Plasma Fibrinogen: A New Factor of the Metabolic Syndrome

A population-based study

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OBJECTIVE — To evaluate whether hyperfibrinogenemia represents a component of the metabolic syndrome.

RESEARCH DESIGN AND METHODS — A cross-sectional study was conducted on the relation between fibrinogen and the metabolic syndrome in a working population of 1,252 nondiabetic men, aged 35–64 years, randomly selected among all men participating in a health screening. We measured anthropometric characteristics, blood pressure, fasting plasma fibrinogen, cholesterol (total, LDL, and HDL), triglycerides, glucose, and insulin. Individuals with two or more metabolic abnormalities (defined as being in the highest quartile of the distribution of diastolic blood pressure, plasma glucose, or triglycerides or being in the lowest quartile of HDL cholesterol) were considered to have the metabolic syndrome.

RESULTS — Age-adjusted fibrinogen levels correlated significantly with BMI, waist-to-hip ratio, systolic and diastolic blood pressure, plasma total cholesterol, LDL cholesterol, triglycerides, insulin, and HDL cholesterol (inversely). Subjects with the metabolic syndrome had significantly higher plasma fibrinogen levels than those without (285.1 ± 1.9 vs. 300.2 ± 3.0 mg/dl, mean ± SE, $P = 0.0001$). Plasma fibrinogen concentrations and the prevalence of hyperfibrinogenemia (defined as ≥350 mg/dl) increased progressively from 279 to 307 mg/dl ($P = 0.0001$) and from 9 to 22% ($P = 0.0024$), respectively, across categories with an increasing number of metabolic disorders characterizing the syndrome (only one, any two, three or more). In multivariate analyses, both plasma insulin and the metabolic syndrome were significantly and independently associated with plasma fibrinogen.

CONCLUSIONS — The finding suggests that hyperfibrinogenemia may be considered a component of the metabolic syndrome. This may also explain the increased cardiovascular risk associated with hyperinsulinemia/insulin resistance.

Hyperinsulinemia, which almost always represents an adaptation to a status of impaired insulin action at its target sites (insulin resistance), is associated with several disorders grouped under the name of metabolic syndrome or syndrome X, which classically includes hyperglycemia, high triglyceride, low HDL cholesterol, and high blood pressure; obesity, particularly of the visceral type, is often, but not invariably, present (1,2). This cluster often leads to coronary heart disease.

During the last decade, findings from a number of cross-sectional and prospective epidemiological studies have demonstrated that high plasma fibrinogen levels represent an independent risk factor for coronary heart disease (3). Previous studies have also linked plasma fibrinogen with different expressions of the metabolic syndrome, namely type 2 diabetes, hypertriglyceridemia, hypertension, and hyperinsulinemia (4–10). However, most earlier studies have been done in small and highly selected study populations, such as people with clinically overt diabetes, hypertension, or evident coronary heart disease. Furthermore, few population-based studies have mainly focused on the relation of plasma fibrinogen with single metabolic abnormalities, and to our knowledge, no information is available on the relation of plasma fibrinogen with multiple metabolic abnormalities in healthy people. Therefore, it remains unknown whether, on a population basis, high plasma fibrinogen levels are associated with the clustering of disorders described in the metabolic syndrome.

The aim of this study is to assess, in a large, population-based sample of relatively young men, whether elevations of fibrinogen levels are associated with the cluster of disorders described in the metabolic syndrome and to evaluate whether hyperfibrinogenemia may be considered a component of this syndrome.

RESEARCH DESIGN AND METHODS

Subjects

The study population consisted of 2,580 male employees of the Italian Telephone Company, aged 35–64 years, participating in a company-sponsored health screening. Plasma insulin and fibrinogen were measured in a random subset of 1,512 men selected on the basis of their identification code using a computer-generated list of random digits. This group was similar to the total population in terms of age, BMI, lipids, glucose, insulin levels, blood pressure, and the other characteristics listed in Table 1.

Because elevation of fibrinogen levels secondary to atherosclerotic lesions has been described, subjects with evidence of coronary, cerebral, or peripheral arterial disease were excluded from the analyses ($n = 74$). Participants were considered to have cardiovascular disease if they presented one or more of the following conditions: positive history for myocardial infarction, angina, intermittent claudication, or cerebrovascular events (World Health Organization questionnaire) (11); electrocardiographic evidence of prior myocardial infarction or coronary ischemia as defined by the Minnesota codes 1.1, 1.2, 1.3, 4.1, 4.2, 4.3, 5.1, 5.2, 5.3, and 7.1 (12); ankle/brachial pres-

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Table 1—*Partial correlation coefficients between fibrinogen levels and study variables*

Variable	Plasma fibrinogen (mg/dl)	
	r	*P* value
Age (years)	0.2176	0.0001
BMI (kg/m²)	0.0869	0.0021
Waist-to-hip ratio	0.0550	0.0525
Systolic blood pressure (mmHg)	0.0676	0.0169
Diastolic blood pressure (mmHg)	0.0699	0.0134
Total cholesterol (mmol/l)	0.1483	0.0001
LDL cholesterol (mmol/l)	0.1556	0.0001
HDL cholesterol (mmol/l)	–0.1100	0.0001
Triglycerides (mmol/l)	0.1043	0.0002
Fasting plasma glucose (mmol/l)	0.0164	0.5621
Fasting plasma insulin (pmol/l)	0.0987	0.0012
Smoking	0.1296	0.0001

All variables (except age) were controlled for age. *n* = 1,252.

sure index <0.90; or previous vascular surgery or angioplasty at the level of coronary, carotid, or leg arteries.

Additional exclusion criteria were diabetes (defined as fasting plasma glucose ≥126 mg/dl and/or use of hypoglycemic drugs; *n* = 98) (13) and use of antihypertensive (*n* = 70) or lipid lowering drugs (*n* = 18). The study population therefore consisted of 1,252 normoglycemic men, free of clinically evident cardiovascular disease and not taking any drug known to influence fibrinogen levels.

Measurements and sampling procedures

Height, weight, and waist and hip circumferences were taken with subjects wearing light clothing and no shoes. Waist circumference was measured at the level of the umbilicus, and hip circumference was measured at the greater trochanters. The ratio of waist-to-hip circumference was used as an index of fat distribution. BMI was calculated as weight in kilograms (kg) divided by height in meters, squared (m²). Blood pressure was measured in the right arm, with the subject in the supine position after 10 min rest, by using a mercury sphygmomanometer of appropriate cuff size. Two measurements were taken—at the beginning and at the end of a complete medical examination—and the average value was used in the analyses. Smoking status was defined by three categories: current smoker (regularly or occasionally), ex-smoker (who had stopped smoking for at least 1 year before the examination), and nonsmoker.

After an overnight fast, between 8:00 and 9:00 A.M., venous blood was drawn into vacuum tubes (Sarsted) prefilled with EDTA. Tubes were centrifuged at room temperature for 15 min. After separation, plasma aliquots for fibrinogen and insulin measurements were frozen at −70°C and analyzed within 1 year's time. Glucose, total cholesterol, HDL cholesterol, and triglycerides were determined immediately in fresh plasma by dry chemistry methods using an Ektachem DT-60 analyzer (Eastman Kodak, Rochester, NY). LDL cholesterol was calculated by Friedewald's formula with the exception of subjects with plasma triglycerides above 400 mg/dl.

The use of dry chemistry method for large-scale screenings has been validated (14,15). In our hands, accuracy and reproducibility were monitored by daily determinations of all the above parameters on each of two reference sera (normal and high concentration). The accuracy was 4.2 for total cholesterol, 1.2 for HDL cholesterol, 3.6 for triglycerides, and 3.0% for glucose. Reproducibility as assessed by the calculation of the between-day coefficient of variation was 5.0 for total cholesterol, 6.3 for HDL cholesterol, 5.9 for triglycerides, and 3.6% for plasma glucose (16).

Plasma insulin concentrations were determined by radioimmunoassay with a double-antibody, solid-phase method (17). The detection limit was less than 1 mU/l. The intrassay and interassay coefficients of variation were 3.0 and 5.8%, respectively, at the level of 25 mU/l.

Plasma fibrinogen concentration was measured using an immunonephelometric method (18). There was no difference in fibrinogen concentration when samples collected in EDTA-containing tubes were compared with samples collected in vacuum tubes containing 0.13 mol/l of sodium citrate, the most common procedure for plasma collection in fibrinogen analysis, (*n* = 50; 288 ± 1.7 vs. 292 ± 1.8, mean ± SE, *P* = 0.11); furthermore, the correlation coefficient between the two sampling procedures was very high (*r* = 0.98). Intrassay and interassay coefficients of variation for fibrinogen were 2.0 and 3.8%, respectively, at a mean level of 250 mg/dl. To estimate if the duration of storage period at −70°C could have influenced fibrinogen concentration, we compared fibrinogen concentration of 50 samples stored for a period of 1 month, 50 samples stored for 8 months, and 50 samples stored for 14 months. There were no significant differences in mean fibrinogen concentrations between the three groups (analysis of variance, *F* = 2.005, NS).

The metabolic syndrome was defined as the clustering of two or more of the following: plasma triglycerides, glucose, or diastolic blood pressure in the highest quartile of the distribution of these variables in the study population, or HDL cholesterol in the lowest quartile of the distribution. Hyperfibrinogenemia was defined as plasma fibrinogen levels ≥350 mg/dl, in keeping with most previous studies which have demonstrated a definite increase in coronary heart disease risk at fibrinogen concentrations between 330 and 370 mg/dl (3).

Statistical analysis

Data are presented as mean ± SE for normally distributed variables, or as percentage for qualitative variables, or as geometric mean and mean ± SE computed on the log-transformed variable and converted to the original scale of measurement for log-normally distributed variables (triglycerides and fasting plasma insulin). Partial Spearman correlations, adjusted for age, were used to evaluate the association between study variables and fibrinogen levels. To assess whether there was an association between severity of the metabolic syndrome and fibrinogen, the study population was divided into subgroups according to the number of metabolic abnormalities (i.e., plasma triglycerides, glucose, or diastolic blood pressure in the highest, or HDL cholesterol in the lowest quartiles of the distribution). The prevalence of hyperfibrinogenemia was evaluated in participants with none, only one, any two, and three or more metabolic abnormalities.

Comparisons between groups were performed by analysis of variance, controlled for age by covariance analysis for continuous variables and by logistic regression analysis for categorical variables. In logistic regression analysis, indicator variables were used to represent the number of metabolic abnormalities present, and the group with no abnormalities was considered the reference category. Odds ratio and 95% CIs were calculated as described by

Table 2—*Clinical and metabolic characteristics of the study population by fibrinogen levels*

	Fibrinogen levels		
	<350 mg/dl	≥350 mg/dl	*P* value
n	1077	175	
Age (years)	44.2 ± 0.18	46.4 ± 0.52	0.0001*
BMI (kg/m²)	26.2 ± 0.09	26.8 ± 0.23	0.0238†
Waist-to-hip ratio	0.97 ± 0.002	0.98 ± 0.005	0.0232†
Blood pressure (mmHg)			
Systolic	134.4 ± 0.47	136.0 ± 1.17	0.2012†
Diastolic	86.4 ± 0.31	87.7 ± 0.77	0.1092†
Total cholesterol (mmol/l)	5.28 ± 0.030	5.44 ± 0.074	0.0518†
HDL cholesterol (mmol/l)	1.15 ± 0.009	1.09 ± 0.023	0.0122†
LDL cholesterol (mmol/l)	3.37 ± 0.029	3.55 ± 0.071	0.0265†
Triglycerides (mmol/l)	1.47 (1.45, 1.49)	1.57 (1.51, 1.62)	0.1001†
Fasting plasma glucose (mmol/l)	5.51 ± 0.017	5.58 ± 0.044	0.1472†
Fasting plasma insulin (pmol/l)	43.1 (42.5, 43.7)	47.7 (46.1, 49.4)	0.0055†
Smokers (%)	49.7	63.3	0.0010‡

Data are means ± SE for normally distributed variables, or % for qualitative variables, or geometric means and means ± SE computed on the log-transformed variable and converted to the original scale of measurement for log-normally distributed variables (triglycerides and fasting plasma insulin). **P* value from Student's *t* test. †*P* value from analysis of variance; the effect of age was controlled for by covariance analysis. ‡*P* value from logistic analysis controlled for age.

Kleinbaum et al. (19). Covariate-adjusted prevalence rates of hyperfibrinogenemia according to the number of metabolic alterations were calculated from logistic regression models by covariance adjustment of rates to mean values of covariate in the sample (20). Forward stepwise multiple regression with fibrinogen concentration as the dependent variable was used to identify significant predictors, and a selection threshold of $P < 0.05$ was used. All predictor variables were evaluated for interaction.

RESULTS — Mean age ± SE of the study participants was 44.5 ± 0.2 years, mean BMI was 26.3 ± 0.1 kg/m², and mean plasma fibrinogen concentration was 289.5 ± 1.7 mg/dl. Prevalence of overweight (BMI >25 kg/m²) was high (64%), as was the prevalence of current smoking (52%). Plasma fibrinogen levels were strongly correlated with age ($P = 0.0001$). After controlling for age, fibrinogen levels were significantly and positively correlated with smoking, BMI, waist-to-hip ratio, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol, triglyceride, and fasting insulin concentrations and negatively with HDL cholesterol concentration (Table 1).

Subjects with hyperfibrinogenemia had significantly higher BMI, waist-to-hip ratio, plasma total cholesterol, LDL cholesterol, and insulin and significantly lower HDL cholesterol than those without. The prevalence of smoking was significantly higher in subjects with hyperfibrinogenemia than in those without (Table 2).

To evaluate the relationship between plasma fibrinogen levels and the metabolic syndrome, as defined above, the study population was divided according to the presence or absence of the syndrome. Age-adjusted plasma fibrinogen levels were significantly higher in the group with metabolic syndrome than in the group without (Table 3). This difference was independent for smoking, which was equally frequent in the group with or without the metabolic syndrome (53.9 vs. 50.7%, $P = 0.36$) and was still significant after controlling for age, BMI, and LDL cholesterol (297.4 ± 3.1 vs. 286.4 ± 1.9, $P = 0.0029$, for with vs. without the metabolic syndrome).

Plasma fibrinogen levels as well as the proportion of participants with hyperfibrinogenemia were compared across categories of the number of metabolic abnormalities characterizing the syndrome (i.e., glucose, triglycerides, and diastolic blood pressure in the upper quartile or HDL cholesterol in the lower). Both plasma fibrinogen and prevalence of hyperfibrinogenemia, controlled for age, increased in a linear fashion according to the number of metabolic abnormalities present ($P = 0.0001$, $P = 0.0024$, respectively; Table 4). Plasma insulin levels also increased across these four categories with a linear trend (Table 4). These results did not change after controlling for age, smoking habits, LDL cholesterol concentrations, and BMI.

Stepwise multiple regression analysis, performed with fibrinogen level as the dependent variable and with age, BMI, LDL cholesterol, smoking, fasting insulin concentrations, and the presence of the metabolic syndrome as independent variables, showed a significant and independent association between the metabolic syndrome and fibrinogen levels ($P = 0.0001$). Age, smoking, LDL cholesterol, and fasting insulin concentrations were also positively and significantly related to fibrinogen levels (Table 5). However, only 10% of the variance in fibrinogen levels was explained by this model.

CONCLUSIONS — This study demonstrates in a fairly large, relatively young, working population that fibrinogen levels are significantly associated with the metabolic syndrome, defined as the combination

Table 3—*Clinical characteristics of the subjects with and without metabolic syndrome*

	Metabolic syndrome		
	Absent	Present	*P* value
n	895	357	
Age (years)	44.3 ± 0.201	45.0 ± 0.323	0.0717
BMI (kg/m²)	25.9 ± 0.098	27.4 ± 0.156	0.0001
Waist-to-hip ratio	0.97 ± 0.002	0.98 ± 0.003	0.0029
Fasting plasma insulin (pmol/l)	41.6 (41.0, 42.2)	49.5 (48.3, 50.7)	0.0001
Fibrinogen (mg/dl)	285.1 ± 1.916	300.5 ± 3.035	0.0001
LDL cholesterol (mmol/l)	3.36 ± 0.031	3.51 ± 0.050	0.0111
Smokers (%)	50.7	53.9	0.362

Data are means ± SE for normally distributed variables, or % for qualitative variables, or geometric means and means ± SE computed on the log-transformed variable and converted to the original scale of measurement for the log-normally distributed variable (fasting plasma insulin). All variables (except age) were controlled for age.

Table 4—*Insulin, fibrinogen, and prevalence of hyperfibrinogenemia and odds ratio by presence of metabolic abnormalities*

Metabolic abnormalities	*n*	Fasting plasma insulin (pmol/l)	Fibrinogen (mg/dl)	Prevalence of hyperfibrinogenemia (%)	Odds ratio	95% CI
0	433	38.7 (37.9, 39.5)	278.7 ± 2.74	9.1	1	—
1	461	44.1 (43.2, 45.0)	291.1 ± 2.66	14.7	1.8	1.2–27
2	270	48.3 (47.0, 49.6)	298.3 ± 3.47	16.6	2.0	1.3–3.2
≥3	88	55.1 (52.6, 57.8)	306.6 ± 6.08	22.2	2.8	1.5–5.3
		0.0001*	0.0001*	0.0024†		
		0.0001‡	0.0001‡	0.0003‡		

Data are means ± SE for fibrinogen concentration and % for hyperfibrinogenemia. For fasting plasma insulin, the geometric mean and the mean ± SE computed on the log-transformed fasting plasma insulin and converted to the original scale of measurement (in parentheses) are reported. **P* value from analysis of variance; the effect of age was controlled for by covariance analysis; †*P* value from logistic regression controlled for age; ‡*P* value for trend controlled for age.

of at least two of the following: high plasma glucose, triglycerides, blood pressure, and low HDL cholesterol. Both plasma fibrinogen levels and the prevalence of hyperfibrinogenemia increase in a linear fashion with the number of disorders characterizing the syndrome. These associations are independent of major confounders (age, smoking, plasma cholesterol, coexisting inflammatory diseases, and use of drugs). Unlike most other studies, the present study did not include people with clinically evident atherosclerotic vascular disease, which is related to both high fibrinogen levels and the metabolic factors under study; also excluded from the study were a number of people highly likely to have cardiovascular disease in the preclinical stage (i.e., men with diabetes or those taking antihypertensive or lipid-lowering drugs). So far, existing studies have mainly focused on the relationship of fibrinogen with clinically overt conditions such as hyperlipidemia, hypertension, and diabetes (4–8); in addition, the confounding role of cardiovascular disease, often associated with these conditions, has not always been taken into account. Population studies are few and have related fibrinogen to single metabolic abnormalities (8–10,21,22). However, for a group of conditions to be considered a syndrome, each factor should be related not only with single disorders, but with multiple disorders. To our knowledge, this is the first study to examine on a population basis the relationship between hyperfibrinogenemia and the clustering of metabolic abnormalities defined as syndrome X.

Insulin resistance and/or hyperinsulinemia have been suggested as the common link for the various metabolic abnormalities described in this syndrome. In agreement with what is reported for the other components of the metabolic syndrome, in this study hyperfibrinogenemia is significantly associated with high insulin levels in both univariate and multivariate analyses. Previous studies on this issue are contradictory. The Atherosclerosis Risk in Communities Study (21) reported that fibrinogen was associated with serum insulin concentrations in women but not in men. A study conducted on a relatively small sample of adult healthy men showed a significant and independent association between fibrinogen levels and fasting insulin (22). A weak relationship of insulin with fibrinogen levels was found in patients with angina after indexes of acute inflammation accompanying atherosclerosis (e.g., white blood cell count and C-reactive protein) were taken into account (7). In the Northern Sweden MONICA Study (23), fibrinogen levels were not related to insulin levels after adjustment for other risk factors. The inconsistency of the results might be accounted for by a number of methodological problems, including small sample sizes, selection criteria, and lack of control for the confounding effect of concomitant cardiovascular disease. In any case, the link between hyperfibrinogenemia and hyperinsulinemia is not fully elucidated; insulin resistance, a condition frequently underlining hyperinsulinemia, may be suggested as a possible pathogenetic link. Data on this topic are scarce, but fairly consistent: increases in fibrinogen levels were repeatedly found in the offspring of hypertensive subjects, who are often insulin resistant (4,6,24). In addition, the only study, to our knowledge, that has investigated the association between fibrinogen and insulin resistance, as evaluated by the euglycemic insulin clamp, reports a significant increase in fibrinogen in individuals with insulin resistance, in a group of 22 subjects, 11 of whom had mild untreated hypertension (25). Plasma insulin concentrations represent a reasonably good marker of insulin resistance in normoglycemic individuals (26). There are data indicating that the effect of insulin on plasma fibrinogen synthesis is inhibitory rather than stimulatory (27). Because insulin resistance is a condition of impaired insulin action at its target sites, it seems plausible to consider the rela-

Table 5—*Multivariate regression analysis: stepwise method*

Variable	Dependent variable: fibrinogen levels (mg/dl) B	SE	*P* value
Age	2.03622	0.2861	0.0001
LDL cholesterol	0.23129	0.0482	0.0001
Smoking	14.87011	3.4968	0.0001
Metabolic syndrome	11.21701	3.9797	0.0001
Fasting plasma insulin	23.80275	10.1859	0.0026
BMI	1.10739	0.6093	0.0694
R^2	0.10		

All variables are included in the model.

tionship between hyperinsulinemia and hyperfibrinogenemia found in this and in other studies to be an epiphenomenon of the condition of insulin resistance underlying hyperinsulinemia. The divergent effects of insulin and insulin resistance on plasma fibrinogen closely resemble those observed on triglyceride-rich lipoproteins. In fact, in epidemiological studies, hypertriglyceridemia is associated with hyperinsulinemia, but the true effect of insulin per se on plasma triglyceride-rich lipoprotein metabolism is inhibitory, because of its effect at the level of both synthesis and catabolism (28,29). Therefore, insulin resistance presumably represents a key pathogenetic factor of hyperfibrinogenemia as well as of hypertriglyceridemia, whereas hyperinsulinemia is very likely only a marker of insulin resistance and therefore only indirectly associated.

In this study, insulin levels were measured by a nonspecific assay. At variance with what is observed in diabetic patients, both absolute and relative concentrations of proinsulin-like molecules are low in nondiabetic people, making it improbable that these molecules confound interpretations based on nonspecific insulin assay. However, because intact proinsulin and proinsulin split products show relationships with a number of cardiovascular risk factors similar to or stronger than those of insulin (30), a potential confounding role of these molecules cannot be excluded.

Prevalence of smoking is high in our study population. Smoking is strongly associated with fibrinogen levels, and there is also evidence that smoking induces insulin resistance (31) Therefore, it might represent a confounding factor of the association between the metabolic syndrome and fibrinogen levels. This has been carefully ruled out in the analysis.

Cross-sectional studies do not permit definition of the time sequence of events and causal relations. Unfortunately, the few prospective analyses on the relation between hyperinsulinemia/insulin resistance and development of metabolic disorders have not included fibrinogen (32). The effects on fibrinogen concentration of behavioral interventions, such as restricting caloric intake and increasing physical activity, which are able to reduce insulin resistance, are still contradictory (33–38). In any case, the factors investigated in this study explain only a small percentage of the variation of fibrinogen levels, and this suggests that other determinants are at work.

In conclusion, this study demonstrates, in a large, unselected group of relatively young men, that high fibrinogen levels are consistently associated with the individual components of the metabolic syndrome and with their cluster, independent of major confounders. These observations nominate fibrinogen as a candidate of the hyperinsulinemia/insulin-resistance family. Because we have studied only Caucasian men, these data need to be confirmed in women and in other ethnic groups. The hyperfibrinogenemia linked to the presence of the metabolic syndrome is a tempting partial explanation for the association between insulin resistance and high cardiovascular risk. Furthermore, if a role for insulin resistance in hyperfibrinogenemia is confirmed, it would have implications for prevention, because insulin resistance is potentially amenable to correction, and modulation of hemostatic function is likely to be a potent complementary approach to the prevention of coronary heart disease.

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