Severity of Coronary Atherosclerosis in Relation to Hypertension and Dyslipidemia

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The association of the severity of coronary atherosclerosis with hypertension and dyslipidemia, independent of other known coronary risk factors, was examined in 313 men and 155 women who underwent coronary angiography. The severity of coronary atherosclerosis was quantified using Gensini's scoring system. The following criteria were used to define dyslipidemia: hypercholesterolemia (total serum cholesterol concentration \( \geq \) 220 mg/dl), hypertriglyceridemia (serum triglyceride concentration \( \geq \) 150 mg/dl), and low HDL-cholesterolemia (serum HDL-cholesterol concentration < 40 mg/dl). In men, age, total cholesterol, fasting blood sugar, uric acid, and plasma fibrinogen levels were significantly higher in patients with coronary atherosclerosis than in those without. Significantly higher frequency of hypertension and lower levels of HDL-cholesterol were also found in male patients with coronary atherosclerosis. In women, age, total cholesterol, fasting blood sugar, and plasma fibrinogen levels were significantly higher in patients with coronary atherosclerosis than in those without. No significant interaction between hypertension and each dyslipidemia was found after adjustment for the other coronary risk factors; only hypercholesterolemia in men was significantly associated with coronary atherosclerosis. However, the degree of coronary atherosclerosis was most severe among patients with both hypertension and hypercholesterolemia in both sexes. The combination of hypertension and hypercholesterolemia seems to be important in the progression of coronary atherosclerosis. J Epidemiol, 1995; 5: 17-22.

Community-based studies have demonstrated that coronary heart disease remains prevalent despite optimal management of hypertensive patients. Dyslipidemia and other coronary risk factors have been reported to be more prevalent in hypertensives than in normotensives. Thus, controlling hypertension alone may be inadequate to prevent coronary heart disease unless other risk factors also are controlled. It becomes particularly important, therefore, to determine the relation of hypertension and dyslipidemia to coronary atherosclerosis. This study correlates the severity of angiographically determined coronary atherosclerosis with hypertension and dyslipidemia, independent of other known coronary risk factors.

SUBJECTS AND METHODS

Subjects

Our study population consisted of 313 men and 155 women whose ages ranged from 35 to 82 years. All study subjects underwent coronary angiography for suspected or known coronary heart disease at Fukuoka University Hospital between April 1988 and March 1993. They were consecutively examined with the exception of those taking lipid-lowering or anti-hypertensive agents which affect serum lipid metabolism (\( \beta \)-blockers and diuretics), patients admitted with acute myocardial infarction, patients with a history of valvular disease, prior myocardial infarction or a history of coronary artery surgery.
Angiography

Coronary angiography was performed using either a Judkins or Sones technique, and multiple views of all vessels were obtained. The right, left anterior descending, and left circumflex coronary arteries were evaluated with respect to the degree of maximal coronary obstruction, i.e., normal (0%), 25%, 50%, 75%, 90%, or 99% occluded. The evaluation was performed by three well-trained cardiologists, and the overall severity of coronary atherosclerosis was evaluated by Gensini's severity score.7)

Determination of hypertension and dyslipidemia

Hypertension was defined as a systolic blood pressure greater than equal to 160 mmHg or a diastolic blood pressure less than or equal to 95 mmHg. Patients receiving medication for hypertension were also classified as hypertensives regardless of their blood pressure. A venous blood sample was taken from all patients in the next morning after admission. Serum concentrations of total cholesterol, triglyceride, and high density lipoprotein cholesterol (HDL-cholesterol) were measured by enzymatic methods. The following criteria were used to determine the presence or absence of dyslipidemia in accordance with guidelines established at a consensus conference of the Japanese Atherosclerosis Society: hypercholesterolemia (total cholesterol ≥220 mg/dl), hypertriglyceridemia (triglyceride ≥150 mg/dl) and low HDL-cholesterolemia (HDL-cholesterol <40 mg/dl).

Other coronary risk factors

Serum uric acid and fasting blood sugar levels were also measured by routine enzymatic methods. Plasma fibrinogen level were assayed using the thrombin time method. The body mass index (kg/m²) was used as a measure of obesity. Smoking and drinking habits of all patients were obtained by physicians at the time of admission. The amount of alcohol intake was determined from the reported frequency and quantity of each alcoholic beverage (sake, beer, shochu and spirits) and was divided into four categories: none, light (1-99 ml ethanol per week), moderate (100-299 ml/week), and heavy (≥300 ml/week). Cigarette-years (the number of cigarette smoked per day multiplied by years of smoking) were used as a cumulative exposure to cigarette smoking. Our analysis excluded past drinkers who had ceased drinking for at least one year and past smokers who had quit smoking for at least 5 years.14)

Statistical analysis

Because serum triglyceride and plasma fibrinogen were log-normally distributed, statistical analysis of these variables were always done in the log-transformed scale. Means of serum triglyceride and plasma fibrinogen presented were geometric, and standard deviations were approximate. Differences between groups were tested with unpaired Student's t-test or chi-square test. Multiple linear regression analysis were employed to control for confounding effects of other coronary risk factors and to examine the interaction between hypertension and dyslipidemia. Indicator terms were used for dichotomous variables of hypertension and dyslipidemia. Adjusted means of Gensini scores according to the combination of hypertension and dyslipidemia were derived from analysis of covariance. In these statistical procedures, age, body mass index, uric acid, fasting blood sugar, plasma fibrinogen, and cigarette smoking were handled as continuous variables. Assuming a non-linear relation between

### Table 1. Characteristics and laboratory data of study subjects with and without coronary atherosclerosis by sex.

| Variables                      | Men                           | Women                          |
|-------------------------------|-------------------------------|-------------------------------|
|                               | GS=0 | n=189 | GS>0 | n=278 | p-value* | GS=0 | n=87 | GS>0 | n=68 | p-value* |
| Age (years)                   | 55.4±10.3 | 61.1±9.4 | <0.01 | 57.5±10.3 | 65.0±8.7 | <0.01 |
| Total cholesterol (mg/dl)     | 193.2±39.2 | 207.7±48.4 | <0.01 | 196.4±42.2 | 227.1±60.4 | <0.01 |
| Triglyceride (mg/dl)†         | 113.8±1.6 | 121.0±1.5 | 0.10 | 101.1±1.6 | 110.5±1.6 | 0.31 |
| HDL-cholesterol (mg/dl)       | 44.3±12.1 | 40.1±10.8 | <0.01 | 46.0±12.5 | 430.0±12.5 | 0.14 |
| Fasting blood sugar (mg/dl)   | 88.8±17.9 | 96.0±26.6 | <0.01 | 88.4±17.6 | 104.6±35.8 | <0.01 |
| Uric acid (mg/dl)             | 5.3±1.3 | 5.7±1.3 | <0.01 | 4.7±1.1 | 5.0±1.2 | 0.08 |
| Fibrinogen (mg/dl)†           | 266.5±1.3 | 296.7±1.3 | <0.01 | 266.6±1.2 | 289.5±1.3 | 0.02 |
| Body mass index (kg/m²)       | 23.9±3.3 | 23.6±3.0 | 0.40 | 24.0±3.6 | 24.1±3.7 | 0.09 |
| % smokers                     | 71.6 | 76.2 | 0.38 | 14.9 | 25.0 | 0.12 |
| % drinkers                    | 74.5 | 68.6 | 0.28 | 23.0 | 11.8 | 0.07 |
| % hypertension                | 30.4 | 42.4 | 0.04 | 31.0 | 45.6 | 0.06 |

* Values are expressed as the mean±SD with the exception of % smokers, % drinkers, and % hypertension.
† Means were geometric and standard deviation were approximate.
* Based on unpaired t-test or chi-square test.
GS = Gensini's score
alcohol consumption and severity score \cite{15}, we used indicator terms for alcohol consumption rather than a continuous or ordinal variable. A Bonferroni’s correction was made for the multiple comparison \cite{16}. Two-sided p-values of less than 0.05 were regarded as statistically significant. Statistical analyses were performed using the Statistical Analysis System (SAS) \cite{17}.

RESULTS

Table 1 presents the clinical characteristics and laboratory data for patients with and without coronary atherosclerosis by sex. In men, age, total cholesterol, fasting blood sugar, uric acid, and plasma fibrinogen levels were significantly higher in patients with coronary atherosclerosis than in those without. Significantly higher frequency of hypertension and lower HDL-cholesterol level were also noted in male patients with coronary atherosclerosis. In women, age, total cholesterol, fasting blood sugar, and plasma fibrinogen levels were significantly higher in patients with coronary atherosclerosis than in those without.

In patients with and without hypertension, the relation between severity of coronary atherosclerosis and hypercholesterolemia is shown in Figure 1, between atherosclerosis and hypertriglyceridemia in Figure 2, and between atherosclerosis and low HDL-cholesterolemia in Figure 3. Coronary arteries were most severely affected among men and women having both hypertension and hypercholesterolemia, but statistical significance was not found after Bonferroni’s correction for the multiple comparison (Figure 1). Men with hypertension and hypertriglyceridemia also had the highest score of coronary atherosclerosis, but without statistical significance (Figure 2). Hypertensive men with low HDL-cholesterolemia had higher mean of severity scores than any other group, again without statistical significance, while men with either hypertension or low HDL-cholesterolemia had almost the same severity score as those without the two conditions (Figure 3).

Independent effects of hypertension and dyslipidemia were also assessed in relation to the severity score, also controlling for the other coronary risk factors (Table 2). In men, both hypercholesterolemia significantly correlated with severity score. Low HDL-cholesterolemia tended to correlate with severity score but the relation was not statistically significant. Hypertension and triglyceridemia, however, had no significant correlation with severity score. Similarly, in women there was no apparent relation between severity score and hypertension and dyslipidemia. The interaction between hypertension and hypercholesterolemia (p=0.15 for men and p=0.21 for women), hypertriglyceridemia (p=0.13 for men and p=0.16 for women), low HDL-cholesterolemia (p=0.24 for men and p=0.64 for women) was not found in either men or women.

DISCUSSION

Although men and women with both hypertension and hypercholesterolemia had the highest score of coronary atherosclerosis, our study did not indicate the existence of interaction between hypertension and hypercholesterolemia in the severity of coronary atherosclerosis. A similar observation has been reported in several prospective studies on incidence of myocardial infarction \cite{18,19} and on mortality from coronary heart disease \cite{20}.

The combined influence of hypertension and cholesterol has also been examined in experimental studies \cite{21-24}. In a study involving cynomolgus monkeys, hypertension in-
Figure 2. Relation between severity of coronary atherosclerosis and hypertriglyceridemia in patients with and without hypertension: adjusting for age, fasting blood sugar, uric acid, fibrinogen levels, body mass index, smoking and alcohol intake. P-value denotes the overall differences.

Figure 3. Relation between severity of coronary atherosclerosis and low HDL-cholesterolemia in patients with and without hypertension: adjusting for age, fasting blood sugar, uric acid, fibrinogen levels, body mass index, smoking, and alcohol intake. P-value denotes the overall differences.

Table 2. Multiple regression analysis† of severity of coronary atherosclerosis in relation to hypertension, hypercholesterolemia, hypertriglyceridemia, and low HDL-cholesterolemia

| Independent variable                | Men (n=313) |          |          | Women (n=155) |          |          |
|------------------------------------|-------------|----------|----------|--------------|----------|----------|
|                                    | β          | S.E.     | p        | β            | S.E.     | p        |
| Hypertension                       | 4.74       | 2.92     | 0.11     | 2.91         | 4.38     | 0.51     |
| Hypercholesterolemia               | 7.81       | 3.43     | 0.02     | 5.05         | 4.65     | 0.28     |
| Hypertriglyceridemia               | 1.10       | 3.47     | 0.75     | 1.22         | 5.36     | 0.82     |
| Low HDL-cholesterolemia            | 5.70       | 2.92     | 0.05     | 0.93         | 4.69     | 0.84     |

†Adjusting for age, fasting blood sugar, uric acid, body mass index, fibrinogen, cigarette-years and three indicator terms of alcohol use.
duced by surgical coarctation of the midthoracic aorta caused arterial changes such as a thickening of the intima and media and fragmentation of the intra elastic layer of the arteries. The combination of hypertension and hypercholesterolemia (induced by cholesterol feeding), not hypercholesterolemia alone, increased the severity of atherosclerosis in the major coronary arteries and its branches. In another study of stump-tailed macaques, hypertension induced by bilateral renal artery stenosis did not aggravate the extent of coronary atherosclerosis. However, when hypertension developed following two years of cholesterol feeding, the extent of coronary atherosclerosis was significantly greater in hypertensive-hypercholesterolemic stump-tailed macaques than in animals with hypercholesterolemia alone. Other studies also have shown that hypertension alone does not contribute to atherosclerosis and that the combination of hypertension and hypercholesterolemia, has been demonstrated to have a potent effect on the development of atherosclerosis. A lack of an independent effect of hypertension in the present study are thus congruent with these experimental studies.

In the present study, low HDL-cholesterolemia had a tendency to be related to the severity of coronary atherosclerosis in men. Our findings corroborate the previous observations that HDL-cholesterol is protective against coronary atherosclerosis. In contrast, hypertriglyceridemia was not related to severity of coronary atherosclerosis. This finding is in agreement with a previous study reported by Noma et al. Metabolic interrelationships between triglyceride levels and HDL-cholesterol may make it difficult to evaluate the independent risk due to hypertriglyceridemia.

Plasma fibrinogen levels vary from time to time even in healthy individuals and respond to physiological changes such as pregnancy, injury, inflammation and malignancy. Although we did not allow for these factors, we demonstrated higher fibrinogen levels in patients with coronary atherosclerosis than in those without. An association between fibrinogen and the binding of low density lipoproteins within the intima has been reported, and it has been suggested that an early event in the development of atherosclerosis is the adsorption of low density lipoproteins to the endothelial fibrin lining. An elevated fibrinogen level is likely to promote atherosclerosis in patients with hypercholesterolemia. However, hypercholesterolemia was associated with coronary atherosclerosis independently of fibrinogen levels in the present study.

In summary, hypercholesterolemia was independently related to severity of coronary atherosclerosis in men, but not in women. The present study provides no clear evidence that either hypertension, hypertriglyceridemia, or low HDL-cholesterol independently aggravates coronary atherosclerosis. Yet, the combination of hypertension and hypercholesterolemia appear to be important in the development of coronary atherosclerosis in men and women.

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