Strong and Significant Relationships Between Aggregation of Major Coronary Risk Factors and the Acceleration of Carotid Atherosclerosis in the General Population of a Japanese City

The Suita Study

Toshifumi Mannami, MD; Shunroku Baba, MD; Jun Ogata, MD

Background: Carotid arterial intimal-medial thickness (IMT) measured by high-resolution B-mode ultrasonography has come to be used as a noninvasive surrogate end point to measure progression of atherosclerosis. However, there are no detailed data on the relationship between aggregation of coronary risk factors and carotid atherogenesis.

Methods: Cross-sectional assessment of the relationship between carotid atherosclerosis detected by high-resolution ultrasonography and integration of major coronary risk factors by age and sex. Subjects aged 30 to 86 years were randomly selected from Suita, located in Osaka, the second largest urban area of Japan, including 1896 men and 2102 women. Carotid atherosclerosis was evaluated by using our atherosclerotic indexes of IMT, plaque number, plaque score, and percentage of stenosis of the carotid artery assessed using ultrasonography by sex and age group classified by number of major coronary risk factors (ie, hypertension [diastolic blood pressure $\geq$ 90 mm Hg and/or systolic blood pressure $\geq$ 140 mm Hg or receiving medication], smoking [current smoker], and hypercholesterolemia [serum total cholesterol level $\geq$ 5.68 mmol/L [220 mg/dL] or receiving medication]).

Results: The mean carotid atherosclerotic index value, especially the mean IMT value, of the subjects with 1 major coronary risk factor was on average 0.028 mm (3.2%) higher for men and 0.025 mm (2.9%) higher for women than that of the subjects without major coronary risk factors; for subjects with 2 risk factors, 0.054 mm (6.3%) higher for men and 0.053 mm (6.2%) higher for women; and for high-risk subjects with 3 major risk factors, 0.135 mm (15.8%) higher for men and 0.137 mm (15.4%) higher for women. The percentage of the subjects with severe stenosis of at least 50% increased stepwise with increases in the number of coronary risk factors and showed a significant difference ($P<.05$) between men and women, ie, 2.4% vs 0.6% ($P=.01$) among the subjects with no risk factors; 6.7% vs 1.5% ($P<.001$), subjects with 1 risk factor; 10.7% vs 2.7% ($P<.001$), subjects with 2 risk factors; and 18.6% vs 5.0% ($P=.01$), high-risk subjects.

Conclusions: Aggregation of established major coronary risk factors strongly influenced carotid atherogenesis in both sexes. There were significant differences between sexes in the acceleration or progression of carotid atherosclerosis.

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ith the aid of high-resolution B-mode ultrasonography, we can evaluate early carotid atherosclerosis precisely and noninvasively. There is growing evidence that carotid arterial intimal-medial thickness (IMT) measured by B-mode ultrasonography has come to be used as a noninvasive end point in epidemiological studies and clinical trials to gauge progression and regression of atherosclerosis.\textsuperscript{1,2} Futhermore, its IMT has been used recently not only as a surrogate end point for atherosclerosis of the coronary artery but also as a good indicator of the presence and extent of coronary artery disease.\textsuperscript{3,10}

A close histological relationship between carotid and coronary atherosclerosis has been seen in an autopsy study,\textsuperscript{11} and both arterial beds share major coronary risk factors that contribute to the progression of atherosclerosis.\textsuperscript{12,13}

The effect of major coronary risk factors such as high levels of serum cholesterol and high-density lipoprotein (HDL) cholesterol, high blood pressure, and cigarette smoking on the incidence of coronary disease in middle-aged people has been well described and well known.\textsuperscript{14-16} In addition, it is well known that there is a strong relationship between the incidence of coronary events and the aggregation of major coronary risk factors, as shown in the Framingham Study.\textsuperscript{17} How-
SUBJECTS AND METHODS

SUBJECT POPULATION

The population for our present study is based on a random sample selected from the residents of Suita. The sample consisted of 12,200 men and women aged 30 to 79 years, although 3000 men and woman were added randomly in the same way in 1996 and 1997. The basic sampling of the population started in 1989 with a cohort study base. The subjects have been visiting the National Cardiovascular Center every 2 years since then for regular health checkups. In addition to performing a routine blood examination that included total serum cholesterol, HDL cholesterol, triglyceride, and glucose levels and blood pressure and anthropometric measurements, a physician or nurse administered questionnaires covering personal and family history of cardiovascular and other diseases and smoking and drinking habits. The carotid ultrasonic examinations were begun in April 1994 and performed by a single physician (T.M.). The subjects in our present study included 1896 men and 2102 women, aged 30 to 86 years, who attended regular health checkups from April 1, 1994, through October 31, 1998.

STUDY VARIABLES

The definitions of major coronary risk factors (ie, hypertension, smoking, and hypercholesterolemia) were as follows. Subjects were classified as current smokers if they smoked at least 1 cigarette per day, nonsmokers if they had never smoked, and past smokers if they had quit smoking for more than 1 year. Subjects were defined as hypertensive if diastolic blood pressure (DBP) was at least 90 mm Hg and/or systolic blood pressure (SBP) was at least 140 mm Hg or if they were taking antihypertensive medication. Those subjects whose serum total cholesterol levels were at least 5.68 mmol/L (≥220 mg/dL) or who were taking antihypercholesterolemic medication were defined as having hypercholesterolemia. Those subjects whose fasting blood glucose levels were at least 7.00 mmol/L (≥126 mg/dL) based on the new criteria or who were taking antidiabetic medication were defined as diabetic. Subjects who had a history of coronary heart disease or cerebrovascular disease were excluded from this study (122 men and 60 women). Blood samples were obtained after overnight fasting, resulting in 85 men and 104 women being excluded because they did not meet this condition. Altogether, 207 men and 164 women among the total of 3998 subjects were excluded from this analysis. The details of the method of carotid ultrasonic examination have been published elsewhere.18 The method used in our present study was the same. We used a high-resolution B-mode ultrasonic machine with 7.5-MHz transducers yielding an axial resolution of 0.2 mm. The regions between 30 mm proximal from the beginning of the dilation of the bifurcation bulb and 15 mm distal from the flow divider of both common carotid arteries (CCAs) were scanned. All measurements were made at the time of scanning using the instrument’s electronic caliper and were recorded as photocopies. The IMT was measured on a longitudinal scan of the CCAs at a point 10 mm proximal from the beginning of the dilation of the bulb. We defined the IMT as the mean of the IMT of the near and far walls at the point of measurement. We defined a plaque as an area where IMT was at least 1.10 mm and calculated the plaque number (PN) by counting the number of plaques in the bilateral carotid arteries in the scanning area. We also calculated the plaque score (PS) by totaling the maximum thickness of all the plaques in the same area. Finally, we defined stenosis as a condition in which a plaque occupied more than half of the luminal circumference of an artery on a cross-sectional scan, and the degree of stenosis was calculated as a percentage ratio of the area of the plaque to that of the lumen, using the following formula:

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\frac{\text{Lumen Area} - \text{Residual Lumen}}{\text{Lumen Area}} \times 100.
\]

Both areas were measured automatically by the system on a frozen transverse section at the maximal narrowing site. If there was at least 50% stenosis, another skilled ultrasonographer performed color flow Doppler examination to confirm the stenosis.

Blood samples drawn from the subjects after a fast of 12 hours or more were collected in EDTA-containing tubes. Total cholesterol and triglyceride levels were assayed enzymatically with a biochemical discrete analyzer (Toshiba TBA-80RM; Toshiba, Tokyo, Japan). Glucose level was assayed enzymatically, and HDL cholesterol level was measured after precipitation with heparin and calcium ions with a different biochemical discrete analyzer (Toshiba TBA-20R; Toshiba). The measurements of total cholesterol, HDL cholesterol, and triglyceride levels were standardized in accordance with the protocol of the Centers for Disease Control and Prevention, Atlanta, Ga.

STATISTICAL METHODS

We used the Statistical Package for the Social Sciences (SPSS Inc, Chicago, Ill) for the analysis. The mean levels of all numerical values were tested using the t test, and those of all the categorical values were tested by means of the \( \chi^2 \) test. Mean levels of the 3 indexes of carotid atherosclerosis (IMT, PN, and PS) in each age group by sex and the number of major coronary risk factors were obtained and tested by means of 1-way analysis of variance. Values of \( P < .05 \) were considered significant.
Our present aim was to investigate, through a cross-sectional analysis, whether aggregation of major coronary risk factors (ie, hypertension, smoking, and hypercholesterolemia) may affect carotid atherogenesis and to obtain the fundamental data for the third step.

### RESULTS

The **Table** shows the characteristics of the subjects by age group and sex. In all age groups, the percentage of men with diabetes mellitus was significantly higher than that of women, and the smoking rate for men was also much higher than that for women \((P<.05)\). Also, the percentage of both sexes with hypertension, except for the group aged 30 to 44 years, was high because of our definition of hypertension. On the other hand, in all the other age groups, the mean total and HDL cholesterol levels for women were significantly higher than those for men \((P<.05)\).

**Figure 1** shows the mean IMT values of both sexes divided into 4 classes by the number of major coronary risk factors, which were hypertension, smoking, and hypercholesterolemia, in each age group. The IMT values of subjects of either sex with 3 risk factors was significantly higher in all age groups \((P<.05)\), and the values of the highest-risk subjects were almost equal to those of the lowest-risk subjects 20 years older. Furthermore, the IMT value increased with the increase in number of coronary risk factors in each age group for both sexes. There were no female subjects with 3 risk factors in the group aged 30 to 44 years. As shown in **Figure 2**, the mean IMT value of the subjects with 1 risk factor was on average 0.028 mm (3.2%) higher for men and 0.025 mm (2.9%) higher for women than that of the subjects with no risk factors. Similarly, that of the subjects with 2 risk factors was on average 0.054 mm (6.3%) higher for both sexes than that of subjects with no risk factors. Also, that of the high-risk subjects with 3 risk factors was significantly higher than that of the lowest-risk subjects 20 years older. Furthermore, the IMT value of the healthy subjects without risk factors increased on average 0.135 mm (15.8%) higher for men and 0.137 mm (15.4%) higher for women. The mean IMT value of the healthy subjects without risk factors increased on average 0.0075 mm/y for men and 0.0069 mm/y for women.

In other words, these findings suggest that the aggregation of major coronary risk factors accelerated the carotid atherogenesis and that this process is accelerated earlier in men than in women.
rotid atherosclerosis, and that the presence of 1 major coronary risk factor advances the carotid atherosclerosis about 3 to 4 years, the presence of 2 risk factors advances the disease about 7 to 8 years, and the presence of a higher number of major coronary risk factors advances the disease about 17 to 20 years.

Figure 3 shows the mean PN values of both sexes divided into 4 classes by the number of major coronary risk factors in each age group. The results were roughly similar to those shown in Figure 1.

Figure 4 shows the mean PS values of both sexes divided into 4 classes by the number of major coronary risk factors in each age group. These results were also roughly similar to those shown in Figures 1 through 3.

Figure 5 shows the percentage of subjects with 2 grades of stenosis divided by the number of coronary risk factors. The percentages of the 2 grades of stenosis increased as the number of risk factors increased for both sexes.

COMMENT

To our knowledge, this is the first report showing that there are strong relationships between the aggregation of major coronary risk factors and differences of carotid atherosclerosis based on a large general population of both sexes. As shown in Figures 1 through 5, carotid atherosclerotic indexes became higher with increasing numbers of coronary risk factors. Our results suggest that the carotid atherosclerosis of a high-risk person who has all major coronary risk factors progresses roughly 20 years ahead of that of a person with no major coronary risk factors. There are uncertainties when we compare the IMT of CCAs because there are several differences (ie, the apparatus, the techniques, the method of measuring carotid IMT, and the background of the population). However, if the findings in the Atherosclerosis Risk in Communities cohort (a US study) that the IMT of CCAs increases approximately 0.011 mm/y in men and 0.009 mm/y in women19 are applied to our present data, the IMT of a person with a single major coronary risk factor will advance about 2 to 3 years, that of a person with 2 risk factors will advance about 5 to 6 years, and that of a high-
A risk person with 3 major coronary risk factors will advance about 12 to 16 years. These results are similar to our present results, which indicates that our data seem to be reasonable.

Furthermore, our present data showed that there was a strong and significant sex difference in the genesis of carotid atherosclerosis, as we had expected, and that the atherosclerotic process in men seemed to be about 10 years ahead of that in women. There have been few data published so far on this subject based on a general population study, and our data seem to provide fundamental and valuable information on carotid atherosclerosis. Also, there have been few data or analyses published so far on these aspects of carotid atherosclerosis, although it has been reported that there were strong relationships between each coronary risk factor, including aging, and ca-
rotid atherosclerosis. In fact, a similar analysis has been reported in a previous study. Some authors have reported recently that IMT of the carotid artery is a reliable and powerful predictor of incident coronary events, although its index differs slightly among the studies. An autopsy study also has shown that there was a histologically close relationship between the carotid and coronary arteries. Furthermore, it is well known, as shown in the Framingham Study, that there is a strong relationship between the integration of major coronary risk factors and the incidence of coronary events. Taking these findings into consideration, our data suggest that it is possible to infer noninvasively and correctly the extent of coronary atherosclerosis on the basis of evaluation of the extent of carotid atherosclerosis.

In fact, Salonen and Salonen reported that a 1-time measurement of the maximal common arterial IMT of greater than 1.0 mm on the basis of a categorical system describing carotid artery structural changes was a predictive index for acute myocardial infarction during a period of 1 month to 3 years (relative risk, 2.2 [confidence interval, 0.7-6.7]). Belcaro and colleagues also reported that a 1-time IMT measurement of greater than 1.0 mm in asymptomatic patients was predictive of a cardiovascular event during a 6-year period using a categorical system describing the severity of atherosclerosis at the carotid and femoral artery bifurcations. Certainly, our atherosclerotic indexes are a little different from those of both studies because our indexes are not categorical, but our definition of a plaque as an abnormal condition of IMT has similar because early-phase atherosclerosis IMT values of less than 1.0 mm were considered the referent category in these studies. Furthermore, a previous report has found that there were strong and significant relationships between cardiovascular risk factors and our carotid atherosclerotic indexes (ie, IMT, PN, and PS). In addition, carotid artery wall thickness measured by ultrasonography has been documented as a good measure for evaluating regression or progression of atherosclerosis in clinical trials. A study has recently shown that for each 0.03-mm increase per year in common carotid arterial IMT, the relative risk for nonfatal myocardial infarction or coronary death was 2.2, and the relative risk for nonfatal myocardial infarction, coronary death, or a revascularization procedure was 3.1, although the participants of this study were limited to those who had previously had coronary artery bypass graft surgery. Our present results suggest that aggregation of coronary risk factors may accelerate or progress IMT, and that ultrasonographic monitoring and data of early-phase carotid atherosclerosis may sufficiently incorporate independent information leading to the prediction of coronary events. Furthermore, our present data suggest that the addition of direct ultrasonographic information on carotid atherosclerosis to the data of traditional risk factors derived from blood samples may make it possible to indentify subjects at high risk for the development of symptoms of cardiovascular disease. However, a longitudinal study is necessary as a third step because previous studies from our laboratory and our present study had a cross-sectional design to obtain basic data.

CONCLUSIONS

Our present data showed that there is a strong relationship between the aggregation of major coronary risk factors (ie, hypertension, smoking, and hypercholesterolemia) and acceleration or progression of carotid atherosclerosis in both sexes. Also, our data seem to be helpful in progressing toward our final goal, establishment of a noninvasive screening and prevention system for cardiovascular diseases (ie, stroke or myocardial infarction) using carotid atherosclerotic indexes.


