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Serum Uric Acid, Gout, and Venous Thromboembolism: the Atherosclerosis Risk in Communities Study

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Abstract

Introduction—Inflammatory diseases increase risk of venous thromboembolism (VTE).

Whether gout, the most common rheumatologic inflammatory arthritis, or its cause, elevated serum uric acid (SUA), is associated with VTE incidence is unknown.

Materials and Methods—The Atherosclerosis Risk in Communities Study measured SUA in 14 126 participants aged 45–64, without a history of VTE or gout and not using anticoagulants/gout medications, and obtained information on incident gout between 1987 to 1998 from 10 247. We followed them for VTE occurrence from 1987 to 2011. Hazard ratios (HRs) of VTE were estimated using Cox proportional hazards models.

Results—We documented 632 incident cases of VTE (236 unprovoked and 396 provoked). Age, sex, and race-adjusted HRs for total VTE were 1, 1.40, 1.43, 1.91, 1.71, and 3.25 (*P* for trend<0.001) across levels of SUA (range mg/dL: 4.9, 5.0–5.9, 6.0–6.9, 7.0–7.5, 7.6–8.7, and 8.8). After adjustment for other VTE risk factors, those in the highest level of SUA had HRs [95% confidence interval] of 2.13 (1.47–3.07) for total VTE, 2.07 (1.17–3.67) for unprovoked VTE and 2.16 (1.33–3.50) for provoked VTE. Those with incident gout had a nonsignificantly increased risk of total VTE [HR (95% CI): 1.33 (0.95–1.86)].

Conclusions—Elevated SUA was associated with an increased risk of VTE, suggesting that SUA might be a novel risk factor or marker for VTE. Further studies are needed to assess the association between gout and VTE.

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Conflict of Interest

None.

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Keywords

Arthritis; Gout; Inflammation; Uric Acid; Venous Thromboembolism

Introduction

Venous thromboembolism (VTE), manifested by deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common medical problem with an estimated incidence of 1–2 per 1000 person-years (1, 2). Patients who develop VTE have high mortality rates of 11–30% per annum (1–3). Thus, VTE is an important public health concern and is very important to prevent.

While there are several recognized strong risk factors for VTE, such as immobilization, surgery, and malignancy (4), some rheumatologic diseases are positively associated with VTE (5). Yusuf et al. reported that patients with rheumatoid arthritis or systemic lupus erythematosus had about two- and five-fold higher risks of VTE, respectively, than a control group (6). Chronic inflammation accompanying these rheumatologic diseases is considered to increase the risk of VTE by up-regulating procoagulants, down-regulating anti-coagulants, suppressing fibrinolysis, and causing endothelial dysfunction (7). Gout, another rheumatologic disease caused by elevated serum uric acid (SUA), or hyperuricemia, is primarily characterized by arthritis due to monosodium urate crystals deposition in the joints (8). Monosodium urate crystals are pro-inflammatory stimuli that can initiate, amplify, and sustain an intense inflammatory response. Gout is the most common inflammatory arthritis, with an estimated prevalence in the United States of 38 per 1000 adults (9, 10).

In addition, several studies have suggested that SUA itself has a pro-inflammatory effect on vascular cells (11–13). This effect is one of the potential mechanisms to explain the positive association between SUA and atherothrombotic cardiovascular diseases, such as coronary artery disease, although whether SUA is a causally related still remains controversial (14). Therefore, SUA and gout might be expected to be positively associated with VTE, but, to the best of our knowledge, so far there has been no study investigating these associations.

The objective of this study was to prospectively investigate whether elevated SUA and gout are related to increased risk of VTE in a population-based study in the U.S, namely the Atherosclerosis Risk in Communities (ARIC) Study.

Methods

Study Population

The Atherosclerosis Risk in Communities Study is an ongoing prospective study of multiple cardiovascular diseases. The details of the ARIC Study have been described elsewhere (15). Briefly, the ARIC Study recruited and examined 15 792 mostly Caucasian or African American men and women aged 45–64 from 4 U.S. communities (in Washington County, Maryland; Forsyth County, North Carolina; Jackson, Mississippi (African Americans only); and suburbs of Minneapolis, Minnesota) in 1987–1989 (visit 1). The participants were followed-up in 1990–1992 (visit 2, 93% return), in 1993–1995 (visit 3, 86% return), and

1996–1998 (visit 4, 80% return). The institutional review boards of the collaborating institutions approved the study protocol, and each participant provided written informed consent.

Main Exposures: Serum Uric Acid and Incident Gout

One of the exposures of interest was SUA. After an overnight fast before ARIC visit 1, blood was drawn from the participants into tubes with sodium citrate for hemostatic factors, EDTA for lipids, and serum separator gel. Blood samples were centrifuged at 3000 g for 10 min at 4°C and stored at –70°C. SUA was measured within a few weeks using the uricase method (16). A previous study documented a reliability coefficient of 0.91, and a coefficient of variation of 7.2%, by repeated measurements of SUA in 40 individuals, taken at least one week apart (17).

Another exposure of interest was gout history. Participants were asked at visit 4 to provide information on physician-diagnosed gout, including the age of gout onset. Specifically, they were asked, “Has a doctor ever told you that you had gout?” If the answer was yes, they were further asked, “How old were you when you were first told that you had gout?” From these, participants with gout history prior to visit 1 were considered to have a history of gout at baseline. Participants were considered to have incident gout—a main study exposure—if they either reported gout onset from visit 1 to visit 4 or reported the use of colchicine, probenecid, or allopurinol for the first time at visit 2, 3 or 4. Self-report of incident gout in the ARIC Study was shown to be both reliable (3-year reliability kappa=0.73) and sensitive (sensitivity=84%) (18). We obtained information on gout history from 11 506 participants.

For analyses of SUA, starting with 15 642 participants with visit 1 SUA measurements, we excluded those with VTE history or taking anticoagulants prior to visit 1 (n=343), those with gout history or taking gout medications at visit 1 (n=508), participants whose data on any covariates (n=571) were missing, and non-whites in Washington County and Minnesota or non-white/black in Forsyth County (n=94) [the last exclusion allowed us to conduct multivariable adjustment for race and study site (19)]. For analyses of gout, starting with 11 423 participants with visit 1 SUA measurements, similarly we excluded those with VTE history or taking anticoagulants (n=298), those with gout history or taking gout medications at visit 1 (n=439), participants whose data on any covariates (n=378) were missing, and non-whites in Washington County and Minnesota or non-white/blacks in Forsyth County (n=61). After exclusions, 14 126 participants with baseline SUA measurements and 10 247 with information on incident gout at baseline were left for the present analyses.

Potential Confounding Factors

At baseline, ARIC measured a broad set of potential confounding factors for the association of SUA with VTE. They included age (continuous), sex, race/ARIC field center (whites in Washington County, Forsyth County, or Minnesota, or African Americans in Jackson or Forsyth County), body mass index (continuous), prevalent diabetes, smoking status (current, former or ever), glomerular filtration rate (eGFR) (continuous), von Willebrand factor, factor VIII, antithrombin III, protein C and fibrinogen. Body mass index was calculated as weight (kg)/height (m)², prevalent diabetes was defined as a fasting blood glucose of 126 mg/dl or

higher, non-fasting blood glucose of 200 mg/dl or higher, a physician diagnosis of diabetes, or use of antidiabetic medication in the past 2 weeks, and eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (20, 21).

Confirmation of Venous Thromboembolism

ARIC contacted participants annually or semi-annually by phone to ask about all hospitalizations in the previous year through 2011. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) discharge codes were obtained for every hospitalization. Cases of VTE were identified using the following ICD-9-CM codes: 415.1x, 451, 451.1x, 451.2, 451.8x, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7x, 997.2, and 999.2, as well as procedure code 38.7. After identification through ICD-9-CM code, hospital records including additional hospitalizations within the previous 3 months, physician and consultant reports, discharge summaries, and vascular and radiologic studies were copied. Two physicians then validated possible VTEs using them (1). VTEs associated with cancer, major trauma, surgery or marked immobility were classified as “provoked VTE” while all others were classified as “unprovoked VTE”.

Statistical Analysis

We constructed cubic spline graphs with 3 knots at 25, 50 and 75 percentiles in order to investigate the shape of the association between SUA levels and VTE risk (Figure). The risk appeared to be significantly higher at levels of SUA around 8 mg/dL (around 90th percentile). Therefore, to investigate the VTE association for levels of SUA over the 75 percentile in detail, we classified SUA level into 6 categories as follows: 25, 25–50, 50–75, 75–85, 85–95, and 95 percentiles.

Mean values and prevalences of selected factors were compared among the 6 SUA categories using linear or logistic regression analysis, and between the 2 categories of incident gout (yes or no) from visit 1 to visit 4 using ANOVA or χ^2 tests, respectively. The person-years of follow-up for each participant were calculated from the baseline (1987–1989) to the first endpoint: VTE, death, loss to follow-up, or the end of follow-up (2011). Hazard ratios (HRs) and their 95% confidence intervals (CIs) of VTE occurrence were calculated after adjustment for potential confounding factors using Cox proportional hazard models. Model 1 adjusted for age, sex, and race/ARIC field center; Model 2 additionally for body mass index, diabetes status, smoking status, eGFR, von Willebrand factor, and factor VIII. The linear trend of HRs across the level of SUA was tested using Cox-model by including the median value of SUA for each category.

For sensitivity analysis, we (i) additionally adjusted for diuretics and prevalent coronary heart disease, stroke and heart failure (Model 3) and (ii) also ran models using shorter-follow-up time for VTE (10 years from baseline).

The proportional hazards assumption in Cox regression was tested using risk factor-by-time interactions and was not violated. Since we found no statistical interactions between sex or race and exposures in relation to VTE risk, an analysis pooled across sex and race was conducted. SAS version 9.3 software (SAS Institute Inc., Cary, NC) was used for statistical

analyses. All statistical tests were two-tailed and *P* values <0.05 were regarded as significant.

Results

Baseline Characteristics According to Serum Uric Acid Level or Incident Gout

The mean value $\pm$ S.D. of baseline SUA in 14 126 ARIC participants was 6.0 ± 1.5 . Their mean age was 54.6 years, 55.6% participants were female, 25.8% were African Americans, and 18.7% were diuretic-users. As shown in Table 1, those with higher SUA or incident gout were more likely to be African American, have a history of diabetes, heart failure, and coronary heart disease, have higher body mass index and coagulation factors, and use diuretics than those with lower SUA or with no incident gout.

Association of Serum Uric Acid with Venous Thromboembolism

During 279 741 person-years of follow-up, over a median of 22.5 years, we documented 632 incident cases of VTE (236 unprovoked and 396 provoked) among participants with SUA measurements (Table 2). The age-, sex-, and race-adjusted model showed a positive association between SUA levels and VTE risk, with HRs for total VTE across the six categories of SUA being 1.00, 1.40 (95% CI: (1.10–1.78), 1.43 (1.11–1.84), 1.91 (1.41–2.57), 1.71 (1.25–2.34), and 3.25 (2.32–4.56) (*P* for trend <0.001). A similar trend was observed for VTE subtypes. Further adjustments for body mass index, diabetes status, smoking status, eGFR, von Willebrand factor, factor VIII, antithrombin III, protein C and fibrinogen (Model 2) attenuated the associations, but the highest level of SUA was still associated with elevated risks of total VTE [HR (95% CI): 2.13 (1.47–3.07)], deriving from both unprovoked VTE [2.07 (1.17–3.67)] and provoked VTE [2.16 (1.33–3.50)].

Association of Incident Gout with Venous Thromboembolism

The age-, sex-, and race-adjusted model showed a positive association between SUA levels and VTE risk, with the HR for total VTE for those with incident gout being 1.49 (95% CI: (1.07–2.08). Further adjustment (Model 2) attenuated the total VTE HR to 1.33 (0.95–1.86), which was no longer significant.

Sensitivity Analysis

When we further adjusted for diuretic use, history of heart failure and coronary heart disease (Model 3 in Table 2), we found almost identical associations of SUA levels and incident gout and VTE risk. When we ran models using shorter follow-up intervals (within 10 years from baseline), similar trends were observed although the analyses were less likely to be statistically significant, due to the smaller number of VTE events (137 cases for 10 years follow-up) (data not shown).

Discussion

In this prospective population-based cohort, we found elevated SUA was associated with increased risk of VTE. Those with incident gout were also likely to have a higher risk of VTE although the association was not statistically significant. To the best of our knowledge,

this is the first study to investigate the association of SUA or gout with VTE occurrence. The association was moderately strong, with little elevation of VTE risk until levels well above the highest quartile of SUA. Yet, generally, the association of SUA or gout with VTE (1 to 2 times risk) seemed weaker than VTE associations with more severe rheumatologic diseases, like systemic lupus erythematosus (5 times risk) or rheumatoid arthritis (2 times risk) (5–7).

Serum Uric Acid and Venous Thromboembolism: Risk Factor or Marker?

Inflammation is considered to be a key mechanism by which rheumatologic diseases such as rheumatoid arthritis may increase the risk of VTE. The inflammatory process initiates clotting, impairs the fibrinolytic system and decreases the activity of natural anticoagulation mechanisms (22). During states of endothelial disturbances, release of platelet activating factor and endothelin-1 promotes vasoconstriction, whereas production of von Willebrand factor, tissue factor, plasminogen activator inhibitor-1, and Factor V augment thrombosis (23). Furthermore, endothelial cells are activated, resulting in increased surface expression of certain cell adhesion molecules, promoting the adhesion and activation of leukocytes (23). This event initiates and amplifies inflammation and thrombosis (23). It has been suggested that SUA has proinflammatory effects on vascular cells (14, 24). Intracellular uric acid could induce oxidative stress whereas in blood vessels, SUA decreases nitric oxide production while increasing production of reactive oxygen species, vascular inflammation and proliferation of vascular smooth muscle cells with inhibition of endothelial-cell growth (14, 24). In fact, a previous population-based study reported elevated SUA was positively associated with inflammatory cytokines, interleukin-6, C-reactive protein and tumor necrosis factor- α (25). Therefore, it seems plausible that elevated SUA may increase the risk of VTE through inflammation. At this time, however, we clearly cannot conclude whether elevated SUA is a causal risk factor or merely a risk marker for VTE, and further studies will be needed. Yet, SUA is a low-cost biomarker that could be studied for adding to VTE risk prediction.

Incident Gout and Venous Thromboembolism

Although we did not observe a significant association between incident gout and VTE probably because of limited statistical power (only 40 gout cases), those with incident gout tended to have an elevated risk of VTE. This is consistent with the association between SUA level and VTE risk. Another reason for no significant association may be that gout treatment with anti-inflammatory or SUA-lowering drugs, especially during acute flare-ups may sufficiently reduce vascular inflammation so as to prevent the excess VTE risk of hyperuricemia. Chronic inflammation as well as acute inflammation might be key in the pathophysiology of VTE, as it is for atherothrombosis (26).

Strengths and Limitations

The strengths of our study include its prospective design, long follow-up, and validated VTE events.

Nonetheless, some limitations need to be addressed. First, as already noted, statistical power was limited for the gout group. Second, incident gout history was obtained by self-report, not by documentation of monosodium urate crystals in joint fluid or application of published

gout classification criteria (27). Although self-report of gout in ARIC Study has good reliability and sensitivity (18), we cannot rule out the possibility of misclassification of gout status, which would likely attenuate observed associations. Second, ascertainment of gout was conditional on survival to and participation in visit 4, when gout status was assessed. If gout patients who did not complete visit 4 had more severe disease, their omission could have masked an association between gout and VTE.

Conclusion

We found in the prospective population-based ARIC cohort that elevated SUA was associated with a higher risk of VTE and those with incident gout were also likely to have an elevated risk of VTE although the association was not statistically significant. Elevated SUA might be a novel risk factor or marker for increased VTE risk. Further studies are needed to investigate whether elevated SUA or gout is a causal risk factor or a marker for VTE.

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Highlights

- Whether serum uric acid (SUA) and gout are associated with VTE is unknown.
- We examined the associations of SUA and gout with VTE risk using ARIC study.
- Elevated SUA was associated with increased risk of VTE, but gout was not.
- Elevated SUA might be a novel risk factor or marker for increased VTE risk.

Figure. Multivariable adjusted (Model 2) association of serum uric acid (SUA, mg/dL) with total venous thromboembolism. Solid, dashed lines, and dots represent hazard ratios, 95% confidence interval, and 25, 50, and 75 percentiles, respectively. The reference value was a median value of the lowest SUA category.

Baseline Characteristics of Participants According to Serum Uric Acid Level at Visit 1, 1987–89 and Incident Gout from Visit 1 to 4, 1987–1998.

Table 1

	Serum uric acid, median (range) mg/dL							Incident gout	
	4.3 (4.9)	5.4 (5.0–5.9)	6.4 (6.0–6.9)	7.2 (7.0–7.5)	8.0 (7.6–8.7)	9.3 (8.7)		No	Yes
No. at risk	3633	3701	3349	1368	1432	643		9600	647
Age, years	53.6±5.7	54.6±5.7	55.0±5.6	55.3±5.9	55.3±5.8	55.3±5.8		54.3±5.7	53.5±5.6
Female, %	85.4	62.3	41.4	33.6	28.4	30.9		56.7	51.6
African American, %	21.1	24.8	25.4	28.2	32.1	41.2		19.3	45.4
Body mass index, kg/m ²	25.2±4.4	27.2±5.0	28.4±5.3	29.2±5.2	29.7±5.2	30.6±5.7		27.3±5.0	28.8±5.8
Diabetes, %	8.7	10.7	11.6	12.9	14.7	18.5		8.3	12.2
Current smoker, %	27.9	27.5	25.9	24.7	23.7	24.4		21.5	29.5
eGFR, ml/min/1.73m ²	107±13	104±14	101±15	99±16	98±18	93±22		102±14	104±17
von Willebrand factor, %	112±43	115±47	117±47	120±46	126±52	136±59		113±44	120±47
Factor VIII, %	127±36	129±38	130±38	134±40	138±43	147±51		127±36	136±40
Antithrombin III, %	111±21	111±22	111±22	112±22	112±22	114±23		110±21	112±22
Protein C, µg/mL	3.1±0.6	3.2±0.6	3.2±0.6	3.2±0.6	3.2±0.6	3.3±0.7		3.2±0.6	3.2±0.6
Fibrinogen, %	295±61	301±63	305±66	308±68	310±69	316±72		296±61	304±60
Diuretic use, mg/dL	9.3	13.3	19.0	24.9	35.0	51.3		15.8	24.4
History of heart failure, %	2.1	2.9	4.4	6.0	8.1	12.4		3.0	4.9
History of coronary heart disease, %	1.8	3.3	5.4	6.7	8.4	9.8		3.0	4.6

All differences among groups were statistically significant at $p < 0.05$.

Values are mean ± standard deviation for continuous variables and % for categorical variables.

Table 2

Hazard Ratios and 95% Confidence Intervals for Venous Thromboembolism (VTE) According to Serum Uric Acid Level at Visit 1, 1987–89 and Incident Gout from Visit 1 to 4, 1987–1998.

	Serum uric acid, median (range) mg/dL							Incident gout	
	4.3 (4.9)	5.4 (5.0–5.9)	6.4 (6.0–6.9)	7.2 (7.0–7.5)	8.0 (7.6–8.7)	9.3 (8.7)	P for trend	No	Yes
No. at risk	3633	3701	3349	1368	1432	643		9600	647
Person-years	75 445	74 852	66 048	26 057	26 452	10 887		208 704	13 403
Total VTE, cases	118	167	147	77	69	54		408	40
Model 1	1	1.40 (1.10–1.78)	1.43 (1.11–1.84)	1.91 (1.41–2.57)	1.71 (1.25–2.34)	3.25 (2.32–4.56)	<0.001	1	1.49 (1.07–2.08)
Model 2	1	1.24 (0.98–1.59)	1.16 (0.89–1.51)	1.46 (1.07–2.00)	1.25 (0.90–1.74)	2.13 (1.47–3.07)	0.001	1	1.33 (0.95–1.86)
Model 3	1	1.23 (0.96–1.57)	1.12 (0.86–1.46)	1.39 (1.02–1.91)	1.15 (0.82–1.62)	1.90 (1.30–2.78)	0.014	1	1.32 (0.94–1.84)
Unprovoked VTE, cases	50	55	56	25	26	24			
Model 1	1	1.10 (0.74–1.61)	1.29 (0.87–1.93)	1.48 (0.90–2.45)	1.53 (0.93–2.53)	3.45 (2.06–5.77)	<0.001		
Model 2	1	0.95 (0.64–1.41)	1.01 (0.67–1.53)	1.11 (0.66–1.87)	1.05 (0.62–1.79)	2.07 (1.17–3.67)	0.054		
Model 3	1	0.95 (0.64–1.40)	0.99 (0.65–1.50)	1.07 (0.63–1.82)	0.99 (0.57–1.69)	1.90 (1.05–3.42)	0.129		
Provoked VTE, cases	68	112	91	52	43	30			
Model 1	1	1.63 (1.20–2.21)	1.53 (1.10–2.12)	2.23 (1.53–3.25)	1.85 (1.24–2.76)	3.18 (2.03–4.98)	<0.001		
Model 2	1	1.46 (1.07–2.00)	1.26 (0.90–1.78)	1.74 (1.17–2.59)	1.39 (0.91–2.13)	2.16 (1.33–3.50)	0.010		
Model 3	1	1.44 (1.06–1.96)	1.21 (0.86–1.71)	1.64 (1.10–2.44)	1.27 (0.82–1.96)	1.89 (1.15–3.12)	0.054		

Model 1: Adjusted for age, sex, and race/ARIC field center.

Model 2: Adjusted for Model 1 + body mass index, diabetes, smoking status, eGFR, von Willebrand factor, factor VIII, antithrombin III, protein C, and fibrinogen.

Model 3: Adjusted for Model 2 + diuretic use, history of heart failure and history of coronary heart disease.

The linear trend of HRs across the level of SUA was tested using Cox-model by including the median value of SUA for each category.