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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 14126 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 and 1998 from 10247. 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.

1. 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.

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2. Methods

2.1. 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.

2.2. 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.

2.3. 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].

2.4. 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: 415.1×, 451, 451.1×, 451.2, 451.8×, 451.9, 453.0, 453.1, 453.2, 453.8, 453.9, 996.7×, 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”.

2.5. 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 (Fig. 1). 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

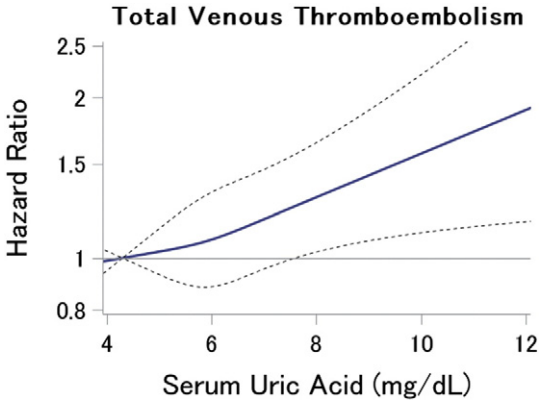

Fig. 1. Multivariable adjusted (Model 2) association of serum uric acid (SUA, mg/dL) with total venous thromboembolism. Solid, dashed lines, and dots represent hazard ratios, 95% confidence interval, and 25, 50, and 75 percentiles, respectively. The reference value was a median value of the lowest SUA category.