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Serum urate levels and the risk of hip fractures: data from the Cardiovascular Health Study☆

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ABSTRACT

Purpose. Uric acid inhibits vitamin D activation experimentally and higher serum urate levels are associated with higher parathyroid hormone levels in humans suggesting a link between uric acid and bone health. We hypothesized that hyperuricemia may increase the risk of fractures in older adults.

Methods. 1963 men and 2729 women ≥65 years of age who participated in the Cardiovascular Health Study and had baseline serum urate levels were included in the study. The primary outcome was incident hip fracture, assessed prospectively through June, 2008 by inpatient and outpatient records. The analysis was stratified by sex a priori.

Results. There was a U-shaped relationship between serum urate levels and hip fractures in men. Men in the lowest and the highest urate quartiles (<4.88 and ≥6.88 mg/dL respectively) had a significantly higher rate of fractures in unadjusted analysis. However, upon multivariate adjustment, only the HR for hip fracture in highest quartile versus the reference remained significant (HR 1.9; 95% C.I. 1.1, 3.1; p value 0.02). High serum urate levels were not associated with hip fractures in women.

Conclusion. In this large prospective cohort of community-dwelling older adults, increased serum urate levels were associated with an increased risk of hip fractures in men. Further studies are needed to confirm these findings and to understand the mechanisms that underlie them.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; 1,25(OH)$_2$D, 1,25 dihydroxyvitamin D; 25(OH)D, 25 hydroxyvitamin D; U.S, United States; CHS, cardiovascular health study; BMI, body mass index; HOMA-IR, homeostatic model of insulin resistance; CRP, C-reactive protein; cys eGFR, cystatin C estimated glomerular filtration rate; PA, physical activity.

☆ Disclosures: Tapan Mehta, Petra Bůžková, Mark J. Sarnak, Michel Chonchol, Jane Cauley, Erin Wallace, Howard A. Fink, John Robbins, and Diana Jalal declare that they have no conflict of interest.

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1. Introduction

Low bone mineral density (BMD) is common and leads to an increased risk of fractures in the aging population. Recent analysis of the National Health and Nutrition Examination Survey (NHANES) estimates that 19% of older men and 30% of older women are at increased risk of fractures [1].

Hyperuricemia may affect vitamin D metabolism as patients with gout have lower $1,25(OH)_2D$ levels than normal controls. Treatment of hyperuricemia in such individuals increases $1,25(OH)_2D$ levels with no change in 25(OH)D [2] suggesting that hyperuricemia may have a suppressive effect on 1-α hydroxylase activity. Consistent with this, we recently published that uric acid suppresses 1-α hydroxylase protein expression and activity [3]. In addition, we and others have shown that higher serum urate levels correlate with higher parathyroid hormone levels [3,4]. Such data would suggest that high urate levels may be associated with impaired bone health. Yet, several recent observational studies have shown the contrary. Increased serum urate levels have been associated with increased BMD in men [5] and in women [6]. In recent analyses, high serum urate levels were associated with a lower risk of fractures in Korean [7] and American men [8] and lower serum urate levels (rather than higher) were associated with a higher odds or fracture in Korean women [9]. These studies, however, are limited by the small number of participants [6], inclusion of younger participants [5,7], and their cross sectional nature [5,9,10]. Importantly, the majority of these studies were performed outside the United States (U.S.) where the prevalence of metabolic syndrome and its definition differ from Asian and other populations [11–13].

The Cardiovascular Health Study (CHS) is a population-based longitudinal study of older adults (aged 65 years or more) [14]. The study collected serum urate levels and hip fracture data. Thus, we utilized data from CHS to examine the hypothesis that higher serum urate levels are associated with a higher risk of hip fracture in older adults in the U.S.

2. Methods

2.1. Study population

CHS is a prospective observational study consisting of community-dwelling adults aged 65 years or older. The primary objective of the study was to identify risk factors for coronary artery disease and stroke in older adults. Details of the study design, sampling, and recruitment were published elsewhere [14]. Briefly, the main cohort (5201 participants) was recruited between 1989 and 1990 from a random sample of Medicare-eligible individuals in the following communities: Forsyth County, NC; Sacramento County, CA; Washington County, MD; and Pittsburgh, PA. In addition, 687 African–American men and women were recruited in 1992 and 1993. Participants were seen yearly. Subjects were excluded from the original study if they were institutionalized, had cancer or other life-threatening diseases, were planning to move out of the area in the next 3 years, or required a proxy to give consent [14]. Study visits ceased after 1999 but data collection continued with telephone interviews that obtained information on hospitalizations. Medicare administrative claims data were used to help enhance the surveillance of events and deaths. The institutional review board at each site approved the study methods, and all participants gave written informed consent.

2.2. Exposure variable and outcomes

Serum urate was the exposure variable. Serum urate levels were measured during the 1992/93 visit after an 8 h fast. A Kodak Ektachem 700 analyzer was used; the detailed method including the lab draw, quality assurance, and assay performance was previously published [15]. The primary outcome was incident hip fracture. This was defined as first hospitalization for hip fracture after the 1992/93 visit by International Classification of Diseases, Ninth Revision (ICD-9) code 820.xx as per previous CHS publications [16,17]. This included inpatient fracture data from CHS 1992/93 until June 30 2008, death, or non-fatal censoring.

2.3. Covariates

Covariates were chosen for inclusion in the multivariate models based on physiological relevance or reports of association with serum urate levels, hip fracture, or BMD. Age, race, and smoking status were determined by patient self-report. Body weight was measured using a calibrated balance beam scale. Height was measured with a wall-mounted stadiometer. Body mass index (BMI) was calculated as kg/m^2. Smoking was defined as current, former, or never. Alcohol intake was defined as none, 1–7 drinks per week, and 7 or more drinks per week. A physical activity score (PA) was calculated based on the type and intensity of physical activity reported by participants [18]. We summed leisure-time activity measured by kilocalories expended per week (ordinal score of 1–5 for quintiles) and pace of walking (ordinal score of 1–3 for pace <2 mph, 2–3 mph, and >3 mph respectively) and categorized as 0 for score 2 to 3, 1 for score 4 to 6, and 2 for score 7 to 8, with higher scores representing greater physical activity.

Other measures such as difficulty getting out of a bed or chair (yes/no) and history of falling in the last year (yes/no) were included. Blood pressure was measured in a sitting position after at least 5 min of rest using standard sphygmomanometry. Hypertension was defined as systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg or if the individual was taking anti-hypertensive medications. A participant was considered to have diabetes if he/she used hypoglycemic agents or had a fasting glucose level ≥126 mg/dL. Prior history of cardiovascular disease was defined as self-reported history of angina, myocardial infarction, coronary angioplasty, coronary bypass surgery, or death due to coronary heart disease. Homeostatic model of insulin resistance (HOMA-IR) was calculated using the following formula: [fasting glucose (mmol/L)]*[fasting insulin (U/mL)]/22.5 [19]. High sensitivity C-reactive protein (CRP) was measured as mg/L using an automated assay on the BNII nephelometer from Dade Behring (N High Sensitivity CRP, Dade Behring, Deerfield, IL, USA). Detailed optimization of the