Plasma Fibrinogen and Its Correlates in Children from a Biracial Community: The Bogalusa Heart Study

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ABSTRACT. Fibrinogen levels were measured in 5- to 17-y-old children ($n = 3047$; 40% black and 49% female), from a well-defined biracial community. No significant race and sex differences in fibrinogen levels were observed, but levels increased ($p < 0.001$) with age or sexual maturation in black females. Adjusted for age, fibrinogen concentrations were positively correlated with ponderal index (weight/height³) (0.09–0.22, $p < 0.01$), triceps skinfold thickness (0.10–0.23, $p < 0.05$), and subscapular skinfold thickness (0.13–0.24, $p < 0.01$) in all race-sex groups. Weak correlations were found between fibrinogen level and blood pressure and lipoprotein components for some of the race-sex groups, but these become nonsignificant or minimal after adjustment for ponderal index and skinfolds. A positive correlation (0.12–0.16, $p < 0.01$) was found between fibrinogen and white blood cell count for Caucasians, which still held after adjustment for ponderal index and skinfolds. In a stepwise regression, ponderal index, white blood cell count, and HDL cholesterol showed an independent association with fibrinogen. (*Pediatr Res* 33: 323–326, 1993)

Abbreviations

WBC, white blood cell count

Fibrinogen levels, involved in both blood clotting and the rheologic characteristic of blood flow (1–5), have been proposed as a cardiovascular risk factor variable; numerous studies (6–12) have shown a positive relationship between coronary heart disease and elevated fibrinogen levels. It has also been suggested (6, 13, 14) that fibrinogen deposition may be one of the mechanisms leading to coronary atherosclerosis and coronary occlusion.

Although the relationships of fibrinogen to other coronary heart disease risk factors have been studied extensively in adults, information on children is limited. Observations from the Bogalusa Heart Study show that coronary atherosclerosis has a childhood onset (15, 16). Racial (black-Caucasian) differences in cardiovascular risk factor variables also occur in children. The objective of this study is to describe the distribution of plasma fibrinogen levels in children and to examine the association of fibrinogen with other cardiovascular risk factor variables.

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MATERIALS AND METHODS

Population. The study population is made up of children from Bogalusa, Louisiana, a semirural, biracial (36% black, 64% Caucasian) community and surroundings with a defined population of approximately 22 000 people. Demographic, health history, anthropometric, blood pressure, serum lipids and lipoproteins, nutrition, and biobehavior data were collected at various intervals from this population. During 1987–1988, a cross-sectional survey of children aged 5–17 y was conducted in which 3047 children, 40% black and 49% female, had fibrinogen levels measured. It was reported that 2610 of these individuals were fasted before screening.

General examinations. The details of the various aspects of the overall cardiovascular risk factor screening have been described previously (15, 16). In summary, this screening included a complete physical examination, anthropometric measurements, blood pressure determinations, estimation of sexual maturity with the Tanner Scale, and blood samples.

A health habits questionnaire was administered to obtain information including cigarette smoking (for subjects in the 3rd grade or higher), alcohol consumption (for subjects in the 7th grade or higher), and oral contraceptive use by females (for those in the 7th grade or higher). A subject was classified as a smoker or a drinker if he or she was an adopter or experimenter (17). During the survey, 2043 subjects completed (answered "yes" or "no") the questions for smoking, 2039 completed those for drinking, and 551 females completed those for oral contraceptive pill use.

A questionnaire for the presence of parental history of cardiovascular disease such as myocardial infarction, stroke, and diabetes mellitus was also obtained from parents of the study subjects.

Laboratory procedure. Hematologic data were determined using a Technicon H6000 (Technicon Instrument Corp., Tarrytown, NY). Plasma fibrinogen levels were determined using a method described by Swaim and Feders (18), a modification of the Jacobsson procedure (19). Serum total cholesterol and triglycerides were measured with a Technicon Auto Analyzer II (Technicon Instrument Corp.) according to the protocol developed by the Lipid Research Clinics Program (20). Serum VLDL, LDL, and HDL cholesterol fractions were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures (21).

Statistical analyses. The mean and standard error of fibrinogen were calculated for each age-, race-, and sex-specific group. Age or sexual maturation, race, and sex differences were studied in an analysis of covariance after examining the interactions. The effect of age or sexual maturation was also studied for each race-sex group. The association of fibrinogen and obesity, blood pressure, or lipoprotein components were then inspected through Spearman correlation coefficients by race and sex adjusted for

age. Fibrinogen levels were also compared between cigarette smokers and nonsmokers, alcohol users and nonusers, and oral contraceptive users and nonusers (females only), as well as between subjects with or without parental history of myocardial infarction, stroke, or diabetes mellitus. A stepwise regression was applied to determine the relative importance of the risk factor variables on fibrinogen concentration. Predictive variables were further examined through presenting levels for each quintile of fibrinogen. An increasing or decreasing linear trend was tested, adjusting for age and ponderal index (for blood pressure and lipoprotein cholesterol).

RESULTS

Fibrinogen levels. The mean and standard error are given in Table 1 for each age-race-sex group. Mean fibrinogen levels were compared between race and sex groups with and without controlling for age. No significant race or sex difference was found. Fibrinogen was found to increase significantly with age ($r = 0.17$, $p = 0.0001$) or Tanner stage ($r = 0.18$, $p < 0.001$) in black females only.

Correlations between fibrinogen levels and other cardiovascular risk factor variables. Figure 1 shows age-adjusted Spearman correlation coefficients between fibrinogen concentration and selected cardiovascular risk factor variables for each race-sex group. A positive correlation was observed between fibrinogen concentration and ponderal index (0.09–0.22), triceps skinfolds (0.10–0.23), and subscapular skinfolds (0.13–0.24) in all race-sex groups. This correlation tended to be stronger in magnitude for Caucasian females. For some race-sex groups, positive correlation also existed between fibrinogen and blood pressure, LDL cholesterol, and VLDL cholesterol. These correlations were low in magnitude (0.07–0.15) and became nonsignificant or minimally significant after adjustment for ponderal index and skinfolds. Similar observations apply to the negative correlation between fibrinogen and HDL cholesterol. Fibrinogen correlated positively with the WBC (0.12–0.16) in females of both races and Caucasian males. This correlation still held after the adjustment for ponderal index and skinfolds.

Fibrinogen level was compared between cigarette smokers and nonsmokers, alcohol users and nonusers, and female oral contraceptive users and nonusers, as well as children with or without a positive parental history of myocardial infarction, stroke, or diabetes mellitus. No significant difference was found.

Relative predictability of these risk factor variables for fibrinogen was assessed in a stepwise multivariate regression. Independent variables used were height, ponderal index, systolic and diastolic blood pressure, VLDL cholesterol, LDL cholesterol, HDL cholesterol, WBC, cigarette smoking, alcohol use, and oral contraceptive use in girls. Significant predictors by each race-sex group are listed in Table 2. Generally, ponderal index, WBC, and HDL cholesterol had a stronger independent association with fibrinogen. However, variability explained by these independent variables only ranges from 3 to 9%.

To detail the association between fibrinogen level and its predictive risk factors, Figure 2 provides the risk factor levels for each age group-specific quintile of fibrinogen. It is seen that ponderal index had a precipitous rise over the upper 40% rank-

ings of fibrinogen. The linear trend of increase is significant ($p \leq 0.001$) for all the race-sex groups.

HDL cholesterol decreased in Caucasian males ($p \leq 0.01$), Caucasian females ($p = 0.0001$), and black females ($p \leq 0.001$). Except for the lowest quintile of fibrinogen, WBC levels increased for males ($p < 0.05$) and Caucasian females ($p < 0.01$).

It is observed from Figure 2 that children with the highest fibrinogen concentration (5th quintile) were more likely to show increases in other risk factors. Further analysis also showed this group to have a significantly higher prevalence of positive parental history for maternal diabetes mellitus (7.6 versus 5.4%) and paternal hypertension (23.4 versus 17.9%).

DISCUSSION

This study demonstrated an interesting and consistent increase in fibrinogen levels with ponderal index and skinfolds in children. Also found were some positive associations of fibrinogen level with blood pressure, VLDL cholesterol, LDL cholesterol, and WBC and a negative association with HDL cholesterol. The positive correlations with obesity and WBC and negative association with HDL cholesterol were stronger than with other risk factors. The magnitudes of these correlations were generally low, as found in adult studies (13, 22, 14) (approximately 0.1–0.2); however, these may not mean that fibrinogen is less predictive of cardiovascular disease than other risk factors (23, 24). Fibrinogen values did not differ essentially between blacks and Caucasians or males and females in our study, although an increase in levels with age or sexual maturation was noted in black females. In a large four-community study involving 12 000 men and women aged 45–64 y, Folsom *et al.* (22) found that fibrinogen levels are higher in blacks than Caucasians and higher in females than males. Our current study suggests that fibrinogen increases earlier or to a greater extent for black females which results in the highest adulthood level seen in black females.

Epidemiologic studies in adults (13, 14, 22, 23) have shown the association between fibrinogen concentration and obesity, blood pressure, lipoprotein cholesterol, and WBC. The correlations were generally less than 0.3 and explained 10 to 20% of the variability of fibrinogen level. Our observation confirmed that similar associations also occur in children and adolescents. Among the risk factors selected, obesity index, WBC, and HDL cholesterol contributed significantly toward the prediction of fibrinogen level. Numerous indices reflecting obesity exist in the literature. Derived from weight and height, ponderal index (weight/height³) instead of quetelet index (weight/height²) was reported in the current study. For children, ponderal index is more independent of height than quetelet index ($r = -0.10$ versus $r = 0.66$), and it reflects both subscapular (central) and triceps (peripheral) skinfolds ($r = 0.56, 0.62$) in the current data. It is of interest to see that even though ponderal index and subscapular and triceps skinfold thickness reflect somewhat different aspects of obesity their associations with fibrinogen were similar.

An increase by age in fibrinogen has been shown for adults (14, 22, 24–27). As reported by Lee *et al.* (14), based on 8824 subjects aged 40 to 60 y, older people had higher fibrinogen levels compared with younger people. In children, which we studied, this relationship to aging was only present for black

Table 1. Fibrinogen levels (g/L) by age, race, and sex: the Bogalusa Heart Study

Race-sex group	Age 5–9 y		Age 10–13 y		Age 14–17 y	
	<i>n</i>	Mean (SE)	<i>n</i>	Mean (SE)	<i>n</i>	Mean (SE)
Caucasian males	422	2.58 (0.04)	301	2.69 (0.05)	223	2.63 (0.05)
Caucasian females	372	2.60 (0.04)	304	2.68 (0.04)	210	2.65 (0.06)
Black males	246	2.64 (0.05)	213	2.64 (0.05)	163	2.61 (0.06)
Black females*	239	2.40 (0.06)	194	2.71 (0.05)	160	2.81 (0.07)

* Fibrinogen levels increased with age ($p = 0.0001$).

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$

Fig. 1. Age-adjusted race- and sex-specific Spearman correlation between fibrinogen concentration and height (HT), ponderal index (PI = weight/height³), subscapular skinfold thickness (SSF), systolic and diastolic blood pressure (SYS and DIAS), LDL, VLDL, and HDL cholesterol (LDLC, VLDLC, and HDLC), and WBC from the Bogalusa Heart Study.

Table 2. Significant predictors of fibrinogen by race and sex: the Bogalusa Heart Study*

	Caucasian males (n = 905)	Caucasian females (n = 851)	Black males (n = 597)	Black females (n = 567)
	PI -HDL-C WBC	PI WBC Height LDL-C	PI WBC	Height PI -HDL-C
R ²	0.0416	0.0903	0.0296	0.076

* PI, ponderal index (weight/height³); HDL-C, HDL cholesterol; LDL-C, LDL cholesterol.

females. Comparison of mean levels across different studies is often difficult because of the methodologic differences. Similarly, for males and females, children's fibrinogen levels in the current study were lower than the adults' levels in the Framingham Study (11) (2.8–3.1 g/L for adults aged 47–79 y) or the four-community study (22) (2.9–3.4 g/L) but higher than the adults' levels in the Scottish Heart Study (14) (2.2–2.5 g/L for adults aged 40–59 y). Some of these differences may be due to genetic factors (28).

Several studies (14, 22, 29–31) demonstrated in adults that fibrinogen increases in smokers and decreases in drinkers. The relationships between fibrinogen and cigarette smoking or alcohol consumption were not seen in this study. Only a tendency of increased fibrinogen level was noted with smokers. A positive relationship between cigarette smoking and WBC and platelets was found in the Oslo Youth Study (32). The lack of significant associations between these risk factors and fibrinogen levels may be due to the low statistical power or to a shorter duration and lower intensity of smoking and alcohol consumption in childhood versus adulthood. This lack of statistical power may also result in no consistent association between levels of fibrinogen and oral contraceptive use.

Sugrue *et al.* (33) observed elevated fibrinogen levels in subjects with familial history of myocardial infarction, whereas others (34) did not confirm such a finding. In our study, no significant association was observed. The relationship between fibrinogen

Fig. 2. Selected risk factor levels for age-group-specific quintiles of fibrinogen by race and sex. With fibrinogen level increased, ponderal index and WBC increased with an accelerating rate ($p \leq 0.001$) and HDL cholesterol decreased ($p \leq 0.01$) except for in black males. The p values are the significance levels of linear trends. Ponderal index was compared after adjusting for age; WBC and HDL cholesterol were compared after adjusting for age and ponderal index.

and parental diabetes mellitus, as suggested by others (35, 36), was only found in children with the highest fibrinogen concentrations; the same was true of the relationship between fibrinogen and parental hypertension. The lack of significance may be due to the age of the parents, which was younger than the age at which clinical disease is manifest. Although family history is only a surrogate measure of cardiovascular disease, there may be important genetic and environmental implications underlying the familial aggregation of a high risk profile.

Unlike in adults, in children the relationship of fibrinogen levels to myocardial infarction, stroke, and peripheral vascular disease cannot be determined. The pathophysiologic mechanisms of fibrinogen, through involvement in platelet aggregation, blood rheology, and endothelial cell injury, which play a key role in thrombosis and atherosclerosis, need to be further understood (37–43). However, because higher fibrinogen levels have been shown to have a positive relationship with coronary heart disease and other risk factors, these relationships may reflect on the thrombotic mechanism that is considered to contribute to arterial intimal atherosclerotic changes. The influence of childhood fibrinogen levels may also come from the potential “tracking” of childhood levels into adulthood. Obesity seems to have the strongest association with higher fibrinogen levels and is also a risk factor for peripheral thrombosis. This consistent relationship may also imply that the genetic factors that control obesity may also affect fibrinogen levels. Although methods are not established to control fibrinogen directly, control of other accepted risk factors (23, 44), such as weight control, exercise, diet management, and smoking cessation in adults, should apply to children as well. Because it is important to begin the prevention of atherosclerotic disease in early life, the factors that influence fibrinogen levels should also be considered, starting in childhood.

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