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ORIGINAL ARTICLE

Association between serum uric acid and bone health in adolescents

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Abstract

Summary Previous studies are suggestive of the protective role of uric acid on bone in the middle-aged and elderly. Whether this association exists in younger individuals has not been examined. This investigation showed a significant positive association between serum uric acid and bone parameters among Iranian adolescents.

Introduction Uric acid (UA) might be linked to bone health, but it is unclear whether its effects on bone are limited to certain population subgroups. This study is aimed at investigating the correlation between serum uric acid levels and bone mineral density (BMD) in Iranian adolescents.

Methods This cross-sectional study was conducted on 413 (221 girls and 192 boys) Iranian adolescents aged 9–19 years. An analysis of anthropometric, biochemical parameters and bone density was performed on the participants. Measurements included serum uric acid, calcium, phosphorus, alkaline phosphatase, albumin, and vitamin D. They were divided according to their serum UA into the low UA group who had UA ≤ 6 mg/dL and the high UA group with UA > 6 mg/dL. BMD and bone mineral content (BMC) were measured in the total body, lumbar spine, and left femoral neck, using dual energy X-ray absorptiometry (DXA), and bone mineral apparent density (BMAD) was calculated.

Results A Pearson correlation analysis revealed a significant correlation between UA and bone parameters. In multiple regression analyses adjusted for potential confounders, serum UA was proven to be associated with BMD and BMC at all sites. There was no association between UA, serum calcium, and vitamin D concentrations.

Conclusion Our study, as the first research on adolescents, demonstrated a higher bone density in those who had higher UA levels.

Keywords Adolescent · Bone mineral apparent density · Bone mineral content · Bone mineral density · Uric acid

Introduction

Peak bone mass acquisition which is affected by both genetic and environmental factors is established during adolescence. Indeed, maximum bone mass and further bone loss are two important determinants of osteoporosis development in later life period [1, 2]. An increasing number of recent studies have shown that oxidative stress has adverse effects on bone health and might play a role in the pathogenesis of osteoporosis [3, 4]. In vitro, reactive oxygen species are able to suppress the osteoblast generation and development, and on the other hand, it enhances osteoclast differentiation and activity [3]. Likewise, in the Framingham osteoporosis study, antioxidants such as vitamin C and carotenoids revealed to have bone protective effects [5]. Recent literature review have suggested that UA which has historically been viewed as a waste by product, might actually be beneficial for bone metabolism through its antioxidant effects [6]. However, the importance of UA, as a potent antioxidant in humans, is still controversial and the results of previous studies were inconclusive. In this regard, some of the cross-sectional surveys revealed greater BMD and lower prevalence of osteoporosis in middle-aged and older individuals with higher serum uric acid levels [6–8]. In addition, it was suggested

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that uric acid, through its dual suppressive effects on vitamin D activation or parathyroid hormone (PTH) production, might be linked to bone health [9].

Objectives

Up to now, the exact role of UA in the musculoskeletal system has not been fully explained. Meanwhile, whether serum UA is independently associated with bone mineral density in the general population or its beneficial bone effects are limited to certain population subgroups still needs to be answered. To the best of our knowledge, no study has been performed in this regard among adolescents. For this reason, the present research was designed to examine the relationship between serum UA and BMD in Iranian adolescents.

Patients and methods

This cross-sectional study was conducted in the county of Kawar. It is a community with an urban structure situated 50 Km east of Shiraz, the capital of Fars province, southern Iran, during 2010–2011. The data used in this analysis were from the baseline phase of the study which aimed to provide the first reference values for BMC and BMD in Iranian adolescents [10].

Subjects

Our participants were selected from girls and boys aged 9–19 years. After applying an age-stratified systematic random sample of 7.5%, using systematic random sampling method, eventually, 413 participants (221 girls and 192 boys) were enrolled in this research. The exclusion criteria were having any disease or using medication which could affect bone density or serum UA level, such as renal failure; endocrine, rheumatologic, and musculoskeletal disorders; or consumption of allopurinol, glucocorticoids, anticonvulsant drugs, and contraceptives. The study protocol was approved by the local Ethics Committee of Shiraz University of Medical Sciences. After explaining the research objectives, written informed consents were obtained from the participants' parents/guardians.

Anthropometric measurements and Tanner stage

The participants were referred to the healthcare center where they answered a short health questionnaire. Parents/guardians helped the younger children to answer the questions. Body weight was measured using a standard scale (Seca, Germany), while they wore light clothes and no shoes. Height was measured while they were in the upright position and barefooted using a wall-mounted meter. The weight and height values were rounded to the nearest 0.1 Kg and 0.5 cm, respectively. Body mass index (BMI) was calculated for each person as the body weight in kilogram divided by height in meters squared. Next, they were divided into two groups according to their calculated BMI centile values, determined based on their own BMI cut-off points [11] and also age and gender-specific cut-off points, as defined by the IOTF [12]. Group 1 was considered normal (BMI ≤ 85th centile), and group 2 was overweight or obese individuals (BMI > 85th centile). We also stratified the participants according to the recommendation by the American College of Sports Medicine into those with fewer and those with more than three times physical activity per week [13]. The Tanner puberty classification was determined by an endocrinologist, and children at stages I and II were classified as pre-early puberty, those at stages III and IV as mid puberty, and children at stage V were classified as full puberty.

Bone densitometry

Bone mineral density (g/cm2) and bone mineral content (g) in the total body, lumbar spine, and left femoral neck were measured using the Hologic system (Discovery QDR, USA). All measurements were performed on the same machine by an experienced operator in accordance with standardized procedures for subject positioning. Coefficients of variation based on preliminary measurements in 10 participants were 2.4% for BMD of the femoral neck, 0.51% for the lumbar spine, and 1% for the total body. The measurements were in accordance with international standards. In order to overcome the effect of bone size on BMD and BMC interpretation, bone mineral apparent density for the lumbar spine (LS BMAD) and the femoral neck (FN BMAD) was calculated to estimate the bone density per unit volume according to the following equations [14]:

$$\text{LS BMAD}\left(\text{g/cm}^3\right) = \text{BMC of L2–L4/area}^{1.5}$$
$$\text{FN BMAD}\left(\text{g/cm}^3\right) = \text{BMC of femoral neck/area}^2$$

Laboratory data

Venous blood samples were collected during early morning after an overnight fasting. Serum separation was performed immediately and kept frozen at − 70 °C until assayed. Biochemistry included serum uric acid, total calcium, phosphorus, alkaline phosphatase, and albumin. Serum calcium values were adjusted for circulating albumin levels. All of the tests were performed in the Endocrinology and Metabolism Research Center of Shiraz University of Medical Sciences, using standard techniques on a Dirui autoanalyzer (Dirui, CS-T240, China). The serum level of 25-hydroxy vitamin D

(25OHD) was measured by high-performance liquid chromatography (Young Lee 9100, South Korea).

Statistical analysis

Statistical analysis included student's *t* test which was used for comparing the mean levels of anthropometric, body composition, and bone density parameters. A Chi-square test was used for comparison of categorical variables. Pearson's linear correlation was used for the analysis of correlation. Multiple regression analysis was used to evaluate the influence of different factors on bone parameters at different sites. Data were analyzed using SPSS v. 18 software (Chicago, IL, USA). A P value of < 0.05 was considered to be statistically significant.

Results

This cross-sectional study included 413 participants, 192 (46.5%) boys and 221 (53.5%) girls, aged 9–19 years with a mean age of 13.99 ± 2.63 years. Basal characteristics of the studied participants, including their anthropometric measurements, serum biochemistry, and bone parameters are presented in Table 1.

Uric acid had a mean level of 5.60 ± 1.25 mg/dL for the total participants (5.28 ± 1.07 in girls and 5.96 ± 1.34 in boys). In total, 84.5% of the subjects had normal BMI (≤ 85th centile), and only 15.5% were overweight or obese (> 85th centile). Severe vitamin D deficiency (≤ 8 ng/mL) was present in 5.8%, while deficient (> 8 ng/mL and ≤ 20 ng/mL), insufficient (> 20 ng/mL and < 30 ng/mL), and sufficient (≥ 30 ng/mL) levels were detected in 78.4%, 13.8%, and 2%, respectively. The subjects were stratified according to their serum UA into low (≤ 6 mg/dL) and high (> 6 mg/dL) UA groups. Those in the high UA group were older and had a higher BMI, but there were no differences between the two groups regarding the stage of puberty, vitamin D, corrected calcium, and phosphorus concentrations. Serum levels of albumin and alkaline phosphatase were significantly higher among those with higher UA concentrations. Pubertal status was appropriate for age in all subjects; all girls over 14 years of age had experienced menarche and all boys over 14 years had a Tanner stage grade of 3 or more. There were no significant differences between the low and high UA groups regarding the frequency of self-reported fractures.

Except for LS BMAD, all other bone parameters showed significantly higher values in the high UA group. The Pearson correlation test also showed a significant correlation between UA and bone parameters at all sites. On univariate analysis, serum vitamin D and corrected calcium levels had no significant association with the bone parameters in either skeletal site, but there was a significant relationship between bone parameters, gender, age, BMI, stage of puberty, serum UA, and physical activity of the participants. In multiple regression analysis after adjustment for gender, age, BMI, puberty stage, and physical activity of the subjects, the serum UA level remained positively correlated with skeletal parameters at all sites.

Moreover, 65% of those in the high uric acid group were male, 63% of those with low uric acid were female and also those in the high uric acid group had greater BMI values. Therefore, in order to determine the potential confounding effects of gender and BMI, further analysis was done for each gender and then in the two BMI groups (≤ 85th centile and > 85th centile) separately. At first, the adjusted regression analysis after splitting for gender revealed a significant association of uric acid and bone parameters in both genders again, except for LS BMC and FN BMC in girls and LS BMC, FN BMAD and Z-scores in boys. Furthermore, splitting of our subjects according to their BMI groups also showed a significant relationship between uric acid and most of the bone indices (Tables 2 and 3).

Finally, we concurrently repeated our analysis after splitting the participants according to their gender and BMI. This subgroup's analysis clearly revealed positive association between UA and bone parameters in girls with BMI ≤ 85th centile and in boys who had BMI > 85th centile (Tables 4 and 5).

Discussion

This study is aimed at examining the potential link between bone density and serum UA levels in adolescents, showing a significant association between them. To the best of our knowledge, this is the first research on this issue among adolescents.

Although hyperuricemia, through endothelial cell damage, has been associated with deleterious effects such as insulin resistance, heart failure, and renal disease [15], its role in musculoskeletal health is controversial. There is an increasing body of evidence stating that higher serum uric acid levels have a protective role against bone loss in old people. For example, Nabipour et al. in their population-based research on men > 70 years showed higher BMD, lower prevalence of fractures, and lower levels of bone resorption markers in subjects who had higher serum UA concentrations [6]. Several other reports also revealed lower prevalence of osteoporosis and higher BMD in those who had higher serum UA levels [7, 8]. Hence, it has been hypothesized that UA has beneficial effects on the bone health only in older people who have higher rates of bone resorption. Also, in spite of the studies that were in favor of beneficial influence of UA on the bone health, there are a few reports that did not confirm this point [16, 17].

Table 1 Basal characteristics of all of the participants and in the high and low uric acid groups

	All	Serum uric acid ≤6 mg/dL	Serum uric acid >6 mg/dL	*P* value
Sex	F: 221 M: 192	F: 172 M: 100	F: 49 M: 92	0.0001
Age (year)	13.99 ± 2.63	13.80 ± 2.70	14.37 ± 2.46	0.03
Weight (kg)	43.83 ± 13.29	41.12 ± 11.58	49.09 ± 14.79	0.0001
Height (cm)	154.93 ± 14.00	152.89 ± 13.15	158.89 ± 14.76	0.0001
BMI (kg/m^2)	17.87 ± 3.27	17.28 ± 2.94	19.01 ± 3.57	0.0001
Vitamin D (ng/mL)	15.25 ± 5.67	15.29 ± 5.39	15.18 ± 6.20	0.86
Corr. calcium (mg/dL)	9.22 ± 0.52	9.19 ± 0.53	9.26 ± 0.50	0.26
Phosphorus (mg/dL)	4.04 ± 0.75	4.06 ± 0.83	4.01 ± 0.57	0.52
Albumin (g/dL)	4.84 ± 0.49	4.81 ± 0.49	4.92 ± 0.50	0.03
ALP (U/L)	367.96 ± 185.83	350.23 ± 181.06	404.62 ± 191.06	0.01
UA (mg/dL)	5.60 ± 1.25	4.88 ± 0.78	6.99 ± 0.68	0.0001
Exercise	Yes: 136 No: 277	Yes: 72 No: 189	Yes: 64 No: 88	0.003
Total BMD (g/cm^2)	0.88 ± 0.11	0.86 ± 0.11	0.91 ± 0.11	0.0001
FN BMD (g/cm^2)	0.71 ± 0.13	0.69 ± 0.12	0.76 ± 013	0.0001
LS BMD (g/cm^2)	0.85 ± 0.17	0.84 ± 0.17	0.88 ± 0.17	0.044
Total BMC (g)	1481.40 ± 441.51	1404.33 ± 394.96	1630.06 ± 487.74	0.0001
FN BMC (g)	3.45 ± 0.88	3.29 ± 0.78	3.77 ± 0.96	0.0001
LS BMC (g)	41.88 ± 16.40	40.27 ± 15.85	44.99 ± 17.04	0.005
Total Z-score	− 0.83 ± 0.92	− 0.94 ± 0.92	− 0.61 ± 0.87	0.001
FN Z-score	− 1.14 ± 1.09	− 1.30 ± 1.15	− 0.84 ± 0.89	0.0001
LS Z-score	− 1.01 ± 1.04	− 1.10 ± 1.08	− 0.85 ± 0.95	0.023
Total BMAD (g/cm^3)	0.88 ± 0.12	0.86 ± 0.12	0.91 ± 0.11	0.0001
FN BMAD (g/cm^3)	0.15 ± 0.02	0.14 ± 0.02	0.15 ± 0.02	0.0001
LS BMAD (g/cm^3)	0.20 ± 0.03	0.20 ± 0.03	0.20 ± 0.03	0.70

Data are given as mean ± SD

F, female; *M*, male; *BMI*, body mass index; *Corr. calcium*, corrected calcium; *ALP*, alkaline phosphatase; *UA*, uric acid; *FN*, femoral neck; *LS*, lumbar spine

Table 2 Association between serum UA and bone parameters adjusted for age, BMI, puberty category, and exercise status of all of the participants, and after splitting them for gender

	All			Girls			Boys		
	β^a	ρ	R^2	β^a	ρ	R^2	β^a	ρ	R^2
LS BMC (g)	0.11	0.002	0.55	0.08	0.08	0.57	0.1	0.06	0.56
LS BMD (g/cm^2)	0.11	0.001	0.61	0.1	0.021	0.64	0.12	0.022	0.58
LS BMAD (g/cm^3)	0.11	0.006	0.46	0.13	0.006	0.55	0.14	0.045	0.26
FN BMC (g)	0.13	0.0001	0.55	0.09	0.08	0.47	0.11	0.05	0.51
FN BMD (g/cm^2)	0.14	0.0001	0.48	0.14	0.008	0.48	0.13	0.038	0.39
FN BMAD (g/cm^3)	0.11	0.026	0.17	0.16	0.009	0.28	0.11	0.14	0.07
Total BMC (g)	0.15	0.0001	0.65	0.1	0.012	0.67	0.14	0.004	0.64
Total BMD (g/cm^2)	0.13	0.0001	0.61	0.12	0.007	0.64	0.15	0.006	0.58
Total BMAD (g/cm^3)	0.12	0.001	0.55	0.12	0.007	0.64	0.12	0.046	0.46
LS Z-score	0.16	0.002	0.12	0.26	0.0001	0.21	0.1	0.22	0.07
FN Z-score	0.1	0.050	0.14	0.14	0.038	0.14	0.07	0.34	0.08
Total Z-score	0.13	0.012	0.13	0.25	0.0001	0.19	0.05	0.5	0.09

LS, lumbar spine; *FN*, femoral neck

[a] Standardized β coefficient

Table 3 Association between serum UA and bone parameters adjusted for gender, age, puberty category, and exercise status of all of the participants, and after splitting them for BMI

	All			BMI ≤ 85th centile			BMI > 85th centile		
	β^a	ρ	R^2	β^a	ρ	R^2	β^a	ρ	R^2
LS BMC (g)	0.11	0.002	0.55	0.1	0.011	0.55	0.2	0.055	0.53
LS BMD (g/cm^2)	0.11	0.001	0.61	0.1	0.005	0.60	0.2	0.049	0.61
LS BMAD (g/cm^3)	0.11	0.006	0.46	0.1	0.017	0.53	0.2	0.11	0.31
FN BMC (g)	0.13	0.0001	0.55	0.12	0.002	0.54	0.23	0.031	0.56
FN BMD (g/cm^2)	0.14	0.0001	0.48	0.13	0.003	0.46	0.23	0.037	0.51
FN BMAD (g/cm^3)	0.11	0.026	0.17	0.1	0.06	0.14	0.16	0.22	0.30
Total BMC (g)	0.15	0.0001	0.65	0.14	0.0001	0.65	0.21	0.024	0.64
Total BMD (g/cm^2)	0.13	0.0001	0.61	0.11	0.003	0.61	0.25	0.012	0.61
Total BMAD (g/cm^3)	0.12	0.001	0.55	0.1	0.012	0.53	0.25	0.012	0.61
LS Z-score	0.16	0.002	0.12	0.14	0.012	0.07	0.37	0.01	0.21
FN Z-score	0.1	0.050	0.14	0.08	0.13	0.10	0.3	0.044	0.15
Total Z-score	0.13	0.012	0.13	0.11	0.041	0.06	0.26	0.09	0.08

BMI, body mass index; *LS*, lumbar spine; *FN*, femoral neck

[a] Standardized β coefficient

However, several possible mechanisms have been suggested to explain the association between bone health and UA. One proposed mechanism is the potential antioxidant effects of uric acid, which in turn might inhibit osteoclastic bone resorption and promote bone formation [3]. For example, Dong et al. suggested that the increased serum uric acid could accelerate the recovery of fractures via its antioxidative effects [18].

Furthermore, the effect of elevated serum UA on 25OHD metabolism has been suggested as another mechanism, which links UA with osteoporosis. In fact, hyperuricemia and vitamin D deficiency are recognized as major public health concerns worldwide. Whereas several studies have detected an inverse relationship between them, other published reports have shown a positive or even no association [6, 19–21]. For example, Takir et al. showed lower vitamin D levels only

Table 4 Association between serum UA and bone parameters adjusted for age, puberty category, and exercise status of the participants after concurrent splitting them for gender and BMI (girls and boys with BMI ≤ 85th centile)

	BMI ≤ 85th centile			BMI ≤ 85th centile		
	Girls			Boys		
	β^a	ρ	R^2	β^a	ρ	R^2
LS BMC (g)	0.1	0.052	0.57	0.07	0.24	0.56
LS BMD (g/cm^2)	0.11	0.02	0.62	0.08	0.13	0.59
LS BMAD (g/cm^3)	0.13	0.013	0.54	0.08	0.21	0.44
FN BMC (g)	0.08	0.15	0.43	0.09	0.12	0.48
FN BMD (g/cm^2)	0.15	0.011	0.42	0.09	0.18	0.36
FN BMAD (g/cm^3)	0.2	0.006	0.20	0.05	0.5	0.07
Total BMC (g)	0.11	0.014	0.65	0.12	0.02	0.63
Total BMD (g/cm^2)	0.11	0.016	0.63	0.11	0.046	0.57
Total BMAD (g/cm^3)	0.11	0.016	0.63	0.09	0.16	0.43
LS Z-score	0.26	0.001	0.14	0.05	0.5	0.04
FN Z-score	0.13	0.07	0.05	0.03	0.7	0.04
Total Z-score	0.28	0.0001	0.08	0.004	0.9	0.05

BMI, body mass index; *LS*, lumbar spine; *FN*, femoral neck

[a] Standardized β coefficient

Table 5 Association between serum UA and bone parameters adjusted for age, puberty category, and exercise status of the participants after concurrent splitting for gender and BMI (girls and boys with BMI > 85th centile)

	BMI > 85th centile			BMI > 85th centile		
	Girls			Boys		
	β^a	ρ	R^2	β^a	ρ	R^2
LS BMC (g)	0.01	0.9	0.57	0.32	0.037	0.61
LS BMD (g/cm^2)	0.06	0.6	0.67	0.33	0.04	0.56
LS BMAD (g/cm^3)	0.16	0.2	0.59	0.5	0.038	0.18
FN BMC (g)	0.16	0.28	0.45	0.22	0.16	0.61
FN BMD (g/cm^2)	0.1	0.47	0.52	0.36	0.04	0.58
FN BMAD (g/cm^3)	0.02	0.9	0.44	0.44	0.047	0.31
Total BMC (g)	0.08	0.47	0.66	0.24	0.08	0.67
Total BMD (g/cm^2)	0.16	0.18	0.62	0.35	0.012	0.70
Total BMAD (g/cm^3)	0.16	0.17	0.62	0.35	0.012	0.70
LS Z-score	0.41	0.02	0.25	0.45	0.047	0.28
FN Z-score	0.23	0.23	0.13	0.41	0.07	0.27
Total Z-score	0.13	0.5	0.05	0.51	0.038	0.23

BMI, body mass index; *LS*, lumbar spine; *FN*, femoral neck

[a] Standardized β coefficient

in old hyperuricemic females, especially those who had severe vitamin D deficiency [19]. To explain this relationship, there are some reports which indicate a direct effect of UA on 25OHD metabolism by inhibiting 1α-OH activity, leading to higher PTH and lower 1,25-dihydroxy vitamin D (1,25OH2D) levels [9]. Similarly, Hsu and colleagues showed that sodium urate infusion in rats inhibited the calcitriol synthesis [22].

In the present study, we found no correlation between serum UA and vitamin D concentrations, although a significant number of our subjects were vitamin D deficient or insufficient. Therefore, the likelihood of an association between UA and vitamin D metabolism was not supported in our study. Of note, it has been shown that conversion of 25OHD to 1,25OH2D is substrate independent in individuals with normal renal function and in the absence of severe vitamin D deficiency [23]. Thus, our findings might be due to the degree of vitamin D deficiency in the participants. Meanwhile, it should be noted that the primary enzymes for UA and 25OHD production are abundantly found in the hepatocytes. Therefore, it is possible that old people in previous reports who had lower UA levels had greater age-related impairment of the liver function, which manifested as both decreased production of uric acid and defective hydroxylation of vitamin D [24].

In addition, other investigations have found a positive relationship between UA and PTH in healthy subjects [25]. Hence, this relationship might be another explanation for some of the observed metabolic changes associated with osteoporosis. Indeed, PTH involvement in renal handling of UA was proposed by some authors and urate transporter 1 was considered a potential candidate site [26, 27]. For example, hyperuricemia was stated as a side effect of recombinant PTH treatment [28] and patients who had PTH resistance at the renal tubules usually have reduced serum UA [27]. Also, hyperparathyroid subjects usually have high FGF23 and UA levels which decrease after surgical treatment [29, 30].

It is noteworthy that a recent study performed on children suggested a direct relationship between FGF23 and UA, independent of PTH effect [31]. Gutierrez et al. also showed a direct association between UA and FGF23 levels, regardless of age [32]. Taken together, the correlation between serum uric acid and bone metabolism might be explained by other possible factors. Although we did not measure PTH in our subjects, there was no significant correlation between UA and calcium or phosphorous concentrations in our study. This finding was in contrast to Valdemarsson et al. study who observed a positive correlation between the serum UA and serum calcium levels in patients with primary hyperparathyroidism [33]. However, further studies are warranted to elucidate the potential mechanisms of this association.

Other findings of our investigation consisted of a significant positive association between UA and BMI, and on the other hand, between UA level and BMD, even after adjustment for BMI. In fact, BMI has been considered an important modifiable risk factor for hyperuricemia [34], and their positive relationship has been shown among adult individuals in several investigations [35]. On the contrary, there are few reports about the relationship between UA and obesity in children and adolescents [36]. Our study revealed a significant association between UA and obesity in this age group. Although purine metabolism in the adipose tissue has not been defined clearly, it is possible that impaired adipocyte function in obese subjects could lead to increased production of uric acid. In this regard, experimental studies on mice have shown that the adipocytes have abundant expression of xanthine oxidoreductase (XOR) activity which can result in higher UA levels [37]. In addition, it has been suggested that XOR might play a role in differentiation of the adipocytes in obese subjects [38]. Tamba et al. also showed a significant association between visceral fat area and adiponectin concentration with the serum UA level and lowering UA after reducing the visceral fat [39]. Moreover, other reports attributed the hyperuricemia in obese individuals to an impaired renal excretion of UA rather than its overproduction [40].

However, the influence of obesity on bone density is still controversial. Whereas some reports showed a reverse relationship between adiposity and bone metabolism, other reports have indicated a protective role of overweight against osteoporosis. For example, Cervellati et al. demonstrated an inverse relationship between BMI and BMD in postmenopausal women [41], but Nabipour et al. reported a positive association between them in old men [6]. Muka et al. found no modification effect by BMI for the association of UA with bone parameters [42]. Similarly, we observed a significant relationship between UA and bone health indices even after splitting our subjects based on their BMI. However, after concurrent splitting of our subjects on the basis of their gender and BMI, the association between UA and bone parameters in girls remained significant in those who had BMI ≤ 85th centile and in boys with BMI > 85th centile in most studied areas. Therefore, it could be suggested that the effects of UA and BMI on the bone might be gender dependent. However, this point of view needs to be investigated thoroughly in later studies.

Lastly, the UA levels and its effects on the bone health might vary among different ethnicities. In this regard, Cauley et al. in a large population-based study reported race/ethnicity as the strongest determinant of BMD in older men [43]. Also, the positive correlation of UA and BMD was reported in both cross-sectional and longitudinal studies on middle-aged and older subjects in Asian population [7, 8], but not in Western people [16, 17]. Moreover, epidemiological studies suggested a strong genetic influence upon serum UA concentrations. Indeed, genome-wide association studies exhibited that up to 73% of UA variations could be explained by the genetic background [21, 26, 44]. Therefore, other potential

causes for disparity in various studies might be due to different ethnicities and genetics of their participants or differences of potential cofounder variables considered in previous studies. However, the UA-bone association in specific population subsets and in a variety of populations worldwide requires further investigation before reaching a conclusive result.

Our study had some limitations including its cross-sectional design which limits the inferences regarding causation and temporality. In addition, we did not evaluate other potential antioxidants such as dietary intake of calcium, vegetable, and fruit in the participants. Also, we did not measure GFR and PTH levels in this investigation.

Conclusion

This research on adolescents showed the significant association of UA with BMD, similar to older subjects. Therefore, the hypothesis that UA has beneficial effects only on older individuals who are at a higher risk of bone loss was not supported in our study. However, our results indicated the need for further basic studies to evaluate the relative importance of UA in bone metabolism over long term and in different age groups. Also, it is necessary to determine the potential level of serum UA which would be beneficial for bone health without deleterious effects.

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Compliance with ethical standards

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest None.

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