Components of the Metabolic Syndrome and Carotid Atherosclerosis
Role of Elevated Blood Pressure

Concetta Irace, Claudio Cortese, Elio Fiaschi, Claudio Carallo, Giorgio Sesti, Eduardo Farinaro, Agostino Gnasso

Abstract—Elevated blood pressure is among the factors that contribute to the metabolic syndrome (MetS). It is not known whether subjects with MetS and elevated blood pressure are at the same cardiovascular risk as subjects with MetS but without elevated blood pressure. To clarify this point, we have evaluated the prevalence of carotid atherosclerosis in subjects with MetS with or without elevated blood pressure. A large population was examined (842 women and 1011 men). Blood pressure, lipids, glucose, and waist were measured by routine methods. Carotid atherosclerosis was evaluated by echo Doppler examination. The prevalence of MetS was 24.4% in women and 28.7% in men. The prevalence of carotid atherosclerosis was 35.1% in women and 37.3% in men (p=NS), and increased with increasing number of MetS components. Age, smoking, and systolic blood pressure (SBP) were associated with the presence of carotid atherosclerosis (logistic model), whereas age, high-density lipoprotein cholesterol, and SBP were associated with the extent of atherosclerosis (linear model). When comparing subjects with an equal number of MetS components, the prevalence of carotid atherosclerosis was significantly higher in subjects with elevated blood pressure than in those without. No difference in carotid atherosclerosis prevalence was found in subjects bearing or not bearing components of the syndrome other than elevated blood pressure. The present findings demonstrate that subjects with MetS and elevated blood pressure have increased carotid atherosclerosis compared with subjects with MetS but without elevated blood pressure. The diagnosis of MetS per se might not adequately identify subjects at elevated cardiovascular risk. (Hypertension. 2005;45:597-601.)

Key Words: atherosclerosis ■ carotid arteries ■ hypertension

Metabolic syndrome (MetS) represents a combination of at least 3 of the following conditions: elevated triglycerides, blood pressure, glucose, waist, or low high-density lipoprotein (HDL) cholesterol, as set forth by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III. Insulin resistance probably plays a central pathophysiological role in the development of the syndrome, and genetic and environmental factors have been associated with the disease. The MetS is quite diffuse and its prevalence has been reported to exceed 40% in subjects aged older than 40 years. Several studies have demonstrated that MetS is associated with increased cardiovascular morbidity and mortality, both in the general population and in subjects with type 2 diabetes.

Although there is no doubt that multiple risk factors markedly increase the risk of cardiovascular events, little, if any, information is available on the impact of peculiar clustering of risk factors and on the clinical relevance of each single risk factor within the syndrome. In particular, it is not known whether MetS clusters including or not including elevated blood pressure are equally associated with carotid atherosclerosis. To this aim, we have examined the impact of MetS and its components on carotid atherosclerosis in a large sample of participants in a Cardiovascular Disease Prevention Campaign.

Subjects and Methods
We used data on 842 women and 1011 men, 30 to 80 years of age, who were participants in a regional Cardiovascular Disease Prevention Campaign. Subjects, who were all white, were examined between January 2001 and October 2003, according to a previously standardized protocol. Briefly, participants were residents in the region and no exclusion criteria was adopted except age younger than 30 years. All participants were informed about the aim of the campaign and an informed consent was obtained before examination.

Cardiovascular Risk Factors Assessment and Metabolic Status Classification
All subjects were examined in the morning in a room at 22°C, after overnight fasting. Well-trained personnel measured blood pressure,
height, and weight by routine methods. The mean of 2 sitting blood pressure readings was used. Body mass index (BMI) was computed as weight (in kilograms) divided by height (in squared meters). Waist circumference was measured midway between the lower rib margin and the iliac crest. A questionnaire was administered to evaluate smoking habit and drug use. Current smokers recorded the number of cigarettes smoked each day. Subjects were asked to record the age at which they started to smoke and, for those who stopped smoking, also the age at which they gave up. Pack-years of cigarette consumption were calculated from these data assuming that smoking pattern indicated was stable throughout the life. A pack-year was defined as 20 cigarettes per day for 1 year. Blood was withdrawn from an antecubital vein after echo Doppler examination. Blood lipids and glucose were measured by commercially available kits. Low-density lipoprotein cholesterol was calculated using the Friedewald formula.

MetS was defined as the presence of 3 or more of the following: (1) waist circumference >88 cm in women and >102 cm in men; (2) fasting triglycerides ≥150 mg/dL; (3) HDL cholesterol <50 mg/dL in women and <40 mg/dL in men; (4) systolic blood pressure/diastolic blood pressure ≥130/85 mm Hg or use of antihypertensive drug therapy; and (5) fasting glucose ≥110 mg/dL or use of hypoglycemic agents, according to the third report of the NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III).14

**Carotid Atherosclerosis Assessment**

Echo Doppler examination of carotid arteries was performed using an instrument equipped with a 5- to 10-MHz multifrequency high-resolution linear probe, as previously described.11 The subjects were kept in the supine position with their heads slightly extended. External, internal, bulb, and common carotid arteries were examined to evaluate the presence of plaques and/or stenoses. Plaque was defined as localized lesion encroaching the lumen of thickness ≥1.3 mm, no spectral broadening, or only in deceleration phase of systole and systolic peak velocity <120 cm/s. Stenosis was defined as spectral broadening throughout systole and/or peak flow velocity ≥120 cm/s. Normal segments were scored 0, those with plaque were scored 1, and those with stenosis were scored 2. A global score was computed by adding the scores of all segments, as previously reported.11 For logistic regression analyses, subjects were classified as with atherosclerosis if they had at least 1 plaque and/or stenosis in the carotid tree, and as without atherosclerosis if they had completely normal echo Doppler examination.

**Statistical Analyses**

All statistical analyses were performed by SPSS 8.0 for Windows. Triglycerides were not normally distributed and were therefore log-transformed.

Student t test and ANOVA were used to compare continuous variables among women and men, and across subjects with different number of MetS components. The difference in smoking habit between women and men was tested by the Mann-Whitney test. Differences in carotid atherosclerosis between groups were assessed by χ2 test. The association between components of the MetS and extent of carotid atherosclerosis was estimated by multiple linear regression analysis, using the log-transformed echo Doppler score. Logistic regression analysis was used to obtain adjusted estimates of the odds of having carotid atherosclerosis in relation to cardiovascular risk factors and MetS components.

**Results**

Table 1 shows clinical and biochemical characteristics of participants, according to gender. Women were slightly older and had higher values of BMI, total and HDL cholesterol, and lower levels of triglycerides and glucose. Cigarette consumption was higher and diabetes mellitus was more prevalent in men.

Among women, 177 had none of the components of the MetS, 238 had 1, 221 had 2, 119 had 3, 58 had 4, and 29 had all the components. For men, the figures were 130, 304, 287, 196, 79, and 15, respectively. As expected, age, blood pressure, BMI, waist, blood lipids, and glucose significantly increased with increasing number of MetS components, in both men and women (data not shown).

Overall, 206 women (24.4%) and 290 men (28.7%) were defined as having MetS. In these subjects, increased waist, increased blood pressure, and reduced HDL were more frequent in women; increased triglycerides and blood glucose were more frequent in men (all P<0.05). When those with diabetes were considered separately, 163 women (19.3%) and 213 men (21.1%) were defined as having MetS only, and 43 women (5.1%) and 77 men (7.6%) were defined as having diabetes.

In the entire population investigated, the prevalence of carotid atherosclerosis was 35.1% in women and 37.3% in men (p=NS) and increased with increasing number of components of the MetS (Figure 1). The contribution of MetS components to carotid atherosclerosis was first estimated by using variables as quantitative traits together with age, gender, pack-years of cigarette, low-density lipoprotein cho-

**TABLE 1. Clinical and Biochemical Characteristics of Participants According to Gender**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women</th>
<th>Men</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>842</td>
<td>1011</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>52.8±9.6</td>
<td>51.8±9.9</td>
<td>0.03</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132±20</td>
<td>132±18</td>
<td>NS</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81±9</td>
<td>82±10</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3±4.8</td>
<td>27.7±3.7</td>
<td>0.0008</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>87.7±12.0</td>
<td>94.4±9.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>5.92±1.24</td>
<td>5.79±1.19</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.42±0.39</td>
<td>1.14±0.31</td>
<td>0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.87±1.15</td>
<td>3.83±1.17</td>
<td>NS</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.38±0.88</td>
<td>1.78±1.15</td>
<td>0.0001</td>
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<tr>
<td>Glucose, mmol/L</td>
<td>5.44±1.50</td>
<td>5.88±1.89</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>2.37±6.13</td>
<td>7.94±10.58</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>6.2</td>
<td>10.9</td>
<td>0.0004</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Figure 1. Prevalence of carotid atherosclerosis according to number of components of the MetS and gender.
TABLE 2. Multiple Regression Analyses

Model 1

Stepwise multiple logistic regression analysis. Outcome: carotid atherosclerosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.076</td>
<td>1.059–1.092</td>
<td>0.0001</td>
</tr>
<tr>
<td>Smoking, pack-years</td>
<td>1.028</td>
<td>1.014–1.039</td>
<td>0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>1.023</td>
<td>1.015–1.030</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Model 2

Stepwise multiple linear regression analysis. Outcome: carotid atherosclerosis extent (log of carotid atherosclerosis score)

<table>
<thead>
<tr>
<th>Variable</th>
<th>β-coefficient</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>0.225</td>
<td>4.936</td>
<td>0.0001</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>−0.145</td>
<td>−3.235</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>0.118</td>
<td>2.610</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Both models included the following variables: age, gender, systolic blood pressure, diastolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, blood glucose, body mass index, waist circumference, pack-years of cigarette, antihypertensive therapy. 

CI indicates confidence interval; OR, odds ratio.

The MetS arises from the association of at least 3 among 5 components of the syndrome compared with 30.5% in subjects with elevated blood pressure among the 196 men (Table 2, second model). Among all participants, 178 were using antihypertensive medications (renin-angiotensin-system blocker=30; diuretic=11; calcium channel blocker=45; β-blocker=24; clonidine=2; association of at least 2 drugs=66). When subjects using antihypertensive therapy were excluded from the analyses the results were unaltered.

The association between elevated blood pressure and carotid atherosclerosis was further explored by looking at the prevalence of carotid atherosclerosis in subjects with different numbers of MetS components according to presence/absence of elevated blood pressure. Figure 2 shows that the prevalence of carotid atherosclerosis increases with increasing number of MetS components, in subjects with or without elevated blood pressure. The former group, however, the prevalence is significantly higher than in the latter one, up to the presence of 3 MetS components. To further define the role of elevated blood pressure, the analysis was restricted to subjects with only 3 factors of the syndrome (119 women and 196 men) by selectively including or excluding 1 component from the analysis. The overall prevalence of carotid atherosclerosis was 41.5% (42% in women and 41% in men), with 44.9% in subjects with elevated blood pressure among the components of the syndrome compared with 30.5% in subjects with clusters not including elevated blood pressure (P<0.05). The statistical significance was mainly caused by the male sex component and was significant also after adjustment for smoking status. When pooling subjects with 3 and 4 components together, results were unchanged. No difference in carotid atherosclerosis prevalence was found in subjects whether bearing components of the syndrome other than elevated blood pressure.

On logistic regression analysis, after adjustment for age, gender, smoking, and low-density lipoprotein cholesterol levels, MetS (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 1.402 (95% CI, 1.088 to 1.808) (Table 3, model 1). When including the various components of the MetS separately in the same model, only elevated blood pressure resulted significantly associated with carotid atherosclerosis (OR, 1.683; 95% confidence interval, 1.327 to 2.134) (Table 3, model 2). Finally, in a multivariable model including the same variables as in model 2 plus the number of MetS components (from 0 to 5), number of MetS components and elevated blood pressure were significantly associated with carotid atherosclerosis (Table 3, model 3). These results were unaltered after exclusion of subjects with diabetes mellitus.

Discussion

The MetS is a complex of symptoms, highly prevalent in the industrialized countries. The strong association with cardiovascular diseases makes it a great burden for societies and a challenge to health care in these countries. The prevalence of MetS exceeds 20% in individuals aged 20 or older and 40% in older age groups.4,12–16 In the present study, the prevalence was 24.4% in women and 28.7% in men, very similar to that reported in other countries.

Genders were different also in the prevalence of each component of the syndrome: in women increased waist and blood pressure and decreased concentration of HDL were more frequent, whereas in men increased triglycerides and glucose were more frequent.

The MetS arises from the association of at least 3 among 5 alterations. Possible combinations are therefore 16, or, in other words, there are 16 possible phenotypes of the MetS, and even among subjects with only 3 components of the
syndrome the possible phenotypes are 10. What we do not know is whether these phenotypes are all equally associated with cardiovascular risk and/or whether the presence of a particular component confers an increased risk. In the present study, elevated blood pressure is strongly associated with carotid atherosclerosis, independently of possible confounding factors and even of MetS presence. Other authors have investigated the impact of MetS and its components on coronary heart disease and have reported different findings. Anderson et al.17 tested the ability of MetS and its components to predict angiographic coronary heart disease and incident death/myocardial infarction in a large cohort of patients undergoing angiography. They found that the presence of coronary artery disease was predicted by MetS and, individually, by high glucose and low HDL. The incidence of death/myocardial infarction was predicted only by high glucose, and this risk was carried by diabetes. Girman et al.18 used the placebo data from the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) to estimate the long-term relative risk of major coronary events associated with MetS. They found that subjects with MetS were 1.5-times more likely to have a major coronary event. Of the components of MetS, low HDL levels were associated with major coronary events in both studies, high triglycerides in 4S, and high blood pressure in AFCAPS/TexCAPS. Malik et al.15 reported low HDL cholesterol to predict coronary heart disease mortality, hypertension to predict cardiovascular disease mortality, and hyperglycemia to predict overall mortality. However, these studies have investigated the coronary district and have used very hard end points like death, myocardial infarction, and major coronary events. For these events to occur, pro-atherogenic and pro-thrombotic factors have to play a role. Fibrinolytic dysfunction (elevated levels of plasminogen activator inhibitor-1) appears central to the pathogenesis of cardiovascular events for individuals with the MetS.19 Our study investigated the association between components of the MetS and carotid atherosclerosis. Some components of the MetS might be implicated in atherogenesis and plaque formation, and others might have a prominent role in plaque complication, thrombosis, and clinical event. The present findings suggest that elevated blood pressure fosters the development of plaques. The fate of the plaque, either stabilization or complication with following clinical event, may depend on different components of the syndrome or on other intervening factors.

The association between hypertension and carotid atherosclerosis is well known and widely reported.20–23 Our findings support that the association between elevated blood pressure and presence, as well as extent of carotid atherosclerosis, persists even in subjects with multiple risk factors and is appreciable in a range of blood pressure that cannot be defined as hypertension, according to current World Health Organization classification. Furthermore, subjects with only 3 or 4 components of the syndrome are more likely to have carotid atherosclerosis if they have elevated blood pressure. Overall, it seems that the different MetS phenotypes have different impact on atherosclerosis, at least in terms of carotid involvement.

We found that clusters including elevated blood pressure and those with increased number of MetS components were more strongly associated with carotid atherosclerosis. Even after taking into account each individual component of the MetS, the increasing number of components was independently associated with carotid atherosclerosis. This indicates that the components of MetS interact to synergistically impact vascular wall and cause atherosclerosis. These results completely agree with the findings by Scuteri et al.,24 who recently found that MetS is independently associated with intima-media thickness and stiffness of the carotid artery, even after taking into account each individual component of the syndrome.

Our results also confirm the known association between age and atherosclerosis. In all the analyses performed in the present study, age was significantly and markedly associated with carotid atherosclerosis. This indicates that the different MetS phenotypes have different impact on atherosclerosis, at least in terms of carotid involvement.

The exact definition of the risk associated with MetS and its components are of utmost importance for clinical and therapeutic purposes. The coronary heart disease risk in patients with MetS is variable,25 and some patients might be at only moderate risk, depending on their phenotype. The present study demonstrates that among subjects with MetS, those with elevated blood pressure and those with elevated number of MetS components are likely to be at higher risk for carotid atherosclerosis. Our data strongly support that the simple diagnosis of MetS is not sufficient to define the coronary heart disease risk of the patient and that it might be recommendable to consider all the components of the syn-
drome, both qualitatively and quantitatively. As a matter of fact, our results seem to suggest that when elevated blood pressure is among the components of the MetS, particular care might be convenient in the diagnostic and therapeutic approach.

A possible limitation of the present study is its cross-sectional design. However, the large and well-characterized population, especially the large number of subjects who received carotid ultrasound, represents a strong point, together with the careful application of the suggested NCEP-PATP III criteria to classify MetS. The finding that within subjects with MetS there are subgroups that deserve particular attention from both clinical and therapeutic points of view seems therefore reliable. Further investigation is needed to better characterize these subgroups and address treatment strategies.

References
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