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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.

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Results

There were 460 female twin participants who had completed their last follow-up visit: 96 monozygotic (MZ) and 134 dizygotic (DZ) pairs. After randomly excluding one member of each MZ twin pair ($n=96$) and subjects taking allopurinol ($n=4$), thiazides ($n=2$) or loop diuretics ($n=2$), 356 women with a mean age of 60.4 (range 45–83) years remained for analysis.

Cross-sectional analyses

The main anthropometric, biochemical and lifestyle characteristics of these subjects at the final visit, stratified by tertiles of UA levels are presented in Table 1. There were 26 hyperuricemic women (serum UA levels ≥0.41 mmol/L) in the highest tertile of UA. As expected final visit UA levels were higher than baseline levels. Women with higher serum UA levels were older, heavier and correspondingly had higher BMI than those with lower UA concentrations. Total serum cholesterol, LDLC, triglyceride, calcium and creatinine levels were all significantly higher in the higher UA tertiles. Serum CTX-I levels were higher in the highest UA tertile, but no between-tertile differences were seen for any of the other bone-related biochemical parameters. There was no significant difference in history of smoking, alcohol intake or physical activity between groups. There were 40 incident self-reported fractures during the follow-up period with no apparent difference in fracture rates between UA tertiles.

Crude bone density measures of the study cohort at the final visit are shown in Table 2a. When analysed by tertile of serum UA, women with higher UA levels had significantly higher absolute BMD at all skeletal sites at baseline (data not shown) and follow-up visits. Adjusted means for final visit bone density measures at different skeletal sites across tertiles of UA are presented in Fig. 1. Unadjusted body composition measures of the study cohort at the final visit are shown in Table 2b. Both body fat and lean mass measures as well as the body fat to lean mass ratio were significantly higher in the medium and high UA group. Similar results were obtained for baseline body composition characteristics (data not shown). Adjusted means for the final visit body weight, lean mass and fat mass measures across tertiles of UA are presented in Fig. 2.

Multiple regression analysis was performed to examine the cross-sectional associations between serum uric acid levels and final visit BMD measures at different skeletal sites. Estimates of the fully adjusted regression models are presented in Table 3. Serum UA levels were positively associated with baseline and final visit cross-sectional bone density measures at all skeletal sites after adjustment for GFR, serum Ca and CTX-I levels, age, FM/LM/Ht^2, smoking, alcohol, HRT use and physical activity.

Longitudinal analyses

Mean duration of follow-up was 9.7 ± 1.8 years and did not differ between UA tertiles. Longitudinal bone density and body composition

Table 1
Demographic, biochemical and lifestyle characteristics of the study subjects at final visit stratified by tertiles of serum uric acid levels (Final Visit).[a]

	Tertiles of uric acid levels				
	All	1	2	3	Sig.
	(*N*=356)	(*N*=122)	(*N*=106)	(*N*=128)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age (years)	60.44 ± 7.89	59.23 ± 7.88	60.47 ± 8.30	61.57 ± 7.43	**0.019***
Duration of Follow-Up (years)	9.68 ± 1.84	9.87 ± 1.51	9.45 ± 2.09	9.69 ± 1.89	0.450
Weight (kg)	69.44 ± 12.36	63.58 ± 9.61	70.63 ± 13.06	74.00 ± 11.88	**<0.000**§
Height (m)	1.61 ± 0.06	1.61 ± 0.06	1.62 ± 0.06	1.60 ± 0.06	0.190
BMI (kg/m^2)	26.83 ± 4.92	24.48 ± 3.83	27.09 ± 5.19	28.85 ± 4.68	**<0.000**§
Biochemistry measures:					
Uric Acid Baseline Visit (mmol/L)	0.26 ± 0.06	0.22 ± 0.05	0.25 ± 0.05	0.30 ± 0.05	<0.000§
Uric Acid Final Visit (mmol/L)	0.29 ± 0.07	0.21 ± 0.04	0.28 ± 0.01	0.36 ± 0.05	<0.000§
A%ΔChange in Uric Acid (% per yr)	1.36 ± 3.16	0.26 ± 3.84	1.59 ± 2.37	2.36 ± 2.67	<0.000§
Total Cholesterol (mmol/L)	5.47 ± 0.96	5.41 ± 0.92	5.33 ± 0.93	5.63 ± 1.01	0.060
HDLC (mmol/L)	1.45 ± 0.38	1.50 ± 0.42	1.45 ± 0.36	1.41 ± 0.36	0.053
LDLC (mmol/L)	3.39 ± 1.02	3.21 ± 1.17	3.30 ± 0.87	3.63 ± 0.94	0.001±
Triglycerides	1.20 ± 0.60	1.08 ± 0.41	1.19 ± 0.72	1.31 ± 0.63	0.003±
Calcium (mmol/L)	2.30 ± 0.09	2.28 ± 0.09	2.30 ± 0.09	2.32 ± 0.09	<0.000§
Creatinine (micromol/L)	68.99 ± 11.06	65.48 ± 9.14	68.45 ± 9.29	72.79 ± 12.82	<0.000§
C-Reactive Protein (nmol/L)	2.80 ± 3.65	2.28 ± 3.94	2.79 ± 3.74	3.30 ± 3.22	0.027*
Serum CTX-I (μg/L)	283.97 ± 157.86	260.71 ± 142.58	290.35 ± 157.08	300.67 ± 170.37	0.047*
PINP (μg/L)	46.14 ± 20.20	46.82 ± 20.39	47.10 ± 20.13	44.73 ± 20.17	0.410
GFR	85.53 ± 22.84	83.26 ± 18.58	88.26 ± 27.44	85.44 ± 22.26	0.466
Fractures:	39 (11.0%)	12 (9.8%)	16 (15.1%)	11 (8.6%)	0.200
Lifestyle characteristics:					
Smoking History: (*N* (%))					0.620
Never	224 (62.9%)	72 (59.0%)	72 (67.9%)	80 (62.5%)	
Current	21 (6.9%)	7 (5.7%)	7 (6.6%)	7 (5.5%)	
Ex-smoker	111 (31.2%)	43 (35.2%)	27 (25.5%)	41 (32.0%)	
Alcohol intake (*N*(%))					0.411
≤ 1 drink per week	142 (39.9%)	50 (41.0%)	43 (40.6%)	49 (38.3%)	
2–14 drinks per week	207 (58.1%)	71 (58.2%)	62 (58.5%)	74 (57.8%)	
≥ Drinks 14 per week	7 (2.0%)	1 (0.8%)	1 (0.9%)	5 (3.9%)	
Physical activity (*N* (%))					0.788
None	18 (5.1%)	4 (3.3%)	7 (6.6%)	7 (5.5%)	
< 30 min per day	167 (46.9%)	58 (47.5%)	47 (44.3%)	62 (48.4%)	
≥ 30 min per day	171 (48.0%)	62 (50.8%)	50 (47.2%)	59 (46.1%)	

[a] ANOVA and test of linearity were performed.
* $p<0.05$.
± $p<0.01$.
§ $p<0.001$.

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Table 2a
Cross-sectional (final visit) and longitudinal bone mineral density measures of the study subjects, stratified by tertiles of serum uric acid levels.[a]

	Tertiles of uric acid				
	All	1	2	3	Sig.
	(N = 356)	(N = 122)	(N = 106)	(N = 128)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Cross-sectional BMD (g/cm²)					
Lumbar spine	0.952 ± 0.158	0.923 ± 0.157	0.949 ± 0.148	0.982 ± 0.164	0.003±
Femoral neck	0.751 ± 0.120	0.726 ± 0.111	0.761 ± 0.112	0.767 ± 0.132	0.007±
Hip total	0.896 ± 0.125	0.869 ± 0.123	0.907 ± 0.119	0.914 ± 0.129	0.005±
Forearm total	0.522 ± 0.058	0.511 ± 0.061	0.527 ± 0.054	0.528 ± 0.057	0.022*
Whole body total	1.089 ± 0.116	1.071 ± 0.116	1.091 ± 0.120	1.105 ± 0.113	0.021*
A%ΔChange in BMD (% per year)					
Lumbar spine	−0.50 ± 0.83	−0.58 ± 0.85	−0.57 ± 0.76	−0.37 ± 0.86	0.044*
Femoral neck	−0.45 ± 0.75	−0.46 ± 0.76	−0.45 ± 0.78	−0.44 ± 0.72	0.794§
Hip total	−0.38 ± 0.61	−0.39 ± 0.67	−0.39 ± 0.52	−0.36 ± 0.61	0.636
Forearm total	−0.62 ± 0.58	−0.62 ± 0.62	−0.66 ± 0.61	−0.59 ± 0.52	0.630
Whole body total	−0.21 ± 0.65	−0.25 ± 0.67	−0.24 ± 0.62	−0.14 ± 0.65	0.200

[a] ANOVA and test of linearity were performed.
* $p<0.05$.
± $p<0.01$.
§ $p<0.001$.

measures of the study cohort stratified by tertiles of UA are shown in Tables 2a and 2b. Annual rates of increase in body weight and lean body mass (LM) over the preceding 9 years were significantly related to higher serum UA levels and these associations remained after adjusting for potential confounders: age, height, history of smoking, alcohol intake, HRT use and physical activity (data not shown). There was a general trend for women in the highest tertile of UA to be losing bone at a slower rate than those with lower UA level. However this relationship was statistically significant only for A%ΔLSBMD. Women in the highest UA tertile had gained more weight and more lean mass over time, but changes in fat mass were not significantly different by UA tertiles (Fig. 2).

Multiple regression analyses were performed to examine the associations between serum UA and longitudinal BMD measures at different skeletal sites (Table 4). Higher rates of annual change in UA levels were associated with slower rate of decline in BMD at all skeletal sites. When the regression models were adjusted for A%ΔFM (model 2) or A%ΔLM (model 3), the associations between change in UA levels and change in BMD measures remained significant at the spine only.

The results of the time dependent mixed model regression analyses confirmed these findings (not shown).

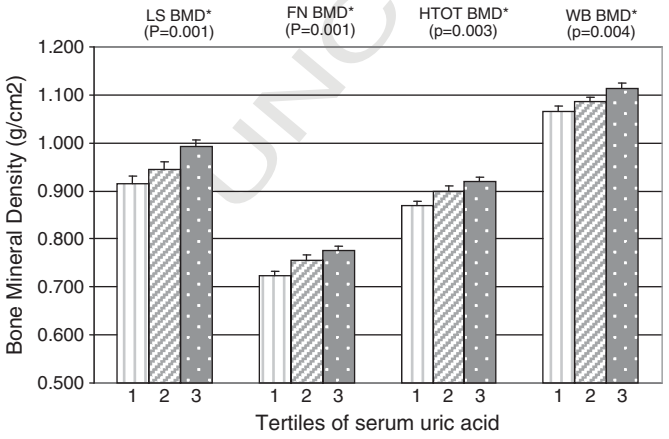

Fig. 1. Adjusted means of Lumbar Spine, Femoral Neck, Total Hip and Whole Body cross-sectional BMD measures (final visit) across tertiles of Serum Uric Acid ($N = 356$)*. * BMD means adjusted for GFR, serum Ca and CTX-I levels, age, height; history of smoking, history alcohol intake, history HRT use and physical activity.

Discussion

In a previous cross-sectional study [31] the CHAMP consortium has reported that higher serum UA levels are associated with greater BMD at all skeletal sites in an older male population. In the present study, we have confirmed, for the first time, that a similar relationship exists between serum UA and BMD in peri- and postmenopausal women. In addition, we have shown that serum UA is also associated with the rate of change in BMD over time in women. In the lumbar spine, forearm and total body, those with higher UA levels were relatively protected from bone loss compared to those with lower levels. However the protective effect of UA on longitudinal BMD appeared to be weaker at hip sites.

Body weight is well known to be related to BMD [27]. However, there has been considerable controversy about the association between fat body mass and lean body mass and their relationship to BMD [27,28,30]. Gender and age are likely to be important factors in modifying this relationship given we showed previously in a cross-sectional study of opposite sex twins that lean mass had stronger relationships with most bone variables than fat mass in both genders at all ages, but fat mass had a positive relationship with total body and hip BMD in women under 50 and men over 50 years of age [29]. Body weight and in particular obesity are also associated with serum UA levels [12,20,42]. In the present study, UA was also associated with cross-sectional weight, FM and LM measures and the rate of change over time in lean body mass. Those women with high UA levels gained more lean body mass without much change in fat mass. However after adjusting for lean mass or fat mass, the relationship between UA and BMD remained.

As noted above, UA is the end product of purine metabolism which in turn is related to lean body mass. However our analyses of changes in body composition do not explain the relationship observed between serum UA and cross-sectional or longitudinal BMD. We found modestly higher serum CTX-I values in women in the highest tertile of UA, which might be expected to be associated with increased bone loss over time rather than what was actually observed. Taken together, these longitudinal data suggest that the relationship between serum UA and lumbar spine BMD in women, both cross-sectionally and longitudinally, is not mediated to any great extent by the relationship between body composition and UA or by direct effects on bone remodeling. Evidence from observational and epidemiological studies has linked oxidative stress to reduced BMD and osteoporosis [9–11] and since UA accounts for approximately

t3.1 **Table 2b**
t3.2 Cross-sectional (final visit) and Longitudinal Body composition measures of the study subjects, stratified by tertiles of serum uric acid levels.[a]

	Tertiles of uric acid				
	All	1	2	3	Sig.
	(N = 356)	(N = 122)	(N = 106)	(N = 128)	
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Cross-sectional (kg):					
Whole body fat mass	23.84 ± 7.88	20.11 ± 6.05	24.44 ± 8.30	26.87 ± 7.68	<0.000§
Whole body lean mass	40.07 ± 5.55	38.30 ± 4.30	40.34 ± 6.75	41.51 ± 5.06	<0.000§
Fat mass/lean mass	0.59 ± 0.16	0.52 ± 0.14	0.59 ± 0.15	0.64 ± 0.16	<0.000§
Longitudinal (% per year)					
A%Δ Whole body fat mass	0.09 ± 2.09	0.09 ± 2.06	0.07 ± 2.20	0.11 ± 2.03	0.947±
A%Δ Whole body lean mass	0.72 ± 0.69	0.49 ± 0.60	0.70 ± 0.70	0.95 ± 0.70	<0.000§
A%Δ Fat mass /lean mass	−0.57 ± 2.00	−0.36 ± 1.98	−0.58 ± 2.08	−0.75 ± 1.97	0.131*

[a] ANOVA and test of linearity were performed.
* $p<0.05$.
± $p<0.01$.
§ $p<0.001$.

half of the antioxidant properties of human plasma [3], this mechanism of action as an explanation of our findings requires further investigation. The lesser protective effect of UA on hip BMD in our longitudinal analyses may reflect that hip BMD is more influenced by body composition measures [43,44] and local environmental factors such as weight bearing and also deserves further study.

Although we have demonstrated that higher serum UA values are associated with higher BMD and lower rates of bone loss in women,

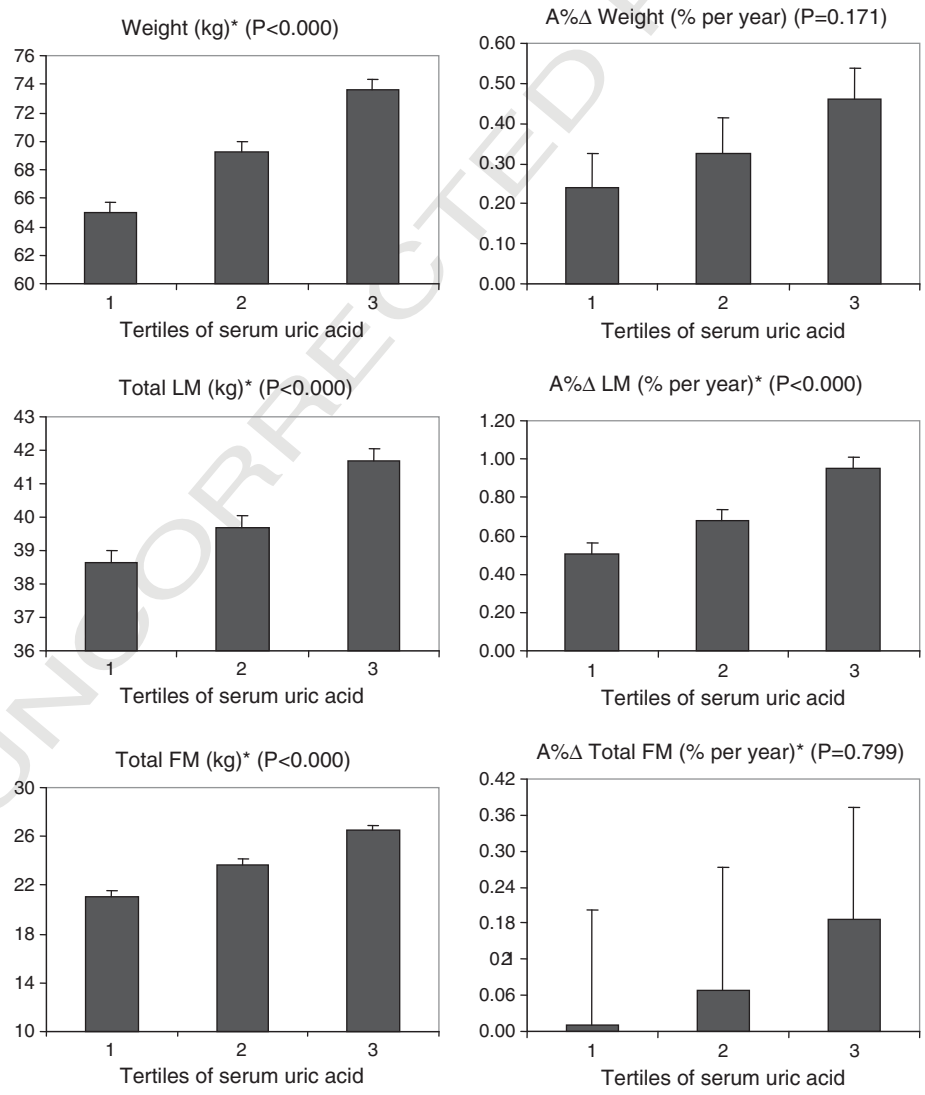

Fig. 2. Adjusted means of body weight and body composition measures across tertiles of uric acid*. *Means adjusted for UA, GFR, serum Ca and CTX-I levels, age, height; history of smoking, history alcohol intake, history of HRT use and physical activity.

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Table 3
Multiple regression analysis of the association between serum uric acid and cross-sectional BMD measures at different skeletal sites.

Regression models	Baseline visit*		Final Follow up visit**	
	β^*	Sig.	β^*	Sig.
BMD (g/cm^2)				
Lumbar spine	0.190	0.000§	0.243	0.000§
Femoral neck	0.169	0.002$^{\pm}$	0.221	0.000§
Total hip	0.167	0.002$^{\pm}$	0.195	0.000§
Total forearm	0.136	0.012*	0.191	0.000§
Whole body	0.170	0.001$^{\pm}$	0.230	0.000§

Each regression model included one BMD measure as dependent variable.
Independent variables included in the regression analyses were: Bsl UA, Bsl: age, LM/FM/height^2; history of smoking, history alcohol intake, history HRT use, and physical activity.
Final Visit UA, Final visit: age, LM/FM/height^2; history of smoking, history alcohol intake, history HRT use, and physical activity.
*$p<0.05$.
$^{\pm}p<0.01$.
$^{\S}p<0.001$.

those with higher UA values also had a more adverse lipid profile with higher total cholesterol, lower LDLC and higher triglyceride values and the clinical significance of these opposing effects need further evaluation. The existence of a possible link between bone, fat and atherogenic pathways has been recognised for some time and serum UA should now be added to consideration of any such interactions. Previous studies in this regard are conflicting. Early postmenopausal women with an atherogenic lipid profile have been reported to have lower lumbar and femoral neck BMD and an increased risk of osteopaenia than those with a normal lipid profile [45], which differs from our findings. In a longitudinal study in postmenopausal women aged 50–75 years, those with the largest increases in serum cholesterol showed the greatest decreases in spine BMD independently of change in the body mass index [46]. We have also previously reported a modest inverse relationship between total serum cholesterol and spine but not hip BMD in perimenopausal women [35], but none of these studies considered the influence of serum UA.

Our study has a number of strengths. We measured change in BMD and body composition measures in women over almost 10 years and UA levels at baseline and final visits. For the first time the associations between serum UA and BMD and body composition measured by DXA were studied on a relatively healthy population of peri- and postmenopausal women. Our study also has some limitations. Only UA levels were measured at the two end points of the study. Bone markers or other biochemical characteristics were only measured at the final visit. Whereas DXA is regarded by majority as a reference technique for the measurement of the bone mineral, fat and fat-free soft tissue compartments of the body, it is not without limitations. Several studies suggest that long term DXA precision results may be affected by substantial weight gain [47–50]. In our study subjects with severe obesity that affected the quality of DXA scans were excluded and regression analyses of the longitudinal BMD measures were adjusted for rates of changes in BMI.

The variability in rates of change in BMD and body composition was high, although we measured change over almost 10 years and the changes we observed are consistent with annual rates of BMD change reported by others [51,52]. With only 40 incident fractures during the follow-up period we lacked power to examine the effect of UA on fractures.

We recently reported that serum UA levels were significantly associated with BMD at various skeletal sites after adjusting for covariates in a large population-based study of older men [30] and have now confirmed a similar relationship exists in peri- and postmenopausal women.

For decades it has been hypothesised that the antioxidant properties of uric acid might be protective against aging, oxidative stress, and oxidative injury of cells, including cardiac, vascular, and neural cells. However, recent epidemiological and clinical evidences suggest that hyperuricaemia might be a risk factor for cardiovascular disease, where enhanced oxidative stress plays an important pathophysiological role. It has also been hypothesised that hyperuricaemia might be involved in chronic heart failure and metabolic syndrome [7,53,54]. The apparent paradox between protective and toxic effects of UA is supported by clinical evidence that antioxidant compounds may become pro-oxidant compounds in certain situations, particularly when they are present in blood at abnormally high levels [7].

The present study suggests that serum UA, when present at higher physiological concentrations, may have protective effects on BMD, most likely through its antioxidant properties. However, further studies are needed to establish the precise mechanism of action and whether serum UA plays a role in antagonising oxidative stress-induced bone loss.

Table 4
Multiple regression analysis of the association between longitudinal measures of uric acid and BMD at different skeletal sites.

Regression models	Model 1		Model 2		Model 3	
	β^*	Sig.	β^*	Sig.	β^*	Sig.
A%ΔBMD (% per year):						
Lumbar Spine	0.170	0.006$^{\pm}$	0.161	0.009$^{\pm}$	0.134	0.036*
Femoral Neck	0.121	0.054	0.112	0.073	0.072	0.264
Total Hip	0.121	0.050*	0.108	0.076	0.052	0.405
Total Forearm	0.077	0.207	0.073	0.231	0.038	0.550
Whole Body	0.145	0.022*	0.138	0.029*	0.082	0.202

Each regression model included one BMD measure as dependent variable.
Independent variables included in the regression analyses were:
Model 1: A%ΔUA, Bsl UA, Bsl BMD, GFR, serum Ca, Cholesterol and CTX-I levels, age, height; history of smoking, history alcohol intake, history HRT use, physical activity and ΔBMI.
Model 2: as Model 1 + A%Δ total body fat mass.
Model 3: as Model 1 + A%Δ total body lean mass.
*$p<0.05$.
$^{\pm}p<0.01$.
$^{\S}p<0.001$.

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