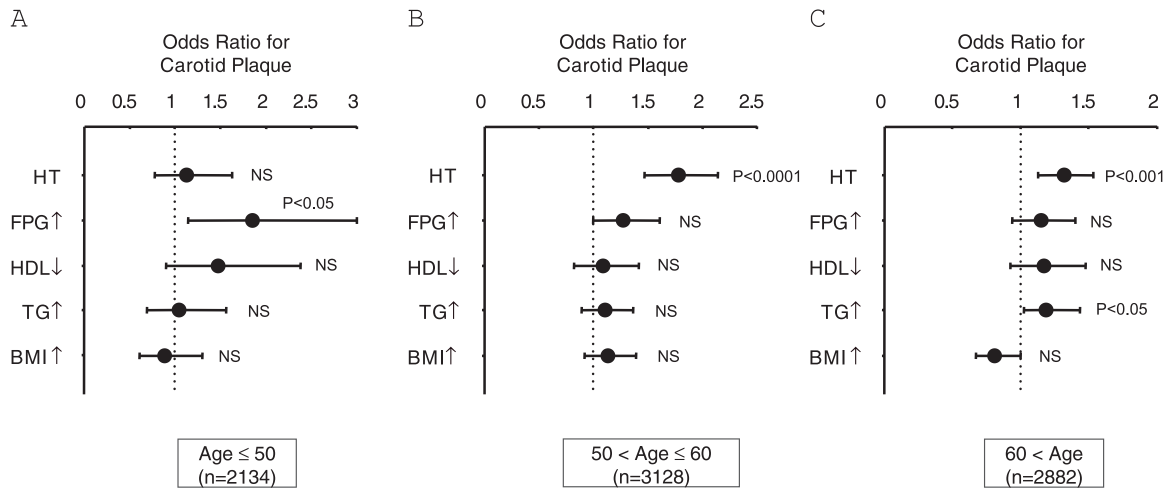

Fig. 4. *Multivariate analysis evaluating each metabolic syndrome (MetS) risk factor as a risk factor for carotid plaque in three age populations. The multivariate analysis was adjusted for all the variables shown, as well as for age, sex, serum TC levels, and smoking status.*

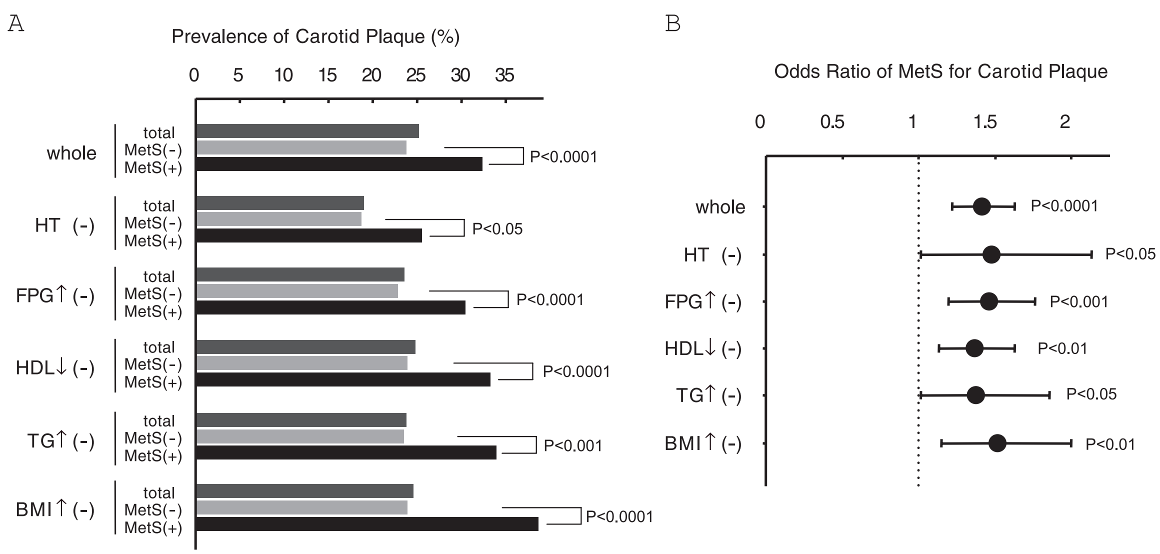

Fig. 5. *Univariate and multivariate analysis evaluating metabolic syndrome (MetS) as a risk factor for carotid plaque in the absence of any one of the MetS risk factors. A: Univariate analysis. B: Multivariate analysis adjusted for age, sex, serum TC levels, and smoking status.*

the metabolic syndrome was found to be 16% in men and 14% in women (*16*). In their analysis of 40,698 Korean metropolitan subjects, Lee *et al.* found that the prevalence of MetS was 13.2% in men and 13.1% in women (*17*). Lawlor *et al.* have reported a diagnosis of MetS in 29% of women (aged 60–79 years) randomly selected from 23 British towns (*18*). Thus, the overall prevalence of MetS in our study can be said to be comparable to the values reported in some of these reports, although one should be cautious when comparing the prevalence of MetS among various studies, as several different types of modified criteria have been used to diagnose MetS, and this could affect the determination of MetS prevalence.

Indeed, by analyzing the same cross-sectional data from a prospective population-based survey, Bonora *et al.* estimated that the prevalence of MetS was 34% according to WHO criteria and 18% according to NCEP-ATPIII criteria (*19*). Most notable in the current study was the low prevalence of MetS in women: the age-adjusted prevalence of MetS in women was found to be about 1/3 of that in men. One may question whether the metabolic parameters observed in the women included in the present study are comparable to those found in the general population in Japan. Yamamoto *et al.* have reported metabolic and hemodynamic data from Japanese women aged 50–69 years obtained in an epidemiological sur-

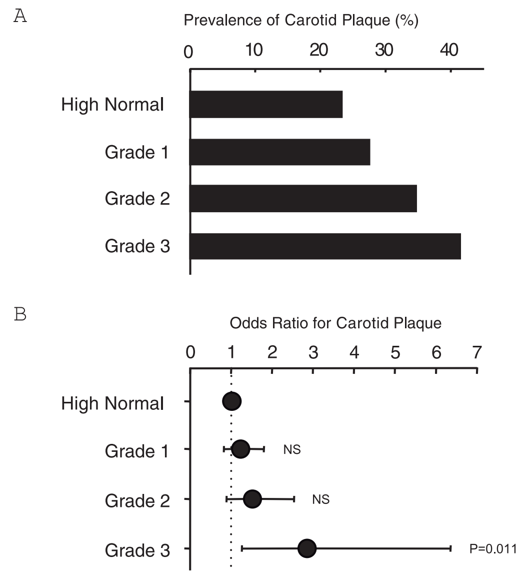

Fig. 6. *Prevalence of carotid plaque according to the blood pressure status. Only individuals with metabolic syndrome who met the criteria of "hypertension," but were not receiving anti-hypertensive drugs were included for the analyses. The severity of hypertension was defined according to the 1999 WHO/ISH guidelines as "high normal" or grade 1, 2, or 3. A: Prevalence of carotid plaque according to the blood pressure levels. B: Multivariate logistic regression analysis adjusted for age, sex, BMI, TC, HDL-C, TG, and FPG. The high normal group was used as reference.*

vey carried out in 1990 (*20*). The metabolic and hemodynamic risk factors in their report *vs.* our age-matched female study population are as follows: hypertension, 32% *vs.* 32%; TC, 213 mg/dl *vs.* 223 mg/dl; TG, 106 mg/dl *vs.* 98 mg/dl; and HDL-C 54 mg/dl *vs.* 70 mg/dl, respectively. Although we cannot easily compare these values, it seems that our female individuals aged 50–69 years had metabolic and hemodynamic cardiovascular risk factors, except for HDL-C, that were similar to those of the general population, as reported by reported by Yamamoto *et al.* (*20*).

In the present study, the prevalence of MetS increased with age in women, whereas it peaked at an age of 55–60 years in the male population. By analyzing the general Japanese population, other investigators reported a similar finding (*21*). Why did the prevalence of MetS in males decrease after 60 years of age? One possibility is that abnormalities in some of the metabolic and hemodynamic risk factors might be ameliorated after 60 years of age. Another possibility is that male subjects with a relatively small number of MetS risk factor components might be more successful in maintaining good or fair health, such that they would be more likely to undergo a general health screening rather than to attend clinics or hospitals for the treatment of specific diseases. These possibilities should be examined in future studies.

A previous study has shown that MetS is an independent risk factor for carotid atherosclerosis and coronary heart disease (*22*). In the current study, MetS was found to be an independent risk factor for carotid plaque after adjustment for age, sex, serum TC levels, and smoking status, with an odds ratio of 1.41 (95% CI 1.22–1.63, $p<0.0001$). More recently, the clustering of MetS risk factor components itself has been suggested to be a risk for carotid arteriosclerosis even after the adjustment for each MetS risk factor component (*23*). Similarly, in our study population, we found that MetS was an independent risk factor for carotid plaque, with an odds ratio of 1.23 (95% CI 1.03–1.48, $p=0.023$) after adjustment for age, sex, BMI, serum levels of TC, HDL-C, and TG, and FPG; this finding may emphasize the importance of controlling blood pressure for reducing the risk of carotid plaque, as hypertension was the most common MetS risk factor component in individuals with MetS. When the analysis was limited to the individuals without hypertension, the prevalence of MetS was found to be only 4.0% in the present population. The finding that hypertension had a greater odds ratio for carotid plaque as compared with other MetS risk factor components may further emphasize the importance of blood pressure control. These findings suggest that controlling blood pressure might have greater beneficial effects than controlling other metabolic risk factors in preventing the development of MetS and carotid arteriosclerosis. Is controlling blood pressure sufficient to prevent carotid arteriosclerosis in individuals with MetS? In the current study, we showed by multivariate analysis that metabolic syndrome significantly increased the prevalence of carotid plaque in individuals without hypertension (Fig. 5). Thus, controlling other MetS risk factor components is also essential to further reduce the risk of arteriosclerosis even in the absence of hypertension in individuals with MetS. As blood pressure levels may be associated with abnormalities of other metabolic parameters (*24*), blood pressure control can be said to be essential in preventing clustering of metabolic abnormalities and arteriosclerosis.

Our study has some limitations. First, there may be some selection bias in terms of the subjects who undergo health checkups. In Japan, however, regular health checkups for employees are legally mandated, rather than being due to the decision or recommendation of a physician. Second, individuals who have had previous cerebrovascular events are less likely to undergo general health screening tests; therefore, the prevalence of MetS and/or carotid arteriosclerosis may be underestimated by this type of analysis. Third, because the current study was cross-sectional in nature, longitudinal observations will be needed to further address the relationship between MetS risk factor components and carotid arteriosclerosis.

In the present study, we assessed the properties of each individual MetS risk factor component as a risk factor for carotid arteriosclerosis. Recent studies have indicated that carotid arteriosclerosis is not merely a marker of early atherosclerosis, but is also a predictor for future coronary events (*25*) and for impaired coronary flow reserve (*26*). Whether or not hypertension possesses the greatest risk factor properties for cardiovascular events among the MetS risk factor components also needs to be elucidated in future studies.

In conclusion, in an analysis of 8,144 individuals who underwent general health screening, we found that hypertension was the most common of the MetS risk factor components in both genders (85% in men and 87% in women). Among the five MetS risk factor components, hypertension and increased levels of FPG were found to be independent risk factors for carotid plaque. As hypertension had the greatest odds ratio for carotid plaque among the MetS risk factor components, the importance of controlling blood pressure cannot be overemphasized in terms of preventing the development of MetS and carotid arteriosclerosis.

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