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ORIGINAL PAPER

Effects of vitamin B_{12}, folate, uric acid, and serum biomarkers of inflammation on bone mineral density in postmenopausal women

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Abstract

Introduction: Despite the accumulating evidence suggesting a possible relationship between femur and lumbar bone mineral density (BMD) and serum uric acid (UA), it is unclear whether alterations in UA levels reflect any underlying subclinical inflammatory conditions in postmenopausal osteoporosis. In addition, the mechanistic link between osteoporosis and dietary factors including vitamin B_{12} and folate in postmenopausal women is still obscure. The aim of the present study is to investigate the association between serum vitamin B_{12}, folate, UA, and subclinical inflammatory markers and BMD measurements in postmenopausal women.

Material and methods: One hundred and eighty-four postmenopausal women were recruited for the present study. Clinical data, as well as serum vitamin B_{12}, folate, UA, conventional inflammatory markers, and other related biochemical markers, were assessed for each subject. Bone mineral density measurements of proximal femur and lumbar spine were taken using dual-energy X-ray absorptiometry. Correlation analysis was performed between serum vitamin B_{12}, folate, UA and other biochemical and metabolic parameters.

Results: Although no association was found between serum inflammatory markers, vitamin B_{12} and folate levels with femur neck and lumbar spine BMD measurements, elevated UA levels were observed in subjects with normal BMD values. Higher BMD values were obtained in higher UA tertiles. UA ($p < 0.001$) and BMI ($p = 0.003$) were found to be correlated with femur neck BMD measurements.

Conclusions: The femoral and lumbar BMD measurements were associated with serum UA levels. Higher serum UA levels were found to have a protective effect on postmenopausal osteoporosis irrespective of inflammation and dietary factors.

Key words: osteoporosis, uric acid, inflammation, vitamin B_{12}, folate.

Introduction

Osteoporosis (OP) and osteopenia are a public health concern associated with an increased risk of bone fractures and related morbidity and mortality, especially in the older population [1]. In fact, postmenopausal women have a substantially increased risk of bone-related disorders, with poorer outcomes than their age-matched male counterparts. A number of studies have reported that serum uric acid (UA), as well as subclinical inflammation, is involved in the pathogenesis of OP by affecting oxidative stress and inflammatory cascades [2]. In this context, growing evidence suggests that serum UA might protect against bone loss by its antioxidant properties and is related to postmenopausal OP [3, 4].

Uric acid is the final oxidation product of purine metabolism and exists either in a crystalline or in a soluble state with either anti-oxidant or pro-oxidant activities depending on various factors including the plasmatic and cellular environment [5, 6]. It is implicated in many disease conditions including gout, metabolic syndrome, cardiovascular and renal dysfunction [7-9]. In contrast, cross-sectional and longitudinal studies have shown that UA is a beneficial factor in distinct disease states including osteoporosis, Alzheimer's disease and dementia in both men and women [4, 10-12]. Moreover, it has been found that after excluding multivariable confounders associated with adiposity including body mass index (BMI), body weight and fat mass, UA levels were positively correlated with bone mineral density (BMD) regardless of adiposity [4, 10, 12].

Clinical, serologic and molecular evidence suggests that systemic inflammation exerts a substantial effect on bone turnover and induces OP [13, 14]. Chronic inflammation and alteration in the immune system, which are characteristics of ageing, as well as other pathological situations linked with OP, might be determinant pathogenetic factors [13]. In this context, it has been found that high-sensitivity C-reactive protein (hs-CRP), which is upregulated by IL-1, IL-6 and TNF-α,

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is associated with BMD, indicating a possible relationship between subclinical systemic inflammation and OP [15]. However, it seems that CRP acts as a surrogate for other factors that directly impact on BMD.

Certain B vitamins and folate play a substantial role in bone health in healthy adults, suggesting that suboptimal B vitamin levels and folate deficiency may contribute to an elevated risk of OP development [16]. Furthermore, large population-based studies have demonstrated that low vitamin B_{12} and folate levels are associated with increased fracture risk and/or decreased BMD values [17]. Although many theories have been put forward in attempts to explain the underlying causal mechanisms between bone health and B vitamins and folate, it is accepted that the main mechanism is via these vitamins' integral roles in one carbon metabolism that is required for the methylation of DNA, proteins, and other molecules via S-adenosylmethionine [16].

Given the emerging evidence that supports the role of UA, B vitamins and inflammation on bone health, as far as we know, until today, no study has looked at the association of these parameters with BMD. The present study aims to explore associations of UA, vitamin B_{12}, folate and conventional inflammatory markers with BMD of the femur and lumbar regions in postmenopausal women.

Material and methods

Participants and study design

The study participants were chosen from consecutive postmenopausal women who came for their regular gynecological visits to our outpatient clinic. In order to examine the relationship between serum vitamin B_{12}, folate, UA, and inflammatory markers, the present study was carried out on 184 postmenopausal women. Menopause was defined as the last natural menstruation when followed by 12 months of amenorrhea, or when the follicle stimulating hormone (FSH) exceeds 40 IU/l in cases of subjects with hysterectomy. Women taking medications affecting bone or calcium metabolism including hormone replacement therapies and anticonvulsants, liver and renal disease, having a malignant or chronic debilitating illness, and a history of alcohol consumption, diabetes mellitus (DM), or other systemic diseases, were excluded from the study. The present study was approved by the Local Ethics Committee and performed according to the guidelines of the Declaration of Helsinki.

All postmenopausal subjects recruited to this study were invited to complete a questionnaire while waiting for further physical examination and laboratory testing. Demographic characteristics, including age, height, body weight, menopausal status, past and present medication history, and tobacco use, were recorded.

All women were asked to go to the appointed laboratory the following morning, after an overnight fast of 12 h. Fasting blood samples were drawn and analyzed immediately for general hematologic, biochemical and lipoprotein profiles. The following laboratory tests were applied for each woman: alkaline phosphatase (ALP), calcium (Ca), phosphor (P), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), UA, vitamin B_{12}, folate, parathyroid hormone (PTH), hs-CRP and erythrocyte sedimentation rate (ESR).

For each woman, weight and height were measured in light indoor clothing without shoes. Body mass index was calculated using the following formula: BMI = weight (kg) : height (m^2).

Body mass index measurement

The areal BMD (grams per square centimeter) measurement of the proximal femur and lumbar spine was done using dual-energy X-ray absorptiometry. All BMD measurements were made by the same experienced operator on the same X-ray machine following standardized procedures to reduce the chance of technical error.

Bone mineral density results of study participants were evaluated according to the World Health Organization criteria in which osteopenia is diagnosed by a $-2.5 < T\text{-score} < -1.0$ standard deviation (SD), and OP is diagnosed by a $T\text{-score} \leq -2.5$ SD at any sites on the lumbar spine, femoral neck, or total hip. A $T\text{-score} > -1$ is considered as normal.

Statistical analysis

All statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 19.0 (SPSS for Windows, SPSS, Chicago). One-way ANOVA was used to compare normally distributed variables. The Kruskal-Wallis test was conducted to compare non-normally distributed variables. The Mann-Whitney *U* test was used to compare continuous variables between the groups. Spearman's correlation coefficient analyses were performed between femur and lumbar BMD measurements with other variables, and a *p*-value < 0.05 was considered statistically significant.

Results

The average age was 57.5 ±10.6 years and the serum mean UA level was 4.9 ±1.2 mg/dl. Postmenopausal women were divided into three groups according to BMD measurements. A *T*-score higher than –1 was considered as normal, women with a *T*-score between –2.5 and –1 were considered as osteopenic, and those with

a score lower than –2.5 were considered as osteoporotic. The demographic and biochemical characteristics of study participants were evaluated both for femur neck and lumbar spine measurements (Table 1). According to the femur neck BMD results, serum UA levels were 5.3 ±1.0, 5.0 ±1.2 and 4.39 ±0.9 in normal, osteopenic and osteoporotic women, respectively (p = 0.001). Body mass index results were also statistically higher in postmenopausal osteoporotic women (p = 0.014). According to lumbar spine BMD measurements, mean serum UA levels were 5.0 ±1.2, 4.9 ±1.2 and 4.3 ±0.9 in normal, osteopenic and osteoporotic women, respectively (p = 0.015). There was no statistically significant difference in other variables between groups (Table 1). According to menopause status, out of 184 women, 44 (23.9%) reported surgical causes and 140 (76.1%) women reported natural causes. Current smoking was only reported in 11 (5.9%) women; 30 (16.3%) women were ex-smokers and 143 (77.8%) women had no history of smoking.

Correlation analysis was also performed between BMD measurements and confounding factors including age, BMI, UA, vitamin B_{12}, folate and hs-CRP levels (Table 2). According to femur neck BMD results, only BMI (r = –0.221, p = 0.003) and serum UA (r = 0.274, $p \leq 0.001$) were found to be correlated with femur neck BMD. Serum UA (r = 0.175, p = 0.017) and creatinine (r = –0.146, p = 0.049) were found to be correlated with lumbar spine BMD measurements. No correlation was observed between BMD measurements and other variables. We also conducted a correlation analysis between UA, hs-CRP and vitamin B_{12} in postmenopausal women with a T-score < –1. In postmenopausal women with a T-score < –1, femur neck (n = 125) and lumbar spine (n = 116) BMD measurements were also correlated with serum UA levels but no correlation was observed in hs-CRP and vitamin B_{12} levels (Fig. 1).

In order to better understand the clinical implications of these results, we categorized the study participants into three groups according to serum UA levels (Table 3). Serum UA levels were statistically significantly elevated in higher tertiles. Although not significant, an increasing trend was observed for ESR, PTH, and phos-

Table 1. Clinical and biochemical characteristics of study participants according to bone mineral density measurements

Factor	Femur neck measurement				Lumbar spine measurement			
	Normal (n = 59)	Osteopenic (n = 68)	Osteoporotic (n = 57)	p	Normal (n = 68)	Osteopenic (n = 94)	Osteo-porotic	p
Age (years)	57.5 ±9.5	57.9 ±10.1	56.0 ±9.0	0.537	57.2 ±9.4	57.4 ±10.1	56.1 ±7.7	0.849
Weight (kg)	83.3 ±9.5	83.3 ±11.8	87.4 ±9.1	0.058	84.0 ±8.7	84.2 ±11.9	87.6 ±7.8	0.337
Height (cm)	156.5 ±3.4	156.4 ±3.8	155.0 ±2.9	0.051	156.4 ±3.6	156.0 ±3.5	154.8 ±2.6	0.168
BMI (kg/m^2)	34.1 ±4.6	34.1 ±5.4	36.4 ±4.2	0.014[a]	34.4 ±4.4	34.7 ±5.5	36.5 ±3.3	0.192
Uric acid (mg/dl)	5.3 ±1.0	5.0 ±1.2	4.39 ±0.9	0.001[b]	5.0 ±1.2	4.9 ±1.2	4.3 ±0.9	0.015[a]
Vitamin B_{12} (pg/ml)	321 ±187	375 ±283	310 ±144	0.199	321 ±220	355 ±225	318 ±181	0.556
Folate (ng/ml)	7.7 ±2.8	7.8 ±2.2	8.1 ±2.6	0.730	7.5 ±2.5	8.1 ±2.7	7.7 ±1.9	0.346
hs-CRP (mg/l)	0.74 ±1.1	0.60 ±0.8	0.56 ±0.81	0.527	0.7 ±1.1	0.6 ±0.7	0.5 ±0.9	0.528
ESR (mm/hr)	11.6 ±12.6	12.6 ±7.5	11.6 ±5.0	0.568	11.5 ±4.2	12.5 ±7.1	11.4 ±3.4	0.458
PTH (pg/ml)	59.6 ±29.9	63.8 ±25.7	61.0 ±17.2	0.635	59.6 ±29.3	62.9 ±23.1	62.3 ±16.9	0.719
ALP (U/l)	94.5 ±88.0	85.6 ±25.2	84.9 ±19.0	0.544	91.3 ±82.7	86.9 ±23.1	84.5 ±16.2	0.819
Total cholesterol (mg/dl)	197.3 ±32.2	199.0 ±28.8	193.5 ±35.3	0.625	201.1 ±33.2	192.9 ±30.8	199.8 ±31.9	0.243
Triglyceride (mg/dl)	164.2 ±75.2	171.1 ±89.4	145.7 ±58.5	0.164	163.9 ±61.8	162.7 ±90.6	145.5 ±48.7	0.594
LDL-C (mg/dl)	115.0 ±27.1	115.1 ±29.1	115.2 ±30.2	0.998	116.9 ±29.5	112.5 ±28.4	119.9 ±27.1	0.437
HDL-C (mg/dl)	53.6 ±11.6	55.3 ±9.5	55.5 ±12.9	0.605	54.1 ±9.9	55.4 ±12.4	54.5 ±10.8	0.775
Calcium (mg/dl)	9.5 ±0.8	9.1 ±0.9	9.2 ±0.9	0.091	9.4 ±0.7	9.2 ±0.9	9.1 ±0.9	0.129
Phosphorus (mg/dl)	3.3 ±0.6	3.3 ±0.5	3.2 ±0.6	0.710	3.2 ±0.5	3.4 ±0.6	3.2 ±0.7	0.306
BUN (mg/dl)	31.7 ±8.5	33.2 ±9.7	31.5 ±7.3	0.484	31.7 ±8.1	32.7 ±9.1	31.1 ±8.5	0.640
Creatinine (mg/dl)	0.7 ±0.2	0.7 ±0.1	0.7 ±0.2	0.308	0.7 ±0.2	0.7 ±0.2	0.7 ±0.1	0.200
Femur neck BMD (g/cm^2)	–0.74 ±0.16	–1.65 ±0.37	–2.7 ±0.18	0.000[b]	–0.91 ±0.37	–2.00 ±0.65	–2.84 ±0.19	0.000[b]
Lumbar spine BMD (g/cm^2)	–0.77 ±0.34	–1.39 ±0.50	–2.34 ±0.48	0.000[b]	–0.70 ±0.19	–1.76 ±0.47	–2.81 ±0.20	0.000[b]

[a]Osteoporotic vs. osteopenic and normal group. [b]Osteoporotic vs. osteopenic vs. normal group
BMI – body mass index, hs-CRP – high sensitivity C-reactive protein, ESR – erythrocyte sedimentation rate, PTH – parathyroid hormone, ALP – alanine aminotransferase, LDL-C – low-density lipoprotein cholesterol, HDL-C – high-density lipoprotein-cholesterol, BUN – blood urea nitrogen, BMD – bone mineral density

Table 2. Correlation analysis between serum uric acid and other metabolic and biochemical parameters according to bone mineral density measurements

	All women (n = 184)	
Femur neck bone mineral density	***r***	***p***
Age	0.045	0.543
BMI	–0.221	0.003
Uric acid	0.274	< 0.001
Vitamin B_{12}	0.009	0.905
Folate	–0.045	0.544
hs-CRP	0.021	0.782
ESR	0.012	0.874
Calcium	0.125	0.092
Phosphorus	0.014	0.853
ALP	–0.052	0.480
PTH	–0.127	0.087
Creatinine	–0.125	0.092
BUN	0.039	0.601
Total cholesterol	0.082	0.269
TG	0.081	0.276
Lumbar spine bone mineral density	***r***	***p***
Age	0.020	0.543
BMI	–0.110	0.137
Uric acid	0.175	0.017
Vitamin B_{12}	–0.046	0.532
Folate	–0.129	0.080
hs-CRP	–0.016	0.831
ESR	–0.024	0.745
Calcium	0.145	0.049
Phosphorus	–0.047	0.529
ALP	–0.016	0.854
PTH	–0.143	0.055
Creatinine	–0.146	0.049
BUN	–0.004	0.962
Total cholesterol	0.108	0.144
TG	0.118	0.11

BMI – body mass index, hs-CRP – high sensitivity C-reactive protein, ESR – erythrocyte sedimentation rate, ALP – alanine aminotransferase, PTH – parathyroid hormone, BUN – blood urea nitrogen, TG – triglycerides, BMD – bone mineral density

phorus levels, and a decreasing trend was observed for serum folate levels (Table 3). The BMD values at the femur neck (p = 0.048) were elevated in the higher tertiles. Although an increasing trend of lumbar spine BMD values in higher UA tertiles was observed, this was not statistically significant (Fig. 2).

Discussion

Our results indicate that serum UA is an important factor for both femur and lumbar spine BMD values among postmenopausal women irrespective of BMI status. Increased UA levels were found to be associated with improved bone health, supporting the original hypothesis that higher serum UA levels have a protective effect on bone loss in postmenopausal OP. We also demonstrated that UA levels are associated with femur and lumbar spine T-scores (r = –0.274, $p \leq 0.001$ and r = –0.175, p = 0.017, respectively). No significant correlation was obtained between serum UA levels and inflammatory markers. Moreover, vitamin B_{12} and folate levels were not correlated with either serum UA levels or BMD measurements.

Although a number of observational and epidemiologic studies suggest similar findings [18, 19] to the present study, a cross-sectional study of a probability sample of the US population reported contrary findings [20]. This study reported that after adjustment for potential confounders including age, BMI, race, and alcohol consumption, serum ALP and CRP levels and serum UA levels were no longer correlated with BMD measurements. Moreover, in order to examine the causal effect of higher serum UA on skeletal health (which is not possible to measure in human subjects), the authors created a rat model of hyperuricemia in which they demonstrated no difference in terms of BMD, volume density and biomechanical properties between hyperuricemic and normouricemic rats.

In this cross-sectional analysis of 184 healthy postmenopausal women, the femoral neck BMD was positively correlated with serum UA levels. In addition, we found that postmenopausal women with a T-score < –2.5 had lower UA levels compared with age- and BMI-matched postmenopausal women with a T-score > –2.5. Similar to our results, Ahn *et al.* [21] found that after adjusting for multiple confounders, serum UA levels were positively associated with BMD at all sites in a large cross-sectional study including 7,502 healthy postmenopausal women. Han *et al.* [4] also confirmed these findings and reported that lumbar BMD was linearly associated with serum UA levels within the normal physiological range of postmenopausal women, and concluded that higher serum UA levels had a protective effect on bone loss in postmenopausal osteoporosis. In a cross-sectional data analysis by Makovey *et al.* [22] women with higher UA levels were found to have significantly higher absolute BMD values for the femur and lumbar spine, which was not affected by changes in body composition measures. Taken together, the results of these studies support the hypothesis that the protective effect of UA relies on its antioxidant effect which participates in antagonizing oxidative stress-induced bone metabolism. Moreover, as postmenopausal women are more prone to oxidative stress development, with higher levels of serum UA there would be a greater antioxidative effect with decreased oxidative stress, which will protect against OP [4, 22, 23].

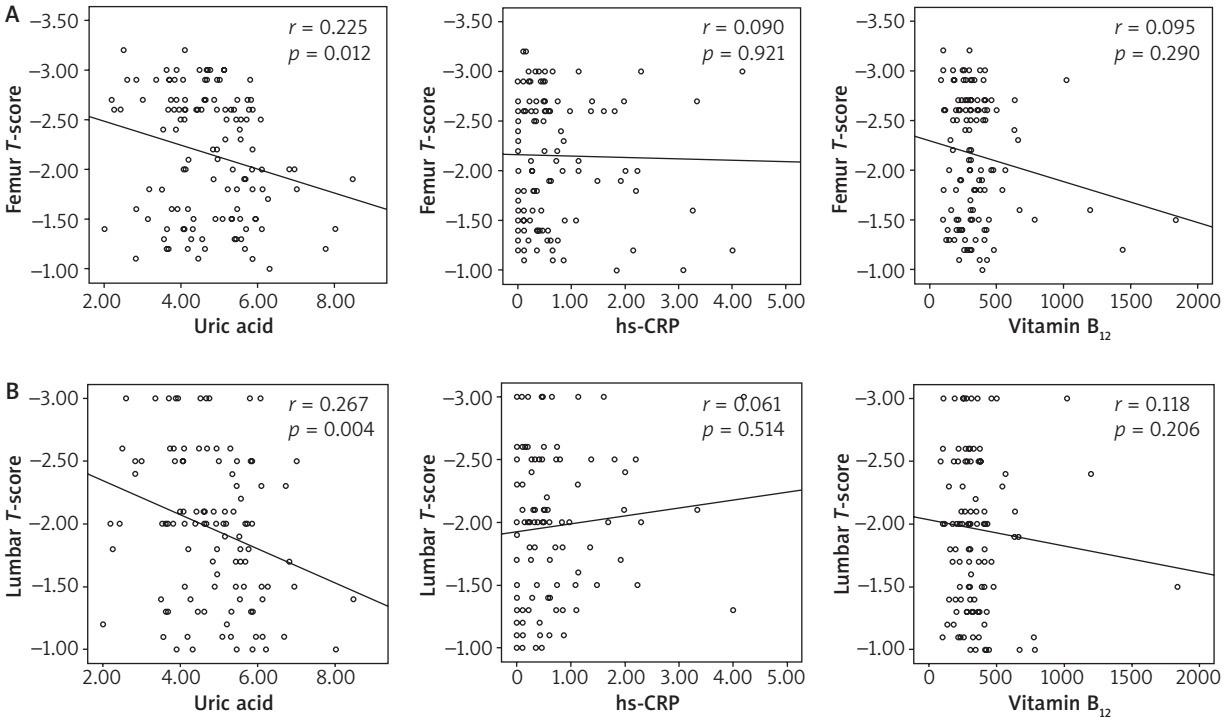

Fig. 1. Correlation analysis between serum uric acid, high-sensitivity C-reactive protein (hs-CRP) and vitamin B_{12} with femur neck and lumbar spine bone mineral density measurements in postmenopausal women **A)** femur neck *T*-score < –1, **B)** lumbar spine *T*-score < –1

In the present study, we did not find any association between serum UA and serum Ca, P, ALP or PTH levels. Similar to our findings, Xiong *et al*. [24] did not detect any causal relationship between serum UA and PTH, Ca, or P levels among a population of postmenopausal women and elderly men. In this Mendelian randomization study, although the authors noted a negative relationship between serum UA and PTH levels, and a positive relationship between serum UA, 25(OH)D, serum Ca and P levels in the adjustment models, these relationships were found to disappear in the two-stage least-squares Mendelian randomization analysis. Contrary to our findings, in a population study by Hui *et al*. [25] it was found that serum PTH levels are independently related to serum UA levels and the frequency of hyperuricemia at the population level. These contrary reports might be due to differences in the methods, scope of analysis and differences in how the methods are applied. Taken together, based on our findings, it seems that PTH, serum Ca, ALP and P levels may have little effect on the role of serum UA in bone metabolism.

Since the association between vitamin B_{12} and folate with BMD in postmenopausal women is controversial, our results suggest that BMD measurements of postmenopausal women are not correlated with vitamin B_{12} and folate levels. Moreover, our results also showed that even in lower UA tertiles, vitamin B_{12} and folate levels were not associated with altered bone mass. Vitamin B_{12} is known to be essential for folate cycling and is a determinant of total homocysteine (Hcy) concentration [26]. Hyperhomocysteinemia leads to an increase in oxidative stress and is related to decreases in bone blood flow, and is independently associated with the occurrence of OP in postmenopausal women [27, 28]. Being a crucial determinant of total Hcy status and affecting osteoblast activity, vitamin B_{12} may have a direct impact on bone metabolism [27, 29]. However, the results of published trials are inconsistent, possibly due to methodological differences across studies. For example, in a cross-sectional analysis by Golbahar *et al*. [30] plasma vitamin B_{12} levels were not found to be a predictor of BMD at either the femoral neck and lumbar spine even adjusted for age and BMI. Similarly, Haliloglu *et al*. [31] revealed that vitamin B_{12}, folate and Hcy levels were not associated with BMD in postmenopausal women. Baines *et al*. [32] reported a strong association between Hcy and vitamin B_{12}, but they also did not demonstrate any association between vitamin B_{12} and BMD. In a recent meta-analysis from China, a total of 16 studies were explored in order to analyze the relationship of Hcy, vitamin B_{12} and folate with BMD. Although Hcy and vitamin B_{12} were found to be associated with postmenopausal BMD, folate levels were not associated with BMD. The evidence from our study indicated that vitamin B_{12} and folate levels did not have a beneficial effect on postmenopausal bone health.

Apart from vitamin B_{12} and folate, certain dietary and metabolic factors are also related to BMD in postmeno-

Table 3. Clinical and biochemical characteristics of study participants according to serum uric acid tertiles

Factor	Tertiles of uric acid levels				
	All (*n* = 184); mean ± SD	1 (*n* = 61); mean ± SD	2 (*n* = 61); mean ± SD	3 (*n* = 62); mean ± SD	*p*
Age (years)	57.2 ±10.6	57.8 ±10.0	56.4 ±8.0	57.3 ±10.6	NS
Weight (kg)	84.6 ±10.5	82.7 ±11.7	86.3 ±8.8	84.7 ±10.5	NS
Height (m)	156.0 ±3.5	156.2 ±2.9	156.0 ±3.9	155.9 ±3.6	NS
BMI (kg/m^2)	34.8 ±4.9	33.9 ±5.2	35.6 ±4.6	34.9 ±4.8	NS
Uric acid (mg/dl)	4.9 ±1.2	3.8 ±0.9	4.9 ±0.4	5.9 ±4.9	0.000[a]
Vitamin B_{12} (pg/ml)	338.3 ±218.3	345 ±252	331 ±233	337 ±163	NS
Folate (ng/ml)	7.9 ±2.5	8.4 ±3.1	7.7 ±2.2	7.5 ±2.1	NS
hs-CRP (mg/l)	0.6 ±0.9	0.53 ±0.70	0.70 ±0.99	0.66 ±1.02	NS
ESR (mm/hr)	12.0 ±5.8	11.3 ±5.3	12.3 ±7.2	12.5 ±4.8	NS
PTH (pg/ml)	61.6 ±24.9	58.3 ±20.5	61.5 ±28.3	64.6 ±25.5	NS
Total cholesterol (mg/dl)	196.7 ±31.9	197.3 ±36.7	195.6 ±29.7	197.3 ±29.3	NS
Triglyceride (mg/dl)	161.1 ±76.7	167.6 ±80.0	151.2 ±53.1	197.3 ±29.3	NS
LDL-C (mg/dl)	115.0 ±28.6	116.2 ±32.4	114.0 ±26.2	114.9 ±27.4	NS
HDL-C (mg/dl)	54.8 ±11.3	54.4 ±14.0	55.5 ±9.8	54.6 ±9.7	NS
Calcium (mg/dl)	9.3 ±0.8	9.2 ±0.8	9.4 ±0.8	9.2 ±0.9	NS
Phosphorus (mg/dl)	3.3 ±0.6	3.2 ±0.5	3.2 ±0.6	3.5 ±0.7	NS
BUN (mg/dl)	32.2 ±8.6	33.3 ±9.7	31.4 ±7.4	31.8 ±8.6	NS
Creatinine (mg/dl)	0.7 ±0.2	0.7 ±0.2	0.7 ±0.2	0.7 ±0.3	NS
ALT (IU/l)	24.7 ±7.8	23.2 ±7.9	26.1 ±7.5	24.7 ±7.8	NS
AST (IU/l)	23.7 ±7.8	23.0 ±7.6	25.0 ±6.4	23.3 ±5.8	NS
Femur neck BMD (g/cm^2)	–1.7 ±0.8	–1.86 ±0.8	–1.74 ±0.92	–1.49 ±0.78	0.048[a]
Lumbar spine BMD (g/cm^2)	–1.5 ±0.8	–1.56 ±0.82	–1.48 ±0.78	–1.49 ±0.77	NS

[a]Group 1 vs. 2 vs. 3
NS – not significant, BMI – body mass index, hs-CRP – high-sensitivity C-reactive protein, ESR – erythrocyte sedimentation rate, PTH – parathyroid hormone, LDL-C – low-density lipoprotein, HDL-C – high-density lipoprotein, BUN – blood urea nitrogen, ALT – alanine aminotransferase, AST – aspartate aminotransferase, BMD – bone mineral density

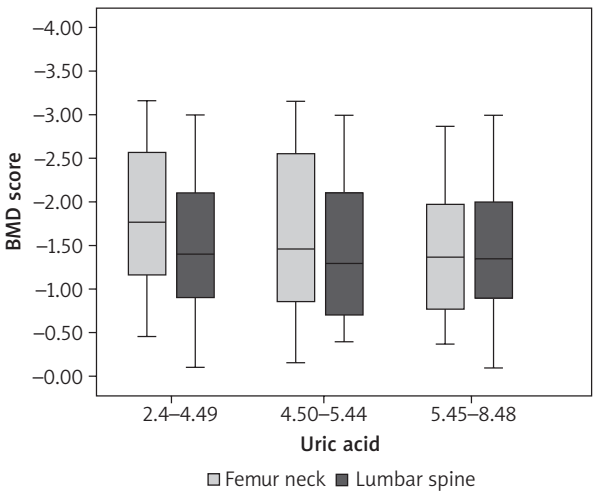

Fig. 2. Femur neck and lumbar spine bone mineral density measurements according to uric acid tertiles

pausal women. It has been shown that distinct factors including dyslipidemia, abnormal glucose metabolism, obesity and hypertension might affect bone mineral dynamics differently. Obesity may lead to increased BMD with causing elevated 17β-estradiol levels and higher mechanical load [33]. Nevertheless, lower serum TG or LDL and higher HDL concentrations were found to be associated with lower trabecular BMD. In this context, dyslipidemic changes occur more prominently in the postmenopausal period including an increase in LDL and TG and a decrease in HDL levels, causing increased hypertension and DM [34]. These metabolic alterations therefore highlight the importance of maintaining glycemic and lipidemic control in postmenopausal women to preserve bone health.

Although in this study we excluded postmenopausal women with DM, serum UA and BMD in type 2 DM

postmenopausal women have been investigated in several studies. In a recent study by Xu *et al*. [35] a positive association between UA and BMD was demonstrated. The authors suggested that relatively high UA might be a protective factor for bone health in postmenopausal diabetic women. Similarly, Ishii *et al*. [36] showed that higher UA levels were linearly associated with higher lumbar spine BMD in peri- and postmenopausal Japanese women.

Pro-inflammatory cytokines including IL-1, IL-6 and TNF-α have been shown to play a substantial role in bone health and metabolism [37]. IL-6 is a soluble mediator with a pleiotropic effect on inflammation and has been shown to increase with estrogen deficiency, and correlates with late life diseases such as osteoporosis, cancers, cardiac issues and frailty [38, 39]. Moreover, an increased level of circulating or locally produced soluble IL-6 receptor induces osteoclast formation by various immunologic mechanisms [40]. In cases of tissue damage, infection and inflammation IL-6 can also lead to CRP secretion from the liver by a direct stimulatory effect. The association between CRP and bone metabolism is therefore attributed to the close relationship between CRP and IL-6 and other pro-inflammatory cytokines [41]. Although we found no association between CRP and BMD measurements in conjunction with other biochemical and metabolic variables in the present study, there are conflicting results [37, 42-44] in the literature on the influence of CRP on progressive bone loss or osteoporosis. In a recent study in which 2,915 members of the Framingham Offspring Study were explored, associations between serum concentrations of IL-6, TNF-α, and CRP with BMD at the femoral neck, trochanter, total femur, and spine were investigated [44]. As a result of this study, statistically significant, modest inverse associations between CRP and femoral neck and trochanter BMD were observed among premenopausal women. But no associations were noted between these parameters and BMD among postmenopausal women who receive no hormone replacement therapy. This lack of consistency suggested that increased levels of circulating inflammatory biomarkers may not be a risk factor for decreased BMD measurements.

There were, however, several limitations related to the present study. First, although we did not calculate fat mass and abdominal visceral fat area in this study, BMI values were similar in each group. The second limitation is the inability to assess changes in CRP in the local bone microenvironment that may have a biological effect, but which may not be detected in the serum. Third, it would be beneficial if bone resorption markers, as well as serum Hcy and IL-6 levels, were included in the results. Finally, the relatively small sample size at a single center necessitates validation of these results with additional multicentre studies.

Conclusions

This study revealed that femur neck and lumbar BMD was associated with serum UA levels irrespective of subclinical inflammation in postmenopausal women. Furthermore, it was found that vitamin B_{12} and folate did not have any significant effect on BMD and UA levels. Nevertheless, further studies focused on the exact underlying mechanisms of how UA affects bone health, particularly in women, need to be undertaken.

Disclosure

The authors report no conflict of interest.

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