Metabolic Syndrome Increases the Risk of Ischemic Stroke in Women

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Abstract

Background Metabolic syndrome is characterized by a cluster of cardiovascular risk factors, including visceral obesity, insulin resistance, dyslipidemia, and hypertension. The criteria for diagnosing metabolic syndrome differ among ethnic groups, due in part to differences in eating habits and body build. Little is known about the relationship between metabolic syndrome and ischemic stroke in Asian countries. The aim of this study was to investigate the relationship between metabolic syndrome and first-time ischemic strokes.

Subjects & Methods Study subjects were 1,493 Japanese adults aged 55 years-old or older with no diabetes mellitus, no history of stroke and no neurological abnormalities, who participated in a voluntary neurological health screening at the Institute of Shimane Health Science, Japan (767 men, 62.0 ± 5.9 years old at entry and 726 women, 61.8 ± 5.1 years old at entry). All subjects were given an annual clinical stroke questionnaire. Clinical details of patients who reported strokes were confirmed with the attending physicians. Each subject was evaluated for an average of 6.4 ± 3.8 years. Metabolic syndrome was defined using the modified criteria for Japanese population published in April 2005.

Results Metabolic syndrome was diagnosed in 11.0% of men and 1.1% of women. Adjusting for age and smoking, female subjects with metabolic syndrome had a 23.1-fold increased risk of suffering ischemic strokes [95% confidence interval (CI), 2.7-196], whereas metabolic syndrome did not increase the risk of ischemic stroke in men.

Conclusions Metabolic syndrome is more likely to influence a risk for ischemic stroke in women than in men.

Key words: metabolic syndrome, ischemic stroke, risk factors, women

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Introduction

Metabolic syndrome is defined as a cluster of risk factors for vascular disease (1). A report by the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) outlines the definition of metabolic syndrome for clinical use in Western countries (2). Based on this definition, metabolic syndrome is diagnosed if the patient has three or more of the following risk factors: high fasting glucose levels, high blood pressure, low high-density lipoprotein levels, high triglycerides, and abdominal obesity. Prospective cohort studies have shown that metabolic syndrome

is associated with increased morbidity or mortality not only from cardiovascular disease (3-9) but also from ischemic stroke (10-13). However, limited information is available regarding the relationship between metabolic syndrome and ischemic stroke in Asian countries. In assessing this relationship in the Japanese population, there are two notable differences between Japanese and Western populations. First, because Asians tend to have smaller body builds and a lower percentage of body fat, the defined cut-off value for the waist circumference is inappropriate. Indeed, this discrepancy has been pointed out in other reports (14, 15). Secondly, based on the Hisayama study in Japan (16) and the Framingham study in United States of America (17, 18), the

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incidence of cerebral infarction in Japanese populations is three to four times higher than in Caucasian populations. In contrast, the incidence of myocardial infarction is five to six times higher in the Caucasian population than in the Japanese population.

In April 2005, the national Metabolic Syndrome Criteria Study Group published criteria for diagnosing metabolic syndrome in the Japanese population (19). Because there are major differences between populations, the relationship between metabolic syndrome and ischemic stroke incidence in Asian populations merits reevaluation. Here, we examined the incidence of ischemic stroke in Japanese subjects with and without metabolic syndrome.

Subjects and Methods

Subjects

Study subjects were 1,563 Japanese adults aged 55 years-old or older with no diabetes mellitus, no history of stroke and no neurological abnormalities, who participated in a voluntary health screening of brain between 1988 and 2002. The subjects wished to receive the health screening of brain at their own expense. Therefore, this was not a population-based study. Information about medical events occurring during the study period was acquired by questionnaire. At the end of 2004, we had obtained regular medical information from 767 men (age range: 55-91 years, mean age: 62.0 ± 5.9 years old at entry) and 726 women (age range: 55-80 years, mean age: 61.8 ± 5.1 years old at entry). The subjects were followed for an average of 6.4 ± 3.8 years (55-5,549 days), with 850 subjects being followed for more than 5 years. The study was approved by the local Ethics Committee of our university hospital and informed consent for this study was obtained from all subjects according to institutional guidelines.

Assessment of ischemic stroke

For subjects who reported having strokes, we confirmed the details of the illness in a telephone interview, and followed up with the attending physician to differentiate between ischemic and hemorrhagic stroke. We also confirmed details of the stroke by direct medical examination and MRI when possible.

Cerebrovascular risk factors

Cerebrovascular risk factors were assessed by interviewing the subjects, and by conducting physical examinations and blood tests. Blood pressure was measured using a sphygmomanometer after 15 min of rest. Complete blood counts, serum lipids [total cholesterol (T-cho), triglycerides (TG), and HDL cholesterol (HDL-C)], fasting blood glucose, electrocardiogram, and body mass index (BMI) were determined on the first day of the study. Hypertension was defined as a systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mm Hg or higher, or a his-

tory of hypertension as reported by the subject. Diabetes mellitus was defined as a fasting blood glucose level ≥ 126 mg/dl (7.0 mmol/L) or diagnosed disease as reported by the subject. Hypercholesterolemia was defined as T-cho ≥ 240 mg/dl. The BMI was defined as baseline weight (kilograms) divided by the square of height (meters). Smokers were defined as any subject whose smoking index (number of cigarettes/day $\times$ number of years) exceeded 200. Regular alcohol consumption was defined as 58 g or more of alcohol per day.

Definition of metabolic syndrome

According to the metabolic syndrome criteria for Japanese subjects, waist circumference is an essential causative component of the metabolic disorder. According to these criteria, metabolic syndrome was diagnosed if the subject had central obesity and two or more of the following components: elevated blood pressure, dyslipidemia, and fasting hyperglycemia. Central obesity was defined as a waist circumference of ≥ 85 cm in men and ≥ 90 cm in women. This cutoff value for central obesity corresponds to ≥ 100 cm² of visceral fat as estimated by abdominal CT scan for the average Japanese person (19). Elevated blood pressure was defined as a systolic blood pressure of ≥ 130 mm Hg and/or a diastolic blood pressure of ≥ 85 mm Hg. Elevated fasting glucose was defined as a fasting glucose level ≥ 110 mg/dl (6.1 mmol/L). Dyslipidemia was defined as a plasma TG level of ≥ 150 mg/dl and/or HDL-C level of < 40 mg/dl. As waist circumference was not measured as a part of our health screening until March 2005, we used BMI for the definition of central obesity. The correlation between waist circumference and BMI was used to determine the appropriate cutoff value for BMI. This correlation was based on data gathered between March 2005 and October 2005. As a waist circumference of ≥ 85 cm in men and ≥ 90 cm in women corresponded to BMIs of ≥ 25 (Fig. 1) and ≥ 29 (Fig. 2), respectively, we used these numbers as cut-off values for central obesity throughout the study.

Statistical analysis

We used Student's t-test for group comparisons of parametric variables. The Fisher exact test or chi-square test was used for nonparametric statistics. The Cox proportional hazards regression model was used to obtain the adjusted relative risks (RRs) and 95% confidence intervals (CIs) in reference to metabolic syndrome. The outcome variable was incidence of ischemic stroke. The data were adjusted for age and smoking. All statistical analyses were performed using SPSS 14.0 statistical package (SPSS Inc). Differences with $P < .05$ were considered significant.

Results

Metabolic syndrome was present in 84 of 767 men (11.0%) and 8 of 726 women (1.1%). Ischemic stroke occurred in 35 of 767 men (4.6%) and in 15 of 726 women

Figure 1. Correlation of body mass index (BMI) and waist circumference (WC) in men (n=104). A WC of ≥ 85 cm in men corresponded to BMIs of ≥ 25 . This data was collected from consecutive participants in our health screening of brain between March 2005 and October 2005.

Figure 2. Correlation of body mass index (BMI) and waist circumference (WC) in women (n=99). A WC of ≥ 90 cm in men corresponded to BMIs of ≥ 29 . This data was collected from consecutive participants in our health screening of brain between March 2005 and October 2005.

(2.1%). Table 1 lists the clinical and biochemical characteristics of the participants. Significant differences between the participants with and without metabolic syndrome were found for all of the components of metabolic syndrome, with the exception of the HDL level among women. There were no significant differences based on age, smoking, atrial fibrillation, T-cho ≥ 240 mg/dl, or follow-up period in both sexes.

Figure 3 shows the cumulative risks for ischemic stroke in men (A) and women (B). The age- and smoking-adjusted RRs for ischemic stroke in women with metabolic syndrome was 23.1 (95% CI: 2.7-196), whereas there was no significant difference between men with and without metabolic syndrome.

We also used Fisher's exact test to compare the incidence of ischemic stroke in subjects with metabolic syndrome to that in women without metabolic syndrome, because the number of women with metabolic syndrome was unexpectedly small (n=8). However Fisher's exact test did not show that metabolic syndrome increases the risk of ischemic stroke significantly even in women ($p=0.16$), when the subset of women subjects followed for 3 to 6 years was analyzed, the difference between the two groups was significant ($p=0.04$, Table 2).

Discussion

This study showed that metabolic syndrome increases the risk of ischemic stroke in women but not in men. To our knowledge, there are currently four published cohort studies that examined the association between metabolic syndrome and stroke. The Northern Manhattan study (10), which included Hispanic, African-American, and Caucasian subjects, reported an increased risk of stroke among women with metabolic syndrome [Hazard ratio (HR)=2.1] compared to men (HR=0.9). Koren-Morag et al similarly reported that

metabolic syndrome without diabetes mellitus was a significant risk factor for ischemic stroke in both sexes, but the effect was more pronounced in women [Odds ratio (OR)=2.10] than in men (OR=1.39) (11). The Framingham Offspring Study also reported that metabolic syndrome without diabetes mellitus was a significant risk factor for ischemic stroke in women (OR=2.8), whereas metabolic syndrome without diabetes mellitus did not increase the risk of ischemic stroke in men significantly (12). In another report, Iglseider et al. investigated the association between metabolic syndrome and early atherosclerosis of carotid arteries and found that the risk of atherosclerosis conferred by metabolic syndrome was more pronounced in females (20). On the other hand, Kurl et al reported that the risk of ischemic stroke is increased in men with metabolic syndrome significantly in Finland (13). The result of theirs might be due to the long follow-up period (average follow-up of 14.3 years). The present findings show that sex differences in the association of metabolic syndrome with ischemic stroke also exist in the Japanese population. Metabolic syndrome is generally considered to be a prediabetic condition (9, 21-23), and type 2 diabetes mellitus has been reported to increase the risk of stroke more in women than in men (24).

Why does metabolic syndrome have a greater influence on the risk of cerebral infarction in women than in men? First, some might think that perhaps the gender difference with respect to ischemic stroke and metabolic syndrome results from gender differences in diagnostic criteria for metabolic syndrome. We used BMI to define central obesity. As waist circumferences of ≥ 85 cm in men and ≥ 90 cm in women corresponded to BMIs of ≥ 25 and ≥ 29 , respectively, we used these numbers as cut-off values for central obesity throughout the study. Using these cut-off values, the rate of metabolic syndrome in women was only one-tenth of that in men. The study might select only extremely obese women as subjects with metabolic syndrome in the study.

Table 1. Clinical and Biochemical Characteristics at Baseline in Subjects with and without Metabolic Syndrome (Mean and SDs)

	Metabolic Syndrome (–)	Metabolic Syndrome (+)	<i>P</i>
Males	n=683	n=84	
Age, y	61.9±5.9	62.4±6.4	n.s.
BMI, kg/m ²	22.7±2.4	26.7±1.5	<0.001
Smokers, %	53.6 %	61.9 %	n.s.
Alcohol habit, %	25.9 %	41.7 %	0.009
Systolic BP, mmHg	128.6±19.5	143.8±18.6	<0.001
Diastolic BP, mmHg	77.0±11.5	85.9±11.5	<0.001
Fasting glucose, mg/dl	100.9±8.5	109.3±9.7	<0.001
T'cho, mg/dl	200.4±33.6	200.6±33.2	n.s.
Triglycerides, mg/dl	116.3±70.6	169.3±90.6	<0.001
HDL, mg/dl	53.9±15.1	44.8±12.0	<0.001
Af on ECG, %	1.5 %	1.1 %	n.s.
Hypertension, %	47.4 %	79.8 %	<0.001
T'cho ≥240mg/dl, %	12.6 %	12.0 %	n.s.
Antihypertensive drugs, %	19.6 %	36.9 %	<0.001
Follow-up period, y	6.5±3.8	6.9±3.8	n.s.
Females	n=718	n=8	
Age, y	61.8±5.1	59.5±4.2	n.s.
BMI, kg/m ²	22.8±2.7	29.9±8.5	<0.001
Smokers, %	4.6 %	0 %	n.s.
Alcohol habit, %	2.2 %	0 %	n.s.
Systolic BP, mmHg	126.9±20.1	146.4±20.1	0.006
Diastolic BP, mmHg	74.2±12.3	83.3±10.5	0.038
Fasting glucose, mg/dl	98.7±8.9	110.4±11.8	<0.001
T'cho, mg/dl	220.6±34.5	252.0±33.4	<0.01
Triglycerides, mg/dl	102.4±55.4	143.4±41.4	0.03
HDL, mg/dl	60.6±14.8	52.1±10.8	n.s.
Af on ECG %	0.6 %	0 %	n.s.
Hypertension, %	43.9 %	62.5 %	n.s.
T'cho ≥240mg/dl, %	27.4 %	50.0 %	n.s.
Antihypertensive drugs, %	19.9%	12.5%	n.s.
Follow-up period, y	6.3±3.9	4.5±2.7	n.s.

BMI:body mass index, BP:blood pressure, HDL: high-density lipoprotein cholesterol
, Af:Atrial fibrillation, T'cho: total cholesterol

Therefore, we recalculated the data using lower BMI cut-off values for women (27 or 25). After altering the diagnostic criteria, metabolic syndrome was associated with an even higher incidence of ischemic stroke in women. A change in the BMI cut-off value for the male subjects (27 or 29) did not result in an association between metabolic syndrome and ischemic stroke in men. This indicates that the gender difference for ischemic stroke in relation to metabolic syndrome was not due to gender differences in the diagnostic criteria

for metabolic syndrome. Secondly, although there were no differences in total cholesterol between men with and without metabolic syndrome, total cholesterol in women with metabolic syndrome was significantly higher than in women without metabolic syndrome in the study. It is well known that lipid abnormalities are associated with atherosclerosis. Metabolic syndrome might influence lipid abnormalities in women more than in men. Third, the circulating adiponectin level is inversely related to obesity (25) and has antidiabetic

Figure 3A. Cumulative risks adjusted age and smoking for ischemic stroke in men with metabolic syndrome.

Figure 3B. Cumulative risks adjusted age and smoking for ischemic stroke in women with metabolic syndrome.

Table 2. The Incidence of Ischemic Stroke in Women Subjects with or without Metabolic Syndrome Followed-up 3 to 6 Years

	Metabolic Syndrome (–) (n=196)	Metabolic Syndrome (+) (n=4)	<i>P</i> *
Ischemic stroke	1	1	0.04

* Fisher's exact test

Values are number of subjects

and anti-atherogenic effects (26). However the adiponectin level is generally higher in women than in men (27), Kojima et al showed that a reduction from high plasma adiponectin concentrations could trigger the progression of coronary atherosclerosis, especially in women (28). Although we did not examine the adiponectin level, we think that it is possible that the reduction in adiponectin with metabolic syndrome might induce the onset of ischemic stroke in women.

Central obesity is the essential component for the diagnosis of metabolic syndrome in Japan. This diagnostic criterion is based on the hypothesis that metabolic syndrome does not result from the coincident combination of risk factors, but rather from visceral obesity, which predisposes individuals to the development of diabetes mellitus, dyslipidemia, and hypertension (29). Two previous cohort studies showed that BMI is a risk factor for stroke in men (30, 31). These results seem to be inconsistent with our results, although the follow-up periods in those studies (15 years and 12.5 years) were longer than in our study (6.3 ± 3.8 years). Had we followed the male subjects in our study for a longer period of time, the occurrence of ischemic stroke might have been dif-

ferent in male subjects with metabolic syndrome than in those without metabolic syndrome.

One limitation of our study is that it was not a community-based study. The study subjects were individuals who volunteered for neurology checkups in the interest of their own health, and might not be representative of the general population. Another limitation is that there were only a few women with metabolic syndrome in the study. This might have been due to the metabolic syndrome criteria for Japanese populations published in April 2005. Using these criteria to diagnose metabolic syndrome, the rate of excess waist circumference in women subjects might be extremely low in Japan.

Although the generalization is limited by the potential bias in subject selection, this study suggests that metabolic syndrome is more likely to influence the risk for ischemic stroke in women than in men. Further community-based studies in Asia are necessary to confirm these results.

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