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Fibrinogen and other coronary risk factors

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Abstract

The association between plasma fibrinogen concentration and other coronary risk factors diverged in previous studies, and the impact from complex lipoprotein patterns has not been studied. Our research involved 24 healthy subjects without coronary heart disease (control) and 22 patients who had survived having acute myocardial infarction before the age of 41 years (cases), overall 40 men and 6 women with age range of 34 to 54 years. In multiple linear regression analyses concerning control subjects, family disposition, social class, a score based on serum triglyceride and high-density lipoprotein (HDL) cholesterol concentrations, and fasting capillary blood glucose concentration were significantly associated with plasma fibrinogen concentration ($P < .00005$, $R^2 = 0.81$). For case subjects, the ratio between serum low-density lipoprotein cholesterol and high-density lipoprotein cholesterol concentrations was significantly associated with plasma fibrinogen concentration ($P = .0018$, $R^2 = 0.39$). Thus, for healthy subjects, 4 coronary risk factors explained three quarters of the variation of plasma fibrinogen concentration, and for patients with a previous acute myocardial infarction, another coronary risk factor explained one third of the variation. In conclusion, the pattern of coronary risk factors associated with plasma fibrinogen concentration differed between those without coronary heart disease and those with a previous acute myocardial infarction.

1. Introduction

Plasma fibrinogen concentration is considered to be a complementary coronary risk factor in the recent guidelines from the Third Joint European Societies' Task Force on Cardiovascular Disease Prevention in Clinical Practice [1]. In addition, recent studies stress the importance of plasma fibrinogen concentration as a coronary risk factor. Northern Ireland has more cases of coronary heart disease than France, and plasma fibrinogen concentration was associated with 30% of the excess risk of coronary heart disease in Northern Ireland, whereas only 25% was explained by a combination of other coronary risk factors [2]. A Danish case-control study of 28 coronary risk factors showed that plasma fibrinogen concentration was a significant coronary risk factor, in addition to smoking and serum low-density lipoprotein (LDL) cholesterol concentration [3].

Several other coronary risk factors are associated with plasma fibrinogen concentration [4-13], for example, age, social class, physical fitness, smoking, obesity measured as body mass index, abdominal obesity measured as waist-to-hip ratio, serum concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, triglyceride, insulin, and proinsulin. However, studies using multiple regression analyses showed inconsistent associa-

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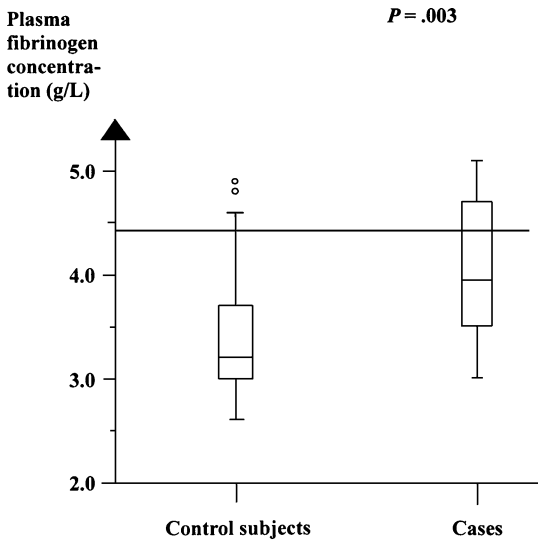

Fig. 1. Boxplot shows the plasma fibrinogen concentration for 24 control subjects and 22 case subjects. Boxes show the interquartile ranges (25% and 75%) and the median values (50%). The whiskers show the ranges (0% and 100%). The circles show the outlier values. The horizontal line shows the upper limit of reference range for plasma fibrinogen concentration. *P* value is calculated by Mann-Whitney *U* test.

tions as different subgroups and different covariates were evaluated based on a single large Swedish cohort [8,12,13].

Accordingly, we undertook an investigation based on the findings of a Danish case-control study of plasma fibrinogen concentration and 27 other coronary risk factors [3,14]. The aims of the present cross-sectional investigation were to evaluate whether these coronary risk factors had significant associations with plasma fibrinogen concentration and whether subjects with and without coronary heart disease differed with regard to significant associations.

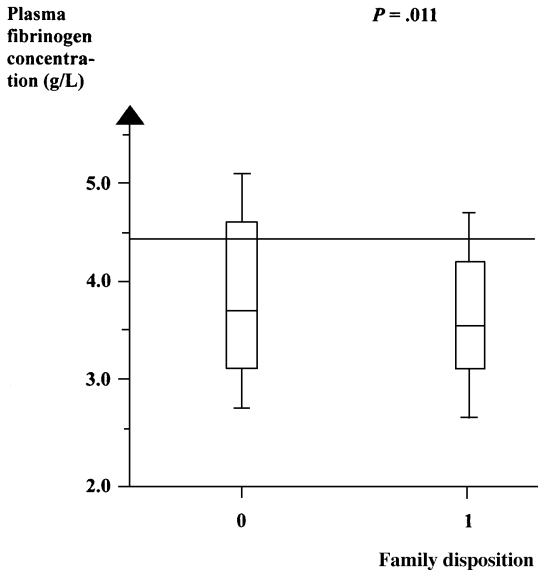

Fig. 2. Relation for 46 subjects between family disposition to acute myocardial infarction and plasma fibrinogen concentration. 0 indicates absence of family disposition; 1, presence. The horizontal line shows the upper limit of reference range for plasma fibrinogen concentration. *P* value shows the significance in univariate linear regression analyses.

2. Materials and methods

2.1. Subjects

Twenty-two cases were included among 77 patients who had been admitted to 4 hospitals in Jutland, Denmark, with acute myocardial infarction before the age of 41 years [3,14]. Twenty-four control subjects were selected of the 84 patients without coronary heart disease who had been treated for appendicitis or hernia at one of the hospitals. The 2 groups were matched for age and gender. The study included 40 men and 6 women. All 46 subjects underwent clinical

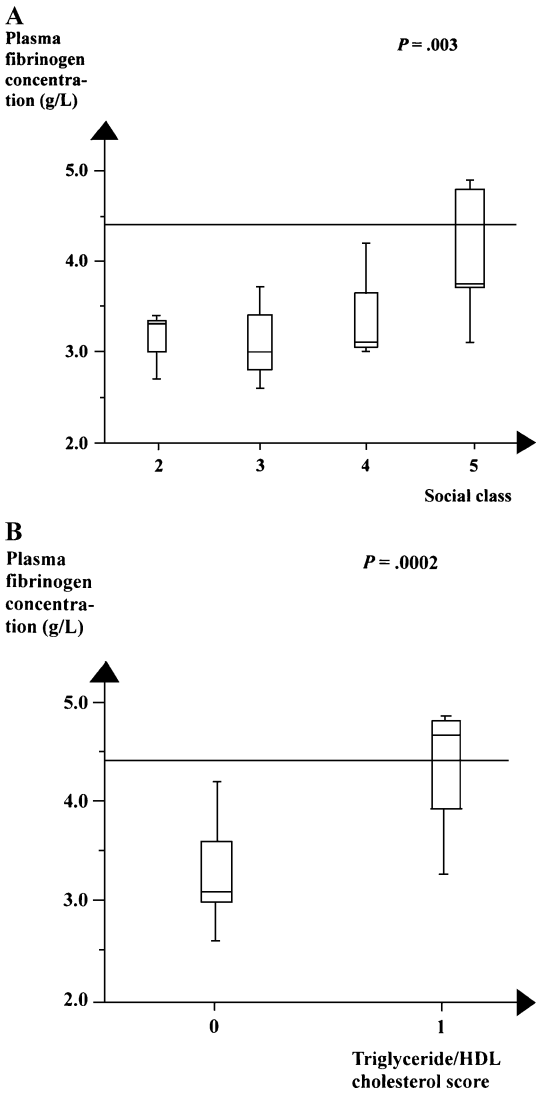

Fig. 3. The relation for 24 control subjects between coronary risk factors and plasma fibrinogen concentration. The horizontal line shows the upper limit of reference range for plasma fibrinogen concentration. *P* value shows the significance in univariate regression analyses. A, Boxplot for the relation between social class and plasma fibrinogen concentration. B, Boxplot for the relation between the triglyceride/HDL score and plasma fibrinogen concentration. 0 indicates negative score; 1, positive score.

Table 1
Multiple linear regression analyses concerning the association between plasma fibrinogen concentration and other coronary risk factors

Independent variables	Control subjects (n = 24)			Case subjects (n = 22)		
	Regression coefficient		*P*	Regression coefficient		*P*
	B	SE		*B*	SE	
Family disposition	−0.44	0.15	.011	–	–	–
Social class	0.24	0.060	.001	–	–	–
LDL/HDL cholesterol ratio	–	–	–	0.28	0.080	.002
Triglyceride/HDL cholesterol score	1.08	0.18	<.0005	–	–	–
Fasting capillary blood glucose concentration	0.53	0.17	.006	–	–	–

Only the 4 significant coronary risk factors for the control subjects and 1 significant coronary risk factor for the case subjects are shown. – indicates insignificant findings.

examinations for our study between April and August 1999. In 1999, the subjects were 34 to 54 years, all were in good health, and none of them had diabetes mellitus. Our examinations were carried out more than 2 years after the case subjects had been admitted for acute myocardial infarction and the control subjects for abdominal surgery.

All gave informed written consent. The study was done in accordance with the Helsinki II Declaration, and it was approved by the regional Science-Ethical Committee of Ringkoebing County and by the Danish Data Protection Agency.

2.2. Determinations of fibrinogen and other variables

Venous blood samples for measurements of fibrinogen were drawn between 8 to 10 AM after a 10-hour overnight fast. Blood was centrifuged at 1500*g* for 10 minutes before plasma was carefully pipetted off. Plasma fibrinogen concentration was measured immediately on a Cobas Fara instrument (Roche Diagnostics, Mannheim, Germany) by use of an immunoturbidimetric method and reagents from DAKO (DakoCytomation Denmark A/S, Glostrup, Denmark) according to the instructions of the manufacturer. The quality control of the assay used a calibrator of standardized human plasma from Dade Behring (Dade Behring Diagnostics GmbH, Marburg, Germany) as an external standard. The assay for plasma fibrinogen concentration had a reference interval of 2.0 to 4.4 g/L, a within-run coefficient of variation of 3.3%, and a day-to-day coefficient of variation of 5.1%.

Family disposition to acute myocardial infarction and social class were judged based on information stated in questionnaire forms. Family disposition was defined as parents, uncles, aunts, or siblings having acute myocardial infarction before 55 years. Social class was classified according to a classification by Svalastoga [15] as modified by Hansen [16]. Social class I included university graduates and self-employed with more than 20 employees and salaried employees with more than 50 subordinates; social class II included self-employed with 6 to 20 employees and salaried workers with 11 to 50 subordinates; social class III included self-employed with less than 6 employees and salaried employees with 1 to 10 subordinates; social class IV included salaried employees without subordinates and skilled manual workers; and social class V included unskilled manual workers, unemployed, and pensioners.

Serum concentrations of total cholesterol and triglyceride were measured with a Vitros 950 apparatus (Kodak Ektachem, Johnson & Johnson, Clinical Diagnostics, Inc, Rochester, NY). Serum HDL cholesterol concentration was measured with a Cobas Fara apparatus (Roche Diagnostics). We calculated serum LDL cholesterol concentration according to the Friedewall formula: serum LDL cholesterol concentration (mmol/L) = serum total cholesterol concentration (mmol/L) − serum HDL cholesterol concentration (mmol/L) − 1/2.2 × serum triglyceride concentration (mmol/L) [17]. Fasting capillary blood glucose concentration was measured using a HemoCue apparatus (Angelholm, Sweden) and a hexokinase method.

All subject were classified according to a score based on the serum triglyceride and HDL cholesterol concentrations [18]. The score was either positive—with serum triglyceride concentration within the upper tertile (>1.68 mmol/L)

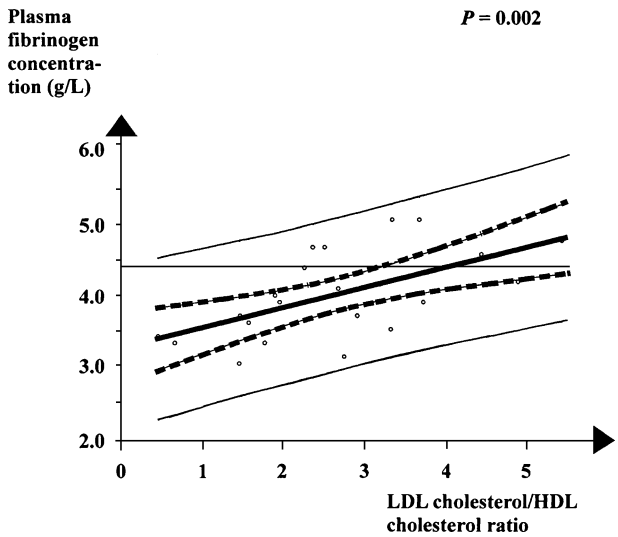

Fig. 4. Scatterplot for 22 case subjects concerning the relation between the LDL/HDL cholesterol ratio and plasma fibrinogen concentration. Bold line indicates the regression line according to linear regression analysis, the bold stippled lines show 95% confidence interval for the regression line, and the thin lines 95% confidence interval for the individual values. The horizontal line shows the upper limit of reference range for plasma fibrinogen concentration.

combined with serum HDL cholesterol concentration within the lower tertile (<1.16 mmol/L)—or negative. We also evaluated the ratio between the serum LDL cholesterol and HDL cholesterol concentrations and classified the subjects according to the metabolic syndrome as defined by the World Health Organization [19].

2.3. Statistical analyses

Statistical analyses were performed using Stata version 7.0 (Stata Corp, College Station, Tex). All univariate and multiple linear regression analyses were calculated using the stepwise function of Stata. The tests were 2-sided, and a P value <.05 was considered statistically significant.

3. Results

The median values and the ranges for plasma fibrinogen concentration and the 27 other coronary risk factors have been reported previously [3]. Fig. 1 shows that case subjects had significantly higher plasma fibrinogen concentration than control subjects.

Fig. 2 shows that all subjects—both control and cases—with a family disposition had lower plasma fibrinogen concentration than those without. For control subjects, as shown in Fig. 3A, plasma fibrinogen concentration increased from social classes II to V. Fig. 3B shows that control subjects with a positive triglyceride/HDL cholesterol score had a higher plasma fibrinogen concentration than those with a negative score.

Table 1 shows the findings in multiple linear regression analyses. For control subjects, family disposition, social class, triglyceride/HDL score, and fasting capillary blood glucose concentration were significantly associated with plasma fibrinogen concentration (final model: $P < .00005$, $R^2 = 0.81$). Other coronary risk factors were not significant, including body mass index, waist-to-hip ratio, body fat percentage, extent of intra-abdominal fat, systolic and diastolic blood pressure, plasma activity of von Willebrand factor ristocetin factor and plasminogen activator inhibitor 1, C-reactive protein concentration, glycosylated hemoglobin, HbA1c, and urinary albumin concentration. For control subjects, the final regression model had the equation:

$$\begin{aligned}\text{Plasma fibrinogen concentration (g/L)} &= -0.41 - (0.44 \times \text{family disposition}) \\ &\quad + (0.24 \times \text{social class}) \\ &\quad + (1.1 \times \text{triglyceride/HDL cholesterol score}) \\ &\quad + (0.53 \times \text{fasting capillary blood glucose concentration (mmol/L)}).\end{aligned}$$

In multiple linear regression analyses for case subjects, the LDL/HDL cholesterol ratio was significantly associated with plasma fibrinogen concentration (final model: $P = .0018$, $R^2 = 0.39$), whereas the other evaluated coronary risk factors were not significant. Fig. 4 shows that plasma fibrinogen concentration increased from 3.1 to 4.5 g/L with low to high LDL/HDL cholesterol ratios. For case subjects, the final regression model had the following equation:

$$\text{Plasma fibrinogen concentration (g/L)} = 3.24 + (0.29 \times \text{LDL/HDL cholesterol ratio}).$$

4. Discussion

For control subjects, 4 coronary risk factors had significant associations with plasma fibrinogen concentration: family disposition, social class, triglyceride/HDL cholesterol score, and fasting capillary blood glucose. In contrast for case subjects, LDL/HDL cholesterol ratio was significantly associated with plasma fibrinogen concentration.

The study design supports our findings. Our evaluations included all studied subjects and all measured coronary risk factors. The sample size was large enough to allow that multiple linear regression analyses gave a valid estimate of the association between plasma fibrinogen concentration and up to 4 independent variables [20]. There was no indication of lack of external and internal validity because our control and case subjects had similar distributions of major coronary risk factors as the control and case subjects in a previous Danish case-control study [21]. We examined all subjects according to the same protocol during the same period, without the investigator's knowledge of the subjects' status (whether control or case). Case subjects had a long time span between admissions for acute myocardial infarction and our clinical examinations, so had control subjects after the surgery for abdominal disorders. The long interval implies that an elevation of plasma fibrinogen concentration due to the acute phase of previous diseases was eliminated before the examinations in our study.

Our subjects with a family disposition to acute myocardial infarction had a lower plasma fibrinogen concentration than those without. In contrast, a larger study found a positive association between family history score and plasma fibrinogen concentration [22]. Similarly, there is a moderate heritability for plasma fibrinogen concentration [23].

Like our study, a study by Danish Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) investigators found that social class was significantly associated with plasma fibrinogen concentration [4,24]. Furthermore, this study showed that plasma fibrinogen concentration changed more with social class (positive relation) than did systolic and diastolic blood pressure, serum total cholesterol concentration (positive relations), and serum HDL cholesterol concentration (inverse relation) [24]. There was more increase for the plasma fibrinogen concentration in our control subjects between social classes II and V than there was for other coronary risk factors between social class I and IV in the Copenhagen Male Study [25,26]. Nevertheless, the trend with social class was not present in a Swedish

study [27]. The Copenhagen Male Study group has used the classification of social class in the analyses of coronary risk factors, and several publications showed that a low social class increased the risk of coronary events [4,24,25]. Accordingly, fibrinogen can be a biologic mediator between low social class and increased risk of coronary events [28]. Interleukin 6 (IL-6) can mediate the link between social class and plasma fibrinogen concentration. Stimulated by IL-6, hepatocytes produce fibrinogen [29].

Before our study, no investigation has pointed to a significant association between the triglyceride/HDL cholesterol score and plasma fibrinogen concentration. For our control subjects, the median plasma fibrinogen concentration increased from 3.1 to 5.3 g/L, with the change from a negative to a positive score. Similarly, another study showed a link between hypertriglyceridemia and hypercoagulation [30]. A positive score is equivalent to the dyslipidemia of the metabolic syndrome, and as expected from the definition of the World Health Organization for metabolic syndrome [19], our subjects had a significant link between a positive score and the metabolic syndrome ($P = .0009$, Mann-Whitney U test). In a previous cohort study, a positive score predicted cardiovascular events [18]. Thus, plasma fibrinogen concentration can be a biologic link between a positive score and the increased risk of coronary heart disease. Thereby, the metabolic syndrome can cause some of the increased coronary risk through plasma fibrinogen concentration. In previous analyses of our data, a high extent of intra-abdominal fat was associated with both a high serum triglyceride concentration and a low serum HDL cholesterol concentration [14]. Large intra-abdominal fat causes an increased level of IL-6 in the blood, and this can contribute to the associations. In another study, serum IL-6 correlated positively with fasting triglycerides and negatively with HDL cholesterol [31].

Our case subjects had a relatively strong association between LDL/HDL cholesterol ratio and plasma fibrinogen concentration. To our knowledge, an association of plasma fibrinogen concentration with LDL cholesterol has been described previously but not with the LDL/HDL cholesterol ratio. In our series, only the triglyceride/HDL cholesterol score for our control subjects had a larger impact on plasma fibrinogen concentration. These aspects are the reasons why our 2 study groups differed in the associations. A Canadian study showed that the ratio between serum LDL and HDL cholesterol concentrations predicted later coronary heart disease [32], whereas in logistic regression analyses of our case-control study, plasma fibrinogen concentration was a significant coronary risk factor independent of serum LDL cholesterol concentration [3].

Coronary risk factors contributed to 81% of the variation for plasma fibrinogen concentration of our control subjects and to 39% of the variation for our case subjects. Contrarily, in previous studies, other coronary risk factors accounted for only 10% to 32% of the variation [4,8,13]. For our control subjects, the significant coronary risk factors were associated with a larger change of plasma fibrinogen concentration than the coronary risk factors highlighted previously. Although many had acknowledged that smoking has an impact on plasma fibrinogen concentration [1,3], the significant coronary risk factors in our study had a larger impact on plasma fibrinogen concentration than had smoking, for both our healthy subjects and patients with previous acute myocardial infarction.

Combined, our previous investigations and present analyses suggest a complex network of relationship between a series of coronary risk factors. Thus, the full extent of risk for all coronary risk factors cannot be disclosed with the use of only logistic regression analyses.

Our study had several limitations. It included a small number of Danish, white, and middle-aged subjects, and it did not measure serum concentrations of insulin and proinsulin (elevated in connection with the metabolic syndrome), acute phase reactants such as orosomucoid and haptoglobin, fibrinogen degradation products (results of fibrinolysis), or IL-6. A polymorphism in the promoter for the β-fibrinogen gene has an influence on the plasma fibrinogen concentration [33-38], but we did not analyze these genetic aspects.

It is of interest that interventions for weight reduction and increased physical activity, known to reduce coronary risk, can reduce plasma fibrinogen concentration [39-41]. Studies based on increased serum concentrations of clotting factors should elucidate whether our findings can be reproduced in other and larger settings. It also remains to be shown for subjects followed over time whether the interindividual findings of our cross-sectional study can be extrapolated to describe intra-individual changes. Further studies are also warranted to investigate the biologic substrate (eg, adipocytokines) mediating the associations between coronary risk factors and plasma fibrinogen concentration.

In conclusion, for healthy subjects, 4 coronary risk factors explained three quarters of the variation of plasma fibrinogen concentration, and for patients with a previous acute myocardial infarction, another coronary risk factor explained one third of the variation. Those without coronary heart disease and those with a previous acute myocardial infarction differed regarding the pattern of coronary risk factors associated with plasma fibrinogen concentration.

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