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ORIGINAL ARTICLE

Higher serum uric acid is associated with higher lumbar spine bone mineral density in male health-screening examinees: a cross-sectional study

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Abstract

Bone health has been associated with oxidative stress and antioxidants have received interest to this end. Serum uric acid (SUA), an end product of purine metabolism in humans, has recently shown antioxidant properties regarding bone health, but there are conflicting results. The aim of this study was to investigate the relationship between SUA levels and lumbar spine bone mineral density (BMD) in clinically apparently healthy males aged 40–60 years. We performed a cross-sectional study of 6588 Korean males who completed a health-screening program from January 2011 to December 2014. Of the study participants, the mean age was 48.2 ± 10.7 years. Multiple regression analyses resulted in a significant positive association with lumbar spine BMD across SUA quintiles in a dose–response manner after adjusting for various confounding factors ($p = 0.013$); for each 1 mg/dl increase of SUA, BMD rose by 0.0054 g/cm^2 ($p = 0.004$). Stratified analyses revealed that this association between SUA and lumbar spine BMD was consistently observed across all clinically relevant subgroups. The present study demonstrated a positive association in males between SUA and lumbar spine BMD, suggesting that SUA could have a profitable effect on bone metabolism.

Keywords Uric acid · Bone mineral density · Bone health · DXA · Male

Introduction

An aging society is sparking renewed discussion about the prevention of age-associated diseases and their risk factors [1]. One of those concerns is bone health, which encompasses bone loss, including osteopenia and osteoporosis, fragility fractures, and disabilities leading to low quality of life, morbidity, and mortality [2]. Researchers have mainly studied postmenopausal osteoporosis in women; recently, however, the underdiagnosis of male osteoporosis and the ripple effect of disease burden have attracted research interest [3].

Pertaining to bone pathophysiology, studies have shown an association with oxidative stress characterized by an elevated level of reactive oxygen species (ROS), which was indicated in primary male osteoporotic patients, and dietary and endogenous antioxidants were markedly decreased in aged osteoporotic women as well [4–6]. Accordingly, it has been suggested that targeting ROS production could be a meaningful approach in the prevention of bone loss. In this regard, the application of antioxidants is of interest with regard to potential treatments

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for osteoporosis using either pharmacological or nutritional means. In the shape of hormone replacement therapy, 17β-estradiol prevented ROS-induced apoptosis of osteocytes [7] and raloxifene, selective estrogen-receptor modulators, had potent effects in the enhancement of antioxidant defense systems [8]. Polyphenols and lycopene, representative antioxidant components in grapefruit and red tomatoes, respectively, have also displayed beneficial effects [9, 10].

Uric acid, an end product of purine metabolism in humans, is considered a risk factor for various diseases, including gout, metabolic syndrome and cardiovascular disorders [11, 12]. Despite these unhealthy contributions, researchers have demonstrated a helpful association with bone health through its antioxidant properties. Higher serum uric acid (SUA) either within or above a normal range was associated with higher bone mineral density (BMD) both in peri- and postmenopausal women and in men [13–16] and has been suggested to be a protective factor against incident osteoporotic fractures [17, 18]. Other prior studies, however, exhibited conflicting results that SUA was inversely associated with BMD and the finding was replicated not only in a larger human population, but also in a rat model [19].

Although SUA has been shown to play a role in bone metabolism as an endogenous antioxidant, there have been inconsistent reports. Furthermore, most studies have focused on postmenopausal women and elderly men; few have included relatively younger men. Thus, we performed this cross-sectional study to assess the effect of SUA on bone metabolism using a large and relatively younger male population who underwent comprehensive health screening exams.

Materials and methods

Study participants

Between January 2011 and December 2014, 10,241 males who participated in the health check-up program, which was held at one of the Kangbuk Samsung Hospital Total Healthcare Centers located in Seoul and Suwon and included a BMD test, were screened. Since the South Korean Industrial Safety and Health Law requires annual or biennial health screening of employees, more than 80% of the participants were employees of various companies and local governmental organizations; the remaining participants voluntarily purchased self-paid screening exams at the health screening center. Among these participants, those who had missing SUA values and covariates ($n = 405$), had gout ($n = 172$), or took gout medication ($n = 78$) were excluded. We also excluded those who had taken medication for osteoporosis ($n = 17$), calcium supplementation ($n = 61$), steroids ($n = 14$), hypertension ($n = 2048$), hyperlipidemia ($n = 777$), and/or malignancy ($n = 40$) which could affect bone metabolism or SUA level. Patients with diabetes ($n = 1360$), rheumatoid arthritis ($n = 84$), and/or chronic kidney disease ($n = 203$) were excluded, as these conditions might affect bone metabolism. Some individuals met more than one exclusion criterion (Fig. 1). Finally, this

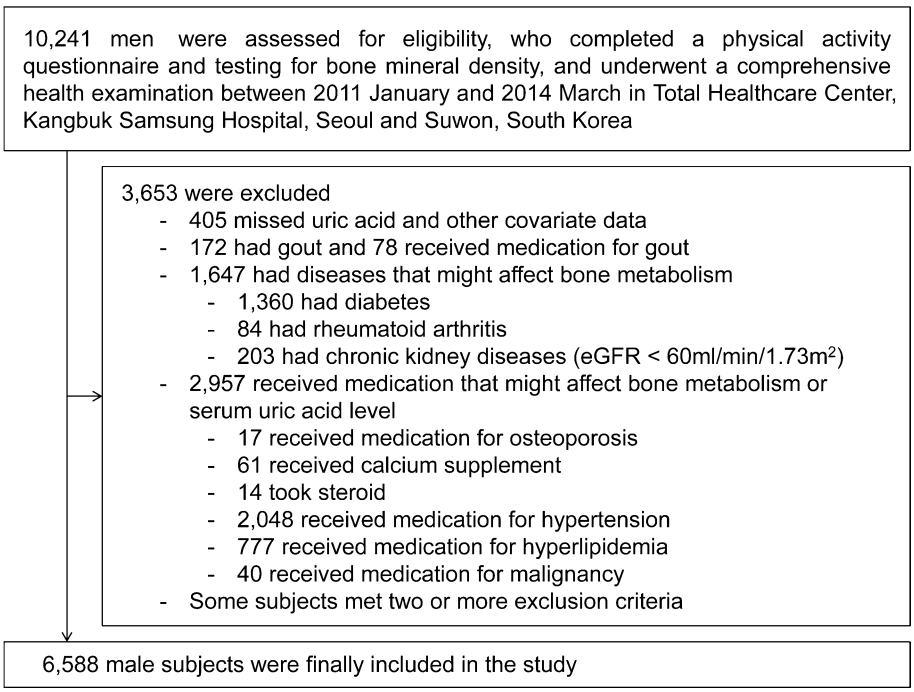

Fig. 1 Selection of study participants. *eGFR* estimated glomerular filtration rate

cross-sectional study included 6588 male participants who were divided into 5 groups according to their SUA level quintile. The study protocol was reviewed and approved by the Kangbuk Samsung Hospital Institutional Review Board (KBSMC #2015-12-044). The requirement for informed consent was waived because the patients were not identifiable from the data that were used.

Data collection and measurements

When visiting Kangbuk Samsung Hospital Total Healthcare Centers, all participants completed a standardized, self-administered questionnaire for the following parameters: demographic features including education, smoking status, alcohol intake, physical activity, diet, medication history, and current medications. Smoking status was categorized into never, former, or current smoker. Alcohol intake was classified as none, moderate (< 20 g/day), or high (≥ 20 g/day). Physical activity levels were categorized into inactive, minimally active (600 metabolic equivalent of task (MET)-minutes per week), or health-enhancing physically active [HEPA; 3000 MET-minutes per week] and were assessed using the validated Korean version of the International Physical Activity Questionnaire Short Form, as previously described [20, 21]. The respondents' usual diet was evaluated with a 103-item, self-reported food frequency questionnaire designed and validated in Korea [22]. Total energy intake (kcal/day) was calculated using a food composition table developed by the Korean Nutrition Society [22]. Blood pressure and anthropometry items were measured by trained registered nurses as part of a health check-up program. Body mass index (BMI) was calculated as the weight (kg) divided by height squared (m^2) and obesity was defined as BMI ≥ 25 kg/m^2, the proposed cutoff for Asian populations [23].

Blood samples were obtained in the morning after 10 h of fasting. Serum levels of the following items were measured, as described elsewhere: calcium, phosphorus, glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), alkaline phosphatase (ALP), alanine aminotransferase, and high-sensitivity C-reactive protein (hsCRP). The homeostasis model of assessment-insulin resistance (HOMA-IR) was calculated as the fasting insulin (mU/l) × fasting glucose (mmol/l)/22.5. Hyperuricemia in males was defined as SUA ≥ 7 mg/dl.

BMD was measured at the lumbar spine (L1–L4) using dual-energy X-ray absorptiometry (Lunar Prodigy; GE, Madison, WI, USA), and the results were expressed as g/cm^2. Calibration with a machine-specific phantom was standardized each day prior to the examination of patient samples.

Statistical analysis

Continuous variables are reported as mean ± standard deviation or the median and interquartile range, while categorical variables are presented as numbers and percentages. Categories of SUA included the following quintiles: < 5.1 mg/dl in Q1, 5.1–5.6 mg/dl in Q2, 5.7–6.2 mg/dl in Q3, 6.3–6.9 mg/dl in Q4, and ≥ 7.0 mg/dl in Q5. Variables of the participants in each quintile were compared using an analysis of variance (ANOVA). To examine the relationship between SUA and BMD, we performed a multiple linear regression analysis, in which the mean value of the lumbar BMD (L1–L4) expressed in g/cm^2 served as the dependent variable and SUA categorized into quintiles served as the independent variable, after adjusting for potential confounders. Age was adjusted for in the first simple model. Then, multivariable model 1 was further adjusted along with age for smoking status, alcohol intake, physical activity, total calorie intake, and BMI. Model 2 was the full model, which was additionally adjusted for calcium and vitamin C intake, serum calcium, serum phosphorus, ALP, and hsCRP. To identify effect modification, we also carried out stratified analyses with prespecified subgroups as follows: age (< 50 vs. ≥ 50 years), smoking history (never or ex-smoker vs. current smoker), alcohol intake (< 20 g vs. ≥ 20 g of alcohol per day), HEPA (no vs. yes), BMI (< 25 vs. ≥ 25 kg/m^2), hsCRP (< 1.0 vs. ≥ 1.0 mg/l), HOMA-IR (< 2.5 vs. ≥ 2.5), dietary calcium intake (< 500 vs. ≥ 500 mg/day), and dietary vitamin C intake (< 100 vs. ≥ 100 mg/day). Each stratum was analyzed using the full model. Interactions between subgroups were tested using likelihood ratio tests to compare models with and without product terms. All significance tests were two-tailed, and p values < 0.05 were considered statistically significant. We used STATA software, version 14.1 (Stata, College Station, TX, USA), to analyze the data.

Results

Characteristics of the study participants

Table 1 shows the baseline characteristics of the 6588 eligible male participants according to their SUA quintiles. The mean age was 48.2 ± 10.7 years, and the mean BMI was 24.0 ± 2.8 kg/m^2. The average SUA level was 5.92 ± 1.20 mg/dl, and the prevalence of hyperuricemia was 17.9%. Men with a higher SUA quintile were younger and more obese than their counterparts with lower SUA quintile values. Furthermore, a higher SUA quintile was associated positively with the frequency of current smokers, an alcohol intake > 20 g/day, higher education, hypertension, TC, LDL-C, TG, hepatic enzymes, hsCRP, and HOMA-IR, but negatively associated with physical

Table 1 Baseline characteristics of study participants

Characteristics	Overall	Uric acid quintiles (mg/dl)					*p* for trend
		Q1 (< 5.1)	Q2 (5.1–5.6)	Q3 (5.7–6.2)	Q4 (6.3–6.9)	Q5 (≥ 7.0)	
Number of participants	6588	1456	1292	1387	1273	1180	
Age (years)[a]	48.2 (10.7)	50.9 (10.8)	49.9 (10.8)	47.7 (10.5)	46.8 (10.1)	44.7 (9.9)	< 0.001
BMI (kg/m^2)[a]	24.0 (2.8)	23.1 (2.7)	23.5 (2.6)	23.9 (2.5)	24.6 (2.6)	25.2 (2.9)	< 0.001
Obesity (%)[c]	33.6	23.1	26.0	31.2	40.5	50.4	< 0.001
Current smoker (%)	35.0	32.5	33.5	36.0	35.9	37.3	0.007
HEPA (%)	20.8	24.3	19.6	21.4	20.2	17.5	0.001
Alcohol intake (%)[d]	38.8	36.4	32.6	38.0	41.3	46.0	< 0.001
Highest education level (%)[e]	76.8	71.7	75.1	76.7	79.4	82.2	< 0.001
Hypertension (%)	10.5	7.9	10.2	10.1	12.1	13.0	< 0.001
History of CVD (%)	3.0	3.3	3.3	2.5	3.1	2.5	0.257
Systolic BP (mmHg)[a]	114.2 (12.2)	112.2 (11.7)	113.4 (12.4)	114.1 (12.4)	114.9 (12.5)	116.7 (11.7)	< 0.001
Diastolic BP (mmHg)[a]	74.2 (9.2)	72.8 (8.8)	73.9 (9.4)	73.9 (9.3)	74.6 (9.3)	76.0 (9.1)	< 0.001
Serum calcium (mg/dl)[a]	9.37 (0.3)	9.29 (0.3)	9.33 (0.3)	9.37 (0.3)	9.42 (0.30)	9.48 (0.3)	< 0.001
Serum phosphorus (mg/dl)[a]	3.44 (0.4)	3.36 (0.4)	3.13 (0.4)	3.45 (0.4)	3.47 (0.4)	3.51 (0.4)	< 0.001
Glucose (mg/dl)[a]	94.0 (9.1)	94.4 (8.9)	93.9 (9.0)	93.8 (9.0)	94.0 (9.5)	94.0 (9.5)	0.321
Total cholesterol (mg/dl)[a]	202.3 (33.5)	196.2 (31.6)	199.3 (32.2)	203.2 (33.0)	205.5 (35.3)	208.8 (34.0)	< 0.001
LDL-C (mg/dl)[a]	128.5 (30.5)	122.3 (29.1)	126.5 (29.7)	130.0 (30.4)	131.2 (31.4)	133.3 (30.8)	< 0.001
HDL-C (mg/dl)[a]	53.4 (13.3)	56.2 (14.3)	54.6 (13.0)	53.1 (12.8)	51.7 (12.7)	50.5 (12.7)	< 0.001
Triglycerides (mg/dl)[b]	106 (75–154)	91 (69–130)	97 (70–136)	107 (75–154)	114 (81–167)	129 (88–196)	< 0.001
ALT (u/l)[b]	23 (17–32)	21 (16–28)	21 (16–29)	22 (17–32)	24 (18–34)	28 (20–39)	< 0.001
ALP (u/l)[b]	62 (53–72)	62 (53–74)	63 (53–73)	62 (53–72)	61 (53–72)	62 (53–71)	0.015
hsCRP (mg/l)[b]	0.5 (0.3–1.0)	0.4 (0.2–0.9)	0.5 (0.2–1.0)	0.5 (0.3–1.0)	0.6 (0.3–1.1)	0.8 (0.4–1.3)	< 0.001
HOMA-IR[b]	1.09 (0.70–1.64)	0.94 (0.62–1.46)	1.00 (0.64–1.52)	1.10 (0.74–1.59)	1.15 (0.73–1.68)	1.34 (0.84–2.00)	< 0.001
Calcium intake (mg/day)[b,f]	292.8 (180.4–442.1)	307.0 (189.5–445.0)	301.6 (187.1–458.3)	286.0 (183.7–443.7)	285.4 (172.0–435.5)	272.5 (169.6–423.7)	0.002
Vitamin C intake (mg/day)[b,f]	69.8 (44.5–108.3)	70.4 (45.9–107.4)	74.0 (46.2–112.8)	69.3 (43.8–106.5)	66.7 (43.4–107.4)	68.0 (41.3–105.7)	0.004
Total energy intake (kcal/d)[b,f]	1611.6 (1316.3–1994.7)	1633.2 (1325.7–1997.0)	1639.2 (1352.1–2031.1)	1583.4 (1299.0–1934.2)	1616.4 (1304.4–1990.7)	1578.1 (1282.9–1999.9)	0.301

Data are expressed as [a]mean (standard deviation), [b]median (interquartile range) or percentage

BMI body mass index, *HEPA* health-enhancing physical activity, *CVD* cardiovascular diseases, *BP* blood pressure, *LDL-C* low-density lipoprotein-cholesterol, *HDL-C* high-density lipoprotein-cholesterol, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *hsCRP* high-sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment of insulin resistance

[c]BMI ≥ 25 kg/m^2

[d] ≥ 20 g of ethanol per day

[e] ≥ College graduate

[f]Among 3477 participants with plausible estimated energy intake levels (within three standard deviations from the log-transformed mean energy intake)

activity, lower dietary intake of calcium and vitamin C, and HDL-C. There was no significant association with a history of cardiovascular diseases, glucose level, or total energy intake and SUA quintiles.

Relationship between SUA levels and BMD

Of all participants, the mean BMD was 1.17 ± 0.16 g/cm^2. The average BMD gradually increased across SUA quintiles (p for trend < 0.001, Fig. 2). A multiple linear regression analysis was conducted sequentially to investigate the relationship between SUA levels and BMD after controlling for potential confounders (Table 2). There was a clear

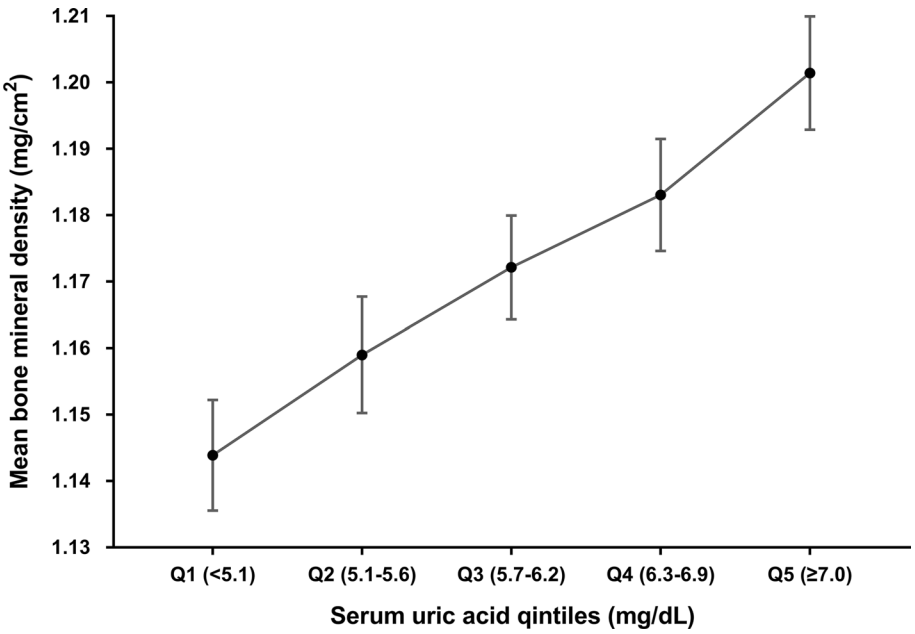

Fig. 2 Increase of the mean bone mineral density in the lumbar spine according to quintiles of serum uric acid. A *closed dot* for each quintile of SUA indicates the mean BMD (± standard error of the mean), and the *solid line* connects *individual dots* to highlight the increasing tendency of a mean BMD according to the increase in SUA. *BMD* bone mineral density, *SUA* serum uric acid

Table 2 Relationship between serum uric acid levels and bone mineral density

Uric acid levels	Quintiles (mg/dl)						Per 1 mg/dl increase
	Q1 (< 5.1)	Q2 (5.1–5.6)	Q3 (5.7–6.2)	Q4 (6.3–6.9)	Q5 (≥ 7.0)	p for trend	
Age-adjusted model	Reference					< 0.001	
Coefficient		0.0147	0.0271	0.0377	0.0552		0.0161
95% CI		0.003–0.026	0.016–0.039	0.026–0.049	0.043–0.067		0.013–0.019
p value		0.013	< 0.001	< 0.001	< 0.001		< 0.001
Multivariable-adjusted model 1	Reference					0.002	
Coefficient		0.0093	0.0122	0.0157	0.021		0.0064
95% CI		−0.003 to 0.022	−0.0002 to 0.025	0.003 to 0.029	0.008 to 0.034		0.003 to 0.010
p value		0.144	0.054	0.016	0.002		< 0.001
Multivariable-adjusted model 2	Reference					0.004	
Coefficient		0.0116	0.0142	0.0186	0.0263		0.0053
95% CI		−0.001 to 0.024	0.002 to 0.026	0.006 to 0.031	0.013 to 0.040		0.002 to 0.009
p value		0.065	0.023	0.004	< 0.001		0.004

Multivariable model 1 was adjusted for age, smoking status, alcohol intake, physical activity, total calorie intake, and BMI; multivariable model 2 was adjusted for calcium and vitamin C intake, serum calcium, serum phosphorus, ALP, and hsCRP in addition to the variables listed in model 1

CI confidence interval, *BMI* body mass index, *BP* blood pressure, *ALP* alkaline phosphatase, *hsCRP* high-sensitivity C-reactive protein

dose–response relationship between SUA quintiles and BMD (p for trend < 0.001). In an age-adjusted model, the average difference (95% confidence interval (CI)) of BMD comparing quintiles 2–5 vs. quintile 1 of SUA was 0.015 (0.003–0.026), 0.027 (0.016–0.039), 0.038 (0.026–0.049), and 0.055 (0.043–0.067), respectively. These results did not change after further adjusting for smoking status, physical activity, total calorie intake, and BMI. When adjusted for potential intermediate variables, the association was still highly statistically significant. The respective average differences (95% CI) in BMD for quintiles 2–5 vs. quintile 1 of SUA were 0.012 (−0.001 to 0.024), 0.014 (0.002 to 0.026), 0.019 (0.006 to 0.031), and 0.026 (0.013 to 0.040), respectively. When SUA was introduced as a continuous variable in multivariate models, BMD was higher by 0.005 g/cm^2 with an increase of 1 mg/dl in SUA (p = 0.004). The adjusted dose–response association curve for this relationship is shown in Fig. 3.

Effect modification by age, smoking status, alcohol intake, physical activity, BMI, hsCRP, HOMA-IR, and dietary intake of calcium and vitamin C

We also performed stratified analyses (Table 3). The positive associations of SUA with BMD were similar across pre-specified subgroups of study participants. SUA was significantly more strongly associated with BMD in non-obese compared to obese men (adjusted coefficients: 0.019 vs. 0.010, respectively; p for interaction = 0.028).

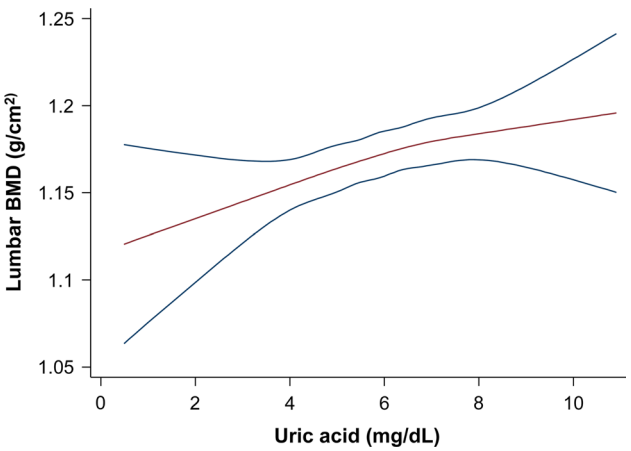

Fig. 3 The relationship between serum uric acid levels and lumbar bone mineral density. The *curves* were estimated from a linear regression model representing the adjusted dose–response associations between serum uric acid levels and lumbar bone mineral density based on restricted cubic splines with knots at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the serum uric acid distribution (p = 0.0004). Models were adjusted for age, smoking status, alcohol intake, physical activity, total calorie intake, BMI, serum calcium, serum phosphorus, ALP, and hsCRP. *BMI* body mass index, *ALP* alkaline phosphatase, *hsCRP* high-sensitivity C-reactive protein

Discussion

The present study of male health examinees investigated the relationship between SUA levels and BMD at the lumbar spine. A significant positive association between SUA quintiles and lumbar spine BMD was observed in a dose–response manner after adjustment for potential confounders. Indeed, the association between SUA and BMD was significantly stronger among non-obese men compared to obese men (the coefficient in the non-obese men = 0.191 vs. the coefficient in the obese men = 0.096). To our knowledge, this is the largest number of Korean male participants in a general population that has been assessed for this condition to date. The examined cohort was also a low-risk, asymptomatic population of Korean men aged 40–60 years undergoing a yearly screening. Study participants with high-risk conditions that could potentially affect bone metabolism or the SUA level were excluded. This meticulously refined population is an additional strength of our study.

The heterogeneity of the results of prior studies could be explained by the following variations: population characteristics (e.g., ethnicity, sex, age, etc.), study design, study size, and covariates adjusted for [24]. Nevertheless, the favorable association between SUA and BMD was homogenously observed in males, especially in Asians and at the lumbar spine [15, 16, 24, 25], while the National Health and Nutrition Examination Survey (NHANES; 2005–2010) study demonstrated no associations in the lumbar spine, femur neck, or hip [19]. Higher SUA levels have been associated with a reduced risk of osteoporotic fractures of the hip and vertebrae [18, 26] and a better overall bone quality [27].

Taken together, our findings were compatible with the majority of the prior studies conducted in males, which advocate the hypothesis that SUA is good for bone health in humans. Our study population covered men aged 40–60 years, and the findings were in keeping with previous cross-sectional studies both in younger [25] and elderly males [15, 16, 24, 28]. A more recent prospective Rotterdam study of a general population showed a positive association between SUA and BMD at the femur neck, and there was no effect modification due to sex or age [28]. To assess the effect modification of age, we examined the association between SUA and BMD stratified by age < 50 or ≥ 50 years. We observed an even stronger positive association in both stratified groups, which suggests that the impact of uric acid on bone may start at an early age and could be maintained throughout the lifespan, although causality still needs to be determined. In our stratified analyses, none of the clinically relevant subgroups modified the relationship between SUA and BMD

Table 3 The relationship between serum uric acid levels and lumbar bone mineral density in clinically relevant subgroups

Subgroup	Number	Per 1 mg/dl increase in uric acid			*p* for interaction
		Coefficient	95% CI	*p* value	
Age (years)					0.220
< 50	3769	0.0078	0.004 to 0.012	< 0.001	
≥ 50	2819	0.0075	0.001 to 0.014	0.018	
Current smoker					0.204
No	3822	0.0078	0.003 to 0.012	< 0.001	
Yes	2056	0.0076	0.001 to 0.014	0.016	
Alcohol intake (g/day)					0.240
< 20	4075	0.0065	0.005 to 0.015	0.001	
≥ 20	1067	0.0096	−0.002 to 0.009	0.029	
HEPA					0.145
No	3727	0.0099	0.003 to 0.011	< 0.001	
Yes	2358	0.0038	0.001 to 0.018	0.185	
BMI (kg/m^2)					0.028
< 25	4373	0.0191	0.014 to 0.024	< 0.001	
≥ 25	2214	0.0096	0.004 to 0.015	0.001	
hsCRP (mg/l)					0.128
< 1.0	4569	0.0086	0.004 to 0.013	< 0.001	
≥ 1.0	2019	0.0065	0.0003 to 0.013	0.039	
HOMA-IR					0.695
< 2.5	5646	0.0062	0.002 to 0.010	0.001	
≥ 2.5	448	0.0073	−0.008 to 0.023	0.353	
Calcium intake (mg/day)					0.680
< 500	3527	0.0066	0.002 to 0.011	0.003	
≥ 500	791	0.0059	−0.003 to 0.016	0.235	
Vitamin C intake (mg/day)					0.492
< 100	3179	0.0073	0.003 to 0.012	0.002	
≥ 100	1139	0.0059	−0.002 to 0.014	0.153	

The multivariable model was adjusted for age, smoking status, alcohol intake, physical activity, total calorie intake, BMI, calcium and vitamin C intake, serum calcium, serum phosphorus, ALP, and hsCRP

CI confidence interval, *HEPA* health-enhancing physical activity, *BMI* body mass index, *hsCRP* high-sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment of insulin resistance, *ALP* alkaline phosphatase

(*p* for interaction > 0.05 except BMI strata). This finding may empower the positive association between SUA and BMD to be coherent, irrespective of a seemingly unsafe condition, including current smokers and heavy drinkers.

We observed a different effect size of the association between SUA and BMD in the BMI subgroups that revealed a qualitatively stronger association between SUA and BMD in non-obese males rather than in the obese subgroup. This outcome might have been because the percent body fat and fat mass index had an unfavorable impact on BMD in obesity [29]. Therefore, the effect of SUA on BMD might appear to be roughly doubled in non-obese males, although there was still a positive association of SUA on BMD in obese males. Intriguingly, the β-coefficient in the physically active subgroup exercising a minimum of 3000 MET-minute per week seemed weak and meaningless compared to the other stratum. One systematic review reported that the effect of physical exercise on BMD varied according to the type of exercise; a walking trial alone had a limited effect, but resistance training alone or in combination with impact-loading activities was most osteogenic [30]. Therefore, our less active exercisers were still able to show a meaningfully strong association, although the present study did not specify exercise types and only factored in the amount. Additionally, HOMA-IR values have been widely used as an insulin resistance index, and insulin-resistant status is associated with suppressed bone turnover [31]. In fact, marked insulin resistance might have a negative effect on BMD in type 2 diabetes [32]. In this sense, our HOMA-IR-stratified analyses displayed an imaginable association between SUA and BMD in males without insulin resistance (HOMA-IR < 2.5). In the subgroup of HOMA-IR ≥ 2.5, the relatively small number

($n = 448$) of participants could limit the interpretation of a statistical comparison for effect modification. The dietary vitamin C intake did not modify the relation between SUA and BMD, although ascorbic acids were known to boost the role of SUA in plasma [6]. In dietary calcium intake-stratified analyses, clarifying the effect of higher calcium intake was restricted due to the relatively small number ($n = 791$).

The antioxidant properties of SUA are mostly considered a possible mechanism for the favorable associations of this substance. The ability of SUA to act as a scavenger of singlet oxygen molecules and radicals, which protects the erythrocyte from membrane damage that could lead to lysis, was described in the 1970s [33]. The role of SUA as an osteoclast precursor antioxidant has also been investigated using in vitro experiments, which showed that intracellular ROS levels significantly decreased after cells received SUA treatment [17]. SUA's effects on osteogenic differentiation were also demonstrated in vitro, in which the differentiation of human bone mesenchymal stem cells into osteoblasts was promoted, and this mechanism was suggested via the expression of 11β-hydroxysteroid dehydrogenase type 1, Cbfa1/Runx2, and Wnt signaling pathways [34]. Therefore, SUA can be deemed to have a protective role in bone health. There are other possible explanations to support the association between SUA and bone health. Metabolic changes may play a role in the relationship between SUA and BMD via serum parathyroid hormone (PTH) and calcium concentration. For instance, recombinant human PTH has a side effect of hyperuricemia during treatment to stimulate bone formation [35]. Other studies have shown that SUA may reduce the level of serum 1,25-$(OH)_2D_3$ by inhibiting 1α-hydroxylase activity, which suggests that SUA is related to BMD via vitamin D, even though this negative correlation was lost with further adjustment [36, 37]. At the same time, a positive association between lean body mass and BMD is well-established. One recent study showed that the beneficial association between SUA and BMD might be partly mediated by muscle mass, likely in the manner of mechanical loading and muscle-derived cytokines [24]. Despite these possibilities, the causal effect of SUA on BMD still needs further clarification, A Mendelian randomization analysis was performed with a weighted genetic urate score using the SLC2A9, ABCG2, SLC17A1, SLC22A11, and SLC22A12 single-nucleotide polymorphisms (SNPs) [38]. Unfortunately, it did not provide inspiring evidence for the causal effect of SUA on BMD. The investigated SNPs, however, explained 3.4% of the variance in SUA; however, only white European participants were included in the study. As a result, future investigation into the causality of SUA on BMD will require additional methodology other than genetics as well as various populations to cover diverse ethnic backgrounds.

While the recommended target of SUA is < 6 mg/dl to prevent gouty arthritis, an SUA level < 3 mg/dl is not advised because of the protective effect of SUA on neurodegenerative disease in the current guidelines for the management of hyperuricemia in gout [39]. Because the antioxidant properties of SUA may be profitable to enhance BMD, it may be inappropriate to apply uric acid-lowering therapy without evidence of the pro-oxidant status of SUA.

This observational study had some limitations. First, the analysis was constrained to assessing associations only and not causality because of the cross-sectional design. Second, we collected data using a self-administered questionnaire, which might have involved a recall bias regarding smoking, diet and drinking habits, and exercise frequency. Third, information about bone turnover markers and hormonal status, including PTH and gonadal hormones, and the measurement of oxidative stress were unavailable because the study population was not composed for the purpose of study, and the laboratory tests performed by health-promotion centers did not focus on specified pathologic conditions, such as hyperparathyroidism. Fourth, femoral BMD was not involved in our analysis. For instance, positive association between SUA and vascular calcification was reported in obese subjects [40], and lumbar spine BMD could be overestimated by the calcification of the aorta. Nevertheless, our population was not obese on average and its impact might be modest. Finally, the participants included in this study consisted of Korean men aged 40–60 years who regularly attended health-screening exams; thus, our findings might not be generalizable to other age groups, to women, or to other races or ethnic groups.

In conclusion, the present study demonstrated the SUA was positively and significantly associated with the BMD of the lumbar spine in a low-risk population of Korean men aged 40–60 years undergoing a yearly screening. Our findings support the hypothesis that SUA plays a beneficial role in bone metabolism. Due to limited evidence of the causal relationship, further investigations are required to determine the effect of SUA on human bone in particular.

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Compliance with ethical standards

Conflicts of interest All authors have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board and/or national research committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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