Metabolic Syndrome and Carotid Atherosclerosis: Role of Elevated Blood Pressure

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It is not known whether subjects with metabolic syndrome and elevated blood pressure are at the same cardiovascular risk as subjects with metabolic syndrome but without elevated blood pressure. Using B-mode ultrasonography, carotid IMT was measured in 1,297 patients (593 men and 704 women) in the medical department of Seiyo Municipal Nomura Hospital between August 1996 and April 2005. The prevalence of metabolic syndrome was 32.5% among men and 35.9% among women. On comparing subjects with an equal number of components of metabolic syndrome, it was found that the prevalence of carotid atherosclerosis was significantly higher in subjects with elevated blood pressure than in those without, and increased with the number of components in the former group (p for trend = 0.0277), but not in the latter (p for trend = 0.5159). In a stepwise multiple logistic regression analysis, after adjustment for confounding factors, elevated blood pressure (OR, 1.771; 95% CI, 1.246–2.519), low HDL-C (OR, 1.391; 95% CI, 1.053–1.836) and number of components of metabolic syndrome (OR, 1.561; 95% CI, 1.103–2.209) were significantly associated with carotid atherosclerosis. The diagnosis of metabolic syndrome per se might not adequately identify subjects at increased cardiovascular risk. J Atheroscler Thromb, 2005; 12: 268–275.

Key words: Risk factor, Atherosclerosis, Lipid metabolism, Blood pressure

Introduction

Metabolic syndrome is a condition in which people have at least 3 of the following abnormalities: overweight, elevated blood pressure, elevated triglyceride (TG) levels, low HDL cholesterol (HDL-C) levels, and elevated blood sugar levels (1–3). People with metabolic syndrome are at high risk of developing type 2 diabetes (4) and cardiovascular disease (5). Reaven (6) used the term “Syndrome X” for the clustering of cardiovascular risk factors such as insulin resistance, hypertension (HT), glucose intolerance, hypertriglyceridemia, and low HDL-C concentrations. Several other metabolic disorders have been associated with this syndrome, including abdominal obesity, microalbuminuria, and abnormalities in fibrinolysis and coagulation (7, 8). In 1998, the World Health Organization (WHO) initially proposed a unifying definition for metabolic syndrome (2). More recently, the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) proposed a new definition of metabolic syndrome (3).

Although there is no doubt that metabolic syndrome markedly increases the risk of cardiovascular diseases, few, if any, studies have assessed the impact of the clustering of risk factors and the clinical relevance of each single risk factor within the syndrome. In particular, while the association between HT and carotid atherosclerosis...
is well known and widely reported (9, 10), it is not known whether subjects with metabolic syndrome and elevated blood pressure are at the same cardiovascular risk as subjects with metabolic syndrome without elevated blood pressure (11). To clarify this point, we evaluated carotid atherosclerosis in subjects with metabolic syndrome with or without elevated blood pressure.

Materials and Methods

Subjects
Participants were consecutively enrolled from in-patients in the medical department of Seiyo Municipal Nomura Hospital between August 1996 and April 2005. Patients with severe cardio-renal or nutritional disorders that would affect blood pressure, lipids or glucose metabolism were excluded. One thousand two hundred and ninety-seven patients (593 men and 704 women) were enrolled in the study. Informed consent for the procedure was obtained from each patient. All procedures were approved by the Ethics Committee of Seiyo Municipal Nomura Hospital.

Evaluation of risk factors
Information on demographic characteristics and risk factors was collected using the clinical files in all cases. We measured blood pressure in the right upper arm of patients in a sedentary posture using an automatic oscillometric blood pressure recorder. We defined a smoker as a subject with a pack-years index > 0 (pack-years were defined as packs of cigarettes per day multiplied by years smoked). Total cholesterol (T-C), TG and HDL-C were measured within 24 hours after admission under fasting conditions. The LDL cholesterol (LDL-C) level was calculated using the Friedewald formula (12): T-C (mg/dl) – HDL-C (mg/dl) – 0.2 × TG (mg/dl), in the case of less than 400 mg/dl of TG, or T-C (mg/dl) – HDL-C (mg/dl) – 0.16 × TG (mg/dl), in the case of 400 mg/dl or more of TG. History of antihypertensive and antilipidemic drug use was also evaluated.

Ultrasound image analysis
An ultrasonograph (Hitachi EUB-565 or Aloka SSD-2000) equipped with a 7.5 MHz linear type B-mode probe was used by a specialist in ultrasonography to evaluate sclerotic lesions of the common carotid arteries on a day close to the day blood biochemistry was analyzed (within 2 days). Patients were asked to assume a supine position, and the bilateral carotid arteries were observed obliquely from the anterior and posterior directions. The thickness of the intima-media complex (IMT) on the far wall of the bilateral common carotid artery at about 10 mm proximal to the bifurcation of the carotid artery (as the image at that site is more clearly depicted than that at the near wall) (13, 14) as well as near the 10 mm point, was measured on a B-mode monitor. The mean value was then used for analysis and carotid atherosclerosis was defined as IMT ≥ 1.0 mm (15).

Metabolic syndrome
We applied the condition-specific cut off points for metabolic syndrome from the recent World Health Organization (WHO) (2) and NCEP-ATP III report (3), with modifications. Metabolic syndrome was defined as at least 3 of the following 5 conditions: visceral obesity assessed by body mass index (BMI) calculated using weight in kilograms divided by the square of height in meters, elevated blood pressure, hypertriglyceridemia, low HDL-cholesterolemia and elevated blood sugar.

• Visceral obesity shown by BMI ≥ 25.0 kg/m² (15-18).
• Elevated blood pressure was defined as systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg or those who had been treated for HT.
• Hypertriglyceridemia was identified based on TG concentrations ≥ 150 mg/dl.
• Low HDL-C level was identified by an HDL-C < 40 mg/dl in men or < 50 mg/dl in women, or those who had been treated for dyslipidemia.
• Elevated fasting glucose was identified by fasting glucose ≥ 110 mg/dl or those who had been treated for diabetes mellitus (DM).

Statistical analysis
All values are expressed as the mean ± standard deviation (SD), unless otherwise specified. Statistical analysis was performed using SPSS 10.0J (Statistical Package for Social Science, Inc., Chicago, IL, USA). The prevalence among control subjects and metabolic syndrome patients was compared with the χ²-test. Differences among groups were analyzed using the Mann-Whitney U-test. A stepwise multiple linear or logistic regression analysis was employed to evaluate the significant contribution of each risk factor including metabolic syndrome to carotid IMT or atherosclerosis. A value of p < 0.05 was considered significant.

Results

Background of subjects
Table 1 shows the clinical characteristics of subjects, according to gender. Women were older and had higher values for prevalence of antihypertensive drug use, T-C, LDL-C, HDL-C and prevalence of antilipidemic drug use. Cigarette consumption, DBP and carotid IMT were higher in men. Among men, 42 had none of the components of metabolic syndrome, 148 had 1, 210 had 2, 137 had 3, 45 had 4, and 11 had all of the components; while for women, the distribution was 36, 164, 251, 163, 78, and 12, respectively. As expected, BMI, SBP, DBP, preva-
lence of antihypertensive drug use, T-C, TG, LDL-C, prevalence of antilipidemic drug use, blood sugar and history of DM significantly increased as the number of components of metabolic syndrome increased in men, while BMI, SBP, DBP, prevalence of antihypertensive drug use, T-C, TG, LDL-C, prevalence of antilipidemic drug use, blood sugar and history of DM were also significantly increased in women. HDL-C significantly decreased in both men and women (data not shown).

Overall, 193 men (32.5%) and 253 women (35.9%) were defined as having metabolic syndrome. Among these subjects, elevated blood pressure and low HDL-C were more frequent in women; elevated blood glucose was more frequent in men. When those with DM were considered separately, 109 men (18.4%) and 157 women (22.3%) were defined as having metabolic syndrome only, and 84 men (14.2%) and 96 women (13.6%) were defined as having metabolic syndrome and DM.

Table 1. Clinical and biochemical characteristics of participants according to gender.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 593</td>
<td>N = 704</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>68 ± 14</td>
<td>73 ± 12</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Body mass index† (kg/m²)</td>
<td>22.6 ± 4.1</td>
<td>22.6 ± 4.2</td>
<td>0.9277</td>
</tr>
<tr>
<td>Visceral obesity, N (%)</td>
<td>127 (21.4%)</td>
<td>178 (25.3%)</td>
<td>0.1147</td>
</tr>
<tr>
<td>Smoking status‡ (pack-years)</td>
<td>29 ± 27</td>
<td>1.7 ± 9.6</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>136 ± 22</td>
<td>137 ± 21</td>
<td>0.2763</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78 ± 12</td>
<td>76 ± 12</td>
<td>0.0120</td>
</tr>
<tr>
<td>Antihypertensive drug use, N (%)</td>
<td>212 (35.8)</td>
<td>327 (46.4%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Elevated blood pressure, N (%)</td>
<td>410 (69.1)</td>
<td>539 (76.6%)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>103 ± 80</td>
<td>97 ± 72</td>
<td>0.5352</td>
</tr>
<tr>
<td>Hypertriglyceridemia, N (%)</td>
<td>81 (14.2)</td>
<td>80 (11.4)</td>
<td>0.1322</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>170 ± 44</td>
<td>192 ± 43</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>102 ± 38</td>
<td>121 ± 36</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>47 ± 19</td>
<td>52 ± 16</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Antilipidemic drug use, N (%)</td>
<td>12 (2.0)</td>
<td>37 (5.3)</td>
<td>0.0031</td>
</tr>
<tr>
<td>Low HDL-C, N (%)</td>
<td>243 (41.0)</td>
<td>353 (50.1)</td>
<td>0.0010</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>130 ± 56</td>
<td>126 ± 56</td>
<td>0.1311</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
<td>158 (26.6%)</td>
<td>167 (23.7%)</td>
<td>0.2470</td>
</tr>
<tr>
<td>Elevated blood glucose, N (%)</td>
<td>350 (59.0)</td>
<td>377 (53.9)</td>
<td>0.0496</td>
</tr>
<tr>
<td>MS component, N</td>
<td>2.0 ± 1.1</td>
<td>2.2 ± 1.1</td>
<td>0.0606</td>
</tr>
<tr>
<td>Metabolic syndrome, N (%)</td>
<td>193 (32.5%)</td>
<td>253 (35.9%)</td>
<td>0.2179</td>
</tr>
<tr>
<td>Atherosclerotic disease, N (%)</td>
<td>204 (34.4)</td>
<td>228 (32.4)</td>
<td>0.4780</td>
</tr>
<tr>
<td>Ischemic stroke, N (%)</td>
<td>191 (32.2)</td>
<td>201 (28.6)</td>
<td>0.1629</td>
</tr>
<tr>
<td>Ischemic heart disease, N (%)</td>
<td>29 (4.9)</td>
<td>36 (5.1)</td>
<td>0.8988</td>
</tr>
<tr>
<td>Carotid intima-media thickness (mm)</td>
<td>1.00 ± 0.25</td>
<td>0.97 ± 0.21</td>
<td>0.0182</td>
</tr>
</tbody>
</table>

Plus-minus values indicate means ± standard deviation. †Body mass index was calculated using weight in kilograms divided by the square of height in meters. ‡Smoking status: daily consumption (packs) × duration of smoking (years). MS: metabolic syndrome; components of metabolic syndrome defined as the 5 following conditions, high body mass index (≥ 25.0 kg/m²): hypertension (systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg or those who had been treated for hypertension), hypertriglyceridemia (triglyceride ≥ 150 mg/dl), low HDL cholesterolemia (Low HDL-C < 40 mg/dl in men or < 50 mg/dl in women, or those who had been treated for dyslipidemia) and high blood glucose (elevated glucose ≥ 110 mg/dl or those who had been treated for diabetes mellitus). * Mann-Whitney U-test or χ²-test.

Carotid intima-media thickness according to the number of components of metabolic syndrome and gender

In the subjects overall, carotid IMT was 1.00 ± 0.25 mm in men and 0.97 ± 0.21 mm in women (p = 0.0182) and increased as the number of components of metabolic syndrome increased in both men and women (both, p < 0.0001). (Fig. 1).
Metabolic Syndrome and Blood Pressure

Elevated blood pressure and carotid intima-media thickness according to the number of components of metabolic syndrome

The association between elevated blood pressure and carotid atherosclerosis was further explored by looking at carotid IMT in subjects with different numbers of metabolic syndrome components according to the presence/absence of elevated blood pressure. Fig. 2 shows that carotid IMT significantly increases as the number of components increases in subjects with elevated blood pressure ($p$ for trend = 0.0277), but not in those without HT ($p$ for trend = 0.5159). Carotid IMT is significantly higher in the former than latter group, equal to that in the presence of metabolic syndrome components.

The contribution of the components of metabolic syndrome including conventional risk factors to carotid atherosclerosis

On stepwise multiple logistic regression analysis, after adjustment for age, gender, high body mass index, smoking status, and elevated LDL-C, metabolic syndrome (ie,
The presence of at least 3 of the 5 components of the syndrome was associated with carotid atherosclerosis with an odds ratio (OR) of 1.638 (95% confidence interval (CI): 1.274–2.106) (Table 3, model 1). When various components of metabolic syndrome were included in the same model, elevated blood pressure (OR, 2.475; 95% CI, 1.836–3.337) and Low HDL-C (OR, 1.634; 95% CI, 1.279–2.087) were significantly associated with carotid atherosclerosis (Table 3, model 2). In a multivariate model that included the same variables as in model 2 plus history of atherosclerotic disease and number of components of metabolic syndrome, elevated blood pressure (OR, 1.771; 95% CI, 1.246–2.519), low HDL cholesterol (OR, 1.391; 95% CI, 1.053–1.836) and number of components (OR, 1.561; 95% CI, 1.103–2.209) were significantly associated with carotid atherosclerosis (Table 3, model 3).

**Discussion**

Metabolic syndrome, representing a cluster of factors that include insulin resistance, visceral obesity, HT,
dyslipidemia, and glucose intolerance, is a common basis for the development of atherosclerosis, especially coronary heart disease and atherosclerotic brain infarction. In the present study, the prevalence of metabolic syndrome was 32.5% in men and 35.9% in women. Importantly, metabolic syndrome was associated with an independently increased risk for carotid IMT after considering each individual component of metabolic syndrome. When subjects with an equal number of components were compared, carotid IMT was found to be significantly higher in subjects with elevated blood pressure than in those without, and increased as the number of components increased in the former, but not latter group. There were gender-related differences in the prevalence of each component of metabolic syndrome, with elevated blood pressure and low HDL-C more frequent in women.

In the present study, we tentatively defined metabolic syndrome using WHO (7) and NCEP-ATP III (8) criteria modified for a Japanese population. Obesity is frequently accompanied by dyslipidemia, HT, and glucose intolerance but the prevalence of obesity greater than BMI 30 kg/m² is only 2–3% in eastern Asia (17) (3.8% in the present study). The establishment of criteria appropriate for Japanese populations is needed. Therefore, we used BMI ≥ 25.0 kg/m² according to the criteria for obesity of the Japanese Society for the Study of Obesity (15) as the cut-off point for visceral obesity. Most observers would accept BMI as a satisfactory substitute for waist circumference in middle-aged men, since it predicts diabetes development and other metabolic disturbances as strongly as waist circumference (15–18). Indeed, the use of BMI in place of waist circumference was recently adopted by Ridker et al (19) in an analysis of metabolic syndrome in a Women’s Health Study. We were thus able to define a modified metabolic syndrome status at baseline and link this status to the risk for carotid atherosclerosis.

The clinical importance of metabolic syndrome is related to its putative impact on carotid IMT. Moreover, as the degree of risk for metabolic syndrome increased, carotid IMT also increased. In the progression of atherosclerosis, metabolic syndrome was markedly associated with positive remodeling of the common carotid artery. However, we do not know whether the various possible phenotypes of metabolic syndrome are all equally associated with carotid IMT and/or whether the presence of a particular component confers an increased risk. In the present study, elevated blood pressure was markedly associated with carotid IMT, independently of possible confounding factors and even of the presence of metabolic syndrome. Other authors have investigated the impact of metabolic syndrome and have reported the same findings as us. Itrace et al (11) examined the use of metabolic syndrome and its components to predict carotid atherosclerosis assessed by ultrasonography in a large population. They found that the presence of carotid atherosclerosis was predicted by metabolic syndrome, and individually, by elevated blood pressure. Scuteri (20) also reported that metabolic syndrome is independently associated with increased IMT and stiffness adjusted for established risk factors as well as each component of metabolic syndrome. They found that fasting glucose was independently associated with carotid IMT after taking into account metabolic syndrome, and fasting glucose, SBP and DBP were independently associated with carotid stiffness.

As for IMT, several authors have reported that the severity of carotid atherosclerosis as evaluated by ultrasonography is an useful indicator of the risk of ischemic stroke in symptomatic patients (21) and the coronary heart disease event rate (22). However, there are reports pointing out somewhat different results depending on the site or the method of measurement in the carotid artery (23). The common carotid artery is often used for measurements, and IMT at the distal end (24) is usually measured. At this site, the shape of the artery is linear, and therefore, hemodynamic disturbances or tensile stresses in the bifurcation and the curve or the arrhythmic sites are less likely to affect wall thickness (25). The IMT images thus obtained are therefore not eccentric, but show a uniform thickening of the arterial wall and are suitable for observation of the relation with risk factors (23). Therefore, we measured the IMT on the far wall of the bilateral common carotid artery at 10 mm and 20 mm proximal to the bifurcation of the carotid artery in those with or without metabolic syndrome which is associated with serious cardiovascular complications.

The relationship between elevated blood pressure and carotid atherosclerosis is well known and widely reported (9–11, 26, 27). We found that clustering including elevated blood pressure and increased numbers of components was strongly associated with carotid IMT even after adjustment for each individual component of metabolic syndrome. Blood pressure and blood flow are major determinants of mechanical stresses that act on the arterial wall and lumen (20). Scuteri et al. reported that in the context of increased circumferential wall stress, specific alterations in carotid geometry were significantly associated with differing levels of flow-mediated shear stress and resulted in specific patterns of alterations in carotid function (28). Of note, Leoncini (29) also reported that essential hypertensive patients with metabolic syndrome are at greater risk of developing cardiovascular disease. They found that the presence of metabolic syndrome entails a twofold greater risk for microalbuminuria, left ventricular mass index and carotid abnormalities after adjusting for age, gender and duration of HT.

However, we need to be aware of limitations in interpreting the present results. Based on its cross-sectional design, the present study is inherently limited in terms of
the ability to eliminate causal relationships between risk factors and carotid atherosclerosis. Since all participants were hospitalized patients, we could not eliminate the possible effect of underlying diseases on the results. 
We also could not eliminate the possible effects of medications for HT, dyslipidemia and atherosclerotic diseases on the present findings. Antihypertensive drug use varied from 35.8% in men to 46.4% in women. An effect of the latter is unlikely because only 2.0% of men and 5.3% of women received antilipidemic drugs. Anti-platelet agents, which attenuated the progression of carotid atherosclerosis (30), were being used by almost all patients with atherosclerotic diseases. However, we found that elevated blood pressure and number of metabolic syndrome components were strongly associated with carotid atherosclerosis even after adjustment of these drugs and diseases. Secondary preventive interventions after obesity, HT, dyslipidemia and DM may be successful in reducing risk factors, thus attenuating the observed association of risk factors with disease. These points need to be addressed again in a prospective fashion using a large population-based sample.

In summary, we reported a significant association between the cluster of cardiovascular risk factors known collectively as metabolic syndrome and carotid IMT in subjects with risk factors for atherosclerosis. Carotid atherosclerosis was significantly more prevalent in subjects with elevated blood pressure than in those without. Our study suggests that a simple diagnosis of metabolic syndrome is not sufficient to define the risk of carotid atherosclerosis and that physicians should also consider each individual component of the syndrome. Further study is needed to adequately identify these subgroups and address management.

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References

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