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Low protein C and incidence of ischemic stroke and coronary heart disease: The Atherosclerosis Risk in Communities (ARIC) Study

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Summary

Background—Protein C is an important plasma natural anticoagulant. Although protein C deficiency increases risk of venous thrombosis, it remains uncertain whether low protein C increases risk of atherothrombosis.

Objective—To examine whether low protein C may be a risk factor for ischemic stroke or coronary events in a prospective population-based study.

Patients/Methods—The Atherosclerosis Risk in Communities Study assessed protein C antigen by ELISA at baseline in 1987–89 and followed participants (*n*=13,879) for incident ischemic stroke or coronary events through 2005.

Results—Over a median of 16.9 years of follow-up, 613 ischemic strokes and 1,257 coronary heart disease events occurred. Protein C was inversely associated with incidence of ischemic stroke. Adjusted for multiple risk factors, the rate ratios (95% CIs) from highest to lowest quintiles were 1.0, 1.16 (0.90–1.50), 1.22 (0.94–1.58), 1.18 (0.90–1.55), and 1.52 (1.17–1.98). This inverse association was stronger for nonlacunar and cardioembolic stroke than for lacunar stroke. In contrast, there was a positive association between protein C and coronary heart disease in incompletely adjusted models, but no association after adjustment for plasma lipids.

Conclusions—In this cohort study, low protein C was a risk factor for incident ischemic stroke but not coronary heart disease. Levels of protein C associated with stroke risk were not restricted to the traditional ‘deficient’ range for protein C (<0.5 percentile), suggesting that other etiologies for a lower protein C, or genetic variants associated with more subtle changes in protein C, are playing a role in disease pathogenesis.

Keywords

Cerebral infarction; coronary disease; prospective study; protein C; stroke

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Disclosure of Conflict of Interests
None.

Introduction

Protein C is an important plasma natural anticoagulant. After activation by thrombomodulin-bound thrombin, activated protein C in the presence of protein S degrades factor Va and VIIIa, thereby inhibiting coagulation. Hereditary protein C deficiency is an established risk factor for venous thromboembolism [1], and low protein C levels in the general population also increase venous thromboembolism risk [2,3]. However, whether low protein C is also a risk factor for arterial thrombosis is less clear.

A meta-analysis of case-control studies concluded that in children protein C deficiency increases risk of stroke 2-fold [4]. In adults, most evidence linking protein C deficiency with arterial thrombosis derives from case reports. Boekholdt and Kramer concluded that this evidence was currently insufficient to link protein C deficiency and arterial thrombosis in adults [5]. More recently, a large family cohort study demonstrated that hereditary protein C deficiency (i.e., protein C antigen <63 IU/dL and/or activity <64 IU/dL) was associated with increased risk of arterial thrombosis (myocardial infarction, ischemic stroke, or transient ischemic attack) before age 55 years, but not in older subjects [6]. We reported previously in the population-based Atherosclerosis Risk in Communities (ARIC) Study that plasma protein C level was not associated with coronary heart disease (CHD) incidence (n = 348) over 7 years [7]. Protein C was inversely associated with ischemic stroke incidence (n=191), though not statistically significantly so after adjustment for other stroke risk factors [8]. More prospective studies are needed of atherothrombotic disease in relation to low protein C outside the traditional cutpoints for “deficiency”.

ARIC now has more than three times as many incident atherothrombotic events as previously [8,9]. We hypothesized that with longer follow-up a low protein C level is a risk factor for atherothrombotic events.

Methods

Study population

The ARIC Study [9] included a cohort totaling 15,792 persons between 45 and 64 years of age at recruitment and baseline examination in 1987–89, probability-sampled from Forsyth County, North Carolina; Jackson, Mississippi (blacks only); the northwest suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Participants underwent additional examinations in 1990–92, 1993–95, and 1996–98, and were followed throughout via annual telephone contact and hospital surveillance for incident cardiovascular events.

Baseline measurements

Blood was drawn after an 8-hour fasting period with minimal trauma from an antecubital vein. Samples were processed by a standardized protocol and stored at −70°C until assayed within a few weeks at the ARIC Hemostasis Laboratory at the University of Texas Medical School, Houston. Detailed methods for blood processing and measurement of hemostatic variables have been published [10,11]. Protein C antigen and von Willebrand factor antigen were measured by ELISA and fibrinogen by the thrombin-time titration method. Reliability coefficients obtained from repeated testing of individuals over several weeks were 0.56 for protein C, 0.72 for fibrinogen, and 0.68 for von Willebrand factor [12].

Plasma total cholesterol and triglycerides were measured by an enzymatic method, and LDL cholesterol was calculated [13]. HDL cholesterol was measured after dextran-magnesium precipitation of non-HDL lipoproteins. Prevalent diabetes mellitus was defined as a fasting glucose level ≥126 mg/dL, nonfasting glucose level ≥200 mg/dL, and/or a history of or treatment for diabetes. Three blood pressure measurements were taken with a random-zero

sphygmomanometer; the last 2 measurements were averaged. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication.

Ascertainment of incident ischemic stroke and coronary heart disease events

Stroke and coronary heart disease events and deaths after baseline were identified by local hospital surveillance and annual telephone contact with ARIC participants [14,15]. Hospital records were abstracted and death certificates obtained, and events were classified by a combination of computer algorithm and physician review. Strokes were classified according to published criteria based on the occurrence and duration of neurological signs and symptoms, the results of neuroimaging and other diagnostic procedures, and treatments provided [14]. Strokes secondary to trauma, neoplasm, hematological abnormality, infection, or vasculitis were not counted, and a focal deficit lasting <24 hours was not considered a stroke. A stroke was classified as ischemic when neuroimaging showed acute infarction or no evidence of hemorrhage. Ischemic strokes were further classified as lacunar, non-lacunar, or cardioembolic. Lacunar stroke required 2 criteria: (1) typical location of the infarct (basal ganglia, brain stem, thalamus, internal capsule, or cerebral white matter) and (2) infarct size of ≤2 cm or unstated size. Cardioembolic ischemic stroke required either (1) autopsy evidence of an infarcted area in the brain and a source of possible cerebral emboli in a vessel or the presence of an embolus in the brain or (2) medical record evidence of a possible source of embolus, such as moderate or greater valvular heart disease, atrial fibrillation, cardiac or arterial procedure, or intracardiac thrombus.

CHD events included definite or probable myocardial infarctions or definite CHD deaths by published criteria [15].

Data analysis

After excluding those with prevalent CHD or stroke, unknown baseline CHD or stroke status, or missing protein C, 13,879 of the 15,792 ARIC participants were included in the analysis. Follow-up went from baseline to whichever of the following occurred first: incident ischemic stroke (or CHD) event, death, last contact, or December 31, 2005.

Age-, race-, and sex-adjusted means or prevalences of baseline risk factors were computed within baseline protein C quintiles and tested for trend using analysis of covariance. Rate ratios (RR) and 95% CI of incident stroke (or CHD) in relation to protein C quintiles were computed by proportional hazards regression, with the highest quintile as the reference. The linear trend in RRs across categories was tested by inclusion of a variable with median protein C values to designate successive protein C quintiles. The multivariable models adjusted initially for age (continuous), sex, race (black, white), ARIC community, systolic blood pressure (continuous) and antihypertensive medications (yes/no), diabetes (yes/no), smoking status (former, current, never), education (<high school, high school, >high school), and subsequently for HDL and LDL cholesterol, fibrinogen, and von Willebrand factor (all continuous).

Some analyses alternatively examined low protein C as the lowest 20^{th}, 10^{th}, or 5^{th} percentile, compared with everyone else. Tests of 2-way multiplicative interactions were performed in regression models using cross-product terms for protein C ($<20^{th}$ vs $\geq 20^{th}$ percentile) with sex, baseline age (45–54 vs 55–64), race (white, African American), hypertension (yes, no), fibrinogen ($\geq 80^{th}$ vs $<80^{th}$ percentile) or von Willebrand factor ($\geq 80^{th}$ vs $<80^{th}$ percentile).

Results

As shown in Table 1, baseline protein C in the lowest quintile was associated with younger age; a higher proportion of men, African Americans, and smokers; a lower proportion with high blood pressure and diabetes; and lower levels of lipids, fibrinogen, and von Willebrand factor.

Protein C and Stroke Incidence

Over a median of 16.9 years of follow-up, 613 ischemic strokes and 1,257 CHD events occurred. Protein C was inversely but nonlinearly associated with incidence of ischemic stroke (Table 2), with increased stroke risk confined mainly to the lowest quintile of protein C. The fully-adjusted RR for the lowest versus highest quintile was 1.52 (95% CI = 1.17–1.98). When the lowest quintile was split in two, participants with the lowest 10 percent of protein C values had a 1.42-fold (95% CI 1.12–1.80) greater stroke incidence than did the 90 percent with higher values (data not shown). Stratification of low protein C by the 5^{th} percentile showed no further risk gradient.

For overall ischemic stroke, there was no evidence of multiplicative interaction of low protein C ($<20^{th}$ vs $\geq 20^{th}$ percentile) with sex, age, or race (p interaction $\geq$0.10). However, there was modest evidence for synergism of low protein C with hypertension, fibrinogen, and von Willebrand factor (p values for interaction = 0.04 to 0.07, uncorrected for multiple testing). The RR (95% CI) of stroke for low protein C ($<20^{th}$ vs $\geq 20^{th}$ percentile) was 1.59 (1.24–2.03) for hypertensives and 1.01 (0.72–1.40) for normotensives; 1.91 (1.34–2.74) for fibrinogen $\geq$368 mg/dL and 1.17 (0.93–1.49) for fibrinogen <368 mg/dL: and 1.73 (1.25–2.39) for von Willebrand factor $\geq$151% and 1.17 (0.91–1.49) for von Willebrand factor <151%.

As shown in Table 3, low protein C was associated primarily with nonlacunar and cardioembolic ischemic strokes, with a RR of 1.6 to 1.9 for the lowest versus highest quintile. Low protein C was not associated with lacunar stroke.

Protein C and CHD Incidence

For comparison with stroke, we computed the association of protein C with incidence of CHD (Table 4). There was a positive association between protein C and CHD in incompletely adjusted models, but no association after adjustment for plasma lipids.

Discussion

In this prospective population-based study, we found that participants with protein C values in the lowest quintile had a 1.5-fold greater incidence rate of ischemic strokes, particularly ischemic strokes not identified as lacunar, than participants in the highest protein C quintile. The risk gradient was non-linear, that is, only evident for protein C values below the 20^{th} percentile. In a previous ARIC report, an inverse association of protein C with ischemic stroke had been suggested, though not statistically significant, due to considerably fewer events [8]. We also found that protein C was not associated with incidence of CHD independently of other risk factors, confirming a previous ARIC report [7].

Protein C deficiency increases risk of venous thrombosis and, in children, stroke. However, evidence that it increases risk of adult atherothrombotic events, including ischemic stroke, is mixed [5,6,8]. Our data suggest that a low protein C level is associated with increased thrombosis in the large arteries of the neck or heart leading to ischemic stroke. In addition, in some cases low protein C may contribute to paradoxic embolism through a patent foramen ovale. In contrast, in this study, lacunar stroke seemed less related to low protein C. Lacunar

stroke typically arises from occlusion of the small arteries deep in the brain; our findings suggest low protein C does not contribute to this etiology of stroke.

The highest RR for stroke with low protein C levels was, in fact, for cardioembolic stroke, although this was not significantly different from the RR for nonlacunar stroke. This suggests that deficiency of anticoagulant function may play a role in pathogenesis of thrombus formation in the heart. Further studies are indicated, including assessment of the role of lower protein C, not necessarily in the deficient range (<0.5 percentile) [16], and risk of stroke in atrial fibrillation and with valvular heart disease.

Despite low protein C being associated with increased stroke risk, those with low protein C levels had lower average values of fibrinogen and von Willebrand factor. Higher levels of fibrinogen and von Willebrand factor, possibly because they are acute phase reactants, are risk factors for stroke [8,17]. Thus, our results suggest that modulation of anticoagulant function might be more important than high levels of inflammation in stroke etiology.

The contrast between our findings for ischemic stroke and these for CHD is striking. There was a positive, not inverse, association between protein C and coronary events in minimally adjusted models, which was eliminated upon adjustment for plasma lipids. This probably reflects the moderately strong correlation between lipids and protein C and a much stronger role for dyslipidemia in the etiology of CHD than ischemic stroke.

A recent study found protein C (*POC*) and protein C receptor (*POCR*) polymorphisms associated with protein C levels were not associated with CHD or stroke occurrence [18]. Although that may suggest little causal role between low protein C and ischemic stroke, that study was performed in the elderly and may have had low statistical power to detect a modest association of polymorphisms with stroke. Additional prospective population studies of protein C levels and stroke, along with genotyping, would be useful.

The main drawback of this study was having a single measure of protein C which had fairly low repeatability within subjects measured over several weeks. Such measurement error typically would bias RRs toward unity, although this is not guaranteed. We also did not functionally measure protein C deficiency but rather defined the lowest 10^{th}–20^{th} percentile as being low. It did not appear that using the 5^{th} percentile sharpened the risk gradients. Another drawback is that ARIC did not measure C-reactive protein and therefore could not rule out completely inflammation mediating the association of low protein C with ischemic stroke. By necessity, ischemic stroke subtypes were classified by medical record review rather than by patient examination. Any differential error in stroke subtype classification may have contributed to the observed different associations of protein C with lacunar versus non-lacunar stroke. Finally, the numbers of events for stroke subtype analyses were only moderate, so differences in findings for subtypes may have arisen by chance.

Conclusions

In this cohort study, low protein C was a risk factor for incident ischemic stroke but not CHD. Levels of protein C associated with stroke risk were not restricted to the traditional ‘deficient’ range for protein C, suggesting that other etiologies for a lower protein C, or genetic variants associated with more subtle changes in protein C, are playing a role in stroke pathogenesis.

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Table 1

Age, sex, race-adjusted baseline characteristics according to quintiles of protein C, ARIC, 1987–89

	Protein C Percentiles					
	<20th	**20th–39th**	**40th–59th**	**60th–79th**	**≥80th**	**P for trend**
Range, μg/mL	<2.6	2.7–2.9	3.0–3.2	3.3–3.6	≥3.7	
n	2,705	2,650	2,899	2,871	2,754	
Age, year	53.5	53.7	53.9	54.4	54.5	<0.001
Male, %	55.3	49.6	43.9	38.8	29.6	<0.001
African Americans, %	30.3	24.6	24.6	23.3	25.1	<0.001
Systolic blood pressure, mmHg	120	121	121	121	122	<0.001
Use of antihypertensive medication, %	23.1	25.7	26.7	27.8	34.9	<0.001
Current smoking, %	31.5	27.0	26.1	23.1	20.7	<0.001
Diabetes mellitus, %	8.9	9.7	8.5	10.5	14.1	<0.001
LDL cholesterol, mg/dl	122	132	138	143	150	<0.001
HDL cholesterol, mg/dl	52	52	52	53	53	0.02
Fibrinogen, mg/dl	297	298	303	305	308	<0.001
von Willebrand factor, %	115	114	116	118	123	<0.001

Table 2

Rate ratios (RR) and 95% confidence intervals (CI) of ischemic stroke according to quintiles of protein C, ARIC, 1987–2005

	Protein C Percentiles					
	<20th	**20th–39th**	**40th–59th**	**60th–79th**	**≥80th**	**P for trend**
Range, μg/mL	<2.6	2.7–2.9	3.0–3.2	3.3–3.6	≥3.7	
No. at risk	2,705	2,650	2,899	2,871	2,754	
No. of cases	142	109	124	123	115	
Person-years of follow-up	41,829	41,897	46,014	45,524	43,955	
Incidence rate/1000 person-years	3.4	2.6	2.7	2.7	2.6	
Age-, race-, and sex-adjusted RR (95% CI)	1.26 (0.98–1.61)	0.99 (0.76–1.29)	1.04 (0.80–1.34)	1.02 (0.79–1.31)	1.0	0.13
Multivariate-adjusted* RR (95% CI)	1.38 (1.07–1.77)	1.08 (0.83–1.41)	1.13 (0.88–1.47)	1.11 (0.86–1.44)	1.0	0.03
Multivariate-adjusted† RR (95% CI)	1.52 (1.17–1.98)	1.18 (0.90–1.55)	1.22 (0.94–1.58)	1.16 (0.90–1.50)	1.0	0.004

*Adjusted for age, race-field center, sex, systolic blood pressure, use of antihypertensive medication, smoking status, diabetes mellitus, and education.

†Further adjustment for LDL cholesterol, HDL cholesterol, fibrinogen, and von Willebrand factor.

Table 3

Rate ratios (RR) and 95% confidence intervals (CI) of ischemic stroke subtypes according to quintiles of protein C, ARIC, 1987–2005

	Protein C Percentiles					
	<20th	**20th–39th**	**40th–59th**	**60th–79th**	**≥80th**	**P for trend**
Lacunar						
No. of cases	28	24	26	27	29	
Multivariate-adjusted* RR (95% CI)	1.06 (0.61–1.84)	0.96 (0.551.68)	1.00 (0.58–1.71)	1.00 (0.59–1.70)	1.0	0.90
Nonlacunar						
No. of cases	84	62	69	67	66	
Multivariate-adjusted* RR (95% CI)	1.63 (1.15–2.30)	1.18 (0.83–1.69)	1.18 (0.84–1.67)	1.08 (0.77–1.52)	1.0	0.008
Cardioembolic						
No. of cases	30	23	29	29	20	
Multivariate-adjusted* RR (95% CI)	1.88 (1.04–3.43)	1.49 (0.80–2.76)	1.64 (0.91–2.95)	1.66 (0.93–2.94)	1.0	0.06

*Adjusted for age, race-field center, sex, systolic blood pressure, use of antihypertensive medication, smoking status, diabetes mellitus, education, LDL cholesterol, HDL cholesterol, fibrinogen, and von Willebrand factor.

Table 4

Rate ratios (RR) and 95% confidence intervals (CI) of coronary heart disease to quintiles of protein C, ARIC, 1987–2005

	Protein C Percentiles					
	<20th	**20th–39th**	**40th–59th**	**60th–79th**	**≥80th**	**P for trend**
Range, μg/mL	<2.6	2.7–2.9	3.0–3.2	3.3–3.6	≥3.7	
No. at risk	2,705	2,650	2,899	2,871	2,754	
No. of cases	233	236	271	238	279	
Person-years of follow-up	41,323	41,196	45,201	44,857	43,072	
Incidence rate/1000 person-years	5.6	5.7	6.0	5.3	6.5	
Age-, race-, and sex-adjusted RR (95% CI)	0.74 (0.62–0.88)	0.78 (0.65–0.93)	0.85 (0.72–1.00)	0.76 (0.64–0.90)	1.0	0.002
Multivariate-adjusted* RR (95% CI)	0.75 (0.63–0.90)	0.83 (0.69–0.99)	0.92 (0.77–1.09)	0.83 (0.70–0.99)	1.0	0.004
Multivariate-adjusted† RR (95% CI)	0.92 (0.76–1.11)	0.95 (0.80–1.14)	1.01 (0.85–1.20)	0.89 (0.74–1.06)	1.0	0.57

*Adjusted for age, race-field center, sex, systolic blood pressure, use of antihypertensive medication, smoking status, diabetes mellitus, and education.

†Further adjustment for LDL cholesterol, HDL cholesterol, fibrinogen, and von Willebrand factor.