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Serum Uric Acid Status and Its Association with Bone Mineral Density in the Elderly People Aged 60 Years and More

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Abstract

Background: Osteoporosis is associated with decreased antioxidant defenses and serum uric acid (UA) as an antioxidant may exert a protective effect on bone mass.
Objectives: This study aimed to determine the association between serum UA and bone mineral density (BMD) in the elderly population.
Methods: All participants of the Amirkola Health and Ageing Project aged ≥ 60 years entered the study. BMD in the femoral neck (FN-BMD) and lumbar spine (LS-BMD) was determined by dual energy X-ray absorptiometry and osteoporosis was defined as BMD T-score < -2.5 at either FN or LS. The patients were classified according to serum UA levels as < 4; 4 - 4.99; 5 - 5.99; 6 - 6.99 and > 7 mg/dL. In statistical analysis, the value of BMD as well as frequency of osteoporosis in each subgroup were compared with the control group (UA < 4 mg/dL).
Results: A total of 1080 patients were studied. By increasing serum UA from < 4 mg/dL to > 7 mg/dL the BMD at both measurement sites increased as well. The serum UA was associated with decreased risk of osteoporosis. In multivariate analysis, the odds of osteoporosis in the subgroup with serum UA levels between 4 - 4.99 mg/dL was significantly lower than the control group (OR = 0.66, 95% CI, 0.44 - 0.99). Age and female sex were associated with increased odds of osteoporosis (OR = 1.08, 95% CI, 1.05 - 1.10 and OR = 10.62, 95% CI, 7.53 - 14.97 respectively).
Conclusions: These findings indicate a negative association between serum UA and osteoporosis in the elderly population aged ≥ 60 years.

Keywords: Association, Bone Mineral Density, Elderly Subjects, Serum Uric Acid

1. Background

Hyperuricemia is a prevalent biochemical abnormality, which can be associated with uric acid (UA) crystal deposition and gout. High levels of serum UA are also associated with many clinical conditions unrelated to UA crystal deposition such as cardiovascular disease, hypertension, heart failure, chronic renal disease, insulin resistance, and metabolic disease (1, 2). Several observational and randomized controlled studies have linked hyperuricemia with multiple health outcomes including bone health in elderly individuals (3). Serum UA is a powerful scavenger of peroxyl and hydroxyl radicals and at an elevated level is a major antioxidant of the plasma, which may protect cells from oxidative damages (4). Age-related osteoporosis is associated with oxidative stress, and in osteoporotic women antioxidant defense is lower than normal age-matched controls, suggesting a role of oxidative stress in the pathogenesis of low bone mass in the elderly people (5).

Many studies have addressed the association between serum UA and bone mineral density (BMD) in men and women but the results vary according to sex, age and sites of BMD measurements (6-12). The results of a systematic review and meta-analysis of 13 studies comprising a total of 55,859 participants showed a positive association between serum UA levels and BMD values for the spine, and hip in both men and women. An increase of one standard deviation in serum UA levels reduced the number of new fractures during follow-up period (8). Another systematic review and meta-analysis of five prospective studies including 29,110 participants showed a negative association be-

tween serum UA and the risk of bone fracture (9).

In participants of the Rotterdam Study, higher level of serum UA and fracture were associated with higher BMD (12). A large cross-sectional study of healthy postmenopausal women showed higher risk of osteoporosis in the lowest quartile of serum UA by 40% as compared to the highest quartile (7). Nonetheless, the association between serum UA and BMD is influenced by sex and site of BMD measurement (7, 9-11). Since many elderly people have coexistence of two or more common chronic medical conditions such as obesity, diabetes, and metabolic syndrome, these conditions which are also prevalent in the general population of northern Iran, may directly or indirectly confound the association between serum UA and BMD in the elderly people (13-18).

Osteoporosis is an important cause of bone fracture and disability in the elderly population. Hence, identification of the associated factors of low BMD and osteoporosis in susceptible individuals is helpful in preventive measures. Yet, the association between serum UA and BMD has not been investigated in the elderly population of northern Iran and data in this context are scarce.

2. Objectives

The present study was conducted to determine the association between serum UA and BMD in all elderly inhabitants of a small town located in the geographic region of northern Iran.

3. Methods

The population of this cross-sectional study comprised all participants of the Amirkola Health and Ageing Project (13). This project was carried out in Amirkola, Babol. The baseline stage of this project was performed in 2011 and 2012. The proposal of this study was approved by the Ethical Committee of Babol University of Medical Sciences. All inhabitants of the Amirkola town aged 60 years and over were invited to participate in this project and finally 72.3% of the invited subjects completed the study. Exclusion criteria were taking medications affecting serum vitamin D or UA metabolism, diuretics, corticosteroids, anti-osteoporotic drugs, vitamin D, calcium, and the presence of renal failure, systemic inflammatory rheumatic diseases, chronic respiratory, hematologic, renal and gastrointestinal diseases, as well as systemic or localized infectious diseases. BMD in the femoral neck (FN) and lumbar spine (LS) was determined by dual energy X-ray absorptiometry (DXA) method using a Lexxus densitometer, and the results were expressed as BMD g/cm^2, BMD T-score and BMD Z-score. The precision errors of BMD measurements were 1.3% for total hip, 2% for femoral neck and 2.3% for spine. Osteoporosis was diagnosed according to the International Society for Clinical Densitometry criteria defined as BMD T-score < -2.5 at either FN or LS (19). Data were provided for demographic features like age, sex, level of education, coexistent comorbidities (Table 1).

In statistical analysis, patients were classified according to serum UA levels as < 4, 4 - 4.99, 5 - 5.99, 6 - 6.99 and > 7 mg/dL. The magnitude of BMD as well as frequency of osteoporosis in each subgroup was compared to the subgroup of serum UA < 4 mg/dL, which served as the control group. The association was determined by chi square test with calculation of odds ratio (OR) with 95% confidence interval (95% CI).

Pearson correlation test was used to determine correlation between serum UA and BMD. Student *t* test was used for comparison of quantitative variables with normal distribution. Multiple logistic regression analysis with osteoporosis as dependent variable and UA subgroups and demographic variables as predictor variables were used to determine independent association between UA and osteoporosis.

4. Results

A total of 1080 patients (men, 58.3%) were studied. Mean age in men was significantly higher than women (71.3 $\pm$ 7.94 vs. 69.97 $\pm$ 7.3 years, P = 0.0047). Overall, mean UA level was 4.82 $\pm$ 0.88 mg/dL, median was 4.7 (3 - 10.10 mg/dL) (Table 1).

As shown in Table 1, the UA subgroups were similar regarding age, all demographic and biochemical factors (data not shown) except sex, diabetes and frequency of osteoporosis. In the entire study population, by increasing serum UA from < 4 mg/dL to > 7 mg/dL, mean BMD at both FN and LS decreased significantly and prevalence of osteoporosis increased from 48.4% to 24% respectively (Tables 1 and 2). At both measurement sites, the magnitude of BMD in the control group was at the lowest and in the > 7 mg/dL group was at the highest level. In the whole number of patients there was a significant but weak positive correlation between BMD in the femoral neck (FN-BMD) and lumbar spine (LS-BMD) with serum UA (r = 0.079, P = 0.01 and r = 0.108, P = 0.001 respectively. Mean BMD changes from the control group in each subgroup are shown in Table 2. Compared to the control group, the FN-BMD increased by 6.6% (P = 0.001), 6.2% (P = 0.001), 8.37% (P = 0.001) and 8% (P = 0.053) in subjects with serum UA at 4 - 4.99, 5 - 5.99, 6 - 6.99 and > 7 mg/dL respectively. The respective percentages of

Table 1. Characteristics of the Study Population According to Serum Uric Acid Levels[a]

Variables	Uric Acid Levels, mg/dL					P Value
	< 4	4 - 4.99	5 - 5.99	6 - 6.99	> 7	
No.	161	517	288	89	25	
Age, years	68.16 ± 7.2	68.6 ± 7.02	68.3 ± 6.9	68.57 ± 7.1	67.7 ± 6.3	0.933
Men	62 (38.5)	30.7 (59.4)	165 (57.3)	55 (61.8)	14 (56)	0.001
BMI, kg/m^2	27.1 ± 4.66	27.2 ± 4.68	27.24 ± 4.43	27.4 ± 4.62	28.44 ± 3.76	0.767
Abdominal obesity[b]	95 (59)	295 (57.1)	174 (60.4)	46 (51.7)	19 (76)	0.222
Waist circumference, cm	95.86 ± 9.12	95.65 ± 9.30	96.12 ± 9.21	95.21 ± 9.01	95.15 ± 9.29	0.80
Obesity[c]	43 (26.7)	134 (25.9)	68 (23.6)	22 (24.7)	9 (36)	0.701
Metabolic syndrome	127 (78.9)	387 (74.9)	221 (76.7)	65 (73)	20 (80)	0.767
Diabetes	67 (41.6)	157 (30.4)	84 (29.2)	23 (25.8)	9 (36)	0.037
FN-BMD, g/cm^2	0.801 ± 0.148	0.854 ± 0.160	0.850 ± 0.153	0.867 ± 0.163	0.865 ± 0.163	0.002
LS-BMD, g/cm^2	0.803 ± 0.175	0.880 ± 0.192	0.872 ± 0.175	0.881 ± 0.176	0.918 ± 0.258	0.001
Osteoporosis[d]	78 (48.4)	166 (32.1)	98 (34)	29 (32.6)	6 (24)	0.003
Educated[e]	62 (38.5)	194 (37.5)	117 (40.6)	37 (41.6)	7 (28)	0.687
Physical activity score > 150[f]	41 (25.5)	131 (25.3)	73 (25.3)	18 (20.2)	4 (16)	0.698
Creatinin, mg/dL	0.89 ± 0.23	0.95 ± 0.22	0.98 ± 0.21	1.04 ± 0.28	1.14 ± 0.29	0.000

Abbreviations: FN-BMD, BMD in the femoral neck; LS-BMD, BMD in the lumbar spine; PASE, physical activity scale for the elderly.
[a] Values are expressed as mean ± SD or No. (%).
[b] Abdominal obesity was diagnosed with WC > 95 cm.
[c] BMI > 30 kg/m^2.
[d] Defined as BMD T-score < -2.5 at either femoral neck or lumbar spine.
[e] Education level at and higher than primary school.
[f] Determined by PASE.

changes in the LS-BMD were 9.6%, 10.6%, 9.8% and 14.5% (P = 0.001 for all).

The relationship between UA and BMD varied according to sex as well as BMD measurement sites. In men, a statistically significant BMD difference from the control group was observed only at serum UA levels > 7 mg/dL in both measurement sites, whereas in women, significant BMD differences were observed at serum levels of 4 - 4.99 mg/dL for FN-BMD and up to 7 mg/dL for LS-BMD (data not shown).

4.1. Association Between Serum UA and Osteoporosis

Osteoporosis at either FN or LS was found in 377 patients (34.9%). Prevalence of osteoporosis in women was significantly higher than men (58.1% vs. 16.5%, P = 0.001). As shown in Table 1, in the entire population, the prevalence of osteoporosis in UA group > 7 mg/dL (24%) was lower than other subgroups. Prevalence of osteoporosis in the control group (UA < 4 mg/dL) was 48.4 percent; indicating a negative association between serum UA levels and osteoporosis. In multiple logistic regression analysis after adjustment for confounding factors such as age, physical activity, diabetes, abdominal obesity, sex, serum creatinine, and vitamin D deficiency, there was an independent negative association between osteoporosis and serum UA levels of 4 - 4.99 mg/dL (Table 3). There was a trend towards a protective effect at higher levels of serum UA. Furthermore, a significant independent negative association was observed between osteoporosis with physical activity, presence of diabetes and abdominal obesity, whereas age and female sex were independently associated with increased risk of osteoporosis.

5. Discussion

The findings of this study indicate a positive association between serum UA level and BMD at both femoral neck and particularly in the lumbar spine. In multivariate logistic regression analysis, after adjustment for all covariates, there was an independent negative association between serum UA at 4 - 4.99 and osteoporosis in both men and women indicating a negative association between serum UA and osteoporosis in the elderly population. Similarly, physical activity, diabetes, and abdominal obesity were negatively associated with osteoporosis, whereas, age and female sex were positively associated with osteoporosis

Table 2. BMD at FN-BMD and LS-BMD in the Whole Number of Elderly Patients Aged ≥ 60 Years According to Serum Uric Acid Levels

Uric Acid Levels, mg/dL	FN-BMD, g/cm^2	Difference(%)[a]	P Value	LS-BMD, g/cm^2	Difference (%)	P Value[b]
< 4 (n = 161)	0.800 ± 0.1 4 8	-		0.802 ± 0.175	-	
4 - 4.99 (n = 517)	0.853 ± 0.156	6. 6	0.001	0.879 ± 0.191	9.6	0.001
5 - 5.99 (n = 288)	0.850 ± 152	6.25	0.001	0.871 ± 175	8.6	0.001
6 - 6.99 (n = 89)	0.867 ± 0.163	8.37	0.001	0.881 ± 0.176	9.8	0.001
> 7 (n = 25)	0.864 ± 0.184	8	0.053	0.918 ± 258	14.5	0.038
Total (n = 1080)	0.846 ± 0.156	-		0.867 ± 0.187	-	

Abbreviations: BMD, bone mineral density; FN-BMD, BMD in the femoral neck; LS-BMD, BMD in the lumbar spine.
[a] BMD percent difference from the group with uric acid < 4 mg/dL.
[b] ANOVA test was used for comparison.

Table 3. Association between osteoporosis[a] at either femoral neck or lumbar spine with serum UA in elderly women and men aged ≥ 60 years, after adjustment for confounding factors using multiple logistic regression analysis with calculation of unadjusted and adjusted OR with 95% CI

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Serum UA, < 4 mg/dL	1	1
Serum UA, 4 - 4.99 mg/dL	0.50 (0.35 - 0.72)	0.60 (0.39 - 0.92)
Serum UA, 5 - 5.99 mg/dL	0.55 (0.37 - 0.81)	0.66 (0.41 - 1.06)
Serum UA, 6 - 6.99 mg/dL	0.51 (0.30 - 0.88)	0.63 (0.33 - 1.21)
Serum UA, > 7 mg/dL	0.34 (0.13 - 0.89)	0.41 (0.13 - 1.29)
Age, y	1.12 (0.75 - 1.6)	1.08 (1.05 - 1.10)
Gender, female vs. male	16.08 (10.92 - 23.49)	10.62 (7.53 - 14.97)
PASE[b], > 150 vs. < 150	0.74 (0.32 - 1.05)	0.67 (0.47 - 0.95)
Abdominal obesity[c], WC > 95 cm vs. < 95 cm	1.07 (0.69 - 1.75)	0.42 (0.31 - 0.58)
Diabetes presence vs. absence	0.96 (0.98 - 1.59)	0.49 (0.31 - 0.62)
Serum vitamin D, < 20 ng/mL vs. > 20 ng/ mL	1.43 (0.80 - 1.15)	1.33 (0.97 - 1.81)
Serum creatinine, < 1 mg/dL vs. > 1 mg/dL	0.74 (0.32 - 1.95)	0.67 (0.47 - 0.95)

Abbreviations: 95% CI, 95% confidence interval; BMD, bone mineral density; OR, odds ratio; PASE, physical activity scale for the elderly; UA; uric acid; WC, waist circumference.
[a] Defined as BMD T-score < -2.5.
[b] determined by PASE.
[c] Abdominal obesity was diagnosed with WC > 95 cm.

as expected. A sex-difference in the association between serum UA and osteoporosis can be attributed to the variations in the etiology of osteoporosis in men versus women (14, 15, 17).

These findings in agreement with other studies show a positive association between serum UA and BMD (10, 20-23). In a longitudinal study of Korean men aged 50 years and more, over a 3-year follow-up period, higher serum UA was associated with decreased rate of incident fracture (20). A large cross-sectional study showed lower rates of osteopenia and osteoporosis in men and postmenopausal women aged ≥ 50 years who had high levels of serum UA (21). However, another study of Chinese men aged > 50 years, showed a positive association of serum UA only with LS-BMD but not BMD at other skeletal sites (22). Nonetheless, in a cross-sectional study of a community dwelling older men aged > 70 years old, the serum UA level above the median value was associated with lower osteoporosis in the femoral neck as well as decreased rates of vertebral and nonvertebral fractures (23). A study of the Chinese people found an independent association between lower osteoporosis and hyperuricemia only in postmenopausal women but not in men (5). In this study mean age in hyperuricemic men was higher than hyperuricemic women (67.2 ± 2.1 vs. 62.2 ± 4) (6). In another study of peri- and postmenopausal women aged 47 - 89 years, there was a linear correlation between LS-BMD and serum UA. In this study, the third quartile of serum UA was associated with a significant protective effect against bone loss as compared to the first quartile (10). The results of a systematic review

and meta-analysis of 5 prospective studies revealed an association between increased serum UA and lower fractures (9).

Protective effect of UA on bone mass is supposed to be mediated through the antioxidant effect of serum UA on bone metabolism. Elderly osteoporotic women have lower antioxidant defenses as compared to normal age-matched reference population (5). Oxidative stress has a potential to attenuate osteoclastogenesis and bone formation. Whereas, antioxidants reduce osteoclastic activity, increased differentiation of osteoblasts and mineralization process. Uric acid as an antioxidant can decreases bone resorption (7, 23, 24).

This study has some limitations, including low sample size in subgroups with higher serum UA. This issue prevented detection of a significant difference between the control and other subgroups. Data regarding a few demographic features or biochemical parameters such as smoking, history of fractures, and history of family fracture, menopausal duration, parity, serum thyroid hormones, serum cholesterol, triglycerides, and parity have not been collected. These factors may directly or indirectly affect postmenopausal BMD and confound the results (15). Since all comparison groups were recruited from the same cohort comprised of all 60 years and older inhabitants of the Amirkola town, therefore the distribution of all variables are expected to be similar across various subgroups and thus the results are less subject to bias. The study has also some strength in relation to patient selection, which comprised all inhabitants of a small town aged 60 years and over. Homogeneity of the study subjects in regard to ethnicity, lifestyle, diet, physical activity, dressing and data collection regarding several coexistent medical conditions as well as data collection for many biochemical variables including serum Ca, phosphate, vitamin D, PTH, hematological and iron parameters (data not shown) should be considered as a strength.

This study provided additional data to support the protective effect of high serum UA. Yet the clinical implication of high serum UA in the elderly subjects remains to be determined, because, both high and low levels of UA are associated with metabolic, cardiovascular, renal and neurological diseases (1-3). Hence, in patients with asymptomatic hyperuricemia unrelated to gout or nephrolithiasis, the time of initiating treatment and a target level for UA lowering drugs has not been specified (1). The results of a meta-analysis which explored 136 unique health outcomes, showed no convincing evidence to treat asymptomatic hyperuricemia except for gout or nephrolithiasis (3).

In conclusion, the findings of this study indicate a significant positive association between high serum UA and BMD at both femoral neck and spine in elderly men and women. Furthermore, UA at levels between 4 to 4.99 mg/dL decreases the risk of osteoporosis in the elderly people aged 60 years and more. However, regarding an independent association of hyperuricemia with cardiovascular events, the benefits or deleterious effects of high serum UA on BMD or other health outcomes should be investigated with further longitudinal studies. In these studies, patients with and without hyperuricemia should be followed with periodic measurements of serum UA and BMD over a prolonged period. Comparison of the outcomes in subjects with and without hyperuricemia provides additional data on the association between serum UA and osteoporosis.

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Footnotes

Authors' Contribution: All the authors performed the literature search, designed the study, performed data collection, analyzed the data and drafted the manuscript.

Conflict of Interests: The authors report no conflict of interests.

Ethical Approval: The research protocol was approved by Babol University of Medical Sciences (code of ethics: MUBABOL.HRI.REC.1396.69).

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