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Serum albumin and risk of venous thromboembolism

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Summary

The incidence of venous thromboembolism (VTE) is increased in patients with albuminuria. However, whether a low serum albumin concentration is associated with increased risk of VTE has been a matter of controversy. We determined the association of serum albumin with VTE incidence in two large, prospective, population-based cohorts: the Atherosclerosis Risk in Communities (ARIC) Study (*n* = 15,300) and the Cardiovascular Health Study (CHS) (*n* = 5,400). Validated VTE occurrence (*n*=462 in ARIC and *n*=174 in CHS) was ascertained during follow-up. In both studies, after adjustment for age, sex, race, use of hormone replacement therapy, estimated GFR, history of cancer, and diabetes, serum albumin tended to be associated inversely with VTE. The adjusted hazard ratio per standard deviation lower albumin was 1.18 (95% CI = 1.08, 1.31) in ARIC and 1.10 (95% CI = 0.94, 1.29) in CHS. The hazard ratio for albumin below (versus above) the fifth percentile was 1.28 (95% CI = 0.90, 1.84) in ARIC and 1.80 (95% CI = 1.11, 2.93) in CHS. In conclusion, low serum albumin was a modest marker of increased VTE risk. The observed association likely does not reflect cause and effect, but rather that low serum albumin reflects a hyperinflammatory or hypercoagulable state. Whether this association has clinical relevance warrants further study.

Keywords

albumin; prospective study; pulmonary embolism; venous thrombosis

Introduction

The nephrotic syndrome, whose classic sign is macroalbuminuria, is a risk factor for venous thromboembolism (VTE) (1-7). Lesser degrees of albuminuria also are associated with increased risk of VTE in the general population (8). Mechanisms for these associations are unclear, but may relate to enhanced coagulation with albuminuric syndromes (9), possibly through renal loss of smaller anti-thrombotic proteins.

Some studies over the past several decades have suggested a low albumin concentration in the serum also may be a marker of increased VTE risk (10), although the majority of studies have not (1,3,5,7). However, most previous studies of serum albumin and VTE have been small or conducted in patients with renal disease. A rationale for low serum albumin being associated

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with VTE risk is two-fold. Low serum albumin, being an acute phase reactant, may reflect inflammation, which is sometimes linked to VTE occurrence (11). Or, low serum albumin may reflect renal loss of albumin and anti-thrombotic proteins, and thus the same hypercoagulable state apparent in the nephrotic syndrome. In neither case would low serum albumin be considered a direct cause of VTE, but rather a risk marker.

Because of prior conflicting evidence on this topic from previous small clinical studies, we tested the hypothesis that a low serum albumin concentration is associated with increased risk of VTE in a large, prospective, population-based cohort.

Methods

Study population

The Longitudinal Investigation of Thromboembolism Etiology (LITE) (12) comprises the Atherosclerosis Risk in Communities (ARIC) Study (13) and the Cardiovascular Health Study (CHS) (14,15). The ARIC Study is a prospective cohort of 15,792 adults aged 45-64 years from 4 U.S. communities at baseline in 1987-1989. CHS is a prospective cohort of adults 65 years of age and older sampled from Medicare eligibility lists from 4 U.S. communities: 5201 recruited in 1989-1990 and 687 African Americans recruited between 1992 and 1993. Written informed consent was obtained from all participants and protocols were approved by the institutional review boards at the participating universities.

Baseline albumin and protein measurements

In ARIC, serum albumin was measured with a Coulter DACOS instrument (Coulter Diagnostics, Hialeah, Florida) with a bromcresol green colorimetric assay (16). The reliability coefficient of albumin measurements, based on repeated testing of 40 healthy participants over four weeks was 0.69, and the within-person variability was 2.8 percent (17). In CHS, albumin was measured using the Kodak Ektachem 700 analyzer (Eastman Kodak, Rochester, NY) with a CV of 3.2% (18). Total protein was measured in ARIC using a biuret spectrophotometric method.

Other baseline measurements

In both ARIC and CHS, body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Diabetes was defined by fasting blood glucose $\geq$ 7 mmol/L, nonfasting glucose $\geq$ 11.1 mmol/L, a self-report of physician diagnosis, or current medication use for diabetes. A prescription or self-report was used to determine hormone replacement therapy (HRT) use in women at baseline.

Factor VIIIc was measured in ARIC and CHS using coagulation assays by determining the ability of the sample to correct the clotting time of human factor VIII–deficient plasma. Serum creatinine was measured in each study by a modified kinetic Jaffe method, and estimated glomerular filtration rate (eGFR) was calculated using the equations recently developed by Levey et al (19). APTT was measured in ARIC on an automated coagulometer (Coag-A-Mate X-2, General Diagnostics, Morris Plains, NJ).

VTE case ascertainment

ARIC participants had clinic visits every three years through 1998 and were contacted annually by telephone. Participant report and surveillance of local hospital discharge lists were used to identify hospitalizations. The CHS participants had alternating clinic visits and telephone contacts every six months through 1999 and telephone contacts at 6-month intervals since 1999. Participant or proxy report and Health Care Financing Administration record searches identified hospitalizations.

For possible hospitalizations for VTE, research staff copied discharge summaries, physician and consultant reports, and vascular and radiological studies. Two physicians then assigned a VTE classification, and differences in classification were resolved by discussion (12). Secondary VTE was defined as events that were associated with cancer or chemotherapy, or that occurred within 90 days of major trauma, surgery, or marked immobility. Idiopathic VTE events were not accompanied by any of the previous conditions.

Statistical analysis

All analyses were conducted using SAS (SAS Institute, Cary, NC). Of the 21,680 participants in LITE, we excluded those who reported using warfarin (n = 87 ARIC, n = 98 CHS), who self-reported a history of VTE (n =276 ARIC, n = 354 CHS), or had missing serum albumin data (n = 150 ARIC, n = 80 CHS), leaving 20,700 participants (n = 15,300 ARIC, n = 5,400 CHS) for analysis.

Analyses were performed separately for ARIC and CHS because laboratory methods and albumin distributions differed by study, prompting concern over pooling them. The main focus was on ARIC because of its larger size, extra covariates, and longer follow-up. Incident VTE was defined as the first occurrence of validated deep vein thrombosis or pulmonary embolism from baseline through 2005 for ARIC or through 2001 in CHS. Study-specific hazard ratios for VTE by baseline quintile of serum albumin (using the highest quintile as the reference) were estimated using Cox regression after adjustment for the following covariates at baseline: age (continuous), sex, race (African American, other), BMI (continuous), prevalent diabetes (yes, no), history of cancer (yes, no), current HRT use in women (no, yes), cancer history (no, yes), eGFR (continuous), fibrinogen (continuous), factor VIIIc (continuous), fibrinogen (continuous), and in ARIC only, aPTT (continuous). These variables include the factors associated with VTE in the LITE project that were available in both full cohorts (20-22). We also modeled serum albumin two additional ways: as a continuous variable and determined hazard ratios for VTE per 1 standard deviation decrement of serum albumin, and as the lowest 5 percent of albumin values versus the remainder. Hazard ratios were estimated separately for total, idiopathic, and secondary VTE.

Results

At baseline in ARIC, the mean ± SD serum albumin concentration was 38.7 ± 2.7 g/L and for total protein was 72.8 ± 4.5 g/L. As shown in Table 1, serum albumin values tended to be lower in those who at baseline were older, female, African American, HRT users, and diabetic. Lower serum albumin was also associated with greater BMI, fibrinogen, factor VIII, fibrinogen and eGFR and lower aPTT.

Among the 15,300 ARIC participants at risk, 462 VTE events (170 idiopathic, 292 secondary) occurred over a median of 16.9 years of follow-up. After adjustment for age, sex, and race (Model 1, Table 2), lower serum albumin was associated with greater VTE incidence. The hazard ratios of total VTE were 1.57, 1.54, 1.32, 0.74, and 1.00 (p trend < 0.0001) from lowest to highest quintiles of albumin and 1.26 (95% CI = 1.15, 1.39) per standard deviation decrement of albumin. This translates into a 9% greater VTE rate (95% CI = 5, 13%) for each 1 g/L decrement of albumin. The total VTE hazard ratio was 1.66 (p = 0.003) for the approximately lowest 5 percent (<34 g/L) compared with the highest 95 percent of serum albumin values. The association was approximately the same for idiopathic and secondary VTE. Further adjustment for HRT, history of cancer, diabetes, eGFR, and BMI (Model 2) attenuated the association somewhat, so that the VTE hazard ratio per standard deviation decrement of serum albumin fell to 1.18 (95% CI = 1.08, 1.31). Further adjustment for fibrinogen, factor VIII and aPTT attenuated this hazard ratio further, but it remained statistically significant for total and secondary VTE.

In contrast with albumin, there was no association of serum total protein with VTE in ARIC (data not shown). For example, the Model 1 hazard ratio of total VTE per standard deviation decrement of total protein was 0.99 (95% CI = 0.91-1.09).

In CHS, the mean ± SD serum albumin was 40.0 ± 2.9 g/L. There were 174 VTE events among 51,262 person-years of follow-up. Although the hazard ratios for VTE among quintiles and per standard deviation decrement were generally similar to those seen in ARIC, they were not statistically significant (Table 3). For example, each 1 g/L decrement in albumin yielded a nonsignificant 3% (95% CI = -3, 9%) greater VTE rate. However, for the lowest approximate 5% (<35 g/L) in CHS, compared with higher values, the Model 1 hazard ratio was 1.85 (95% CI = 1.14, 3.00) for total VTE and 2.23 (95% CI = 1.26, 3.94) for secondary VTE.

Discussion

In the prospective ARIC study, low serum albumin was a modest marker for increased risk of VTE, both idiopathic and secondary. In the smaller CHS project, very low albumin levels also were associated with VTE incidence. There was no association of VTE with serum total protein in ARIC.

Most previous research has not suggested that low serum albumin is a VTE risk marker. However, existing studies (1,3,5,7,10) were usually small and often cross-sectional or retrospective clinical studies, with possible bias introduced by serum albumin being measured after VTE. They often had limited statistical power. They also often focused on nephrotic syndrome patients, who would have the analytical advantage of having a wider range of serum albumin levels, but the disadvantage of having other confounding conditions. No prospective population-based studies had been previously performed, and our study offered good statistical power. The fact that the association for idiopathic VTE was present for ARIC and weaker for CHS may argue against its importance. However, CHS had relatively few idiopathic events and more limited statistical power than ARIC.

We undertook this research mainly because of reports linking albuminuria and the nephrotic syndrome with increased VTE risk (1-8). Although we did not have urinary albumin measures at baseline to identify nephrotic syndrome patients, the nephrotic syndrome is rare enough that it seems an unlikely explanation for our findings. The inverse association of serum albumin with VTE persisted after adjusting for eGFR, suggesting the association is probably independent of gross renal albumin wasting. Serum albumin is well maintained in chronic kidney disease until the estimated glomerular filtration rate falls below approximately 30 ml/min/1.73 m^2 (23), which was rare in these cohorts.

If the association between low serum albumin and VTE is real, it nevertheless is unlikely to reflect a cause and effect relation. More likely, low serum albumin is an indicator ofpoor general health or a marker of a true cause of VTE, such as a hyperinflammatory or hypercoagulable state. The fact that lower serum albumin was associated with higher fibrinogen and factor VIII levels and shorter aPTT suggests that low serum albumin indeed may reflect a hypercoagulable tendency. Unfortunately, we did not have CRP measurements in the full ARIC and CHS cohorts to further explore whether a hyperinflammatory state may explain our findings; however, adjustment for fibrinogen, which is also an inflammatory marker, only modestly attenuated the association of low serum albumin with VTE.

Other drawbacks of this study, besides the limited sample size for CHS and lack of CRP and albuminuria data, warrant consideration. We had a single measure of serum albumin; within-subject variability would tend to obscure associations with VTE. We did not have information on liver enzymes or cirrhosis diagnosis; we thus could not exclude those with altered serum albumin concentrations due to liver disease.(24) We had a limited set of thrombotic risk factors

for VTE by which to test whether they explained the association of VTE with albumin. D-dimer, factor V Leiden, and other common genetic markers for VTE were unavailable in the whole ARIC and CHS cohorts. Finally, as with all epidemiologic studies of VTE, only clinical cases were detected.

In summary, we found evidence that low serum albumin was a modest marker of increased VTE risk. Whether this association has clinical relevance, for example in identifying those at risk of acute VTE, warrants further study.

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Table 1

Baseline participant characteristics* stratified by serum albumin categories, ARIC, 1987-89

Quintile† **Range (g/L)** ***N***	**Q1** **20-36** **2908**	**Q2** **37-38** **4128**	**Q3** **39** **2407**	**Q4** **40** **3703**	**Q5** **41-51** **2154**	**p-values**
Age, years (SD)	54.6 (5.8)	54.4 (5.9)	54.2 (5.8)	53.9 (5.6)	53.6 (5.7)	<0.0001
Male, *n* (%)	928 (31.9)	1727 (41.8)	1122 (46.6)	1020 (49.3)	2110 (55.7)	<0.0001
African Americans, *n* (%)	1137 (39.1)	1106 (26.8)	553 (23.0)	469 (22.7)	823 (21.7)	<0.0001
HRT Use‡, *n* (%)	473 (23.9)	489 (20.4)	209 (16.3)	163 (15.5)	202 (12.1)	<0.0001
BMI, kg/m^2 (SD)	29.3 (6.6)	27.9 (5.4)	27.2 (4.8)	27.1 (4.7)	26.7 (4.3)	<0.0001
Prevalent Diabetes, *n* (%)	361 (12.5)	289 (7.0)	146 (6.1)	142 (6.9)	190 (5.0)	<0.0001
History of Cancer, *n* (%)	175 (1.15)	226 (1.48)	123 (0.81)	112 (0.73)	211 (1.38)	0.53
$eGFR_{creat}$ (ml/min per 1.73 m^2)	97.3 (17.3)	96.1 (14.8)	95.3 (14.8)	95.5 (14.5)	95.3 (14.4)	<0.0001
Factor VIII, % (SD)	146 (48)	132 (38)	128 (36)	127 (35)	124 (35)	<0.0001
aPTT, seconds (SD)	28.9 (3.2)	29.0 (3.0)	29.1 (2.9)	29.1 (2.9)	29.2 (3.0)	0.0003
Fibrinogen, µmol/L (SD)	9.7 (2.4)	9.0 (1.8)	8.7 (1.8)	8.6-1.7)	8.5 (1.6)	<0.0001

*Values are mean (SD) or *n* (%)

†Quintiles are approximate due to rounding of serum albumin measurements.

‡Women only

Abbreviations: aPTT, activated partial thromboplastin time; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; eGFR, estimated glomerular filtration rate; HRT, hormone replacement therapy; Q, quintile

Table 2

Hazard ratios (HR) (95% CI) of venous thromboembolism for quintiles, per standard deviation decrement, and for very low (<5 percentile) baseline serum albumin levels, ARIC, 1987-2005

		HR (95% CI) per Albumin Quintile							
	Range (g/L) ***N***	**Q1** **20-36** **2908**	**Q2** **37-38** **4128**	**Q3** **39** **2407**	**Q4** **40** **3703**	**Q5** **41-51** **2154**	**Trend p-value**	**HR (95% CI) per SD Decrement of Albumin (2.7 g/L)**	**HR (95% CI) for Bottom 5% of Albumin vs Top 95%**
Total VTE	*N* events	104	151	77	37	93		462	462
	Model 1	1.57 (1.18, 2.10)	1.54 (1.19, 2.00)	1.32 (0.97, 1.78)	0.74 (0.51, 1.09)	1.00	<0.0001	1.26 (1.15, 1.39)	1.66 (1.18, 2.33)
	Model 2	1.35 (1.00, 1.82)	1.47 (1.13, 1.92)	1.29 (0.95, 1.74)	0.73 (0.50, 1.07)	1.00	0.0007	1.18 (1.08, 1.31)	1.28 (0.90, 1.84)
	Model 3	1.24 (0.91, 1.68)	1.42 (1.09, 1.85)	1.26 (0.93, 1.71)	0.73 (0.50, 1.07)	1.00	0.005	1.15 (1.04, 1.27)	1.15 (0.79, 1.66)
Idiopathic VTE	*N* events	36	64	28	11	31		170	170
	Model 1	1.60 (0.98, 2.61)	1.93 (1.25, 2.98)	1.43 (0.85, 2.38)	0.66 (0.33, 1.31)	1.00	0.001	1.28 (1.09, 1.49)	1.91 (1.13, 3.22)
	Model 2	1.36 (0.82, 2.25)	1.82 (1.18, 2.82)	1.39 (0.83, 2.33)	0.64 (0.32, 1.27)	1.00	0.009	1.19 (1.02, 1.40)	1.50 (0.86, 2.61)
	Model 3	1.17 (0.70, 1.98)	1.73 (1.11, 2.68)	1.35 (0.81, 2.26)	0.63 (0.32, 1.26)	1.00	0.04	1.13 (0.96, 1.33)	1.25 (0.70, 2.21)
Secondary VTE	*N* events	68	87	49	26	62		292	292
	Model 1	1.57 (1.10, 2.24)	1.35 (0.97, 1.88)	1.27 (0.87, 1.85)	0.79 (0.50, 1.24)	1.00	0.0002	1.26 (1.12, 1.41)	1.53 (0.98, 2.38)
	Model 2	1.36 (0.94, 1.96)	1.30 (0.93, 1.81)	1.24 (0.85, 1.81)	0.78 (0.49, 1.23)	1.00	0.02	1.18 (1.04, 1.33)	1.16 (0.72, 1.86)
	Model 3	1.29 (0.88, 1.87)	1.27 (0.91, 1.77)	1.22 (0.83, 1.78)	0.78 (0.49, 1.23)	1.00	0.05	1.16 (1.02, 1.31)	1.08 (0.67, 1.76)

Model 1: Adjusted for age (continuous), sex, and race (African American, other)

Model 2: Adjusted for age (continuous), sex, and HRT use (3-level categorical variable), race, diabetes status (yes, no), history of cancer (yes, no), eGFR (continuous), and BMI (continuous)

Model 3: Adjusted for Model 2 + Factor VIII (continuous), aPTT (continuous), and fibrinogen (continuous)

Abbreviations: aPTT, activated partial thromboplastin time; ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HRT, hormone replacement therapy; VTE, venous thromboembolism

Table 3

Hazard ratios (HR) (95% CI) of venous thromboembolism for quintiles, per standard deviation decrement, and for very low (<5 percentile) baseline serum albumin levels, CHS, 1989-2002

		HR (95% CI) per Albumin Quintile							
	Range (g/L) ***N***	**Q1** **28-37** **1076**	**Q2** **38-39** **1330**	**Q3** **40** **742**	**Q4** **41-42** **1270**	**Q5** **43-52** **982**	**Trend p-value**	**HR (95% CI) per SD Decrement of Albumin (2.9 g/L)**	**HR(95% CI) for Bottom 5% of Albumin vs Top 95%**
Total VTE	*N* events	48	32	24	42	48		174	174
	Model 1	1.50 (0.93, 2.41)	0.81 (0.49, 1.34)	1.16 (0.67, 2.00)	1.15 (0.71, 1.85)	1.00	0.38	1.12 (0.96, 1.31)	1.85 (1.14, 3.00)
	Model 2	1.41 (0.87, 2.28)	0.79 (0.47, 1.31)	1.11 (0.64, 1.93)	1.14 (0.71, 1.84)	1.00	0.55	1.10 (0.94, 1.29)	1.80 (1.11, 2.93)
	Model 3	1.33 (0.79, 2.24)	0.78 (0.45, 1.35)	1.01 (0.56, 1.83)	1.21 (0.73, 1.98)	1.00	0.89	1.07 (0.90, 1.27)	1.84 (1.05, 3.21)
Idiopathic VTE	*N* events	16	11	10	16	12		65	65
	Model 1	1.21 (0.56, 2.59)	0.65 (0.29, 1.48)	1.12 (0.48, 2.60)	1.02 (0.48, 2.16)	1.00	0.95	0.99 (0.77, 1.28)	1.28 (0.51, 3.21)
	Model 2	1.10 (0.51, 2.39)	0.62 (0.27, 1.41)	1.07 (0.46, 2.50)	0.99 (0.47, 2.10)	1.00	0.77	0.96 (0.75, 1.24)	1.20 (0.48, 3.03)
	Model 3	1.02 (0.46, 2.28)	0.49 (0.20, 1.21)	0.90 (0.36, 2.21)	0.95 (0.44, 2.03)	1.00	0.53	0.93 (0.70, 1.22)	1.27 (0.46, 3.55)
Secondary VTE	*N* events	32	21	14	26	16		109	109
	Model 1	1.72 (0.93, 3.19)	0.92 (0.48, 1.77)	1.18 (0.58, 2.43)	1.25 (0.67, 2.33)	1.00	0.24	1.20 (0.99, 1.47)	2.23 (1.26, 3.94)
	Model 2	1.65 (0.89, 3.08)	0.90 (0.47, 1.74)	1.14 (0.55, 2.35)	1.25 (0.67, 2.33)	1.00	0.32	1.19 (0.98, 1.46)	2.25 (1.27, 3.99)
	Model 3	1.60 (0.80, 3.18)	1.02 (0.51, 2.07)	1.10 (0.50, 2.44)	1.42 (0.74, 2.74)	1.00	0.51	1.17 (0.94, 1.45)	2.30 (1.18, 4.50)

Model 1: Adjusted for age (continuous), sex, and race (African American, other)

Model 2: Adjusted for age (continuous), sex, and HRT use (3-level categorical variable), race, diabetes status (yes, no), history of cancer (yes, no), eGFR (continuous), and BMI (continuous)

Model 3: Adjusted for Model 2 + Factor VIII (continuous), aPTT (continuous), and fibrinogen (continuous)

Abbreviations: aPTT, activated partial thromboplastin time; BMI, body mass index; CHS, Cardiovascular Health Study; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HRT, hormone replacement therapy; VTE, venous thromboembolism