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Serum uric acid plays a protective role for bone loss in peri- and postmenopausal women: A longitudinal study☆

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ABSTRACT

Objective: Oxidative stress has been linked to osteoporosis. Serum uric acid (UA), a strong endogenous anti-oxidant, has been associated with higher bone mineral density (BMD), lower bone turnover and lower prevalence of fractures in a large cross-sectional study of men. Whether this relationship is present in women and how UA relates to changes in BMD longitudinally has not been examined.
Methods: A sample of 356 peri- and postmenopausal women, mean age 60.5 years was studied. Each individual had baseline BMD and body composition measurements by dual energy x-ray absorptiometry (DXA) and at least one repeat measure, on average 9.7 years later. Annual rate of change in BMD (A%ΔBMD) was calculated. UA was measured at each DXA visit. Calciotropic hormones and bone turnover markers were measured at the final visit only.
Results: Cross-sectional data analyses revealed that women with higher UA levels had significantly higher absolute BMD measures at all skeletal sites. These women also had higher measures of body weight and its components such as lean mass (LM) and fat mass (FM). Results of multiple regression analyses showed a positive association between UA and BMD that remained significant even after accounting for possible confounders including LM and FM. Regression analyses of the longitudinal BMD data demonstrated significant associations between serum UA levels and annual rates of change in BMD at all skeletal sites. After adjustment associations remained significant for lumbar spine, forearm and whole body BMD but not for hip BMD.
Conclusion: Higher serum UA levels appear to be protective for bone loss in peri- and postmenopausal women and this relationship is not affected by changes in body composition measures.

Introduction

Soluble uric acid (UA) is present principally as monosodium urate at physiological pH values and is the final breakdown product of purine metabolism. Historically, UA has been viewed as a waste byproduct, which in excess may cause gouty arthritis and renal stones [1,2]. While it is well recognised that UA in its crystalline state is pro-inflammatory [3], there has been controversy as to the biological roles of soluble UA. Although soluble UA was considered biologically relatively inert, it is now thought that higher serum UA levels within normal physiologic levels (0.15–0.4 mmol/L) [4] may have conferred a selection advantage because of their antioxidant effects [3,5–7].

Indeed, UA accounts for approximately half of the antioxidant properties of human plasma [3]. Evidence from observational and epidemiological studies has linked oxidative stress or low circulating levels of anti-oxidants to reduced bone mineral density (BMD) and osteoporosis [8–11]. On the other hand, increased body weight has been reported as one of the major predictors of elevated levels of serum UA [3,12]. Supranormal serum UA levels (hyperuricaemia) have been associated with presence of the metabolic syndrome [7,12–15] and its components such as diabetes mellitus [16,17], obesity [18–20], hyperlipidemia [21–23] and hypertension [19,24]. Body weight has been related to BMD [25–27]. Numerous previous studies have also reported positive associations between body composition components such as lean body mass and fat body mass and BMD at different skeletal sites [27–30].

In a large population-based study of older men (the CHAMP Study), the CHAMP collaborative recently reported that higher serum UA levels were significantly associated with higher BMD at various skeletal sites after adjusting for covariates [31]. Moreover, higher serum UA levels were associated with a lower prevalence of osteoporosis as determined by either BMD or prevalent non-vertebral fracture status. Whether this relationship is present in women and how UA relates to changes in BMD longitudinally has not been examined.

☆ All authors state that they have no conflicts of interest.

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Methods

Subjects

Study subjects were female twins over 45 years, recruited as part of the Northern Sydney Twin Study, which has been running at the Department of Rheumatology, Royal North Shore Hospital, since 1996. The twins were recruited through the Australian National Health and Medical Research Council (NHMRC) Twin Registry and from local media campaigns. Twins were invited to participate in an investigation into the genetic and environmental determinants of various diseases including osteoarthritis, cardiovascular disease, asthma, and osteoporosis on several occasions. The hospital's Human Research Ethics Committee approved the study. After providing written informed consent, each twin was interviewed separately in accordance with a standard questionnaire to collect demographic, lifestyle and medical history data. The baseline visit was completed by 1980 twins (1997–2006), and 864 of these participants attended at least one follow-up visit (2009–2010).

Except for hormone therapy, twins who used medications or who had medical conditions that could interfere with bone metabolism were excluded from the analysis. Individuals with conditions that might compromise the accuracy of DXA measurements such as severe obesity, the presence of artificial objects such as pacemaker or gallstones, or significant degenerative spine changes were also excluded. Hormone therapy use was recorded and included as a covariate in the statistical analyses. Zygosity in same-sex twins was determined from the twins' self-report using questions from a validated questionnaire [32]. DNA fingerprinting was used to determine zygosity in twin pairs in which their zygosity was either unknown or disputed.

Baseline characteristics and laboratory measurements

Demographic characteristics of the study cohort included age (years), height (m), weight (kg), BMI (kg/m^2), menopausal status (MS), hormone replacement therapy (HRT), physical activity (PA), alcohol intake and smoking history. Menopausal status was categorised as 1 — premenopausal (i.e. having regular menstrual cycles), 2— perimenopausal (i.e. experiencing changes in frequency of their menses or amenorrhoea of at least 3 but less than 12 months) and 3 — postmenopausal (amenorrhoea for 12 consecutive months). Hormone replacement therapy was recorded and accounted for if taken regularly for more than 3 months within the last 12 months. PA was categorised based on time spent on leisure exercise for > 30 minutes per day (0 — none, 1 — <30 min/day, 2 — ≥30 min/day). Alcohol intake was recorded as standard drinks per week and categorised as 0 — none; 1 —≤1 drink per week (social occasions only); 2 — 2–13 drinks per week (moderate) and 3—≥14 drinks per week (excessive). Smoking habits were recorded as 0 — never; 1 — current smoker; 2 — ex-smoker (not smoked in the last 3 months). Self-reported fractures that occurred between baseline and the final visits of the study were also recorded.

Fasting blood samples used in this study were collected at each subject's visit and kept as aliquots at −80° C until analysis. Serum UA was measured from baseline and last visit blood samples. Other biochemical parameters such as creatinine, calcium, albumin and phosphorus and bone markers were measured from the last visit samples only. These tests were performed using standard techniques on a Roche Modular Analytics<P>module (Roche Diagnostics, Germany). The UA assay had a detection limit of 0.01 mmol/L, female reference range of 0.18–0.38 mmol/L and combined measurement of uncertainty of 1.1% at 0.18 and 0.44 mmol/L. Serum calcium was measured by colorimetric assay using p-cresolphthalein. Values were adjusted for circulating albumin levels with a reference range of 2.15–2.5 mmol/L. Glomerular filtration rate (GFR) was calculated using the Cockroft–Gault formula [33,34]. Serum levels of aminoterminal procollagen type I propeptide (PINP) were determined by Electrochemiluminescence immunoassay on a Roche Modular Analytics E170 module (Roche Diagnostics GmbH, Germany). The assay for serum PINP, a marker of bone formation, detects both trimeric and monomeric fractions of PINP. The detection limit was 5 ng/mL with total precision coefficients of variation (CVs) of between 3.8% and 4.2%. Serum concentrations of the aminoterminal cross-linked telopeptide of collagen type I (Serum CTX-I) were measured using a manual immunoassay (Osteomark, Ostex, USA).

Bone Mineral Density and Body Composition Measurements

Lumbar spine (LS), total hip, forearm and whole body scans were performed on a fan beam dual-energy X-ray absorptiometry (DXA) bone densitometer (QDR 4500W, Hologic, Waltham, MA USA) at baseline and follow-up visits. Measurements of bone mineral density (BMD) (g/cm^2) and body composition such as fat mass (FM) (kg) and lean body mass (LM) (kg) were obtained using standard protocols as previously described [29,35]. The same densitometer was used throughout the entire study. Performance of the DXA scanner has been monitored throughout the study. Routine daily QC scans of the Spine Phantom were performed and the coefficient of variation for QC BMD measures in our unit was 0.98%. In vivo reproducibility has been estimated from duplicate scans (155 patients with repositioning between scans) as coefficients of variation (CV) and intraclass correlation (ICC) for BMD and body composition measures. CV and ICC for LS, total hip, femoral neck BMD were 0.74/0.998; 1.23/0.994 and 1.27/0.994 correspondingly. CV and ICC for Total LM were 1.07/0.997 and for Total FM — 1.83/0.997.

Baseline and last visit measurements were used to calculate an annual rate of change in BMD. Commonly accepted annual % change in BMD (%/year ΔBMD) was selected as a longitudinal BMD measure to adjust for difference in time between two end-point visits in study participants [36–41].

Statistical analysis

For comparison between groups of UA tertiles, ANOVA analysis for continuous variables and chi-square tests for categorical variables was performed. Adjusted means across tertiles of uric acid were also reported for bone-related and body composition measures at the final visit. In addition, generalised linear regression models were used to assess the association between UA and BMD at the final visit or annual rate of change in BMD (A%ΔBMD). Lack of independence of BMD measures between dizygotic (DZ) pairs was taken into account using generalised estimating equations. The annual rate of BMD change (A%ΔBMD) was calculated as 100×[BMD at final visit − BMD at baseline]/BMD at baseline/ time interval between the two measurements, and was used to account for differences in the intervals among the study participants. The selection of this common parameter as the outcome variable for the longitudinal data was due to the fact that the vast majority of the participants had only two measurements.

In multivariate regression analysis, BMD or A%ΔBMD were treated as dependent variables, and log UA or A%ΔUA as independent variables. Models were adjusted for known and potential confounders, including GFR, serum calcium and CTX-I levels, age, history of smoking, alcohol intake, HRT use and physical activity. We did not include weight or BMI in models because weight is made up of BMC, lean mass and fat mass. We included both lean mass and fat mass and height as a correction for body size in final models. Regression analyses for relationships between UA and body composition measures were done in a similar manner by treating one of the body composition measures as dependent variable in the regression models. Longitudinal data was also analysed by time dependent mixed regression models.