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Gamma prime (γ') fibrinogen and carotid intima–media thickness: the Atherosclerosis Risk in Communities study

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Abstract

We assessed if γ' fibrinogen, an isoform of fibrinogen, is independently associated with subclinical atherosclerosis beyond total fibrinogen in black and white men and women participating in the Atherosclerosis Risk in Communities study. Fasting γ' fibrinogen was measured in 6847 Atherosclerosis Risk in Communities participants, ages 51–70 years, in 1993–1995. Carotid intima–media far wall thickness (CIMT) was measured by B-mode ultrasonography at the common, internal and bifurcation carotids. The association of γ' fibrinogen tertiles with overall and segment-specific mean CIMT was assessed with linear regression, controlling for fibrinogen as well as cardiovascular risk factors, including high-sensitivity C-reactive protein and D-dimer. γ' Fibrinogen values ranged from 8.0 to 80.3 mg/dl and were positively related to age, female sex, black race, smoking, BMI, lipids and SBP. Crude γ' fibrinogen was directly associated with all CIMT measures except for the internal carotid, but explained less than 1% of the variance in the associations. Adjustment for total fibrinogen eliminated these associations, and total fibrinogen remained an independent predictor of CIMT without explaining additional variance. Adjustment for potential confounding variables did not alter the observed associations, which did not differ by race or sex. In these cross-sectional data, γ' fibrinogen was not independently associated with CIMT when controlling for total fibrinogen. γ' Fibrinogen and total fibrinogen together explained a very small proportion of the variance in CIMT, regardless of the carotid site. If γ' fibrinogen adds to total fibrinogen's ability to predict subclinical atherosclerosis, it may be in younger populations.

Keywords

carotid atherosclerosis; cohort studies; epidemiology; fibrinogen; thrombosis

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Conflicts of interest

There are no conflicts of interest.

Introduction

Fibrinogen has been positively associated with cardiovascular disease prevalence and incidence through hyperviscosity and thrombosis in response to inflammation. The association of fibrinogen as an independent predictor of early atherosclerotic disease such as greater carotid intima-media wall thickness (IMT) has been reported in several studies [1–4]. Associations of fibrinogen with plaque and shadowing have been observed in the Atherosclerosis Risk in Communities (ARIC) study [5]. There have also been reports that the association between fibrinogen and subclinical cardiovascular disease differs by race [6], with whites having stronger associations than blacks.

Recently, an isoform of fibrinogen, γ' fibrinogen, has been proposed as a subtype of fibrinogen that may form clinically relevant clots that are more tightly packed and rigid with thinner fibers and lower porosity than clots from the more common types of fibrinogen [7]. Fibrinogen is a six-chain molecule containing two copies each of the A α , B β and γ chains [8,9]. The fibrinogen γ chain has two isoforms, the γ A isoform and the γ' isoform, that arise from alternative mRNA processing. γ' Fibrinogen normally comprises approximately 7% of the total fibrinogen volume, but there is wide variability. Levels are directly correlated with obesity and BMI, female sex, insulin resistance, diabetes, glucose, age and triglycerides, and inversely correlated with physical activity and HDL-cholesterol (HDL-c) [10,11]. Improvements in assays have made measuring this isoform in large cohort studies feasible, allowing assessment of γ' fibrinogen's role as an independent predictor of subclinical atherosclerosis.

Therefore, the aim of this study was to determine if γ' fibrinogen is independently associated with carotid IMT beyond total fibrinogen in black and white men and women attending the ARIC Study visit 3 examination. Subclinical atherosclerosis was examined as the average of the bilateral IMT measures at the internal carotid, the common carotid and the bifurcation as well as the average of all individual sites to assess the association of γ' fibrinogen with carotid IMT at different locations and type of artery. Finally, we assessed if associations differed by age, race and/or sex.

Methods

Study population

The ARIC Study is a prospective, multicenter investigation of atherosclerotic clinical events and noninvasively measured atherosclerosis, consisting of both a cohort and a community surveillance component. Details of the study have been given elsewhere [12]. In brief, 15 792 predominantly black and white men and women ages 45–64 years from Forsyth County, North Carolina, Jackson, Mississippi, suburban Minneapolis, Minnesota and Washington County, Maryland were enrolled in 1987–1989 for a baseline visit. There were follow-up examinations in 1990–1992, 1993–1995 (visit 3), 1996–1998 and 2011–2013. The institutional review boards at each study site approved the protocol and all participants gave informed consent.

Plasma γ' fibrinogen and total fibrinogen measurements

Fasting γ' fibrinogen was measured in citrated plasma collected at visit 3 and stored at -70°C until assayed in 2014. The Laboratory for Clinical Biochemistry Research at the University of Vermont used the standard sandwich ELISA using anti- γ' mAb developed by Lovely *et al.* [10]. The assay was made available by Gamma Therapeutics (Portland, Oregon, USA) and has a coefficient of variation for control samples of 10.3%. Because of the large number of samples, which required 12 months of laboratory measurement for γ' fibrinogen, the laboratory first analyzed ARIC samples from three of the study centers followed by the Jackson center. In addition to the laboratory's standard assay quality assurance procedures, we instituted two other quality checks on γ' fibrinogen measurement. First, ARIC included blinded duplicate samples split at the time of blood draw to check on reliability. Second, the laboratory included a normal pool to check for long-term drift. The analysis of 75 split specimen pairs during the early phase yielded a coefficient of variation of 27% and an intraclass correlation coefficient (ICC) of 0.59 with 31% downward drift of the measured mean for a normal pool. The laboratory attributed this drift to its learning curve with the γ' fibrinogen assay and changed protocol. For the Jackson samples, the mean of the normal pool showed no significant drift and the reliability coefficient was 0.79. We therefore used the normal pool results to adjust participants' γ' fibrinogen for the earlier period to the later period by multiplying the observed laboratory values by the ratio of the mean γ' fibrinogen levels in the normal pool during the later period compared with the earlier period. Prior to adjustment, 61 values that were above the limit of detection ($>400\text{ mg/dl}$) were excluded, while eight samples that were below the limit of detection (8.0 mg/dl) were set equal to the limit (8.0 mg/dl) [13].

Because total fibrinogen was only measured in a small subsample at visit 3 ($n = 537$), plasma total fibrinogen values were used from visit 1, determined by the thrombin time titration method, with reagents obtained from General Diagnostics Organon Technica Co. The reliability coefficient for measurement of fibrinogen in a sample of ARIC Study participants conducted over several weeks was 0.72 [14].

Ultrasonography

Carotid wall thickness was measured by B-mode ultrasonography using the technique of Pignoli *et al.* [15]. Repeatability of the scanning and reading procedures have been reported elsewhere with an ICC of 0.81 for repeated scans by the same sonographer and a correlation of 0.93 for blinded, repeated readings of the same scan by different sonographers [16,17]. The degree of atherosclerosis was approximated by measuring and then averaging the intima-media far wall thickness of the extracranial common carotid artery, internal carotid artery and carotid bifurcation at 1-mm intervals along a 1-cm segment. Wall thickness was expressed both as the overall mean across all far wall thicknesses and as the average of the left and right mean far wall thicknesses for each of the three carotid artery regions.

Covariates

With the exception of total fibrinogen and C-reactive protein, all variables were collected at visit 3. Participants self-reported their age, race (black or white), educational attainment, smoking and drinking status, and sports-related physical activity. Participants brought all of

the medications that they had taken in the past 2 weeks to the clinic visit, and ARIC staff recorded lipid-lowering and antihypertensive medications used.

Participants fasted for 12 h prior to phlebotomy. Plasma total cholesterol (TC) and HDL-c were assayed by enzymatic methods. Diabetes was defined as fasting serum glucose of at least 126 mg/dl, nonfasting glucose of at least 200 mg/dl, a self-reported physician diagnosis of diabetes or use of antidiabetic medication in the past 2 weeks. Plasma D-dimer was measured in citrated plasma using an immunoturbidimetric assay (Liatest D-DI; Diagnostica Stago, Parsippany, New Jersey, USA). High-sensitivity C-reactive protein (hs-CRP) was measured at ARIC visit 2 (3 years before γ' fibrinogen) using a latex-particle enhanced immunoturbidimetric assay kit (Roche Diagnostics, Indianapolis, Indiana, USA).

Statistical analysis

Of the 12 887 participants who attended ARIC visit 3, 7895 had data on carotid IMT due to an *a priori* decision to randomly scan 50% of the Washington County and Minneapolis participants; 12 516 had data on γ' fibrinogen and 7704 had data on both carotid IMT and γ' fibrinogen. We excluded 631 participants who had prevalent coronary heart disease (CHD) and stroke prior to visit 3, and another 131 with missing fibrinogen at visit 1. After excluding missing visit 3 data for smoking, drinking and education, and a small number of black participants in Minneapolis and Washington County, we were left with an analytic sample of 6847 participants.

To examine nonlinear associations between γ' fibrinogen and carotid IMT (either the combined mean carotid IMT or means of the individual common, internal and bifurcation sites), we divided γ' fibrinogen into tertiles of equal sample size. Crude associations for the covariates of interest by tertiles of γ' fibrinogen were examined and statistical significance assessed with chi-square for categorical variables and *F*-test for continuous variables.

Linear regression models were used to determine the associations between tertiles of γ' fibrinogen and carotid IMT. Least square means for carotid IMT in millimeters were generated for each γ' fibrinogen tertile, and R^2 values for each model described. First, crude models with only γ' fibrinogen were run, and then models were adjusted for total fibrinogen to determine independence of γ' fibrinogen as a risk factor. Additional models controlled for age, sex, race, field center, education, smoking and drinking status, sports-related physical activity, SBP, BMI, diabetes, antihypertensive and lipid-lowering medication use, HDL-c, TC, D-dimer and hs-CRP. Statistical significance for γ' fibrinogen with carotid IMT was assessed overall (2 df) and for the individual tertiles using the lowest tertile as a reference. Additive interactions of γ' fibrinogen with age, race and sex were tested for all outcomes and not found to be statistically significant. Therefore, all models omitted age, race and sex interaction terms. Statistical analysis was performed using SAS v.9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Table 1 presents the characteristics of the participants attending ARIC visit 3 by tertiles of γ' fibrinogen. Participants were ages 51–70 years. As tertiles increased, statistically

significantly higher mean ages as well as BMI, hs-CRP, SBP and total fibrinogen were observed, along with lower mean HDL-c, sports-related physical activity and years of education. Higher tertiles were also associated with greater proportions of women, blacks, current smokers, diabetes, and antihypertensive and lipid-lowering medication use. No associations were observed between TC or D-dimer and tertiles of γ' fibrinogen.

As shown in Table 2, the unadjusted associations between mean carotid IMT and tertiles of γ' fibrinogen were statistically significant for the average of all carotid IMT sites, for the common carotid, and for the carotid bifurcation, but the association was of borderline statistical significance for the internal carotid with the suggestion of a threshold effect in the third tertile. However, when total fibrinogen was added to the unadjusted models (Model 1), γ' fibrinogen was no longer associated with carotid IMT at any site. Additional adjustment for *a priori* selected covariates in Model 2 did not change the lack of association between γ' fibrinogen and mean carotid IMT. The *R*-squared values improved to almost 10% in Model 2, however, predominantly due to the addition of age, diabetes and smoking.

Total fibrinogen was statistically significantly associated with all carotid IMT measures. Table 3 shows the association between mean carotid IMT and tertiles of total fibrinogen adjusted for tertiles of γ' fibrinogen. The correlation between total fibrinogen and γ' fibrinogen was 0.437, but only total fibrinogen was an independent predictor of carotid IMT. Despite statistical significance of total fibrinogen, *R*-squared values for the unadjusted and total fibrinogen-adjusted models were less than 1%. The interaction of γ' fibrinogen and total fibrinogen was not statistically significant and was therefore not included in any of the models (not shown).

Discussion

In this cross-sectional analysis in a cohort of middle-aged black and white men and women, we found that γ' fibrinogen was associated with carotid IMT, but that association was eliminated when total fibrinogen was added to the model. γ' Fibrinogen and total fibrinogen together explained a very small proportion of the variance in carotid IMT, regardless of the carotid site. The findings did not differ by age, race or sex, and additional adjustment for potential confounding variables did not materially alter the lack of association observed.

Our results mirror the results found by Appiah *et al.* [18], who found no association between γ' fibrinogen and incident CHD and ischemic stroke in this cohort. Unlike their finding of a modest association of the higher levels of γ' fibrinogen with incident peripheral artery disease, heart failure and cardiovascular disease deaths, we found no association at any level once total fibrinogen was added to the models.

Total fibrinogen has previously been demonstrated to be an independent predictor of subclinical atherosclerosis. Green *et al.* [19] found that fibrinogen measured in young adulthood (ages 25–37 years) was associated with both coronary artery calcification (CAC) and carotid IMT 13 years later. Fibrinogen measured concurrently with CAC and carotid IMT, however, was not associated once adjusted for confounding variables. The authors concluded that higher levels of fibrinogen during young adulthood are positively related with

incident subclinical atherosclerosis, but that the association is diminished with increasing age, possibly due to competing risk factors such as smoking and obesity. The same authors also found that fibrinogen is more strongly associated with CAC than with carotid IMT, and that CAC was not associated with several other hemostatic factors (Factor VII, Factor VIII or von Willebrand factor activity or antigen). Grebe *et al.* [2] also found an association between fibrinogen and common carotid IMT in adults less than 50 years of age. Folsom *et al.* [1], however, reported that fibrinogen was directly associated with both higher mean carotid IMT and with higher odds of being in the upper 90th percentile of the carotid atherosclerosis distribution in the ARIC baseline cohort, ages 45–64 years, after adjustment for age, race and study center.

Mannila *et al.* [7] found that γ' fibrinogen was related to myocardial infarction (MI) in a matched case–control study of patients who had had a first MI under the age of 60 with population-based controls. The association was even stronger when both γ' fibrinogen and fibrinogen were elevated. Lovely *et al.* [20] also reported an interaction between γ' fibrinogen and total fibrinogen that was associated with a stronger association with MI, but overall, they found that adjustment for total fibrinogen attenuated the statistical significance of the association between γ' fibrinogen and CVD. Kim *et al.* [21] described the kinetics of fibrinogen's role in clotting and lysis, speculating that as the concentration of fibrinogen increases above a physiologically normal level, the balance between fibrinolysis and clotting shifts to clotting. We did not find an interaction between γ' fibrinogen and total fibrinogen such that either association differed by concentration of the other, but total fibrinogen was independently associated with carotid IMT when controlling for γ' fibrinogen.

Limitations of this study include the cross-sectional design, which prevents any causal inferences to be made; nonetheless, there was no evidence to support a relation between γ' fibrinogen and carotid IMT. Total fibrinogen was only measured in the entire cohort at visit 1, 6 years before the γ' fibrinogen and carotid IMT measures. However, total fibrinogen was measured in 537 participants at visit 3 who also had γ' fibrinogen and carotid IMT values, and the correlation between visit 1 and visit 3 total fibrinogen was 0.52, suggesting that fibrinogen tracks well across time. This was also demonstrated by Okwuosa *et al.* [22], who showed that fibrinogen tracked longitudinally with changes in other longitudinal risk factors in a young population that was largely free of cardiovascular risk factors at baseline.

In conclusion, we found no independent association of γ' fibrinogen with subclinical atherosclerosis assessed in the carotid arteries in a large, biracial sample that was free of prevalent cardiovascular disease and stroke at baseline. The lack of association did not differ by race or by sex. In particular, γ' fibrinogen showed no association with carotid IMT after accounting for the more widely measured total fibrinogen. Although the data are cross-sectional, this may suggest that if γ' fibrinogen adds to the predictive ability of total fibrinogen, it may be in other populations, such as younger populations or in populations with elevated fibrinogen.

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Table 1

Characteristics of participants by tertiles of γ' fibrinogen, the Atherosclerosis Risk in Communities Study 1993–1995

Characteristics	γ' Fibrinogen tertiles (mg/dl)			<i>P</i> value ^a
	T1 (8.0–26.3)	T2 (26.3–33.2)	T3 (33.2–80.3)	
<i>N</i>	2282	2283	2282	
Age (years)	59.3 (5.7)	59.7 (5.8)	60.2 (5.8)	<0.0001
Sex (% men)	44.4	41.3	35.2	<0.0001
Race (% black)	24.3	31.2	40.7	<0.0001
Education (years)	14.8 (4.4)	14.6 (4.5)	14.2 (4.5)	<0.0001
Smoking status (%)				<0.0001
Current	15.5	17.9	23.6	
Former	41.0	39.6	33.5	
Drinking status (%)				<0.0001
Current	52.4	47.2	41.9	
Former	21.2	23.6	23.9	
SBP (mmHg)	123.2 (18.3)	125.0 (19.3)	126.5 (20.1)	<0.0001
Antihypertensive medication (%)	28.5	34.0	42.2	<0.0001
BMI (kg/m ²)	27.4 (5.0)	28.2 (5.3)	29.2 (6.1)	<0.0001
Diabetes (%)	10.6	14.5	18.2	<0.0001
Sports index (range 1–5)	2.59 (0.83)	2.50 (0.81)	2.41 (0.77)	<0.0001
Total cholesterol (mg/dl)	205.9 (38.5)	207.9 (36.4)	207.8 (38.8)	0.14
HDL-cholesterol (mg/dl)	54.5 (19.2)	54.4 (18.9)	52.9 (18.2)	0.0084
Lipid-lowering medication (%)	6.5	7.0	7.9	<0.0001
D-Dimer (μg/ml)	0.52 (1.7)	0.46 (1.2)	0.51 (0.94)	0.90
C-reactive protein (mg/l) (visit 2)	3.08 (5.3)	3.89 (5.8)	5.67 (8.4)	<0.0001
Total fibrinogen (mg/dl) (visit 1)	268.8 (49.5)	296.0 (52.0)	329.4 (67.1)	<0.0001

Values are mean (SD) for continuous variables and percentages for categorical variables. IMT, intima-media wall thickness.

^aChi-square for categorical variables and F-test for continuous variables.

Table 2

Mean carotid intima-media wall thicknesses (mm) by plasma γ' fibrinogen tertiles, the Atherosclerosis Risk in Communities Study 1993–1995

	Unadjusted	P	Model 1	P	Model 2	P
Average CIMT						
Tertile 1	0.793	Ref	0.802	Ref	0.808	Ref
Tertile 2	0.803	0.14	0.804	0.85	0.805	0.67
Tertile 3	0.817	0.0002	0.808	0.43	0.806	0.84
2-df test		0.0009		0.71		0.91
R^2	0.00204		0.00864		0.142	
Common carotid						
Tertile 1	0.722	Ref	0.728	Ref	0.737	Ref
Tertile 2	0.728	0.16	0.729	0.82	0.734	0.46
Tertile 3	0.742	<0.0001	0.736	0.12	0.739	0.70
2-df test		<0.0001		0.23		0.50
R^2	0.00278		0.00833		0.153	
Carotid bifurcation						
Tertile 1	0.918	Ref	0.931	Ref	0.944	Ref
Tertile 2	0.938	0.048	0.939	0.43	0.946	0.83
Tertile 3	0.952	0.0005	0.939	0.43	0.938	0.54
2-df test		0.0022		0.67		0.68
R^2	0.00179		0.00730	0.110		
Internal carotid						
Tertile 1	0.740	Ref	0.748	Ref	0.742	Ref
Tertile 2	0.742	0.76	0.743	0.54	0.735	0.43
Tertile 3	0.757	0.038	0.749	0.98	0.743	0.95
2-df test		0.081		0.76		0.63
R^2	0.000735		0.00417		0.0860	

Cutpoints for γ' fibrinogen: tertile 1 = 8.0–26.3 mg/dl; tertile 2 = 26.3–33.2 mg/dl; tertile 3 = 33.2–80.3 mg/dl. Model 1: adjusted for total fibrinogen. Model 2: Model 1 with additional adjustment for age, sex, race, field center, education, smoking and drinking status, sports index, SBP, BMI, antihypertensive medication, diabetes, lipid-lowering medication, HDL-cholesterol, total cholesterol, D-dimer and C-reactive protein. CIMT, carotid intima-media wall thickness, df, degrees of freedom.

Table 3

Mean carotid intima-media wall thicknesses (mm) by total fibrinogen tertiles^a, after controlling for γ' fibrinogen tertiles, the Atherosclerosis Risk in Communities Study 1993–1995

	N	Average CIMT	P value	Common carotid	P value	Carotid bifurcation	P value	Internal carotid	P value
Tertile 1	2249	0.789	Ref	0.718	Ref	0.916	Ref	0.734	Ref
Tertile 2	2315	0.799	0.16	0.730	0.020	0.926	0.31	0.741	0.46
Tertile 3	2270	0.825	<0.0001	0.744	<0.0001	0.967	<0.0001	0.765	0.0008

CIMT, carotid intima-media wall thickness.

^aCutpoints for total fibrinogen: tertile 1 = 97.0–267.0 mg/dl; tertile 2 = 268.0–314.0 mg/dl; tertile 3 = 315.0–806.0 mg/dl.