ORIGINAL CONTRIBUTION

A Case-Reference Study on Plasma Fibrinogen Concentrations and Coronary Atherosclerosis in Japanese

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To examine contribution of plasma fibrinogen concentrations to coronary atherosclerosis in Japanese, a cross-sectional study was conducted from 1991 to 1993 for 169 myocardial infarction cases and 1:1 matched references. All cases had one to three coronary vessels with 50 percent or more stenosis. References were chosen out of Osaka residents who had no cardiac event by matching sex and age (+- 3 years) with cases. Mean (SD) values of plasma fibrinogen concentration were 322 (81) mg/dl in men and 377 (77) mg/dl in women for cases, and were 282 (56) mg/dl in men and 277 (48) mg/dl in women for references; mean plasma fibrinogen was significantly higher in cases than in references for both men and women. Furthermore, mean plasma fibrinogen was progressively higher as the number of stenotic vessels increased for men, and similar trend was seen for women. The case-reference difference remained significant even after adjusting smoking status, hypertension, serum total cholesterol, serum HDL cholesterol. Although plasma fibrinogen concentration was reported lower in Japanese than in American Caucasians, plasma fibrinogen is suggested to be a risk factor for myocardial infarction among Japanese as so among Caucasians. J Epidemiol, 1996; 6: 81-86.

plasma fibrinogen ; cross-sectional study ; myocardial infarction ; coronary artery stenosis ; Japanese

Hypertension, smoking and hypercholesterolemia are three major risk factors for incidence and mortality from coronary heart disease1,2). Recently, in addition to these, a lower serum HDL cholesterol concentration3-6) and a higher plasma fibrinogen concentration7-12) are recognized independent risk factors. According to our follow-up studies in urban Japanese men, hypertension, smoking, hypercholesterolemia10) and a lower serum HDL cholesterol concentration10) have been confirmed coronary risk factors. Regarding plasma fibrinogen, we reported positive associations of plasma fibrinogen concentrations with age, blood pressure, cigarette smoking and serum total cholesterol concentrations, and inverse association with serum HDL cholesterol concentrations in urban Japanese men15). These correlations between plasma fibrinogen concentrations and known coronary risk factors suggest that higher plasma fibrinogen concentrations increase the risk of coronary heart disease in Japanese as so in Caucasians. As the first step to confirm this hypothesis, we conducted a case-reference study to examine the relation between plasma fibrinogen concentrations and coronary atherosclerosis.

MATERIALS AND METHODS

The cases were 207 patients aged 20 to 79 years who undergone coronary angiography (CAG) for suspected or known myocardial infarction at Osaka Medical Center for Cancer and Cardiovascular Diseases. According to the CAG, all cases had one to three vessels (left anterior descending coronary artery, left circumflex coronary artery and right coronary artery) with 50% or more stenosis. All cases had discharged the hospital between November 1991 to October 1993.

The patients were recruited to the hospital after a month from the discharge to examine plasma fibrinogen, serum lipids, blood pressures, and smoking and drinking status. Patients

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with medication lowering the serum total cholesterol or plasma fibrinogen, or without fasting were excluded from this study. Thus, 169 cases left for the analyses.

References were picked up out of Osaka residents who participated in health examination at Osaka Medical Center for Cancer and Cardiovascular Diseases between February 1991 to March 1993 by 1 : 1 matching sex and age (+ - 3 years) with cases. References had no cardiac event. The majority of the cases and references had worked at small companies, and almost the other of these had no job.

Blood was drawn into a citrated, siliconized glass for fibrinogen according to the protocol of the Atherosclerosis Risk in Communities (ARIC) study16, and into a plain, siliconized tube for lipids. The plasma and serum were separated and stored at -70°C for two weeks until the measurement. Fibrinogen was measured by the clotting assay of Clauss17 using reagents obtained from General Diagnostics (Organon-Technika Co., Morris Plains, NJ). Serum total cholesterol was measured by an enzymatic method18 and HDL cholesterol was measured after heparin-manganese precipitation using the Liebermann-Burchard method19. The laboratory has been standardized by CDC-NHLBI Lipid Standardization Program (Center for Disease Control and Prevention, USA, Atlanta)20).

Systolic and diastolic blood pressures were measured using a standard mercury sphygmomanometer on the right arm of seated participants after a five-minute rest. Blood pressure observers were trained according to American Heart Association methods21. An interview was conducted to ascertain smoking status, the number of cigarettes smoked per day, usual alcohol intake per week, for cases a month before myocardial infarction attack, for references at the health examination.

Hypertension was defined as systolic blood pressure of >= 160 mmHg, diastolic blood pressure of >= 90 mmHg, and/or current treatment by antihypertensive medication. Smokers were defined as persons who smoked one or more cigarettes per day regularly. Drinkers were defined as persons who had a drink once or more a week and took 7g or more ethanol at one time.

We used the analysis of covariance for mean values, and chi-square test for proportions to examine differences between cases and references, and differences according to the number of vessels with 75% or more stenosis. Conditional multivariate logistic regression analysis was conducted to examine the relation of plasma fibrinogen concentrations and other related variables with the prevalence of myocardial infarction. All probability values for statistical tests were two-tailed.

RESULTS

Sex-specific cardiovascular risk factors are shown in Table 1. Mean plasma fibrinogen concentration was higher in cases than in references for both sexes. Mean serum total cholesterol concentration was higher in cases than in references for men, but did not differ between cases and references for women. Mean serum HDL cholesterol concentration was lower in cases than in references for both sexes. There was no significant difference in either systolic or diastolic blood pressure between cases and references. However, the proportion of hypertensive persons was significantly higher in cases than in references for both sexes. Mean number of cigarettes per day and the proportion of smokers were higher in cases than in references for both sexes. There was no significant difference between cases and references in mean alcohol intake or the proportion of drinkers for either sexes.

Sex specific findings of the cases according to the number of stenotic vessels, compared to references, were shown in Tables 2 and 3. Mean plasma fibrinogen concentration was progressively higher as the number of stenotic vessels increased for men, and a similar trend was seen for women. Mean serum total cholesterol concentration was also progressively higher with the number of stenotic vessels for men, but did not vary significantly for women. Mean serum HDL cholesterol concentration was lower in cases than in references, but did not

Table 1. Sex-specific mean (SD) values and prevalence of coronary risk factors in myocardial infarction cases and references

|                      | Men             | Women            |
|----------------------|-----------------|------------------|
|                      | Cases 135       | References 135   | Cases 34 | References 34 |
| Plasma fibrinogen    | (mg/dl)         |                  |          |                |
|                      | 322.4 (80.9)    | 281.6 (56.3)**   | 377.2 (77.1) | 277.2 (47.5)** |
| Serum total cholesterol | (mg/dl)      |                  |          |                |
|                      | 216.6 (44.2)    | 204.3 (45.9)*    | 241.1 (61.7) | 233.8 (39.8)   |
| Serum HDL cholesterol | (mg/dl)        |                  |          |                |
|                      | 48.9 (11.5)     | 54.0 (15.8)**    | 50.9 (12.7) | 60.8 (13.3)**  |
| Systolic blood pressure | (mmHg)         |                  |          |                |
|                      | 134.6 (13.7)    | 131.4 (19.0)     | 145.4 (25.2) | 134.3 (19.6)   |
| Diastolic blood pressure | (mmHg)        |                  |          |                |
|                      | 78.1 (8.2)      | 81.1 (11.3)      | 81.1 (8.1)  | 79.3 (10.7)    |
| Hypertensive persons | (%)            |                  |          |                |
|                      | 87.4            | 20.7**           | 100.0     | 29.4**         |
| Number of cigarettes | (per day)       |                  |          |                |
|                      | 33.9 (18.2)     | 11.6 (13.1)**    | 14.6 (5.6)  | 1.8 (5.8)**    |
| Current smokers      | (%)            |                  |          |                |
|                      | 63.4            | 51.1*            | 36.0      | 11.8*          |
| Alcohol intake       | (23g/week)     |                  |          |                |
|                      | 5.0 (6.2)       | 6.8 (7.7)        | 3.1 (7.7)  | 0.3 (0.9)      |
| Current drinkers     | (%)            |                  |          |                |
|                      | 58.4            | 60.7             | 16.0      | 11.8           |

Differences between cases and references *:p<0.05 **:p<0.01
vary among cases according to the number of stenotic vessels for either sex. Mean number of cigarettes per day and the proportion of smokers were higher in cases than in references, but did not vary among cases according to the number of stenotic vessels for either sex. No trend was seen in mean alcohol intake or the proportion of drinkers according to the number of stenotic vessels for either sex.

Table 4 showed the result of conditional multivariate logistic regression analysis. Plasma fibrinogen concentration, hypertension, and the number of cigarettes smoked were significant-

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### Table 2. Mean (SD) values and prevalence of coronary risk factors according to the number of stenotic coronary vessels for men

| The number of stenotic vessels | N | References | One vessel | Two vessels | Three vessels |
|-------------------------------|---|------------|------------|-------------|---------------|
| Plasma fibrinogen (mg/dl)     |   | 281.5 (56.3) | 312.2 (38.7) | 317.4 (67.6) | 338.9 (106.5) ** |
| Serum total cholesterol (mg/dl) | | 204.3 (45.9) | 209.9 (39.3) | 220.7 (43.5) | 222.7 (51.3) * |
| Serum HDL cholesterol (mg/dl) | | 54.0 (15.8) | 48.4 (10.3) | 49.9 (8.7) | 47.3 (14.5) * |
| Systolic blood pressure (mmHg) | | 131.3 (19.0) | 136.9 (13.1) | 129.1 (13.6) | 135.5 (15.9) |
| Diastolic blood pressure (mmHg) | | 81.1 (11.3) | 78.5 (8.4) | 76.2 (9.4) | 78.7 (6.9) |
| Hypertensive persons (%)       | | 20.7 | 86.5 | 83.3 | 85.7 ** |
| Number of cigarettes (per day) | | 11.6 (13.1) | 30.6 (17.2) | 38.3 (20.6) | 35.0 (17.0) ** |
| Current smokers (%)           | | 51.1 | 59.5 | 69.2 | 66.7 * |
| Alcohol intake (23g/week)     | | 6.8 (7.7) | 4.4 (6.4) | 6.1 (5.4) | 4.7 (6.2) |
| Current drinkers (%)          | | 60.7 | 52.3 | 73.1 | 53.3 |

Stenotic coronary vessels were having 75% or more stenosis, three cases having less than 75% stenosis were excluded from the analysis. Differences among references and three subgroups of cases *:p<0.05 **:p<0.01

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### Table 3. Mean (SD) values and prevalence of coronary risk factors according to the number of stenotic coronary vessels for women

| The number of stenotic vessels | N | References | One vessel | Two vessels | Three vessels |
|-------------------------------|---|------------|------------|-------------|---------------|
| Plasma fibrinogen (mg/dl)     |   | 277.1 (47.4) | 334.9 (62.7) | 353.7 (49.7) | 337.5 (109.8) ** |
| Serum total cholesterol (mg/dl) | | 233.8 (39.8) | 238.1 (45.4) | 239.6 (110.3) | 240.7 (47.0) |
| Serum HDL cholesterol (mg/dl) | | 60.8 (13.3) | 54.6 (14.9) | 44.0 (5.3) | 50.8 (13.0) * |
| Systolic blood pressure (mmHg) | | 134.3 (19.6) | 132.5 (22.7) | 162.0 (38.1) | 145.6 (22.0) |
| Diastolic blood pressure (mmHg) | | 79.3 (10.7) | 76.0 (7.1) | 82.7 (14.2) | 82.8 (4.8) |
| Hypertensive persons (%)       | | 29.4 | 100.0 | 100.0 | 100.0 ** |
| Number of cigarettes (per day) | | 1.8 (5.8) | 16.7 (16.7) | 15.0 (21.4) | 10.0 (13.3) ** |
| Current smokers (%)           | | 11.8 | 50.0 | 28.5 | 33.3 |
| Alcohol intake (23g/week)     | | 0.3 (0.9) | 0.6 (1.1) | 0.0 (0.0) | 7.8 (23.3) |
| Current drinkers (%)          | | 11.8 | 33.3 | 0.0 | 16.6 |

Stenotic coronary vessels were having 75% or more stenosis, three cases having less than 75% stenosis were excluded from the analysis. Differences among references and three subgroups of cases *:p<0.05 **:p<0.01

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### Table 4. Results of conditional multivariate logistic regression analysis for prediction of myocardial infarction

| Coefficient | SE  | p value | Odds ratio (95% interval) |
|-------------|-----|---------|--------------------------|
| Plasma fibrinogen (72mg/dl)* | 0.778 | 0.004 | 0.002 | 2.18 | (1.33 - 3.57) |
| Serum total cholesterol (48mg/dl)* | 0.503 | 0.006 | 0.075 | 1.65 | (0.95 - 2.88) |
| Serum HDL cholesterol (14mg/dl)* | -0.197 | 0.021 | 0.503 | 0.82 | (0.45 - 1.47) |
| Hypertensive persons (yes vs no) | 4.294 | 0.812 | <0.001 | 73.22 | (14.92 - 359.47) |
| Number of cigarettes (18/day)* | 2.381 | 0.028 | <0.001 | 10.81 | (4.12 - 28.40) |
| Alcohol intake (210g/week)* | 0.272 | 0.033 | 0.293 | 1.31 | (0.79 - 2.18) |

* Corresponded with one standard deviation of each variable
ly related with myocardial infarction. A 64mg/dl higher plasma fibrinogen concentration was associated with two times higher risk of myocardial infarction.

**DISCUSSION**

In this study we found plasma fibrinogen was higher in cases than in references for both men and women. This relation remained significant even after adjusting smoking status, hypertension, serum total cholesterol and serum HDL cholesterol. Previous cross-sectional studies in Western countries recognized the relation between plasma fibrinogen and coronary heart disease or coronary atherosclerosis. In Japan, one cross-sectional case study reported the relation between plasma fibrinogen concentrations and the number of stenotic vessels: the relation was statistically significant in men but not in women. In the present study, however, we found the statistically significant relation both in men and women.

There are two limitations since this study is based on a cross-sectional design. The first limitation is from case ascertainment. All cases for this study were survivors who discharged the hospital, fatal or severe nonfatal cases were not examined. On the other hand, the cases had at least one stenotic vessel and we probably missed less severe cases. Thus, it is uncertain whether we selected more or less severe cases which may influence the risk factor analyses. The second limitation is on the timing that we examined cases: one month after the discharge. We possibly underestimated the contribution of risk factors which may change rapidly as patients changed their lifestyles after the onset of myocardial infarction. For instance, serum total cholesterol may decline and serum HDL cholesterol may increase after patients reduced fat intake, reduced body weight or quitted cigarette smoking. Blood pressure was more likely to decrease when patients started antihypertensive medication and changed their lifestyles. Increased plasma fibrinogen concentration among smokers, however, would not decline so rapidly even after the cessation of smoking. Several cross-sectional studies suggested that it takes two or more years after the smoking cessation to reach plasma fibrinogen levels in never-smokers. Thus, the contribution of plasma fibrinogen concentration to the risk of myocardial infarction was unlikely to be underestimated.

Prospective studies in Western countries have shown that plasma fibrinogen is a risk factor of myocardial infarction. Our previous cross-sectional study showed that plasma fibrinogen concentrations were positively associated with age, smoking, serum total cholesterol concentration, and inversely associated with serum HDL cholesterol concentration which was consistent with the results of studies in Western countries. Although plasma fibrinogen concentrations were lower in Japanese than in American Caucasians according to our previous cross-cultural study, the present study suggested that plasma fibrinogen is a risk factor of myocardial infarction among Japanese as so among Caucasians. Our prospective study is underway to confirm this hypothesis.

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