ORIGINAL ARTICLE

Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women

S. Ishii · M. Miyao · Y. Mizuno · M. Tanaka-Ishikawa ·
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Abstract

Summary Previous studies on the association between uric acid and bone mineral density yielded conflicting results. In this study, we demonstrated positive association between uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Further research is needed to elucidate the underlying mechanism.

Introduction Oxidative stress has been implicated in the pathogenesis of osteoporosis. Uric acid, a potent antioxidant substance, has been associated with bone mineral density but previous studies have yielded conflicting results. The objective of the study was to examine the association between serum uric acid and lumbar spine bone mineral density (BMD).

Methods This was a retrospective analysis of medical records of 615 women, aged 45–75 years, who had lumbar spine BMD measurement by dual-energy X-ray absorptiometry as a part of health checkup from August 2011 to July 2012.

Results Mean serum uric acid level was 4.7 mg/dL. Serum uric acid level was positively and significantly associated with lumbar spine BMD independent of age, body mass index, smoking, drinking, physical activity, years after menopause, diabetes mellitus, hypertension, serum calcium, estimated glomerular filtration rate, plasma C-reactive protein, and serum alkaline phosphatase (standardized beta=0.078, $p=0.049$). Uric acid rapidly increased until the age of 60 years, and then decelerated but continued to increase thereafter. The association between lumbar spine BMD and uric acid remained significantly positive after excluding women older than 60 years.

Conclusion The present study showed that higher uric acid levels were linearly associated with higher lumbar spine BMD in peri- and postmenopausal Japanese women. Further research is needed to elucidate the underlying mechanism of the association between uric acid and BMD.

Keywords Bone mineral density · Menopause · Osteoporosis · Uric acid

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Introduction

Osteoporosis, a disease characterized by bone fragility and increased risk of fracture, has been chiefly attributed to the decline of ovarian function at menopause and resulting sex steroid deficiency [1]. On the other hand, oxidative stress has also been implicated in the pathogenesis of osteoporosis [1–12]. For example, observational studies suggested that a higher intake of the antioxidant vitamin C was associated with slower decline of bone mineral density (BMD) [10] and lower risk of hip and nonvertebral fractures [9], and that diminution in plasma antioxidant activity or high oxidative stress was observed in patients with osteoporosis compared with those without [4, 6, 8, 11, 12].

In agreement with accumulating evidence supporting the role of oxidative stress as one of the underlying mechanisms of osteoporosis, uric acid, a potent antioxidant substance [13], has been associated with osteoporosis. In a large population-based, cross-sectional study on older men, higher serum uric acid levels were significantly associated with higher BMD at

various sites including the lumbar spine and femoral neck, adjusting for covariates [14]. Higher serum uric acid levels were also associated with a lower prevalence of osteoporosis, vertebral fracture ascertained by lateral spine scans, and history of nonvertebral fracture [14]. Another large cross-sectional study replicated the association of uric acid positively with BMD and negatively with lower prevalence of vertebral fracture in postmenopausal women [15]. This study also demonstrated that uric acid suppressed osteoclastogenesis and reduced the production of reactive oxygen species in osteoclast precursors, providing important evidence that the positive association between uric acid and bone mineral density may be related to the antioxidant effect of uric acid. Moreover, in a longitudinal study on peri- and postmenopausal female twins, higher uric acid levels at baseline were associated with higher BMD at baseline and a slower rate of decline in BMD thereafter, independent of covariates [16].

However, there is also strong evidence linking hyperuricemia with increased risk of cardiovascular disease [17, 18] in which oxidative stress plays an important pathophysiological role [19, 20]. One of the proposed hypotheses explaining this paradox is related to a shift in the prooxidant/antioxidant properties of uric acid depending on its concentration. Experimental studies suggested that uric acid may become prooxidant under certain conditions [21, 22], particularly when it is supersaturated in blood. Therefore, it is conceivable that uric acid may confer protective antioxidant effects or detrimental prooxidant effects when, respectively, present at normal levels or at supersaturated concentrations [23]. One cross-sectional study on young men and women actually demonstrated that *higher* levels of serum uric acid were associated with *lower* BMD at the femoral neck in women after controlling for age, weight, and serum creatinine [24]. Interestingly, uric acid levels in most female participants were within the normal range. Estrogen has an antioxidant property [1] and also reduces serum uric acid by enhancing renal clearance [25]. Therefore, the finding of an inverse association between estrogen and uric acid may be attributable to the confounding effects of estrogen, considering that the women in this study were predominantly premenopausal. However, the effects of age and menopause on the association between uric acid and osteoporosis have not been empirically examined, and further research is needed.

In the present study, we examined the association between uric acid and BMD in peri- and postmenopausal Japanese women. We hypothesized that BMD and uric acid are linearly and positively associated independent of covariates including the menopausal status in the normal range of serum uric acid, but the association becomes inverse in the hyperuricemic range.

Methods

Subjects

This was a retrospective analysis of medical records obtained from Kanto Central Hospital which is a 470-bed urban teaching hospital in Tokyo funded and run by the Mutual Aid Association of Public School Teachers. Teachers who work at public schools and belong to the Association have health checkup annually at the Center for Health Check-up and Preventive Medicine of the Hospital since workers are required by law to have annual health checkup regardless of their age in Japan. Health checkup is performed in a standardized manner, consisting of consultation with a doctor, height and weight measurement, laboratory tests, and several studies including chest X-ray. Lumbar spine BMD measurement by dual-energy X-ray absorptiometry (DXA) is offered optionally for teachers with financial subsidy from the association.

We drew data from the medical records of 3,814 women aged between 45 and 75 years who received a health checkup at the Center from August 2011 to July 2012. Of the women, 638 (16.7 %) out of 3,814 had lumbar spine BMD measurement. Women with chronic kidney disease (estimated glomerular filtration rate (GFR) lower than 60 mL/min/ 1.73 m^2) ($n=10$) or who had received treatment for osteoporosis ($n=8$) were excluded from the analysis. Those who had received treatment for either hypothyroidism ($n=4$) or hyperthyroidism ($n=1$) were also excluded because of the effect of thyroid hormones on bone [26]. No women received oral steroids, loop diuretics, high-dose thiazide diuretics, hormone replacement therapy, or treatment for hyperuricemia or chronic liver disease. After exclusion, 615 women were included in the analysis. This study was approved by the Ethics Committee of Kanto Central Hospital.

Measurements

Standardized interviews and self-reported questionnaires were used to obtain the following information: age (years), smoking habit (current smoker, past smoker, or never smoked), drinking habit [abstainer, infrequent (non-abstainer but one or less drink per week), and light (more than one drink per week but one or less per day), or moderate to heavy (more than one drink per day)], physical activity (any regular exercise or none), age at menopause, medical history, and use of prescription medication. Height and weight were measured using a fixed stadiometer and a digital scale, with the participant wearing light clothing. Body mass index (BMI) was calculated from weight and height.

Fasting blood samples were collected from each participant, and serum uric acid, creatinine, calcium, and alkaline phosphatase were measured using a standard technique with a medical autoanalyzer (BioMajesty JCA-BM2250). The assay

range for serum uric acid was 0.2–200 mg/dL. Plasma C-reactive protein (CRP) was measured using a latex immuno-assay with the assay range of 0.2–4,000 mg/L. Estimated GFR was calculated from age, sex, and serum creatinine [27].

Subjects with a reported history of diabetes mellitus, fasting glucose of 126 mg/dL or higher, or glycosylated hemoglobin levels at 6.5 % or higher were classified as diabetic. Those with a reported history of hypertension, systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher were classified hypertensive.

Bone mineral density measurements

BMD of the lumbar spine was measured by DXA using a GE Lunar Prodigy. A standard quality control program included daily calibrations with machine-specific phantoms to ensure machine accuracy of greater than 98 %.

Statistical analysis

Uric acid becomes insoluble and supersaturated in bodily fluids above a concentration of about 7 mg/dL. The non-parametric locally weighted scatterplot smoothing (LOESS) method was used to determine whether the saturation point affects the functional form of the association between uric acid and BMD. The LOESS method generated a smooth curve of BMD as a function of uric

acid. Visual inspection of the LOESS plot indicated that the relationship between BMD and uric acid was piecewise linear with an inflection (change of slope) at the uric acid value of 4.8, above which the slope appeared steeper (Fig. 1). We then fitted piecewise linear spline models to BMD as a function of uric acid with a fixed knot at 4.8. We also employed generalized additive models to examine the shape of the association between uric acid and BMD accounting for other covariates. The generalized additive model is an extension of the generalized linear model in which one or more independent variables can be modeled with nonparametric smooth functions [28].

The model was initially adjusted for age and BMI (model 1). Covariates for lifestyle risk factors for osteoporosis including physical activity; smoking and drinking habit; years after menopause (coded as 0 if subject had not experienced menopause) (model 2); comorbidity including diabetes mellitus and hypertension (model 3); and serum calcium, alkaline phosphatase (ALP), estimated GFR, and log (CRP) (model 4) were successively added to regression models. The selection of covariates was based on the literature review on factors affecting BMD [29–35].

There were missing values for physical activity in 180 women (29.3 %), years after menopause in 140 women (22.8 %), and drinking habit in 1 woman (0.2 %). These were imputed using the expectation–maximization (EM) algorithm [36].

Statistical analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, NC, USA) and R statistical software

Fig. 1 Plots of lumbar spine bone mineral density against uric acid level. **a** The LOESS plot. **b**–**d** The plots generated using generalized additive models accounting for age (**b**), body mass index (**c**), or estimated glomerular filtration ratio (**d**). The values of the covariates were fixed at their mean when the association between lumbar spine BMD and uric acid were plotted. *BMD* bone mineral density
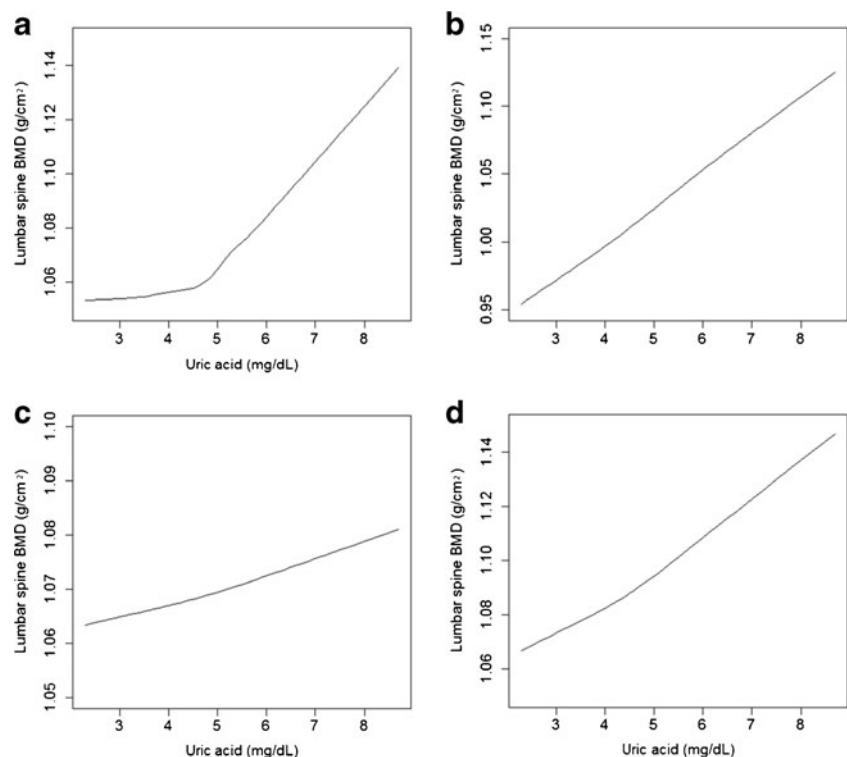
version 2.15.2 (R Foundation, Vienna, Austria). All statistical tests were two-sided, and a p value less than 0.05 was considered statistically significant.

Results

Characteristics of study participants are shown in Table 1. Women included in the analysis were similar to those excluded from the analysis with respect to major characteristics. Of the 615 women included in the analysis, serum uric acid had a mean value of 4.7 mg/dL with standard deviation of 1.0 mg/dL. Only 12 women (2.0 %) had hyperuricemia (i.e., uric acid level higher than 7.0 mg/dL), and 19 (3.1 %)

Table 1 Characteristics of participants

	Participants (n=615)
Uric acid (mg/dL)	4.7±1.0
Lumbar spine bone mineral density (g/cm²)	1.06±0.18
Age (years)	57.6±6.4
Log (CRP in mg/L)[a]	0.12±0.17
BMI (kg/m²)	22.2±3.5
Smoking	
Current	19 (3.1)
Ex	53 (8.6)
Never	543 (88.3)
Drinking[b]	
Abstainer	219 (35.7)
Infrequent	188 (30.6)
Light	171 (27.9)
Moderate to heavy	36 (5.9)
Activity[b]	
Sedentary	283 (65.1)
Active	152 (34.9)
Postmenopausal[b]	373 (78.5)
Age at menopause in postmenopausal women (years)	50.9±3.8
Diabetes	44 (7.2)
Hypertension	114 (18.5)
Serum calcium (mg/dL)	9.3±0.3
Estimated GFR (mL/min/1.73 m²)	97.8±21.6
ALP (IU/L)	223.5±66.3

For continuous variables, the mean is shown with standard deviation. For categorical variables, the number (percentage) is shown. Percentages may not add up to 100 because of rounding errors

BMD bone mineral density, *CRP* C-reactive protein, *BMI* body mass index, *GFR* glomerular filtration rate, *ALP* alkaline phosphatase, *IU* international unit

[a] The natural log (base e) was taken for CRP due to skewed distribution

[b] There were missing values for physical activity in 180 women (29.3 %), years after menopause in 140 women (22.8 %), and drinking habit in 1 woman (0.2 %)

women were obese (i.e., BMI equal to or higher than 30 kg/m²).

Association between BMD and uric acid

In piecewise linear regression of BMD as a function of uric acid with a fixed knot at uric acid level of 4.8 mg/dL, the change in slope at the knot was not statistically significant in univariate analysis and all four models of multivariate analyses (p values=0.31–0.79). The generalized additive models also demonstrated that uric acid was approximately linearly associated with BMD when accounting for each of age, BMI, or estimated GFR (Fig. 1). Therefore, the knot was subsequently dropped. The resulting multiple linear regression models fitted simple linear relationship between uric acid and BMD. Serum uric acid levels were significantly and positively associated with lumbar spine BMD adjusting for age and BMI (model 1, Table 2). The association between uric acid and BMD remained significant after successively adjusting for lifestyle risk factors and years after menopause (model 2); comorbidity (model 3); and serum calcium, estimated GFR, log (CRP), and ALP (model 4). Serum uric acid levels explained 0.48–0.63 % of variance in BMD (R^2=0.187–0.258).

Effect modification

One of the presumed mechanisms of the association between BMD and uric acid is the antioxidant property of uric acid. Considering the complicated and interrelated relationship between oxidative stress and inflammation, we postulated that the degree of inflammation modifies the association between BMD and uric acid. To test this hypothesis, we examined the interaction between log (CRP) and uric acid, but it was not significant (p=0.22).

Table 2 Adjusted associations of serum uric acid with lumbar spine bone mineral density (n=615)

	Beta[a]	%V[b]	p	R^2
Model 1	0.084	0.63	0.03	0.187
Model 2	0.081	0.57	0.04	0.199
Model 3	0.084	0.61	0.03	0.206
Model 4	0.078	0.48	0.049	0.258

Model 1—adjusted for age, BMI; model 2—adjusted for age, BMI, smoking, drinking, physical activity, and years after menopause; model 3—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, and hypertension; model 4—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, hypertension, serum calcium, estimated GFR, log (CRP), and ALP. Abbreviations are as in Table 1

[a] Standardized beta coefficient

[b] Variance of lumbar spine bone mineral density explained by uric acid

Sensitivity analysis

Previous studies have demonstrated that menopause is associated with changes in both BMD and uric acid. Women have a minimal decline in BMD until 1–2 years prior to the final menstrual period when they begin to experience a rapid decline in BMD. The decline in BMD decelerates 1–2 years after the final menstrual period, but continues [37]. On the other hand, postmenopausal status was associated with higher levels of uric acid [38, 39]. Therefore, the associations of age with BMD and uric acid in this study sample of peri- and postmenopausal women may not be linear. The LOESS plots of BMD and uric acid as a function of age demonstrated that both of the relationships were piecewise linear, with an inflection at around the age of 60 (Fig. 2a, b). Uric acid rapidly increased with increasing age until age 60 years, then decelerated but continued to increase. Similarly, lumbar spine BMD declined rapidly with increasing age, but the rate of decline slowed down at the age of 60 years but continued to decline. As a sensitivity analysis, we examined the association between uric acid and BMD after excluding 177 women older than 60. The analysis demonstrated significant and positive associations between BMD and uric acid in all models, with effect sizes slightly larger than those

observed in the main analyses, supporting the robustness of our scientific conclusion (Table 3).

We also conducted another sensitivity analysis after excluding 281 women with any missing values in covariates. This sensitivity analysis revealed slightly larger effect sizes of the association between UA and BMD than those in the main analyses, but the associations failed to reach statistical significance (data not shown).

Discussion

In this cross-sectional analysis of 615 peri- and postmenopausal women aged between 45 and 75 years, higher serum levels of uric acid were significantly associated with higher values of BMD in the lumbar spine, independent of covariates including years after menopause. One standard deviation (1.0 mg/dL in this study population) increment in uric acid was associated with an approximately 0.08 standard deviation increase in lumbar spine BMD. We also demonstrated rapid changes in uric acid and BMD with increasing age until the age of 60, and the rate of changes slowed down thereafter. The positive association between BMD and uric acid remained significant after excluding women older than 60 years.

Our study confirms and extends a previous study that has demonstrated a positive association between BMD and uric acid in peri- and postmenopausal women [15, 16]. We showed that uric acid was positively and linearly associated with lumbar spine BMD, and therefore not only the presence of hyperuricemia but also the magnitude of uric acid elevation plays an important role. Addition of years after menopause did not significantly affect the uric acid–BMD association. We did not observe any sharp inflection point (i.e., change of slope) in the association between uric acid and BMD, incongruent with our hypothesis that the association between uric acid and
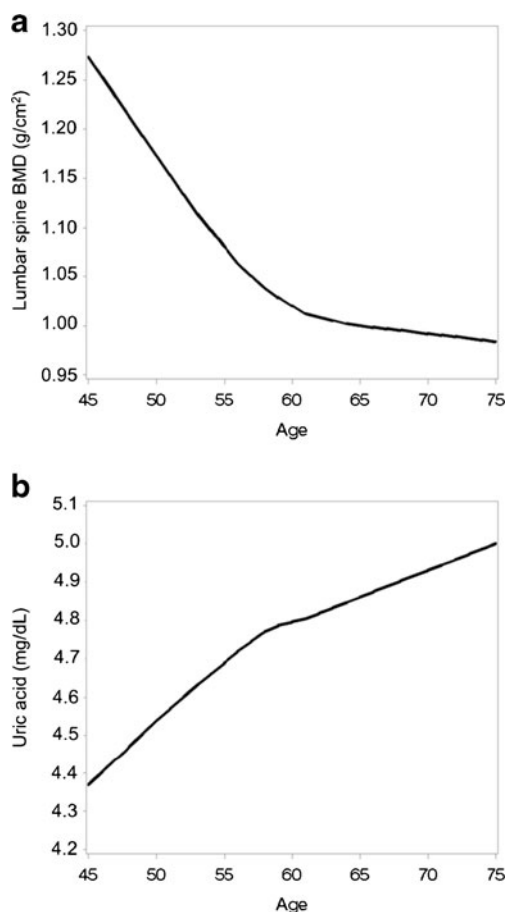

Fig. 2 LOESS plots of bone mineral density and uric acid against age. *BMD* bone mineral density

Table 3 Adjusted associations of serum uric acid with lumbar spine bone mineral density after excluding 177 women older than 60 years ($n = 438$)

	Beta[a]	%V[b]	p	R^2
Model 1	0.103	0.96	0.02	0.284
Model 2	0.091	0.73	0.04	0.294
Model 3	0.101	0.89	0.02	0.304
Model 4	0.107	0.91	0.02	0.359

Model 1—adjusted for age and BMI; model 2—adjusted for age, BMI, smoking, drinking, physical activity, and years after menopause; model 3—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, and hypertension; model 4—adjusted for age, BMI, smoking, drinking, physical activity, years after menopause, diabetes, hypertension, serum calcium, estimated GFR, log (CRP), and ALP. Abbreviations are as in Table 1

[a] Standardized beta coefficient

[b] Variance of lumbar spine bone mineral density explained by uric acid

BMD becomes inverse in the hyperuricemic range. However, it should be noted that only a small portion of women in this study had hyperuricemia, and further study is needed to determine if the association between BMD and uric acid in the hyperuricemic range may differ from that in the physiologic range.

We also demonstrated that there was a period of rapid increase in uric acid until the age of 60 years when the rate of increase slowed. The observed trajectory of uric acid is consistent with menopause-related changes, rather than changes secondary to chronological aging. This is congruent with previous studies showing that uric acid levels were higher in postmenopausal women compared with pre- or perimenopausal women [38, 39]. We observed a similar menopause-related change in BMD, consistent with previous studies [37]. However, the inflection (i.e., change of slope) was observed at around the age of 60 for both uric acid and BMD in the present study, which appears too far apart from the mean age at menopause of approximately 51 years. The possible explanations for the discrepancy include reporting error and the nature of cross-sectional data, which are predisposed to recall bias and are unable to separate the effects of aging from secular trend. Hence, a longitudinal study is warranted to determine the precise trajectory of uric acid during the menopause transition.

This study has several limitations. First, the study design was cross-sectional and did not allow us to infer a cause–effect relationship between uric acid level and BMD. However, one previous longitudinal study demonstrated that higher serum uric acid levels were associated with slower annual decline in BMD in peri- and postmenopausal women [16]. Second, we employed an EM algorithm to impute missing values in covariates. Missing values occurred mostly in two variables—physical activity and age at menopause. Sensitivity analysis excluding women with any missing values in covariates yielded similar, albeit not significant, effect sizes of the association between BMD and uric acid, indirectly supporting the robustness of the approach. The association failed to reach statistical significance due to the reduced number of women included in the sensitivity analysis. Third, the data were obtained from the medical records of female teachers who had received health checkup annually and were therefore expected to be generally in good health and health conscious. In fact, the prevalence of comorbidity such as hypertension and diabetes, and the smoking rate were lower than those in the general population [40–42]. In addition, the women in this study had lower weight compared with peri- and post-menopausal Australian women in a previous study on uric acid and BMD [16]. Thus, the observed associations of uric acid with menopause and BMD were less likely to be confounded by obesity and other comorbidity, but the generalizability of the findings to other populations may be limited. In addition, BMD measurement was performed voluntarily, which could introduce selection bias. However, women in the analysis were comparable to those excluded from the analysis, most of whom had not had BMD measurement and excluded. Fourth, the observed

association was marginally significant. We speculate that it is mostly likely due to relatively small sample size because the finding was consistent throughout various models. Lastly, any observational studies like this one cannot be free of possible confounding due to uncontrolled or unmeasured variables. Several important variables such as bone turnover markers, PTH, and serum 25-hydroxyvitamin D were not measured or available for the analysis.

Despite these limitations, the study has several strengths. Even though this was a retrospective analysis, the data were drawn from medical records for health checkup, which were in general free of missing values except for a few measurements. These measurements were performed voluntarily or as a part of optional examinations. The main finding was robust to the inclusion of a variety of covariates including years after menopause and exclusion of older women.

In conclusion, the present study showed that higher uric acid levels in the physiologic range of uric acid are linearly associated with higher lumbar spine bone mineral density in peri- and postmenopausal Japanese women. Further research is needed to elucidate the precise underlying mechanism of the association between uric acid and bone mineral density and to determine if the positive association between BMD and uric acid is still observed in the hyperuricemic range.

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