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LETTERS TO THE EDITOR

Serum uric acid and its relationship with bone mineral density in middle-aged and elderly men: a cross-sectional study of 571 cases

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Dear Editor,

Uric acid (UA) is an end product of purine metabolism and has attention for its dual role as both an antioxidant and a pro-oxidant[1,2]. While UA's antioxidant properties are believed to protect against oxidative stress, its role in bone health remains controversial[3-5]. Therefore, we conducted a cross-sectional study to investigate the association between serum UA levels and bone mineral density (BMD) in middle-aged and elderly Korean men.

Our study initially included 632 male participants who underwent laboratory tests and dual-energy X-ray absorptiometry (DXA) as part of a general health examination between March 2014 and March 2020. After excluding those under 40 years (n=32), with chronic kidney disease (estimated glomerular filtration rate (GFR) ≤60mL/min/1.73m²) (n=27), or hypothyroidism (n=2), 571 men were analyzed. Participants were divided into quartiles based on their serum UA levels. Categorical variables are expressed as frequencies with percentages, while continuous variables are expressed as means and standard deviations. Between-group comparisons were performed using Pearson's chi-square test or Fisher's exact test for categorical variables, and one-way analysis of variance or the Kruskal–Wallis test was employed for numerical variables, as appropriate. To evaluate the association between serum UA levels and BMD, we performed a multivariate analysis using analysis of covariance, adjusting for covariates such as age, body mass index (BMI), smoking status, diabetes, hypertension, serum alkaline phosphatase, serum vitamin D, and GFR. Bonferroni post-hoc comparisons were performed to assess differences between the quartile groups. All p-values were two-sided, and statistical significance was set at $p < 0.05$.

The mean age of the participants was 54.3 ± 8.7 years, and the mean serum UA level was 5.80 ± 1.20 mg/dL. The baseline characteristics of the study participants stratified by serum UA quartiles are shown in Table I. In the univariate analysis, the BMD of the femur neck, trochanter, and total hip exhibited a significant increase across quartiles of serum UA levels, while there were not significant association at all lumbar spine sites. Furthermore, in the multivariate analysis, a significant association between serum UA levels and BMD was maintained at the trochanter and hip total sites, even after adjusting for covariates (Table I). Bonferroni post-hoc comparisons between the quartiles indicated significant differences, with participants in the fourth UA quartile consistently showing higher BMD than those in the first quartile.

The observed association suggests that elevated serum UA levels may have a protective effect on bone quantity in middle-aged and elderly men. This positive correlation aligns with the hypothesis that UA's antioxidant properties could play a beneficial role in bone metabolism by reducing oxidative stress, which is known to contribute to bone resorption[6]. While this effect has been observed in previous studies, particularly among postmenopausal women,[7,8] evidence regarding older male populations has been limited and inconsistent. For example, the study by Zhang et al[9]. reported no significant association between serum UA and BMD in men. Our study adds to the existing literature by identifying a positive association in middle-aged and elderly Korean men, suggesting potential population-specific or methodological differences that warrant further investigation.

It is important to note, however, that the mechanisms underlying this association are complex. UA may exert its effects not only through its antioxidant capabilities but also through its interactions with other metabolic pathways involved in bone turnover. For example, higher UA levels are often associated with metabolic factors such as higher BMI and better nutritional status, which could also contribute to higher BMD[10]. In our study, this positive relationship between serum UA and BMD remained significant at both the trochanter and total hip sites, even after accounting for such confounding factors. Notably, serum UA levels were associated with hip BMD but not lumbar spine BMD. This differ-

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TABLE I. Data of the study population according to the quartiles of serum uric acid levels

Characteristics	Total (n = 571)	Serum uric acid Quartile 1 ≤ 5.00 mg/dL (n = 146)	Quartile 2 5.01 – 5.70 mg/dL (n = 137)	Quartile 3 5.71 – 6.50 mg/dL (n = 153)	Quartile 4 ≥ 6.51 mg/dL (n = 135)	p value
Baseline characteristic						
Age, years	54.3 ± 8.7	55.6 ± 8.3	54.7 ± 7.7	53.8 ± 8.60	54.9 ± 9.2	0.20
BMI, kg/m^2	24.2 ± 2.9	23.4 ± 2.7	23.7 ± 2.5	24.4 ± 2.8	25.1 ± 3.5	0.17
Current smoker	148 (25.9%)	40 (27.4%)	32 (23.4%)	48 (31.4%)	28 (20.7%)	0.18
Diabetes mellitus	50 (8.8%)	10 (6.5%)	14 (10.2%)	12 (7.8%)	14 (9.6%)	0.31
Hypertension	146 (25.6%)	38 (26.0%)	32 (23.4%)	36 (23.5%)	40 (29.6%)	0.60
Hyperlipidemia	52 (9.1%)	14 (9.6%)	10 (7.3%)	15 (9.8%)	13 (9.6%)	0.87
ALP, IU/L	65.4 ± 21.8	68.5 ± 22.9	65.3 ± 16.7	65.3 ± 16.7	63.7 ± 16.3	0.22
Vitamin.D, ng/ml	19.5 ± 8.0	19.6 ± 7.0	22.1 ± 6.9	17.9 ± 6.6	19.5 ± 6.6	0.48
CRP, mg/L	0.18 ± 0.5	0.16 ± 0.4	0.20 ± 0.6	0.16 ± 0.5	0.18 ± 0.4	0.92
GFR, mL/in/1.73m^2	96.6 ± 23.4	95.5 ± 20.2	95.3 ± 19.3	96.8 ± 23.8	98.9 ±29.1	0.55
BMD (g/cm^2)	0.94 ± 0.14	0.92 ± 0.13	0.93 ± 0.12	0.95 ± 0.15	0.95 ± 0.14	0.14
L1 Spine	0.94 ± 0.14	0.92 ± 0.13	0.93 ± 0.12	0.95 ± 0.15	0.95 ± 0.14	0.14
L2 Spine	1.00 ± 0.15	0.98 ± 0.13	0.99 ± 0.14	1.02 ± 0.15	1.01 ± 0.16	0.05
L3 Spine	1.04 ± 0.16	1.02 ± 0.15	1.03 ± 0.15	1.06 ± 0.17	1.06 ± 0.17	0.07
L4 Spine	1.05 ± 0.17	1.04 ± 0.17	1.04 ± 0.16	1.05 ± 0.16	1.07 ± 0.17	0.29
L Spine, Total	1.01 ± 0.15	0.99 ± 0.14	1.00 ± 0.14	1.02 ± 0.16	1.03 ± 0.15	0.11
Femur Neck	0.79 ± 0.12	0.77 ± 0.11	0.78 ± 0.11	0.81 ± 0.12	0.81 ± 0.13	0.01
Trochanter	0.71 ± 0.12	0.69 ± 0.09	0.70 ± 0.10	0.72 ± 0.10	0.72 ± 0.12	0.04
Hip, Total	0.97 ± 0.13	0.94 ± 0.12	0.95 ± 0.12	0.98 ± 0.12	0.99 ± 0.14	0.00
*Adjusted mean value of BMD (g/cm2)	Coefficient of etermination (Adjusted R2)					
L1 Spine	0.01	0.92 (0.90-0.95)	0.93 (0.91-0.95)	0.95 (0.93-0.97)	0.95 (0.93-0.98)	0.21
L2 Spine	0.01	0.98 (0.96-1.01)	0.99 (0.96-1.01)	1.02 (0.99-1.05)	1.01 (0.99-1.04)	0.06
L3 Spine	0.02	1.01 (0.98-1.04)	1.03 (0.99-1.05)	1.06 (1.03-1.08)	1.06 (1.04-1.09)	0.08
L4 Spine	0.02	1.03 (0.99-1.06)	1.04 (1.01-1.07)	1.06 (1.03-1.08)	1.08 (1.05-1.11)	0.06
L Spine, Total	0.01	0.99 (0.97-1.01)	0.99 (0.97-1.02)	1.02 (1.00-1.05)	1.03 (1.01-1.06)	0.06
Femur Neck	0.05	0.78 (0.77-0.80)	0.78 (0.76-.080)	0.80 (0.79-.082)	0.81 (0.79-0.83)	0.07
Trochanter	0.02	0.69 (0.67-0.71)[a]	0.69 (0.68-0.71)	0.72 (0.70-0.74)	0.73 (0.71-0.75)[a]	0.01
Hip, Total	0.03	0.94 (0.92-0.96)[a]	0.95 (0.93-0.97)	0.98 (0.96-0.99)	0.96 (0.96-1.01)[a]	0.01

Values are shown as mean ± standard deviation or number (%). ALP: Alkaline phosphatase; BMI: Body mass index; CRP: C-reactive protein; GFR: Glomerular filtration rate; BMD: Bone mineral density; L: Lumbar. *Covariates in the multivariate analysis included age, body mass index, current smoking status, diabetes, hypertension, serum alkaline phosphatase, serum vitamin D, and glomerular filtration rate. Adjusted mean values are expressed as means (95% confidence interval). a Same letter indicate statistically significant based on Bonferroni multiple comparison.

ence could be due to the hip's higher cortical bone content, which may be more responsive to UA's antioxidant effects, whereas lumbar spine BMD may be affected by degenerative changes commonly seen in older adults.

Our study has several limitations. This was a single-center study, with all participants self-selecting to visit the hospital for general health screenings, including elective DXA scans, which may introduce potential selection bias and confounding factors. Secondly, our study lacked data on key bone metabolism markers (e.g., calcium, phosphate, iPTH) and other potential confounders, including dietary patterns, alcohol intake, and medications such as allopurinol, febuxostat, steroids. The lack of such data may limit our ability to fully account for these confounding factors. Moreover, our findings may not be generalizable to other populations, as our study was limited to middle-aged and elderly Korean men. Therefore, further research with larger sample sizes and diverse populations are needed to better understand the effects of UA on bone me-

tabolism and to generalize the findings across different ethnicities.

In conclusion, our findings suggest that elevated serum UA levels are associated with higher BMD at the hip sites in middle-aged and elderly Korean men, indicating a potential protective role of UA in bone metabolism. Further research is necessary to explore the mechanisms involved and to determine whether modifying UA levels could be a viable strategy for improving bone health in older men.

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