Heart Vessels (2004) 19:144–148
DOI 10.1007/s00380-003-0753-5

ORIGINAL ARTICLE

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Plasma fibrinogen and its association with cardiovascular risk factors in apparently healthy Japanese subjects

Received: August 8, 2003 / Accepted: November 8, 2003

Abstract Recent evidence has shown the association of increased plasma fibrinogen levels with subsequent coronary heart disease or stroke. Fibrinogen is an acute-phase inflammatory reactant as well as a clotting factor. The authors investigated an association between fibrinogen levels and cardiovascular risk factors in apparently healthy Japanese subjects, while considering C-reactive protein (CRP) levels, a marker of the inflammatory status. Plasma fibrinogen and serum CRP from 2706 participants in an annual mass screening examination, held in Matsukawa, Nagano, Japan were measured. A total of 2355 subjects (816 men and 1539 women) were analyzed after excluding individuals with a history of diabetes mellitus, heart disease, or stroke. Plasma fibrinogen was strongly correlated with CRP levels. After adjusting the CRP levels, fibrinogen was positively associated with age, smoking status, total cholesterol, and hemoglobin A_{1c} (HbA_{1c}) in men, and with age, total cholesterol, and HbA_{1c} in women. On the other hand, high-density lipoprotein (HDL) cholesterol was a strong negative correlate of fibrinogen in both genders. Fibrinogen levels also tended to be associated positively with body mass index in both genders and negatively with exercise habits in men. The present multiple regression analysis has shown that plasma fibrinogen levels are correlated with conventional cardiovascular risk factors even after adjusting for the CRP levels. Persons with cardiovascular risk factors tended to have higher fibrinogen levels, suggesting that all elevated plasma fibrinogen concentration in those with risk factors may further increase the risk of the development of atherothrombosis and subsequent cardiovascular disease through the blood coagulation system.

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Key words Fibrinogen · Cardiovascular disease · Blood coagulation system · Atherosclerosis

Introduction

Increased plasma fibrinogen levels have been shown to be associated with coronary heart disease or stroke.[1–4] Meta-analyses of epidemiological studies estimated that a relative risk of cardiovascular disease was about two times higher in persons with plasma fibrinogen levels in the higher tertile than persons with levels in the lower ones.[1,3,4] Plasma fibrinogen is a major determinant of platelet aggregation and blood viscosity that play a central role in formation of thrombi. High plasma fibrinogen levels may aggravate atherosclerotic vessel lesions and predispose to further cardiovascular disease by its procoagulant actions.[1]

It is indicated that the risk of plasma fibrinogen or cardiovascular risk factors may not have the same effects in different ethnic groups, for example, between Japanese and Caucasian subjects.[5] There are relatively few studies on plasma fibrinogen in the Japanese population compared with American and European populations. The authors conducted a cross-sectional study to investigate the possible association between plasma fibrinogen levels and cardiovascular risk factors in apparently healthy Japanese subjects, while considering C-reactive protein (CRP) levels, a marker for inflammatory status.

Subjects and methods

Apparently healthy Japanese subjects were selected from participants in an annual mass health screening examination in 2000 that was held in a rural community, Nagano Prefecture, Japan. Health screening examinations had been conducted for community inhabitants aged ≥20 years. A total of 2795 subjects (1030 men and 1765 women) participated in the health screening. Among them, 2706 persons

(981 men and 1725 women) gave their informed consent to participation in the present study. Persons with a history of diabetes mellitus, heart disease, or stroke were excluded, leaving a total of 2355 (816 men and 1539 women) subjects for analysis.

The health examination included a questionnaire about medical history and lifestyle (smoking, alcohol, physical activity habits) information as well as anthropometric, physiological, and laboratory measurements. Self-administered questionnaires were completed at home by the participants, and then checked by nurses at the health examination to fill in any missing items. Smoking habits were categorized as current smoker, ex-smoker, and nonsmoker. Drinking habits were divided according to the frequency of alcohol intake: none, 3 or less days a week, and more than 3 days a week. Exercise habits were also defined according to the frequency of exercise: less than once a week, 1–2 times a week, and three or more times a week. Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$ and divided into lean (BMI $<$ 18.5), normal (18.5 $\leq$ BMI $<$ 25), and obese (BMI $\geq$ 25).

Blood samples were obtained from the antecubital vein of a seated subject. The plasma fibrinogen level and serum CRP were analyzed at a laboratory (SRL, Japan). For measurement of the plasma fibrinogen level, 1.8 ml of blood was placed into a tube containing 0.2 ml of 3.8% sodium citrate. Blood plasma was separated by centrifuging the tube at 3000 rpm for 10 min, and the plasma was frozen at $-20°C$ until analysis within several days after blood collection. The fibrinogen level was determined by the thrombin-clotting time measured according to the method of Clauss. Serum samples were also centrifuged and separated after blood collection. The serum CRP level was measured using the latex immunonephelometric method. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and hemoglobin A_{1c} (HbA_{1c}) were analyzed at the laboratory of the Health Examination Center of the Japanese Agricultural Cooperative Associations of Nagano.

Statistical analysis was performed using the Statistical Package for Social Science (SPSS 10.0 J for Windows). One-way analysis of variance was employed for a comparison of the mean values. Further statistical differences between them were analyzed using Dunnett's *t*-test. Multiple regression analysis was made to analyze associations between the fibrinogen level and related factors, such as age, obesity, smoking, alcohol intake, exercise habits, total cholesterol, HDL cholesterol, and HbA_{1c}, while adjusting for the CRP levels.

Results

Mean levels of plasma fibrinogen increased with age in both genders ($P < 0.001$) (Table 1). Compared with the age group under 34 years, fibrinogen was significantly higher in men aged over 35 years ($P = 0.042$ at ages of 35–44 and $P < 0.001$ after age 45). In women, fibrinogen increased sharply after the ages of 45–54 years, and there were significant differences in the age groups over 45 years ($P = 0.022$ at ages of 45–54 and $P < 0.001$ after 55). The fibrinogen level was higher in women than in men after adjustment for age ($P < 0.001$).

Table 1. Mean and standard deviation (SD) of plasma fibrinogen levels (mg/dl) according to age and sex

Age (years)	Men		Women	
	n	Mean (SD)	*n*	Mean (SD)
≤34	42	199.7 (26.4)	129	227.2 (50.7)
35–44	74	223.4 (41.7)*	246	226.0 (39.9)
45–54	147	234.7 (42.8)***	280	240.2 (40.1)*
55–64	223	252.2 (49.3)***	417	260.0 (44.0)***
65–74	246	261.9 (55.8)***	385	268.2 (45.2)***
≤75	84	264.1 (54.7)***	82	281.4 (52.6)***
Total	816	247.9 (52.2)	1539	251.4 (47.5)

* $P < 0.05$, *** $P < 0.001$, by Dunnett *t*-test compared with the age group of 34 years or less

Table 2 shows age-adjusted fibrinogen levels according to BMI, smoking, alcohol intake, and exercise habits. The age-adjusted fibrinogen level tended to be higher in the obese group (BMI $\geq$ 25) among men ($P = 0.023$). Smoking was significantly related to the fibrinogen level in men ($P < 0.001$). The fibrinogen level was higher in the order current smokers, ex-smokers, nonsmokers. A significant association with smoking was not observed in women. Alcohol drinkers tended to have lower fibrinogen in women ($P = 0.094$), a trend not found in men. Exercise habits were negatively associated with the fibrinogen level in men ($P = 0.027$), although there was no significant difference in women.

Plasma fibrinogen was closely correlated with CRP levels ($P < 0.001$ for both genders, Table 3). The levels also increased with total cholesterol ($P = 0.014$ for men, $P = 0.004$ for women), HbA_{1c} levels ($P = 0.005$ for men, $P = 0.011$ for women), and decreased with HDL cholesterol level ($P = 0.004$ for men and $P = 0.001$ for women).

Multiple regression analysis (Table 4) showed that the plasma fibrinogen level was positively associated with age in both genders ($P < 0.001$). Body mass index exhibited a positive trend with fibrinogen in both genders ($P = 0.061$ for men, $P = 0.063$ for women). In men, the fibrinogen level was positively linked with smoking status ($P = 0.003$), and negatively related with exercise habits ($P = 0.030$). However, no significant association with them was observed in women. Alcohol intake was not significantly related with the fibrinogen level in either gender. In both genders, the fibrinogen level was positively related to total cholesterol ($P = 0.003$ for men, $P < 0.001$ for women) and with HbA_{1c} ($P = 0.010$ for men, $P = 0.002$ for women), whereas HDL cholesterol was negatively associated with it ($P < 0.001$ for both genders). Plasma fibrinogen was strongly correlated with CRP levels ($P < 0.001$ for both genders).

Discussion

The present cross-sectional study of apparently healthy Japanese subjects showed that after considering CRP levels,

Table 2. Age-adjusted mean and SD of plasma fibrinogen levels (mg/dl) according to body mass index, smoking, alcohol intake, and exercise habits

	Men		Women	
	n	Mean (SD)	*n*	Mean (SD)
Body mass index (kg/m^2)				
<18.5	40	234.5 (46.0)	169	246.5 (49.2)
18.5–24.9	637	244.4 (48.8)	1168	250.0 (43.5)
≥25.0	139	255.1 (51.3)*	202	250.6 (42.5)
Smoking status				
Nonsmoker	238	238.1 (48.1)	1473	249.6 (43.9)
Ex-smoker	292	243.1 (49.6)	32	254.7 (56.0)
Current smoker	286	254.7 (48.6)***	31	251.0 (36.7)
Alcohol intake				
Nondrinker	171	246.2 (52.0)	1206	250.9 (44.2)
Drinker ≤ 3 days a week	114	241.8 (45.1)	191	247.1 (45.6)
Drinker > 3 days a week	531	246.5 (49.2)	138	243.0 (40.7)#
Exercise habits				
<once a week	490	249.7 (51.3)	881	249.1 (43.3)
1–2 times a week	143	240.2 (43.9)	286	249.2 (43.8)
≥3 times a week	173	240.1 (47.5)*	360	251.6 (46.3)

# $P < 0.1$, * $P < 0.05$, *** $P < 0.001$ by analysis of variance

Table 3. Age-adjusted mean and SD of plasma fibrinogen levels (mg/dl) according to total cholesterol, high-density lipoprotein (HDL) cholesterol, hemoglobin A_{1c} (HbA_{1c}), and C-reactive protein

	Men		Women	
	n	Mean (SD)	*n*	Mean (SD)
Total cholesterol (mg/dl)				
<200	521	242.2 (49.9)	754	246.5 (44.9)
200–239	234	250.8 (47.3)	591	251.1 (41.8)
≥240	61	257.2 (47.8)*	194	257.7 (46.2)**
HDL cholesterol (mg/dl)				
<40	85	257.1 (50.9)	56	256.8 (46.1)
40–69	585	246.7 (49.2)	1076	251.8 (45.0)
≥70	146	235.3 (46.8)**	407	243.1 (40.3)**
HbA_{1c} (%)				
<5.0	272	239.1 (51.0)	478	244.7 (43.2)
5.0–5.4	451	247.3 (46.5)	892	251.7 (45.2)
≥5.5	93	257.3 (54.5)**	169	253.1 (38.7)*
C-reactive protein (mg/dl)				
<0.10	683	235.3 (37.5)	1327	242.2 (36.5)
0.10–0.19	67	273.3 (40.7)	112	272.8 (43.4)
≥0.20	65	327.7 (73.1)***	96	326.5 (56.6)***

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ by analysis of variance

plasma fibrinogen was positively associated with age, smoking status, total cholesterol, and HbA_{1c} in men, and with age, total cholesterol, and HbA_{1c} in women. The levels were negatively associated with HDL cholesterol in both genders. Fibrinogen levels also tended to be associated positively with BMI in both genders and negatively with exercise habits in men. The present plasma fibrinogen levels were generally in accordance with earlier Japanese studies,[6–9] showing that plasma fibrinogen levels were lower in Japanese than Western populations.

The plasma fibrinogen concentration increased with age in both genders, and it was higher in women than in men. These findings are consistent with previous investigations including Japanese studies.[6–18] Plasma fibrinogen levels in women rose especially after age 45 years when most women might be postmenopausal. Menopausal women reportedly have higher plasma fibrinogen values than premenopausal females.[6,8,11–13,16,19]

Obesity evaluated by BMI tended to be positively associated with the fibrinogen level in both genders. Previous Western studies have indicated the relationship of fibrinogen levels with BMI, waist circumference, and the waist-hip ratio in men and/or women.[13,14,16,17] On the other hand, earlier Japanese studies failed to show an association between fibrinogen levels and BMI,[6–8] while a positive association was observed in one study of Japanese men.[9] This may be because extremely obese persons of BMI ≥ 30 kg/m^2 are rare among Japanese.

Smoking has been indicated to be the most striking determinant of plasma fibrinogen levels in men and/or

Table 4. Standardized β in multiple regression analysis with plasma fibrinogen (mg/dl) as dependent valuable

Variables	Men (n = 805)		Women (n = 1518)	
	Standardized β	P value	Standardized β	P value
Age (years)	0.320	<0.001	0.252	<0.001
Body mass index (kg/m^2)	0.066	0.061	0.042	0.063
Smoking status	0.094	0.003	0.022	0.311
Alcohol drinking	0.044	0.166	−0.036	0.113
Exercise habits	−0.067	0.030	0.008	0.715
Total cholesterol (mg/dl)	0.097	0.003	0.141	<0.001
HDL cholesterol (mg/dl)	−0.138	<0.001	−0.109	<0.001
HbA_{1c} (%)	0.085	0.010	0.075	0.002
C-reactive protein (mg/dl)	0.334	<0.001	0.382	<0.001

women.[6–9,11–18,20,21] In the present study, a significant association between plasma fibrinogen and smoking status was encountered only in men, which agrees with a previous Japanese study.[7] A weaker association with smoking in women has been indicated by some studies as well.[14,15,20] Earlier investigations have also shown a positive dose-response relationship with the years of smoking or the number of cigarettes,[7,8,11,12,14,18,20,21] and a negative association with the years of cessation of smoking.[12,18,21,22] The Framingham Study estimated that almost 50% of the cardiovascular risk caused by smoking was mediated through an increase in plasma fibrinogen levels.[20]

A negative association between exercise and fibrinogen levels was encountered in men. Some investigations have also shown an inverse association of fibrinogen levels with physical activity.[13,15,17,23] A study indicated that 6 months of intensive exercise training decreased plasma fibrinogen levels and suggested that habitual physical activity might reduce the risk of cardiovascular disease by the improvement of fibrinogen levels.[24]

The plasma fibrinogen concentration was positively associated with total cholesterol, and inversely related to HDL cholesterol, in accordance with earlier findings.[13.15–18] A positive relationship to HbA_{1c} in the present study is also consistent with previous studies showing a positive association with insulin or glucose levels.[13,16,18] The present findings coincided with earlier Japanese studies as well.[7,8,25] The present study showed that HDL cholesterol was an independent strong negative correlate of plasma fibrinogen. It is known that low levels of HDL cholesterol are an independent risk factor for coronary heart disease.[26–30] The Japan Lipid Intervention Trial study showed that each 10 mg/dl increase in HDL cholesterol concentration reduced the risk of coronary heart disease by 28.3%.[30] The risk of cardiovascular disease in persons with low HDL cholesterol might be affected through the elevation of plasma fibrinogen levels as well.

Inflammation has been recently acknowledged to play a fundamental role in developing atherosclerosis and its thrombotic complications in cardiovascular disease.[31,32] Plasma fibrinogen is an acute-phase inflammatory reactant as well as a clotting agent. The present multiple regression analysis has shown that plasma fibrinogen levels are closely correlated with cardiovascular risk factors even after adjusting for the CRP levels. Persons with cardiovascular risk factors tended to have higher fibrinogen levels, which suggests that elevated plasma fibrinogen in those with risk factors will further increase the risk for the development of atherothrombosis and subsequent cardiovascular diseases through the blood coagulation system. A recent Japanese study indicated that the relative risk for coronary heart disease was 4.8 in the highest fibrinogen quartiles (≥295 mg/dl) compared with the lowest (<228 mg/dl).[32] Modifying the risk factors or maintaining a healthy lifestyle, such as losing excess weight, not smoking, and taking regular exercise, can be a recommended way to reduce plasma fibrinogen levels and the risk of cardiovascular disease.

Acknowledgment The present study was supported by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

References

1. Ernst E, Resch KL (1993) Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Intern Med 118:956–963
2. Meade TW (1995) Fibrinogen in ischaemic heart disease. Eur Heart J 16 (suppl A):31–35
3. Danesh J, Collins R, Appleby P, Peto R (1998) Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 279:1477–1482
4. Maresca G, Blasio AD, Marchili R, Minno GD (1999) Measuring plasma fibrinogen to predict stroke and myocardial infarction, an update. Arterioscler Thromb Vasc Biol 19:1368–1377
5. Kullo IJ, Gau GT, Tajik AJ (2000) Novel risk factor for atherosclerosis. Mayo Clin Proc 75:369–380
6. Iso H, Folsom AR, Wu KK, Shimamoto T, Koike K, Iida M, Komachi Y (1993) Plasma fibrinogen and its correlates in Japanese and US population samples. Arterioscler Thromb 13:783–790
7. Sato S, Iso H, Naito Y, Kiyama M, Kitamura A, Iida M, Shimamoto T, Komachi Y (1996) Plasma fibrinogen and its correlates in urban Japanese men. Int J Epidemiol 25:521–527
8. Ishikawa S, Kario K, Nago N, Kayaba K, Hiraoka J, Matsuo H, Goto T, Miyamoto T, Tsutsumi A, Nakamura Y, Shimada K, Inoue K, Igarashi M (1997) Factor VII and fibrinogen levels examined by age, sex, and other atherosclerotic risk factors in a Japanese population; the Jichi Medical School Cohort Study. Thromb Haemost 77:890–893
9. Takahashi S, Imaki M, Yoshida Y, Ogawa Y, Tanada S (2000) A cross-sectional study on the relationship of plasma fibrinogen concentration and age, physical fitness, lifestyle and health examina-

tion of healthy Japanese males. Nippon Eiseigaku Zasshi 55:508–515
10. Meade TW, Charkrabarti R, Haines AP, North WR, Stirling V (1979) Characteristics affecting fibrinolytic activity and plasma fibrinogen concentrations. Br Med J 1:153–156
11. Balleisen L, Bailey J, Epping PH, Schulte H, van de Loo J (1985) Epidemiological study on factor VII, factor VIII and fibrinogen in an industrial population: I. Baseline data on the relation to age, gender, body-weight, smoking, alcohol, pill-using, and menopause. Thromb Haemost 54:475–479
12. Lee AJ, Smith WCS, Lowe GDO, Tunstall-Pedoe H (1990) Plasma fibrinogen and coronary risk factors: the Scottish Heart Healthy Study. J Clin Epidemiol 43:913–919
13. Folsom AR, Conlan MG, Davis CE, Wu KK, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators (1992) Relations between hemostasis variables and cardiovascular risk factors in middle-aged adults. Ann Epidemiol 2:481–494
14. Krobot K, Hense HW, Cremer P, Eberle E, Keil U (1992) Determinants of plasma fibrinogen: relation to body weight, wast-to-hip ratio, smoking, alcohol, age, and sex, resulting from the second MONICA Augsbury Survey 1989–1990. Arterioscler Thromb Vasc Biol 12:780–788
15. Dotevall A, Johansson S, Wihelmsen L (1994) Association between fibrinogen and other risk factors for cardiovascular disease in men and women results from the Göteborg MONICA Survey 1985. Ann Epidemiol 4:369–374
16. Stefanick ML, Legault C, Tracy RP, Howard G, Kessler CM, Lucas DL, Bush TL (1995) Distribution and correlates of plasma fibrinogen in middle-aged women, PEPI Study. Arterioscler Thromb 15:2085–2093
17. Scarabin PV, Aillaud MF, Amouyel P, Evans A, Luc G, Ferrières J, Arveiler D, Juhan-Vagie I (1998) Associations of fibrinogen, factor VII and PAI-1 with baseline findings among 10 500 male participants in a prospective study of myocardial infarction. The Prime Study. Thromb Haemost 80:749–756
18. Lam TH, Liu LJ, Janus ED, Bourke C, Hedley AJ (1999) The relationship between fibrinogen and other coronary heart disease risk factors in a Chinese population. Atherosclerosis 143:405–413
19. Meade TW, Haines AP, Imeson JD, Stirling Y, Thompson SG (1983) Menopausal status and haemostatic variables. Lancet I:22–24
20. Kannel WB, D'Agostino RB, Belanger AJ (1987) Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study. Am Heart J 113:1006–1010
21. Meade TW, Imeson J, Stirling Y (1987) Effects of changes in smoking and other characteristics on clotting factors and the risk of ischaemic heart disease. Lancet 31:986–988
22. Dobson AJ, Alexander HM, Heller RF, Lloyd DM (1991) How soon after quitting smoking does risk of heart attack decline? J Clin Epidemiol 44:1247–1253
23. Ernst E (1993) Regular exercise reduces fibrinogen levels: a review of longitudinal studies. Br J Sports Med 27:175–176
24. Stratton JR, Chandler WL, Schwartz RS, Cerqueira MD, Levy WC, Kahn SE, Larson VG, Cain KC, Beard JC, Abrass IB (1991) Effect of physical conditioning on fibrinolytic variables and fibrinogen in young and old healthy adults. Circulation 83:1692–1697
25. Kayaba K, Nago N, Miyamoto T, Mizooka M, Terada M, Kario K, Nakamura Y, Igarashi M (1998) Glycated hemoglobin levels and their correlation with atherosclerotic risk factors in a Japanese population – the Jichi Medical School Cohort Study 1993–1995. Jpn Circ J 62:261–266
26. Manninen V, Tenkanene L, Koskinen P, Huttunen JK, Mättäri M, Heinonen OP, Frick MH (1992) Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentration on coronary heart disease risk in the Helsinki Heart Study: implications of treatment. Circulation 85:37–45
27. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F (1997) Relation of high TG-low HDL cholesterol and LDL cholesterol to the incidence of ischemic heart disease. An 8-year follow-up in the Copenhagen Male Study. Arterioscler Thromb Vasc Biol 17:1114–1120
28. Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J (1999) Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. N Engl J Med 341:410–418
29. Després JP, Lemieux I, Dagenais GR, Cantin B, Lamarch B (2000) HDL cholesterol as a marker of coronary heart disease risk: the Québec Cardiovascular Study. Atherosclerosis 153:263–272
30. Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H. J-LIT study group of Japan Lipid Intervention Trial (2002) Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J 66:1096–1100
31. Ross R (1999) Atherosclerosis – an inflammatory disease. N Engl J Med 340:115–126
32. Libby P, Ridker PM, Maseri A (2002) Inflammation and atherosclerosis. Circulation 105:1135–1143
33. Sato S, Nakamura M, Iida M, Naito Y, Kimura A, Okamura T, Nakagawa Y, Imano H, Kiyama M, Iso H, Shimamoto T, Komachi Y (2000) Plasma fibrinogen and coronary heart disease in urban Japanese. Am J Epidemiol 152:420–423