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, 2.05 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

Silent brain infarction (SBI) is defined as a cerebral infarction that is evident by brain imaging but that is without a clinical syndrome characterized by rapidly developing clinical symptoms and signs of focal and at times a global loss of brain function.1 SBI is frequently seen on MRIs in healthy elderly people. The prevalence of these asymptomatic lesions increases with age from ∼5% at 60 years of age to 35% at 90 years of age.2–4 The presence of an SBI can predict clinical overt stroke2,5 or reduced cognitive function.6 To prevent SBI, it is important that its risk factors be identified, especially treatable factors. It has been demonstrated that the risk factors of SBI are not necessarily the same as those of clinical stroke,7 and several studies have consistently found that regardless of race, advanced age2,5,8–12 and hypertension2,4–11 are the most common risk factors for SBI.

The combination of cardiovascular risk factors that compose metabolic syndrome (MetS) are receiving increasing attention from physicians, but no data are available on the association of the syndrome with SBI. A set of metabolic and physiological risk factors linked to cardiovascular disease has been variously defined as insulin resistance syndrome, syndrome X, the deadly quartet, MetS, dysmetabolic syndrome, and cardiovascular dysmetabolic syndrome.13–17 Proposed definitions of MetS differ with respect to its components and component set points. However, recent attempts to define MetS have included 5 conditions: hyper-triglyceridemia (hyper-TG), low high-density lipoprotein HDL cholesterol (HDL-C), elevated blood pressure (BP), abdominal obesity, and impaired fasting glucose (IFG). The intraindividual correlations shown by these factors have provided a rationale for grouping them as a syndrome.

In the present study, we examined the association between SBI with MetS and its components in apparently healthy individuals. In this study, we use the MetS definition published by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).18

Subjects and Methods

Study Population

We studied 1588 healthy consecutive subjects who visited Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Republic of Korea, from October 2003 through December 2004 and who underwent MRI of the brain as part of their routine health check. Subjects who reported that they had experienced a stroke or transient ischemic attack were excluded. Subjects’ ages ranged from 20 to 86 years, there were 927 men and 661 women, and their mean age was 53.6 years. Clinical information was gathered by
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,18 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.19

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 factors20 and was proposed a component of MetS.21 We checked circulating hs-CRP using a latex turbidimetric immunoassay 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 had 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 κ 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,22 with signal intensity corresponding to liquor (ie, hypointense on T2-weighted images and hypointense on FLAIR images). Often, lesions were surrounded by a hyperintense gliotic 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 symmetrically, 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 SBIs (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>
<thead>
<tr>
<th>Age, y</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>1/86 (1.2)</td>
<td>1/57 (1.8)</td>
<td>2/143 (1.4)</td>
</tr>
<tr>
<td>40–49</td>
<td>8/247 (3.2)</td>
<td>4/159 (2.5)</td>
<td>12/406 (3.0)</td>
</tr>
<tr>
<td>50–59</td>
<td>12/315 (3.8)</td>
<td>8/240 (3.3)</td>
<td>20/555 (3.6)</td>
</tr>
<tr>
<td>60–69</td>
<td>21/217 (9.7)</td>
<td>15/164 (9.1)</td>
<td>36/381 (9.4)</td>
</tr>
<tr>
<td>≥70</td>
<td>11/62 (17.7)</td>
<td>7/41 (17.1)</td>
<td>18/103 (17.5)</td>
</tr>
</tbody>
</table>

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 \( \geq 65 \) 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 report2 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

### Table 2. Baseline Characteristics of Subjects With/Without SBI

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (n=1588)</th>
<th>SBI Yes (n=88)</th>
<th>SBI No (n=1500)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>53.6±10.6</td>
<td>60.7±10.0</td>
<td>53.2±10.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>927 (58.4)</td>
<td>53 (60.2)</td>
<td>874 (58.3)</td>
<td>0.717</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>61 (3.8)</td>
<td>11 (12.5)</td>
<td>50 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td>0.235</td>
</tr>
<tr>
<td>Never</td>
<td>807 (50.8)</td>
<td>39 (44.3)</td>
<td>768 (51.2)</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>485 (30.5)</td>
<td>34 (38.6)</td>
<td>451 (30.1)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>296 (18.6)</td>
<td>15 (17.0)</td>
<td>281 (18.7)</td>
<td></td>
</tr>
<tr>
<td>MetS</td>
<td>222 (14.0)</td>
<td>24 (27.3)</td>
<td>198 (13.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Elevated BP</td>
<td>798 (50.3)</td>
<td>73 (83.0)</td>
<td>725 (48.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFG</td>
<td>394 (24.8)</td>
<td>40 (45.5)</td>
<td>354 (23.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hyper-TG</td>
<td>318 (20.0)</td>
<td>26 (29.5)</td>
<td>292 (19.5)</td>
<td>0.022</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>370 (23.3)</td>
<td>27 (30.7)</td>
<td>343 (22.9)</td>
<td>0.092</td>
</tr>
<tr>
<td>High WC</td>
<td>641 (40.4)</td>
<td>41 (46.6)</td>
<td>600 (40.0)</td>
<td>0.221</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.20±0.90</td>
<td>5.28±0.99</td>
<td>5.19±0.90</td>
<td>0.377</td>
</tr>
<tr>
<td>hs-CRP, mg/dL*</td>
<td>0.17±0.47</td>
<td>0.20±0.32</td>
<td>0.16±0.48</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Values are means±SD or Nos. of participants (percentage). \( P \) values were obtained using the \( \chi^2 \) test for categorical data, and the Student \( t \) test for continuous data. *Statistical tests were performed using logarithmically transformed variables.

The relationship between the number of SBIs and components involved in MetS.
1.42 for men with MetS for ischemic stroke in a general population sample based on the NCEP-ATP III definition of MetS. In the present study, we focused on SBI, which has attracted much attention because it increases the risk of future stroke and cognitive decline.\textsuperscript{2,3,5,6} In our analysis, MetS was found to be significantly associated with SBI. According to our MetS component analysis, an elevated BP is most strongly associated with the presence of SBI, which is consistent with previous reports.\textsuperscript{2,4,5} \textsuperscript{11} Some studies have shown that the presence of diabetes mellitus is a lesser risk factor for SBI.\textsuperscript{8} However, our results show a somewhat higher OR (1.74) for IFG. The present study shows that IFG has considerable impact on SBI because of the strong relationship between type 2 diabetes and MetS.\textsuperscript{14} The absence of independent associations between hyper-TG, low HDL-C, and a large WC with SBI may reflect that other components of MetS have a lesser strong effect on SBI. However, hyper-TG and low HDL-C may summon a certain interest as potential risk factors for SBI because those characteristics showed significance as risk factors and marginal significance on univariate analysis (\(P=0.022\) and 0.092, respectively). People with a much higher component of MetS had a tendency to have more SBI. To screen the presence of SBI, we can assume that MRI screening is guaranteed with people with \(\geq 2\) components of MetS (\(P<0.05\)).

In addition to MetS, an older age and CAD have been identified previously as the most important risk factors of SBI. Old age is a known risk factor for the presence of SBI.\textsuperscript{2,5,8,13} SBI was also found to be more advanced in patients with CAD, indicating that small artery disease may play a role in the progression of SBI in parallel with systemic atherosclerosis of large arteries such as coronary artery.\textsuperscript{26,28} It is well known that patients with a history of CAD events tend to experience more cerebrovascular events than those without.\textsuperscript{29}

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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### References


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

<table>
<thead>
<tr>
<th>Component Conditions</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome model</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>Components model</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 (1.08–2.80)</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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