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Plasma fibrinogen and wall thickness in carotid and femoral arteries: finding from the KIHD study

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Summary *Objective*: Previous epidemiologic studies have shown that high plasma fibrinogen concentration is associated with increased risk of cardiovascular events. However, there is less previous information about the impact of plasma fibrinogen on the severity of subclinical atherosclerosis in population samples. The purpose of this study was to test the association of plasma fibrinogen with the wall thickness of carotid and femoral arteries. *Design*: A sample of male participants in the 'Kuopio Ischaemic Heart Disease Risk Factor Study' (KIHD), aged 46–64, were examined in 1991–3 in a cross-sectional study. *Setting*: A study at the Research Institute of Public Health, University of Kuopio, Finland. *Subjects and methods*: For 1014 men, plasma fibrinogen was measured by fibrin clotting and the intima-media thickness (IMT) in distal common carotid arteries was assessed by high-resolution B-mode ultrasonography. *Results*: Variables with the strongest associations with plasma fibrinogen were cigarette-years, body fat percentage, exhaled carbon monoxide, t-PA antigen, age, serum apolipoprotein B, and waist to hip circumference ratio. The relative difference between the lowest and the highest fibrinogen quintile was 14% for unadjusted carotid IMT and 44% for femoral IMT. The respective differences for means adjusted for all the strongest risk factors for IMT, including smoking, were 8% for the carotid and 17% for the femoral IMT. *Conclusion*: Our data confirm previous findings indicating that the major non-genetic determinants of plasma fibrinogen are smoking and obesity and that elevated plasma fibrinogen levels are associated with increased arterial wall thickness in men. This association is stronger for femoral than common carotid arteries.

INTRODUCTION

Previous epidemiologic studies have shown that high plasma fibrinogen concentration is associated with an increased risk of cardiovascular events.[1–4] There is less previous information about the impact of plasma fibrinogen on the severity of subclinical atherosclerosis in population samples. However, a number of previous studies have observed a relationship between elevated plasma fibrinogen levels and the severity of atherosclerosis, assessed non-invasively.[5–14] Most of these studies concern carotid arteries and there are only a few earlier studies in which the impact of plasma fibrinogen has been compared between different arterial beds.[11]

Determinants of, and factors associating with, plasma fibrinogen have been studied in several population studies.[22–24] For example, cross-sectional studies have shown associations between smoking, coffee consumption, moderate exercise, and other dietary factors and fibrinogen levels. We have reported previously inverse associations between plasma fibrinogen levels and e.g. leisure-time physical activity[16] and four measures of socioeconomic status.[17] However, plasma fibrinogen levels are largely genetically determinated[25, 26] and, for this reason, environmental and behavioural factors can account for only a small fraction of the variability of plasma fibrinogen in population studies.

The purpose of this study was to investigate the determinants of plasma fibrinogen levels and to test the association of plasma fibrinogen with the wall thickness of carotid and femoral arteries in a random population sample of middle-aged men.

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SUBJECTS AND METHODS

Study population

The KIHD study is an ongoing, population-based study designed to investigate previously unestablished risk factors for carotid atherosclerosis, ischemic heart disease, mortality, and other outcomes among middle-aged men from the Kuopio region in Eastern Finland, an area of high coronary morbidity and mortality. A total of 2682 participants (82.9% of those eligible), aged 42, 48, 54, or 60 years, were enrolled in the study between March 1984 and December 1989. Follow-up examinations were conducted between March 1991 and December 1993 on those men who had undergone ultrasound examination of the right and left carotid arteries at baseline. A total of 1229 were eligible for the follow-up study; of these, 52 had died, were suffering severe illness, or had migrated away from the region, and 139 could not be contacted or refused to participate. Thus, the follow-up study included 1038 participants or 88.2% of those eligible. Average time to follow-up was 4.1 years (range = 2.3–5.2 years). Both plasma fibrinogen and the ultrasonographic measurements of arterial wall thickness were available for 1014 subjects.

Measurement of plasma fibrinogen

Plasma fibrinogen was determined in fresh samples with a coagulometer based on clotting of extra fibrin (Amelung KC4, Heinrich Amelung GmbH, Lemgo, Germany).

Assessment of atherosclerotic progression

High-resolution B-mode ultrasonography was used to image carotid arteries.[27] The protocol involved the scanning of the right and left common carotid artery (CCA), including the carotid sinus (bulb), as high up as possible. Images were focused on the posterior (far) wall. Ultrasonographic examinations were performed with the subject in the supine position. The ultrasound system used was Biosound Phase 2 equipped with the 8–10 MHz annular array probe. On the basis of wedge phantom studies, the precision in the measurement of distances between interfaces from video recordings of scannings was in the order of 0.03 mm.[28] The calibration of distance measurements was checked against an RMI 414B tissue phantom. Three observers carried out the scannings. They were trained for at least 6 months before the study. Relevant parts of the scannings were recorded by VCR.

The Data Translation DT 2861 video frame grabber installed in an 80486 microcomputer, interfaced to a Panasonic AG 7355 VCR, was used to digitize B-scan frames. The Prosound (University of Southern California, Los Angeles, CA) software with automated boundary detection were used to measure distances. The software is designed to automate tracking of the lumen/intima and media/adventitia interfaces with an advanced algorithm specially designed for ultrasound images.[29]

The IMT of the posterior wall was measured as the distance from the leading edge of the first echogenic (bright) line to the leading edge of the second echogenic line, as explained earlier in detail.[30] Near wall measurements were not done because of their greater measurement variability.[31]

On average 100 IMT measurements were carried out in the distal 1.0–1.5 cm of both the right and the left common carotid artery below the carotid bulb. From these measurements, the following two outcome variables were constructed: 1. the mean of all IMT measurements, averaged over the right and the left CCA; and 2. the mean of two maximum IMT measurements, one from the right and another from the left CCA.

RESULTS

Variables that had the strongest associations with plasma fibrinogen concentration in a linear step-up regression model were cigarette-years, body fat percentage, exhaled carbon monoxide, t-PA antigen, age, serum apolipoprotein B, waist to hip circumference ratio, cholesterol lowering drugs, frequency of drunkenness, and apolipoprotein E4 allele including phenotype, and inversely plasma retinol, oxidation resistance of VLDL+LDL, serum HDL cholesterol, and the ratio of serum polyunsaturated and monounsaturated fatty acids to saturated fatty acids (Table 1). This model including 14 variables accounted for 25.7% of the variation of plasma fibrinogen.

The strongest determinants of the mean and maximal common carotid and femoral intima-media thickness in linear step-up regression models are presented in Table 2.

Table 1 Determinants of plasma fibrinogen concentration

Variable	Standardized regression coefficient	P-value
Cigarette-years	.18	<.0001
Body fat percentage	.15	<.0001
Exhaled carbon monoxide	.15	<.0001
t-PA antigen	.14	<.0001
Age	.13	<.0001
Apolipoprotein B	.11	.0074
Waist/hip circumf.	.10	.0007
Plasma retinol	−.10	.0028
Oxidation resistance of VLDL+LDL	−.07	.0117
Apolipoprotein A1	−.07	.0228
Cholesterol lowering drugs	.07	.0146
Serum P+M/SAFA	−.07	.0235
Frequency of drunkenness	.06	.0434
ApoE4 phenotype	.06	.0432
R squared	.257	<.0001

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Table 2 The strongest risk factors for mean and maximal carotid and femoral intima-media thickness

Risk factor	Mean carotid	Max carotid	Mean femoral	Max femoral	Mean of max carotid and femoral
Age (years)	.33	.29	.27	.28	.30
Cigarette-years	.13	.12	.21	.18	.21
Plasma fibrinogen		.13	.13	.12	
Apolipoprotein B	.08	.07	.09	.13	.10
Antihypertensive medication		.04	.10	.11	.10
Apolipoprotein A1	−.05	−.06	−.07	−.07	−.09
LDL cholesterol	.14	.13			.07
R squared	.24	.21	.27	.27	.33

Age was the single strongest risk factor for all IMT measurements. Of other variables entered, systolic blood pressure, cigarette-years, serum apolipoprotein B, and apolipoprotein AI (inversely) had the strongest associations with both the mean and maximal common carotid IMT (Table 2). The mean and maximal femoral IMT were predicted the strongest, in addition to age, cigarette-years, plasma fibrinogen, serum apolipoprotein B, antihypertensive medication, apolipoprotein AI (inversely), and serum LDL cholesterol. Neither systolic nor diastolic blood pressure had any association with the femoral IMT measurements. The models explained 21–24% of the variability for the carotids and 27% for the femoral measurements. Eight variables accounted for 33% of the variability of the mean of the maximal carotid and maximal femoral IMT (Table 2).

Figures 1 and 2 present the average maximal common carotid (Fig. 1) and femoral (Fig. 2) IMT in the fifths of plasma fibrinogen concentration, both when unadjusted and when adjusted for either age, examination years, time of blood sampling, sonographer, antihypertensive medication (yes vs. no), systolic blood pressure (mmHg), serum apolipoprotein B and AI concentrations, and body fat percentage, or, additionally, for cigarette-years and exhaled carbon monoxide. In this analysis, plasma fibrinogen was associated also with the maximal common carotid IMT although the association was weaker than for femoral IMT. The relative difference between the lowest

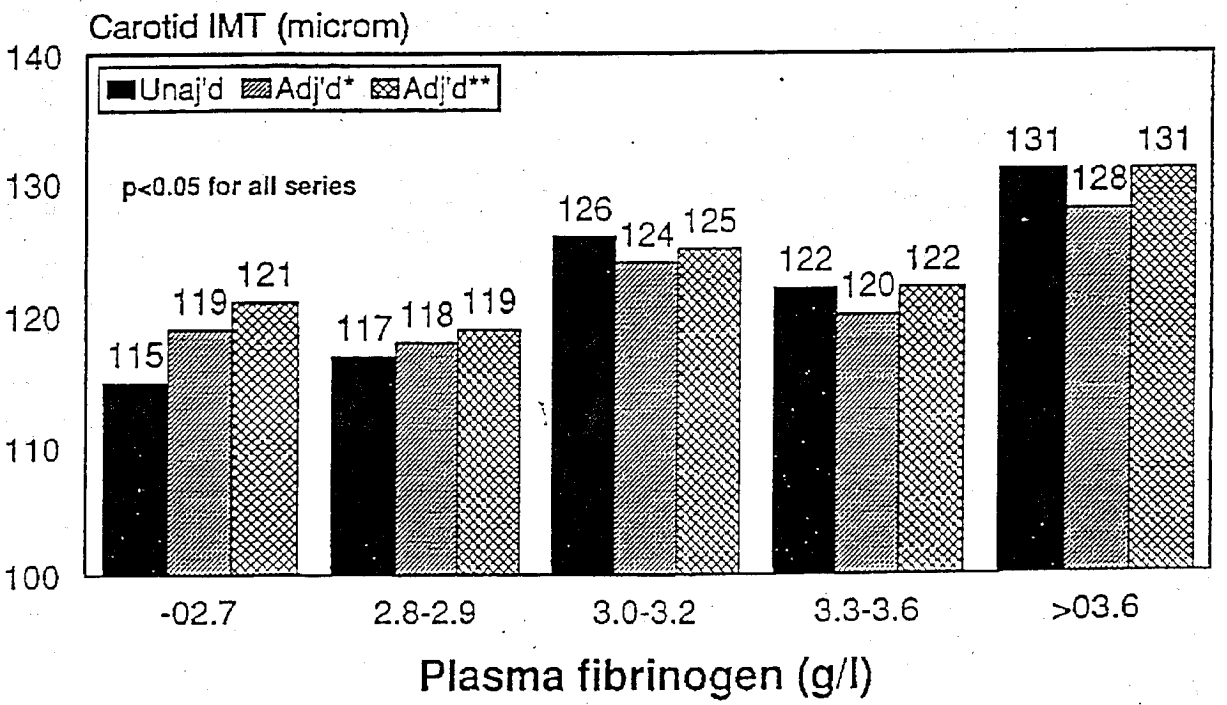

Fig. 1 Average maximal carotid intima-media thickness in fifths of plasma fibrinogen. *Adjusted for age, exam years, time of blood sampling, sonographer, AHT drugs, systolic BP, Apo B, Apo AI, fat %. **Also for cigarette years and exhaled CO.

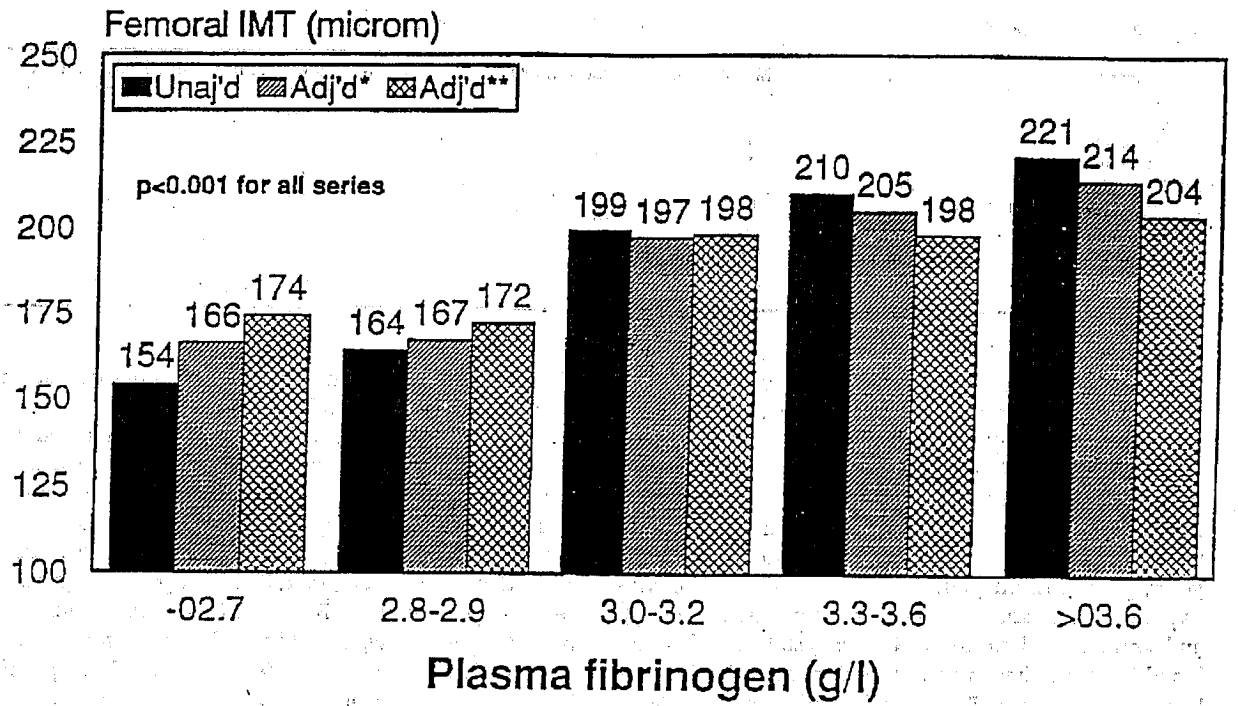

Fig. 2 Average maximal femoral intima-media thickness in fifths of plasma fibrinogen. *Adjusted for age, exam years, time of blood sampling, sonographer, AHT drugs, systolic BP, Apo B, Apo AI, fat %. **Also for cigarette-years and exhaled CO.

and the highest fibrinogen quintile was 14% for the carotid and 44% for the femoral, unadjusted IMT. The respective differences for means adjusted for the second set of covariates (including smoking) were 8% for the carotid and 17% for the femoral IMT (Figs 1, 2). Not surprisingly, smoking-related variables accounted for a large proportion of the relationship between plasma fibrinogen and arterial wall thickness, and possibly more so for the femoral than the carotid arteries. However, plasma fibrinogen had a highly significant association with the femoral IMT both among smokers and non-smokers (Fig. 3).

DISCUSSION

The findings of this study confirm the role of tobacco smoking as by far the strongest non-genetic biological determinant of plasma fibrinogen levels in tobacco-smoking male populations. Two indicators of smoking: the life-time exposure to smoking, as estimated as the product of the years smoked and the number of cigarettes smoked daily currently, and a measure of very recent smoking, the amount of carbon monoxide in the exhaled air, were among the strongest associates of plasma fibrinogen. Both the body fat percentage, estimated by an infrared method, and a measure of central obesity, the waist to hip circumference ratio, were also among the strongest determinants of plasma fibrinogen. This is in agreement with a number of previous observations about the relationship between obesity and plasma fibrinogen.

Our results concerning the risk factors for the common carotid and femoral wall thickness are also mainly confirmatory of previous reports. We have reported previously from two different and independent study populations that while the systolic blood pressure has a strong and consistent association with the common carotid wall thickness, smoking-related measurements are more strongly associated with the thickness of femoral artery wall.[11, 32] This finding has been now confirmed in several cross-sectional population studies using non-invasive methods to image atherosclerotic severity. This finding has relevance both with regard to the selection of outcome variables in clinical trials concerning the prevention of atherosclerotic progression and with regard to recommendations for the public regarding the prevention of atherosclerotic disease in these arterial beds.

The extent to which the associations between plasma fibrinogen and arterial wall thickness reflect the role of coagulation or inflammation in the pathophysiology of early atherogenesis cannot be addressed here. Also, an elevated plasma fibrinogen can be regarded as a simple

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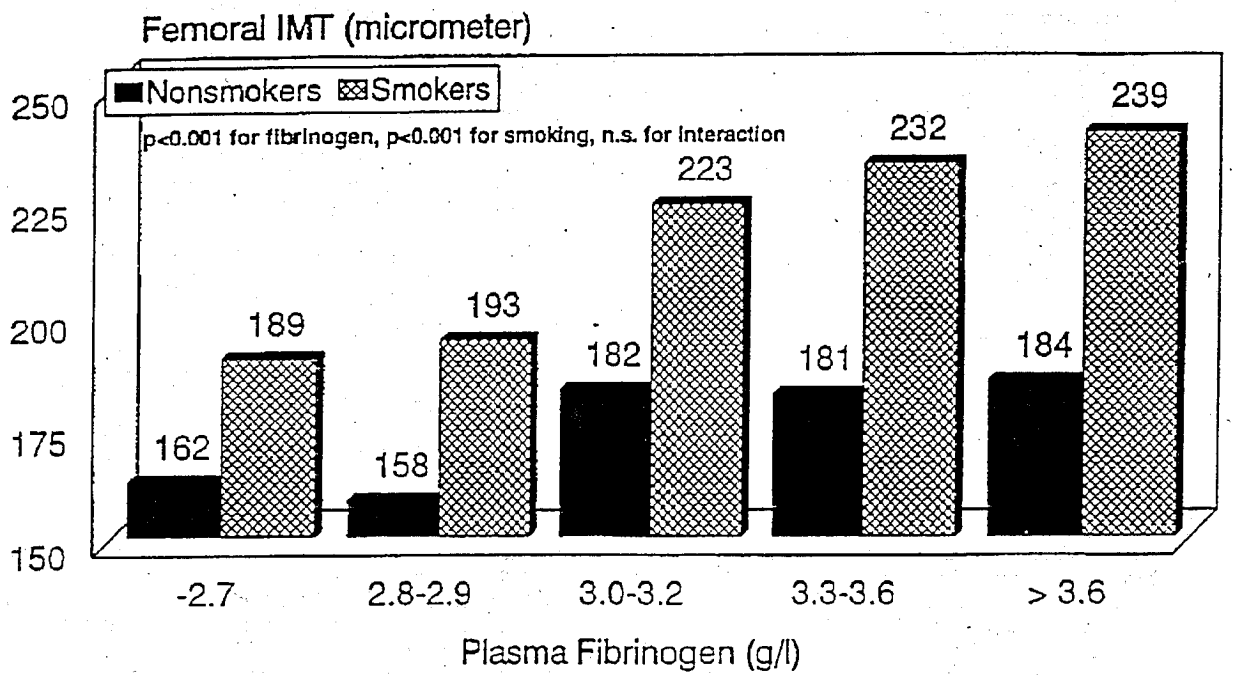

Fig. 3 Average maximal femoral IMT by plasma fibrinogen and smoking status. Adjusted for age, exam years, sonographer, Apo B, Apo AI, systolic BP, antihypertensive medication, and place of residence.

marker for an on-going atherosclerotic process. As a risk factor, it is very proximal in the chain of causation and this is why its strong association with both the severity of early atherosclerosis and cardiovascular events is expectable. Either way, plasma fibrinogen is a useful marker for early atherogenesis and cardiovascular disease.

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