Metabolic Syndrome as an Independent Risk Factor of Silent Brain Infarction in Healthy People

Hyung-Min Kwon, MD; Beom Joon Kim, MD; Seung-Hoon Lee, MD; Seung Ho Choi, MD; Byung-Hee Oh, MD, PhD; Byung-Woo Yoon, MD, PhD

Background and Purpose—Metabolic syndrome (MetS) is associated with an increased risk of the subsequent development of cardiovascular disease or stroke. Moreover, a silent brain infarction (SBI) can predict clinical overt stroke or dementia. We examined the associations between SBI and MetS in apparently healthy individuals.

Methods—We evaluated 1588 neurologically healthy subjects (927 males and 661 females) who underwent brain MRI at Seoul National University Hospital Healthcare System Gangnam Center. MetS was defined using the criteria of the National Cholesterol Education Program Adult Treatment Panel III. We examined associations between full syndrome (≥3 of the 5 conditions) as well as its components and SBI by controlling possible confounders.

Results—Eighty-eight (5.5%) were found to have ≥1 SBI on MRI. Age was found to be significantly related to SBI prevalence (odds ratio [OR], 1.06; 95% CI, 1.04 to 1.09). A history of coronary artery disease was associated with an elevated odds ratio of SBI (OR, 2.83; 95% CI, 1.38 to 5.82), and MetS was significantly associated with SBI (OR, 2.18; 95% CI, 1.38 to 3.44). The components model of MetS showed a strong significance between an elevated blood pressure (OR, 3.75; 95% CI, 2.65 to 6.85) and an impaired fasting glucose (OR, 1.74; 95% CI, 1.08 to 2.80) and the risk of SBI.

Conclusions—MetS was found to be significantly associated with SBI. This finding has clinical utility in terms of identifying healthy people at increased risk of developing SBI. (Stroke. 2006;37:466-470.)

Key Words: cerebral infarction ■ magnetic resonance imaging ■ metabolic syndrome x ■ risk factors
personal interview, and a physical examination was performed by physicians at Seoul National University Hospital Healthcare System Gangnam Center. The term “healthy” was defined as the absence of symptoms or signs of neurological manifestations before and at the time of study enrollment, and all subjects satisfied this criterion. All subjects provided informed consent, and the study was approved by the institutional review board at Seoul National University Hospital.

Vascular Risk Factor
The evaluation of MetS involved data from a questionnaire, an examination at the healthcare center, and laboratory results. We applied the condition-specific cut points for MetS contained in a recent NCEP-ATP III report, with minor modifications. MetS is present when ≥3 of following determinants are met: IFG, elevated BP, hyper-TG, low HDL-C, and abdominal obesity defined by a large waist circumference (WC). In detail, IFG was defined as fasting glucose ≥110 mg/dL; for purposes of this analysis, IFG was also determined using self-reports of the current use of insulin or oral hypoglycemic agents. Elevated BP was defined as a systolic BP ≥130 mm Hg or a diastolic BP ≥85 mm Hg; for purposes of this analysis, elevated BP was also accepted based on a self-report of current use of antihypertension medication. Hyper-TG was determined based on serum triglyceride levels ≥150 mg/dL. Low HDL-C was identified by serum HDL-C of <40 mg/dL in men or <50 mg/dL in women. A large WC defined by NCEP-ATP III report was >102 cm in men or >88 cm in women, but these cutoffs are not suitable for Asian populations. Thus, we adopted the definition of a large WC as a ≥90 cm in men or ≥80 cm in women based on Asia-Pacific consensus.

BP was measured with no knowledge of a history of hypertension. Treatment for hypertension was identified by positive responses to all 3 of the following questions: “Have you ever been told by a doctor or other health professional that you have hypertension, also called high BP?”; “Because of your high BP/hypertension, have you ever been told by a doctor or another health professional to take a prescribed medicine?”; and “Are you now taking such a prescribed medicine?” Fasting plasma glucose was measured using a hexokinase enzymatic method (Roche Diagnostics Ltd.). A history of diabetes was determined based on a positive response to either of the questions “Are you now taking insulin?” or “Are you now taking oral hypoglycemic agents to lower your blood sugar?” Triglycerides and HDL-C were measured using a Hitachi 747 Analyzer (Hitachi Co.). Because fasting may affect hyper-TG and IFG, subjects were tested after fasting for >8 hours. WC was measured by a trained examiner and determined using a measuring tape positioned at the high point of the iliac crest. The measurement was made at minimal respiration to the nearest 0.1 cm, with a snug-fitting tape not compressing the skin.

High-sensitivity C-reactive protein (hs-CRP) has been reported to be associated with SBI independently of traditional cardiovascular risk factors and was proposed as a component of MetS. We checked circulating hs-CRP using a latex turbidimetric immunooassay with a sensitivity of 0.01 mg/dL (Hitachi Co.).

Cigarette smoking status data were collected in a structured interview. The data available was limited to 3 smoking categories: never, past, or current. A history of coronary artery disease (CAD) was elicited based on 2 interview questions: “Has a doctor ever told you that you have experienced a heart attack?” and “Has a doctor ever told you that you have angina pectoris?”

Diagnosis of SBI
MRI examinations were performed at 1.5 T using a CHORUS (ISOL Technology Inc.). The imaging protocol used consisted of: T2-weighted spin-echo (repetition time/echo time [TR/TE]=5800/96 ms), T1-weighted spin-echo (TR/TE=520/14 ms), and fluid-attenuated inversion recovery (FLAIR; TR/TE=8500/96 ms; inversion time=2100 ms) imaging. Images were obtained as 27 transaxial slices per scan. The slice thickness was 3 mm, with no interslice gap. Two trained neurologists (H.M.K. and B.J.K.) blinded to subject history and diagnosis assessed the presence of SBI on magnetic resonance images. The k value of agreement was 0.89. When the 2 investigators decisions were discrepant, SBI was scored by consensus. SBI was defined as a focal lesion of ≥3 mm in diameter, with signal intensity corresponding to liquor (ie, hypointense on T2-weighted images and hypointense on FLAIR images). Often, lesions were surrounded by a hypointense glotic rim on FLAIR images. Lesions were differentiated on FLAIR from periventricular white matter lesions, which were of high signal intensity. Dilated perivascular spaces were distinguished from SBI based on their locations (along perforating or medullary arteries, often bilaterally symmetrical, usually in the lower third of the basal ganglia) and by the absence of gliosis.

Statistical Analysis
To analyze the relationship between SBI and patient characteristics, we used the χ² test for categorical data and Student’s t test for continuous data. P values were 2-tailed, and values of P<0.05 were considered significant. We examined the association between full MetS and SBI by controlling for age, sex, a history of CAD, and hs-CRP as possible confounders. Logistic regression models were also used to determine the associations between the component conditions of MetS and SBI. The component conditions of MetS were included as dichotomous variables based on the NCEP-ATP III–defined cut points. We performed analysis of test for trend between the number of components of MetS and the number of SBI’s (linear by linear association). All statistical analyses were performed using SPSS 11.5 for Windows (SPSS Inc).

Results
Eighty-eight of the 1588 subjects (5.5%) were found to have ≥1 SBI on magnetic resonance images. Sixty-six (75%) subjects had single SBI and 22 (25%) had multiple SBI. Table 1 shows an increase of decade of age was associated with a more prevalent SBI (P<0.001; linear by linear association). There was no sex difference across each age group (P values are not shown). Table 2 shows the prevalence of MetS and of its component conditions among subjects with and without SBI. The prevalence of MetS was significantly higher in the SBI group (27.3%) than in subjects without SBI (13.2%) and in those with elevated BP, IFG, and hyper-TG, although not all comparisons reached statistical significance. By univariate analysis, age, a history of CAD, MetS, and hs-CRP were higher in patients with SBI than in those without. A male gender, smoking status, and low-density lipoprotein cholesterol were no different in the SBI and non-SBI groups. To enhance the causal association of MetS to SBI, analysis of the relationship between number (single or multiple) of SBI lesions and the number of components involved in MetS was performed. The increasing components of MetS showed the more prevalent SBI and multiple SBI (P<0.001; Figure).

| TABLE 1. Demographic Data of Study Subjects and Prevalence of SBI |
|-----------------|-----------------|-----------------|-----------------|
| **Age, y**      | **Male**        | **Female**      | **Total**       |
| <40             | 1/86 (1.2)      | 1/57 (1.8)      | 2/143 (1.4)     |
| 40–49           | 8/247 (3.2)     | 4/159 (2.5)     | 12/406 (3.0)    |
| 50–59           | 12/315 (3.8)    | 8/240 (3.3)     | 20/555 (3.6)    |
| 60–69           | 21/217 (9.7)    | 15/164 (9.1)    | 36/381 (9.4)    |
| ≥70             | 11/62 (17.7)    | 7/41 (17.1)     | 18/103 (17.5)   |

Values in parentheses represent percentages.
Table 3 illustrates the associations between SBI and full MetS and its 5 component conditions. The crude odds ratio (OR) for the association between MetS and SBI was 2.74 (95% CI, 1.76 to 4.25). After adjusting for age, sex, a history of CAD, and hs-CRP level, the OR of MetS was 2.18 (95% CI, 1.38 to 3.44). Age was significantly related to the prevalence of SBI, with an OR of 1.06 per year of age, and a history of CAD also showed an elevated OR for SBI (OR, 2.83; 95% CI, 1.38 to 5.82) after controlling confounders. No significant association was found between hs-CRP and SBI prevalence. People with a much higher component of MetS had a tendency to have more SBI after adjustment for other risk factors. (1 component: OR, 1.49, P = 0.202; 2 components: OR, 3.11, P = 0.014; 3 components: OR, 4.24, P = 0.002; 4 to 5 components: OR, 4.96, P = 0.001). These were compared with people with no components of MetS.

The association between elevated BP and SBI showed strongest significance (OR, 3.75; 95% CI, 2.05 to 6.85) by logistic regression analysis, and IFG was significantly associated with SBI (OR, 1.74; 95% CI, 1.08 to 2.80). Component condition models were also adjusted for age, sex, a history of CAD, and hs-CRP.

Discussion

In the present study, we found that MetS was significantly associated with SBI. The prevalence of MetS and its components were higher in subjects with SBI than in those without. To the best of our knowledge, this is the first study to demonstrate an association between MetS and SBI. These findings suggest that MetS has clinical utility in terms of identifying patients at increased risk of SBI.

The difference in SBI prevalence in the results of our study and those of previous reports appears to be attributable primarily to the relatively wider age range and younger mean age of our study population. In a report on lacunar infarcts in a large group of elderly subjects ≥65 years of age, the prevalence was 23%,23 but that report included subjects with a history of transient ischemic attack or stroke and cannot be a true estimate of the prevalence of clinically “silent” brain lesions. A recent report on the prevalence of SBI in adults that range in age from 55 to 70 years indicates that the prevalence in that particular elderly population is 11%. This is a same estimate in the same age group in our report (11.6%).

A prospective study reported an association between MetS and cardiovascular disease or overall mortality.24 And McNeill et al25 reported hazard ratios of 1.96 for women and
The level of hs-CRP was higher in SBI subjects than in those without (Table 2), suggesting an elevated level of chronic inflammation in SBI subjects. However, this association did not persist when traditional cardiovascular risk factors were taken into account (Table 3). These findings suggest that inflammation is an indirect reflection of pathologic changes in cerebral small vessels that cause lacunar infarction.

It should be noted that our subjects may not have been representative of the general population. Our participants were recruited from among subjects who visited our hospital to check their general health status, and therefore, subjects were enrolled from a population concerned about their health status. In addition, the presence of myocardial infarction and angina history in the present analysis were based on self-reports of physician-diagnosed disease, and therefore, we may have underestimated the number of people with CAD. Furthermore, the racial distribution of the population was overwhelmingly Korean (>99%). The above may thus limit generalizations based on our study results.

However, the present study demonstrates that MetS is associated with SBI independently of traditional cardiovascular risk factors. These findings reaffirm the clinical importance of MetS as a significant risk factor of SBI and the need to develop strategies for controlling this syndrome and its component conditions.

Acknowledgments

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### Table 3. Cross-Sectional Association of SBI With MetS and Component Conditions

<table>
<thead>
<tr>
<th>Component Conditions</th>
<th>Crude OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted* OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Syndrome model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MetS</td>
<td>2.74 (1.76–4.25)</td>
<td>&lt;0.001</td>
<td>2.18 (1.38–3.44)</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (1-year difference)</td>
<td>1.07 (1.05–1.10)</td>
<td>&lt;0.001</td>
<td>1.06 (1.04–1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>1.09 (0.70–1.68)</td>
<td>0.717</td>
<td>1.12 (0.71–1.76)</td>
<td>0.633</td>
</tr>
<tr>
<td>CAD</td>
<td>4.14 (2.07–8.28)</td>
<td>&lt;0.001</td>
<td>2.83 (1.38–5.82)</td>
<td>0.005</td>
</tr>
<tr>
<td>hs-CRP</td>
<td>1.13 (0.81–1.58)</td>
<td>0.469</td>
<td>1.07 (0.92–1.23)</td>
<td>0.404</td>
</tr>
<tr>
<td><strong>Components model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated BP</td>
<td>4.51 (2.53–8.04)</td>
<td>&lt;0.001</td>
<td>3.75 (2.05–6.85)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFG</td>
<td>2.02 (1.29–3.07)</td>
<td>0.002</td>
<td>1.74 (1.06–2.80)</td>
<td>0.022</td>
</tr>
<tr>
<td>Hyper-TG</td>
<td>1.28 (0.77–2.11)</td>
<td>0.343</td>
<td>1.54 (0.91–2.61)</td>
<td>0.111</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>1.25 (0.76–2.06)</td>
<td>0.373</td>
<td>1.08 (0.64–1.82)</td>
<td>0.765</td>
</tr>
<tr>
<td>Large WC</td>
<td>0.92 (0.59–1.45)</td>
<td>0.727</td>
<td>0.70 (0.41–1.18)</td>
<td>0.180</td>
</tr>
</tbody>
</table>

*ORs were calculated using logistic regression model after adjusting age, sex, a history of CAD, and hs-CRP.


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