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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.

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Disclosures:

Tapan Mehta, Petra B žková, 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.

Authors' contributions:

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Diana Jalal: hypothesis conception, data analysis planning, and manuscript oversight and critical editing

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.

Keywords

urate; fractures; bone health

1.0 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 of 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 differs 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.

2.0 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 (5,201 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 hour fast. A Kodak Ektachem 700 analyzer was used; the detailed method including the lab draw, quality assurance, and assay performance were 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 the 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 minutes 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: $[\text{fasting glucose (mmol/L)}] \times [\text{fasting insulin (U/mL)}] / 22.5$ [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 Inc., Deerfield, Ill., USA). Detailed optimization of the assay is as previously published [20]. Participants were asked to bring into the clinic all current prescription and over the counter medications. The following medications were included in the multivariate models: thiazide and loop diuretics, thyroid replacement, and estrogen in women. As described previously [21], cystatin C concentrations were measured using a BN II nephelometer (Dade Behring Inc., Deerfield, Illinois). The intra-assay coefficient of variation was <2.9% and the interassay coefficient of variation was <3.2%. Cystatin C–estimated glomerular filtration rate (cys-eGFR) was calculated using the equation: $\text{eGFR}_{\text{cys}} = 76.7 \cdot \text{cystatin C [mg/L]}^{-1.19}$ [22].

2.4 Statistical Analysis

Given the established differences in serum urate levels and the risk of hip fracture between men and women, all analyses were stratified by sex *a priori*. High serum urate levels are defined as >7 mg/dL in men and >6 mg/dL in women [23]. Baseline characteristics are shown separately for participants with high and normal serum urate levels as mean $\pm$ SD for continuous variables and as count (%) for categorical variables. For skewed variables we provide medians (interquartile range). Clinical and demographic variables across high and normal serum urate groups were compared using t-tests for continuous variables and χ^2 tests for categorical variables.

Time to incident hip fracture was calculated as the interval in years from the visit in 1992/1993 to the earliest date of first incident hip fracture, death, loss to follow-up, or end of follow-up on June 30, 2008. Kaplan-Meier curves were generated to describe incident hip fracture free survival across high and normal serum urate. Log rank test was used to compare the curves. Cox proportional hazards models were used to estimate the hazard ratio (HR) of incident hip fracture associated with serum urate. As a primary predictor, we used the binary high/normal serum urate variable. Normal serum urate was the reference category. To investigate the association of incident hip fracture with continuous serum urate, we explored the serum urate's functional form with splines. There was a strong suggestion of a quadratic association between serum urate and incident hip fracture in men. With a quadratic term, the logarithm of HRs is not necessarily constant across values of serum urate but a linear relationship is allowed. The equation for computation of a HR of incident hip fracture associated with a serum urate increase of x units from level u is $\exp \{ \log \text{HR}_{\text{linear}}$

term* $x + \log \text{HR_quadratic term}*(2ux+x^2)$. For simplicity, we present a table with the HRs for incident hip fracture in men for increases in serum urate levels from 6 mg/dL to 7, 8, 9, and 10 mg/dL. Additionally, we constructed sex-specific quartiles of serum urate. The quartiles in men were < 4.88, 4.88-5.87, 5.88-6.87, and 6.88 mg/dL for quartiles 1, 2, 3, and 4 respectively. In women, serum urate quartiles were defined as: <4.08, 4.08-4.87, 4.88-5.97, 5.98 mg/dL for quartiles 1, 2, 3, and 4 respectively. We repeated the incident hip fracture analysis with the serum urate quartiles, with quartile 2 as the reference category based on the spline.

The multivariate model was adjusted for: demographics (age and race), BMI, smoking status, alcohol intake, PA score, difficulty rising from bed or chair, diabetes, hypertension, HOMA-IR, c-reactive protein (CRP, logarithm), prevalent coronary heart disease, thiazide diuretic use, loop diuretic use, thyroid replacement, and use of estrogen in women. In order to address kidney disease as a potential confounder, we adjusted for cystatin C- estimated GFR (cys eGFR) in addition to the other covariates included in the multivariate model. In each model we evaluated the validity of the proportional hazards assumption graphically and numerically using Schoenfeld residuals and found no meaningful departures.

Two side p-values of <0.05 were considered statistically significant. Analyses were conducted using R (R Development Core Team (2009)) [24].

3.0 Results

3.1.0 Association between serum urate levels and incident hip fractures

3.1.1. Characteristics of the subjects

Men: Of the 5265 CHS participants in 1992/93, 4692 had serum acid levels available and were included in the analysis. The participants with no urate measurement were older, had higher blood pressure, and exercised less. In addition, they were more likely to be women. Of the 4692 with serum uric levels, 1963 were men; the average age was 75 years. 430 (22%) had high urate levels greater than 7 mg/dL. As shown in Table 1, subjects with higher urate levels were heavier, had significantly higher values of insulin, CRP, cystatin C and lower cystatin C- estimated GFR compared to those with normal urate. In addition, those with high serum urate levels were less physically active, and they tended to be black, on diuretics and not in good health.

Women: The clinical characteristics for the women (n=2729) are shown in Table 1. The following were significantly higher in the women with high serum urate levels: age, BMI & weight, time to walk 15 feet (and higher % with low PA scores), black race, diabetes mellitus, serum glucose, insulin, HOMA-IR, use of blood pressure meds (diuretics and β blockers), cystatin C, and CRP. Fewer women with high serum urate levels reported good health compared to the women with normal serum urate levels.

3.1.2 Urate levels and the risk of fractures

Men: There were 156 hip fractures during 18869 person-years of follow-up, yielding an incidence rate of 0.83 hip fractures per 100 person-years. Kaplan-Meier curves and

unadjusted cox regression analyses are shown in Figure 1A and Table 2 respectively. After adjusting for demographics, BMI, smoking, alcohol intake, physical activity, diabetes, HOMA-IR, hypertension, cardiovascular disease, medications, and CRP, men with high urate levels had a 60% increased risk of hip fracture (HR 1.6; 95% C.I. 1.1, 2.5; p value=0.02). This was attenuated slightly after adding cys eGFR to multivariate model but remained significant.

Spline modeling suggested a U-shaped relationship between serum urate levels and risk of hip fractures (Figure 2A), the flex point being 5.94 mg/dL. Thus, specific HRs for hip fracture were calculated for urate levels above 6 mg/dL as compared to 6 mg/dL. As shown in Table 3, urate levels ≥ 8 mg/dL were significantly associated with a higher risk of hip fracture.

Subsequently, when serum urate was categorized into quartiles, the Kaplan- Meier curves (Figure 2B) revealed that more hip fractures occurred in the lowest and highest serum urate quartiles (<4.88 and ≥ 6.88 mg/dL respectively). Cox regression analysis indicated that, when compared to quartile 2, the quartile 4 of serum urate levels was associated with a significantly increased risk of hip fracture in the multivariate model (HR 2.0; 95% C.I. 1.2, 3.2; p value 0.007). This remained significant after cys-eGFR was included in the model. Serum urate levels in quartile 1 were associated with increased HR for hip fractures only in the unadjusted analysis (HR 1.7; 95% C.I. 1.1, 2.6; p value= 0.02). This association was attenuated and no longer significant after adjusting for the variables included in the multivariable model (Table 3).

Women: There were 363 hip fractures during 28790 person-years of follow-up in the women, yielding an incidence rate of 1.22 hip fractures per 100 person-years. We were unable to find an association between baseline serum urate levels and future hip fractures in women. Kaplan-Meier survival curves for high *versus* normal urate levels are presented in Figure 1B. Consistent with the above, high serum urate > 6 mg/dL was not associated hip fractures in Cox regression analysis (Table 2). Similarly, there was no association between serum urate levels and hip fractures when serum urate was modeled as a continuous variable. Generalized additive modeling (spline for urate) did not show a U-shaped relationship between urate and risk of future hip fractures in women (Figure 2C). Kaplan-Meier curves and unadjusted cox regression analyses are shown in Figure 2D and Table 4 respectively. Although we observed an inverse association between urate levels and fracture in unadjusted analyses, the association was attenuated and no longer significant upon multivariate adjustment (Table 4).

The complete multivariate models for the association between serum urate levels and hip fractures are shown in supplementary tables 1S and 2S for both men and women.

3.2.0 Additional Analyses

3.2.1 Interaction with BMI—In an attempt to better understand our results in women, we evaluated the potential interaction of the association between serum urate levels and hip fracture with BMI. First we evaluated the relation between serum urate levels and BMI. Pearson's correlation was 0.33 (95% C.I. 0.29, 0.36) in women, and 0.17 (95% C.I. 0.13,

0.21) in men. We found no interaction in the hip fracture model between serum urate levels and BMI, specifically in the high versus normal serum urate levels: p value for the interaction was 0.65 in men, and 0.87 in women suggesting that BMI does not influence the association between serum urate levels and hip fractures. We then stratified the analysis by BMI ≥ 27 kg/m² and BMI < 27 kg/m². There still was no association between serum urate levels and hip fracture in women in unadjusted or adjusted analysis.

3.2.2 Estrogen replacement therapy—To evaluate whether hormonal factors affected our results in women, we stratified by use of estrogen replacement therapy status. We found 368 women took estrogen versus 2358 did not. Compared to the women who did not take estrogen, the women that did take estrogen had a lower overall incidence of hip fractures (1.1 as opposed to 1.24 per 100 person-year). In addition, the incidence of hip fractures in women with high urate levels who did take estrogen was 0.78 per 100 person-year; lower than the incidence of hip fractures in women with high urate levels who did not take estrogen (1.12 per 100 person-year). We then examined whether high urate levels predict hip fracture in women stratifying by estrogen status. In the 2358 women not taking estrogen, there was no association between high urate levels and future hip fracture in unadjusted or adjusted analysis; the adjusted HR for hip fracture with high versus normal serum urate level was 0.99 (95% C.I. 0.72, 1.36; p value 0.9). In the 358 women taking estrogen there was a trend towards higher risk of future hip fracture in the high urate group compared to the normal urate group, but this did not achieve statistical significance possibly due to the small sample size.

4.0 Discussion

We found that high serum urate levels at baseline were associated with a significantly higher risk of subsequent hip fractures in community-dwelling older men. This association was independent of demographics, smoking, physical activity, and other comorbidities such as diabetes, hypertension, cardiovascular disease, and renal function. In contrast, there was no association between serum urate levels and hip fractures in older women. It is possible that use of a lower cut-off to define hyperuricemia in women as opposed to men (6 mg/dL as opposed to 7 mg/dL) precluded us from identifying an association between high urate levels and hip fractures in women. However, there was no association between serum urate levels and hip fractures in women when serum urate levels were modeled as a continuous variable. In addition, when we examined serum urate levels > 7 mg/dL in women, we still found no association between high urate levels and hip fractures (data not shown). It is likely that factors other than hyperuricemia play a more important role in fracture risk in women such as estrogen deficiency [25]. This is supported by our data above as there was no association between serum urate and future hip fractures in women not taking estrogen replacement therapy. Among the 358 women taking estrogen replacement therapy, there was trend towards a higher risk of future hip fracture in the high urate group as compared to the normal urate group. This did not achieve statistical significance likely due to the small sample size.

Our results differ from the findings of 2 recent studies that examined the association between serum urate levels and fractures in men. Lane et al. found that higher serum urate

levels were associated with a lower risk of nonspine fractures in older men enrolled in the Osteoporotic Fractures in Men study [8]. Hip fractures per se were not associated with serum urate levels in this analysis. In a recent study, Kim et al. [7] also reported that higher serum urate levels were associated with a lower risk of fractures in Korean men. The differences in our findings may reflect differences in the age and race of the populations or available covariates.

Our hypothesis was raised by our experimental finding that uric acid suppressed 1 α -hydroxylase protein expression and activity leading to reduced 1,25 dihydroxy-vitamin D levels [3]. This suppressive effect on vitamin D metabolism could theoretically contribute to our findings. In addition, hyperuricemia has been associated with vitamin D insufficiency [26]. Unfortunately, levels of vitamin D metabolites are unavailable for the participants at the 1992/93 visit. Therefore, we were unable to examine the association between serum urate and fractures in light of vitamin D metabolite levels, and whether the suppressive effect of uric acid on vitamin D activation plays a role in the higher risk of fracture remains unknown.

Urate crystals have been suggested to promote osteoclast development within tophi and their vicinity [27] and may reduce osteoblast activity in vitro [28]. Consistent with these reports fractures have been noted at the site of tophi in patients with tophaceous gout [29]. It is unclear whether hyperuricemia may affect bone health via non-crystal mechanisms in the absence of gout. Although, uric acid has been shown to induce relevant pro- inflammatory pathways in various cell models via non- crystal mechanisms [30, 31], it is unknown if hyperuricemia induces inflammatory pathways in bone tissue by similar mechanisms.

Another potential mechanism by which uric acid may compromise bone health is by impaired nitric oxide (NO) release or availability. Asymptomatic hyperuricemia has been associated with endothelial dysfunction in healthy adults [32, 33]. Although this is controversial [34], in vitro studies have shown that uric acid can suppress NO production by endothelial cells [35]. It may also de-activate NO by reacting with it irreversibly [36]. Organic nitrates have been proposed as a treatment for osteoporosis; one that would improve BMD but also that may improve bone turnover and strength [37], although such therapies have not yet been shown to reduce the risk of fracture. It is possible that hyperuricemia may compromise bone strength indirectly, by impairing NO in the bone and increasing bone fragility and the risk of fracture.

Hyperuricemia has been associated with chronic kidney disease (CKD) in many populations and may contribute to onset and progression of CKD; these studies are reviewed elsewhere [38]. In addition, since uric acid is filtered by the glomerulus, reduced kidney function may lead to hyperuricemia. This association between serum urate levels and estimated GFR is evident in previous analyses of the Cardiovascular Health Study [39]. This raises the concern that the noted association between serum urate and hip fractures maybe be due to CKD and the associated mineral and bone disorder [40, 41]. However, the association between hyperuricemia and hip fractures in men was independent of cys eGFR in our analysis.

Our study has several limitations. First, this is an observational study and not an interventional one. As such treatment of hyperuricemia to prevent hip fractures in older men cannot be justified based on our findings. Second, the study population is restricted to the U.S. and these findings may not be generalizable to other populations. Third, as indicated above, data on bone and mineral metabolism including calcium, phosphorus, vitamin D, and PTH levels are lacking and it remains unclear whether this association is independent of vitamin D deficiency or PTH levels. In addition, we were unable to examine the influence of dietary habits such as vitamin D and caffeine intake on our findings. Finally, although we adjusted for a large number of covariates, the potential for residual confounding remains.

Despite these limitations, our study has several strengths including the long duration of follow up and adjustment for a large number of covariates including age, race, and components of metabolic syndrome.

5.0 Conclusion

We report that high serum urate levels at baseline are associated with a higher risk of hip fractures in older community dwelling men. The adverse effect of uric acid on bone may be mediated via several mechanisms such as reduced vitamin D activation, inflammation, and endothelial dysfunction. . Our findings are in contrast to those by other groups and future studies are needed to better understand the association between serum urate levels and bone health. Such findings may have clinical implications in populations at high risk of fracture such as the elderly and in patients with chronic kidney disease since hyperuricemia is a potentially treatable condition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NHANES	National Health and Nutrition Examination Survey
1,25(OH)₂D	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

References

1. Dawson-Hughes B, Looker AC, Tosteson AN, Johansson H, Kanis JA, Melton LJ 3rd. The potential impact of the National Osteoporosis Foundation guidance on treatment eligibility in the USA: an update in NHANES 2005-2008. *Osteoporos Int*. 2012; 23(3):811–20. [PubMed: 21717247]
2. Takahashi S, Yamamoto T, Moriwaki Y, Tsutsumi Z, Yamakita J, Higashino K. Decreased serum concentrations of 1,25(OH)₂-vitamin D₃ in patients with gout. *Metabolism*. 1998; 47(3):336–8. [PubMed: 9500573]
3. Chen W, Roncal-Jimenez C, Lanaspa M, Gerard S, Chonchol M, Johnson RJ, Jalal D. Uric acid suppresses 1 alpha hydroxylase in vitro and in vivo. *Metabolism*. 2014; 63(1):150–60. [PubMed: 24269076]
4. Hui JY, Choi JW, Mount DB, Zhu Y, Zhang Y, Choi HK. The independent association between parathyroid hormone levels and hyperuricemia: a national population study. *Arthritis Res Ther*. 2012; 14(2):R56. [PubMed: 22405053]
5. Sritara C, Ongphiphadhanakul B, Chailurkit L, Yamwong S, Ratanachaiwong W, Sritara P. Serum uric acid levels in relation to bone-related phenotypes in men and women. *J Clin Densitom*. 2013; 16(3):336–40. [PubMed: 22727551]
6. Makovey J, Macara M, Chen JS, Hayward CS, March L, Seibel MJ, Sambrook PN. Serum uric acid plays a protective role for bone loss in peri- and postmenopausal women: a longitudinal study. *Bone*. 2013; 52(1):400–6. [PubMed: 23111314]
7. Kim BJ, Baek S, Ahn SH, Kim SH, Jo MW, Bae SJ, Kim HK, Choe J, Park GM, Kim YH, Lee SH, Kim GS, Koh JM. Higher serum uric acid as a protective factor against incident osteoporotic fractures in Korean men: a longitudinal study using the National Claim Registry. *Osteoporos Int*. 2014
8. Lane NE, Parimi N, Lui L, Wise BL, Yao W, Lay YA, Cawthon PM, Orwoll E. Association of Serum Uric Acid and Incident Nonspine Fractures in Elderly Men: The Osteoporotic Fractures in Men (MrOS) Study. *J Bone Miner Res*. 2013
9. Ahn SH, Lee SH, Kim BJ, Lim KH, Bae SJ, Kim EH, Kim HK, Choe JW, Koh JM, Kim GS. Higher serum uric acid is associated with higher bone mass, lower bone turnover, and lower prevalence of vertebral fracture in healthy postmenopausal women. *Osteoporos Int*. 2013; 24(12):2961–70. [PubMed: 23644878]
10. Nabipour I, Sambrook PN, Blyth FM, Janu MR, Waite LM, Naganathan V, Handelsman DJ, Le Couteur DG, Cumming RG, Seibel MJ. Serum uric acid is associated with bone health in older men: a cross-sectional population-based study. *J Bone Miner Res*. 2011; 26(5):955–64. [PubMed: 21541998]
11. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. *JAMA*. 2012; 307(5):491–7. [PubMed: 22253363]
12. Reynolds K, Gu D, Whelton PK, Wu X, Duan X, Mo J, He J. Prevalence and risk factors of overweight and obesity in China. *Obesity (Silver Spring)*. 2007; 15(1):10–8. [PubMed: 17228026]
13. IDF. International Diabetes Federation; 2006. http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf
14. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, Kuller LH, Manolio TA, Mittelmark MB, Newman A, et al. The Cardiovascular Health Study: design and rationale. *Ann Epidemiol*. 1991; 1(3):263–76. [PubMed: 1669507]

15. Cushman M, Cornell ES, Howard PR, Bovill EG, Tracy RP. Laboratory methods and quality assurance in the Cardiovascular Health Study. *Clin Chem*. 1995; 41(2):264–70. [PubMed: 7874780]
16. Jovanovich A, Buzkova P, Chonchol M, Robbins J, Fink HA, de Boer IH, Kestenbaum B, Katz R, Carbone L, Lee J, Laughlin GA, Mukamal KJ, Fried LF, Shlipak MG, Ix JH. Fibroblast growth factor 23, bone mineral density, and risk of hip fracture among older adults: the cardiovascular health study. *J Clin Endocrinol Metab*. 2013; 98(8):3323–31. [PubMed: 23771921]
17. de Boer IH, Levin G, Robinson-Cohen C, Biggs ML, Hoofnagle AN, Siscovick DS, Kestenbaum B. Serum 25-hydroxyvitamin D concentration and risk for major clinical disease events in a community-based population of older adults: a cohort study. *Ann Intern Med*. 2012; 156(9):627–34. [PubMed: 22547472]
18. Howe TE, Shea B, Dawson LJ, Downie F, Murray A, Ross C, Harbour RT, Caldwell LM, Creed G. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev*. 2011; (7):CD000333. [PubMed: 21735380]
19. Britton KA, Mukamal KJ, Ix JH, Siscovick DS, Newman AB, de Boer IH, Thacker EL, Biggs ML, Gaziano JM, Djousse L. Insulin resistance and incident peripheral artery disease in the Cardiovascular Health Study. *Vasc Med*. 2012; 17(2):85–93. [PubMed: 22402937]
20. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. *Clin Chem*. 1997; 43(1):52–8. [PubMed: 8990222]
21. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest*. 1999; 59(1):1–8. [PubMed: 10206092]
22. Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, Rossert J, Van Lente F, Bruce RD 3rd, Zhang YL, Greene T, Levey AS. Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis*. 2008; 51(3):395–406. [PubMed: 18295055]
23. Kellgren, JH.; Jeffrey, MR.; Ball, J. The epidemiology of chronic rheumatism. Blackwell Scientific Publications; Oxford: 1963.
24. R: A language and environment for statistical computing. 2009. Available from: <http://www.R-project.org>
25. Khosla S, Melton LJ 3rd, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? *J Bone Miner Res*. 2011; 26(3):441–51. [PubMed: 20928874]
26. Peng H, Li H, Li C, Chao X, Zhang Q, Zhang Y. Association between vitamin D insufficiency and elevated serum uric acid among middle-aged and elderly Chinese Han women. *PLoS One*. 2013; 8(4):e61159. [PubMed: 23585876]
27. Dalbeth N, Smith T, Nicolson B, Clark B, Callon K, Naot D, Haskard DO, McQueen FM, Reid IR, Cornish J. Enhanced osteoclastogenesis in patients with tophaceous gout: urate crystals promote osteoclast development through interactions with stromal cells. *Arthritis Rheum*. 2008; 58(6): 1854–65. [PubMed: 18512794]
28. Bouchard L, de Medicis R, Lussier A, Naccache PH, Poubelle PE. Inflammatory microcrystals alter the functional phenotype of human osteoblast-like cells in vitro: synergism with IL-1 to overexpress cyclooxygenase-2. *J Immunol*. 2002; 168(10):5310–7. [PubMed: 11994489]
29. Nguyen C, Ea HK, Palazzo E, Liote F. Tophaceous gout: an unusual cause of multiple fractures. *Scand J Rheumatol*. 2010; 39(1):93–6. [PubMed: 20132078]
30. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L, Johnson RJ. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen- activated protein kinase and cyclooxygenase-2. *Hypertension*. 2003; 41(6):1287–93. [PubMed: 12743010]
31. Kang DH, Han L, Ouyang X, Kahn AM, Kanellis J, Li P, Feng L, Nakagawa T, Watanabe S, Hosoyamada M, Endou H, Lipkowitz M, Abramson R, Mu W, Johnson RJ. Uric acid causes vascular smooth muscle cell proliferation by entering cells via a functional urate transporter. *Am J Nephrol*. 2005; 25(5):425–33. [PubMed: 16113518]

32. Maxwell AJ, Bruinsma KA. Uric acid is closely linked to vascular nitric oxide activity. Evidence for mechanism of association with cardiovascular disease. *J Am Coll Cardiol.* 2001; 38(7):1850–8. [PubMed: 11738284]
33. Erdogan D, Gullu H, Caliskan M, Yildirim E, Bilgi M, Ulus T, Sezgin N, Muderrisoglu H. Relationship of serum uric acid to measures of endothelial function and atherosclerosis in healthy adults. *Int J Clin Pract.* 2005; 59(11):1276–82. [PubMed: 16236080]
34. Jalal DI, Jablonski KL, McFann K, Chonchol MB, Seals DR. Vascular endothelial function is not related to serum uric acid in healthy adults. *Am J Hypertens.* 2012; 25(4):407–13. [PubMed: 22237152]
35. Zharikov S, Krotova K, Hu H, Baylis C, Johnson RJ, Block ER, Patel J. Uric acid decreases NO production and increases arginase activity in cultured pulmonary artery endothelial cells. *Am J Physiol Cell Physiol.* 2008; 295(5):C1183–90. [PubMed: 18784379]
36. Gersch C, Palii SP, Kim KM, Angerhofer A, Johnson RJ, Henderson GN. Inactivation of nitric oxide by uric acid. *Nucleosides Nucleotides Nucleic Acids.* 2008; 27(8):967–78. [PubMed: 18696365]
37. Jamal SA, Reid LS, Hamilton CJ. The effects of organic nitrates on osteoporosis: a systematic review. *Osteoporos Int.* 2013; 24(3):763–70. [PubMed: 23306823]
38. Jalal DI, Chonchol M, Chen W, Targher G. Uric acid as a target of therapy in CKD. *Am J Kidney Dis.* 2013; 61(1):134–46. [PubMed: 23058478]
39. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF. Relationship of uric acid with progression of kidney disease. *Am J Kidney Dis.* 2007; 50(2):239–47. [PubMed: 17660025]
40. Ensrud KE, Lui LY, Taylor BC, Ishani A, Shlipak MG, Stone KL, Cauley JA, Jamal SA, Antonucci DM, Cummings SR. Renal function and risk of hip and vertebral fractures in older women. *Arch Intern Med.* 2007; 167(2):133–9. [PubMed: 17242313]
41. Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol.* 2006; 17(11):3223–32. [PubMed: 17005938]

Figure 1.

A: Kaplan-Meier curves for hip fractures according to high *versus* normal serum urate levels in men. High= high urate defined as > 7 mg/dL. Normal= normal serum urate level defined as ≤ 7 mg/dL. Individuals with normal serum urate levels had fewer hip fractures on longitudinal follow up; log-rank test P value= 0.095. **Figure 1B:** Kaplan-Meier curves for hip fractures according to high *versus* normal serum urate levels in women. High= high urate defined as > 6 mg/dL. Normal= normal serum urate level defined as ≤ 6 mg/dL. Women had similar rates of fracture in both groups; log-rank test P value= 0.38.

Figure 2.

A: Log hazard ratio (HR) as a function of serum urate levels in men. There is a U-shaped relationship between serum urate levels and future hip fractures in male participants of the Cardiovascular Health Study. **Figure 2B:** Kaplan-Meier curves for hip fractures according to quartiles serum urate levels in men. Serum urate quartiles were defined as: < 4.88, 4.89-5.87, 5.88-6.87, and 6.88 mg/dL for quartiles 1, 2, 3, and 4 respectively. Individuals in the lowest and highest urate quartiles had the most hip fractures during follow up; log rank test p value= 0.028. **Figure 2C:** Log hazard ratio (HR) as a function of serum urate levels in women. The U-shaped relationship seen between serum urate levels and future hip fractures in male participants was not seen in female participants. **Figure 2D:** Kaplan-Meier curves for hip fractures according to quartiles serum urate levels in women. Serum urate quartiles were defined as: <4.08, 4.08-4.87, 4.88-5.97, 5.98 mg/dL for quartiles 1, 2, 3, and

4 respectively. Individuals in the second quartile had the most hip fractures during follow up; log rank test p value= 0.05.

Table 1

Characteristics of participants according to serum urate level (mg/dL) in men and women:

	Men				Women			
	Total n=1963	Normal urate n=1533	High urate n=430	p value	Total n=2729	Normal urate n=2086	High urate n=643	p value
Serum urate (mg/dL)	5.98 ± 1.5	5.39 ± 1	8.08 ± 1.01		5.09 ± 1.5	4.44 ± 0.93	7.18 ± 1.01	
Age (years)	75 ± 5	75 ± 5	76 ± 6	0.16	75 ± 5	74 ± 5	75 ± 5	<0.001
Black Race (%)	16	14	20	0.007	19	17	23	<0.001
BMI (kg/m ²)	26.6 ± 3.8	26.3 ± 3.8	27.5 ± 3.9	<0.001	27.1 ± 5.3	26.3 ± 4.9	29.6 ± 5.7	<0.001
Weight (kgs)	79.3 ± 12.8	78.5 ± 12.7	81.9 ± 12.9	<0.001	68.1 ± 14.3	66.0 ± 13.1	74.7 ± 15.9	<0.001
Smoking (%)								
Current	9	10	7	0.105	10	10.5	9	0.008
Former	61	60	65		33	31.2	38	
Never	30	30	28		57	58.2	53	
Alcohol intake								
0	46	46	47	0.98	61	60	64	0.14
1-7 drinks/week	38	38	38		32	33	29	
7 drinks/week	16	16	15		7	7	7	
PA score								
0	19	18	24	<0.001	29	27	36	<0.001
1	50	50	49		54	54	54	
2	31	32	27		17	19	10	
Good Health	81	83	72	<0.001	78	80	72	<0.001
Time to walk 15 feet (minutes)	5.4 ± 2.3	5.3 ± 1.9	5.7 ± 3.3	<0.001	5.9 ± 3.0	5.8 ± 3.0	6.3 ± 2.7	<0.001
Fallen (yes/no)	11	11	9	0.33	19	19.5	19	0.87
Times fallen	2.0 ± 2.3	2.1 ± 2.4	1.8 ± 1.7	0.56	1.8 ± 1.7	1.8 ± 1.7	1.9 ± 1.8	0.47

	Men				Women			
	Total n=1963	Normal urate n=1533	High urate n=430	p value	Total n=2729	Normal urate n=2086	High urate n=643	p value
Difficulty getting out of bed (%yes)	4	4	6	0.14	9.5	8	13	<0.001
Systolic blood pressure (mmHg)	135 ±21	135 ±21	136 ±22	0.64	137 ±22	137 ±21	139 ±23	0.02
Diastolic blood pressure (mmHg)	73 ±11	73 ±11	73 ±12	0.74	70 ±11	70 ±11	70 ±12	0.67
Glucose (mg/dL)	111 ±36	111 ±37	109 ±28	0.41	107 ±36	105 ±34	115 ±41	<0.001
Insulin (U/mL)	145 ±25	14 ±23	18 ±30	<0.001	14 ±24	13 ±23	19 ±26	<0.001
Diabetes mellitus (%)	19	19	19	0.828	14	11	21	<0.001
HOMA-IR	4.6 ±12.6	4.4 ±12.7	5.3 ±12.3	0.18	4.3 ±11.4	3.7 ±10.2	6 ±14.4	<0.001
Cys C (mg/L)	1.2 ±0.4	1.1 ±0.3	1.4 ±0.4	<0.001	1.1 ±0.3	1.0 ±0.2	1.3 ±0.5	<0.001
Cys C eGFR (mL/min)	69 ±18	72 ±17	59 ±18	<0.001	75 ±19	79 ±17	62 ±19	<0.001
Loop diuretics (%)	8	5	20	<0.001	9	5	19	<0.001
Beta blockers (%)	13	12	17	0.014	12	10	17	<0.001
Thiazides (%)	13	10	23	<0.001	20	15	36	<0.001
Thyroid medications (%)	5	5	5	1	13	13	13	0.72
CRP (mg/L)	2.4 (1.1, 5.3)	2.2 (1.1, 5.0)	3.4 (1.2, 7.2)	<0.001	2.9 (1.3, 6.3)	2.4 (1.1, 5.6)	5.0 (2.3, 9.3)	<0.001
History of CHD (%)	28	25	37	<0.001	17	16	22	<0.001
Follow-up duration (years)	9.6 ±5.0	10.0 ±4.9	8.4 ±4.9	<0.001	10.9 ±4.7	11.1 ±4.7	9.9 ±4.8	<0.001

Values are expressed as means ± standard deviation or %—percent of patients; BMI=body mass index; GFR= glomerular filtration rate; CRP= c reactive protein (reported as median and IQR); CHD= coronary heart disease.

Table 2

Cox regression analysis for hip fractures in men and women:

	Serum urate level as a categorical variable (high versus normal)	
	Men n=1963	Women n=2086
Unadjusted HR (95% C.I.)	1.4 (1.0, 2.0)	0.9 (0.7, 1.2)
P value	P= 0.1	P= 0.4
Multivariate HR (95% C.I.)	1.6 (1.1,2.5)	1.0 (0.8, 1.4)
P value	P= 0.02	P= 0.8
Multivariate + cys eGFR HR (95% C.I.)	1.5 (1.0,2.4)	1.0 (0.7, 1.4)
P value	P= 0.05	P= 0.98

High serum urate defined as > 7 mg/dL for men and > 6 mg/dL for women. Multivariate model adjusted for: age, race, BMI, smoking, alcohol intake, physical activity, diabetes, HOMA-IR, hypertension, cardiovascular disease, meds (thiazides, loop diuretics, & thyroid meds), and CRP. Cys eGFR: cystatin C estimated- Glomerular Filtration Rate

Table 3

Hazard ratios (HR) when serum urate levels increase from 6 mg/dL in men:

Serum uric acid (mg/dL)	Men	
	HR * (95% C.I.)	P value
7	1.1 (1.0, 1.3)	0.07
8	1.4 (1.1, 1.8)	0.01
9	1.9 (1.2, 3.0)	0.004
10	3.0 (1.5, 6.1)	0.003

* adjusted for model including: age, race, BMI, smoking, alcohol intake, physical activity, diabetes, HOMA-IR, hypertension, cardiovascular disease, meds (thiazides, loop diuretics, & thyroid meds), and CRP. Hazard ratios are for serum urate levels increased from 6 mg/dL.

Table 4

Cox regression multivariate analysis for hip fractures according to serum urate quartiles in men and women:

	Men			
	Quartile 1 < 4.88 mg/dL	Quartile 2 4.89-5.87 mg/dL	Quartile 3 5.88-6.87 mg/dL	Quartile 4 6.88 mg/dL
Unadjusted HR (95% C.I.)	1.7 (1.1, 2.6)	REF	1.1 (0.7, 1.8)	1.8 (1.1, 2.8)
P value	P=0.02		P=0.6	P=0.02
Multivariate HR (95% C.I.)	1.4 (0.9, 2.2)	REF	1.3 (0.8, 2.1)	2.0 (1.2, 3.2)
P value	P=0.2		P=0.3	P=0.007
Multivariate + cys eGFR HR (95% C.I.)	1.5 (0.9, 2.3)	REF	1.3 (0.8, 2.1)	1.9 (1.1, 3.1)
P value	P=0.1		P=0.4	P=0.02
	Women			
	Quartile 1 <4.08 mg/dL	Quartile 2 4.08-4.87 mg/dL	Quartile 3 4.88-5.97 mg/dL	Quartile 4 5.98 mg/dL
Unadjusted HR (95% C.I.)	0.8 (0.6, 1.0)	REF	0.7 (0.5, 0.9)	0.7 (0.5, 0.98)
P value	P=0.1		P=0.01	P=0.04
Multivariate HR (95% C.I.)	0.7 (0.5, 0.97)	REF	0.7 (0.5, 0.98)	0.8 (0.6, 1.2)
P value	P=0.04		P=0.04	P=0.32
Multivariate + cys eGFR HR (95% C.I.)	0.7 (0.06, 1.0)	REF	0.7 (0.5, 0.96)	0.8 (0.6, 1.1)
P value	P=0.05		P=0.03	P=0.2

Multivariate model adjusted for: age, race, BMI, smoking, alcohol intake, physical activity, diabetes, HOMA-IR, hypertension, cardiovascular disease, meds (thiazides, loop diuretics, & thyroid meds), and CRP.

Cys eGFR= cystatin C estimated- Glomerular Filtration Rate.