Observational Study

Medicine®

OPEN

Association between serum uric acid and bone mineral density in patients with type 2 diabetes

A 6-year longitudinal study in China

Kun Yang, MD[a], Huilei Miao, MD[b], Ruijie Zhao, MD[c], Xiling Wu, MD[d], Bo Liu, MD[e], Shuiqiao Zheng, MD[e], Dan Huang, MD[e], Zhao Ping, MD[e,*]

Abstract

The relationship between serum uric acid (UA) and bone mineral density (BMD) has been proposed by several researchers. However, there has been no consensus regarding the relationships among serum UA, diabetes, and BMD. The aim of this study is to investigate the association between UA, BMD, and at least osteopenia in type 2 diabetes patients.

This research was a longitudinal study performed at Xiao-Tang-Shan Hospital in Beijing. Type 2 diabetes diagnosis was consistent with the WHO standard classification. Participants with osteopenia or osteoporosis documented by dual-energy X-ray absorptiometry were defined as having "at least osteopenia." A generalized additive model and multivariable logistic regressions were performed to explore the relationship between serum UA and at least osteopenia. Receiver operating characteristic analysis was conducted. Propensity score matching was used to verify the correctness of the cutoff point.

In total, 3476 type 2 diabetes patients free of any osteopenia-related diseases were recruited in 2012 and followed up to 2018. The general proportions of patients with at least osteopenia in 2018 was 16.46% (572/3476). Serum UA was negatively associated with BMD stratified by sex, age group, and BMI level. Setting the first quartile as the reference, the risk of at least osteopenia in the fourth quartile was significant among all patients (odds ratio [OR]: 0.75; 95% confidence interval [CI]: 0.57, 0.98) and specifically in females (OR: 0.79; 95% CI: 0.43, 0.97), patients aged over 50 years (OR: 0.79; 95% CI: 0.60, 0.97) and patients with a BMI greater than 25 (OR: 0.74; 95% CI: 0.47, 0.97). The optimal cutoff point for the serum UA level to distinguish at least osteopenia in diabetic patients was 395 μmol/L.

Serum UA concentration is negatively associated with the occurrence of at least osteopenia in Chinese patients with type 2 diabetes.

Abbreviations: AUC = area under the curve, BMD = bone mineral density, BMI = body mass index, Ca = calcium, CI = confidence interval, Cr = creatinine, eGFR = estimated glomerular filtration rate, GGT = glutamyl transpeptidase, HbA1c = glycosylated hemoglobin, HCT = hematocrit, HDL = high density lipoprotein, HGB = hemoglobin, MPV = mean platelet volume, OP = osteoporosis, OR = odds ratio, PDW = platelet distribution width, PLT = platelets, PSM = propensity score matching, ROC = receiver operating characteristic, SD = standard deviation, T2DM = type 2 diabetes mellitus, TG = triglycerides, UA = serum uric acid, WBC = white blood cells.

Keywords: bone mineral density, osteopenia, osteoporosis Chinese, serum uric acid, type 2 diabetes

Editor: Leonardo Roever.

The study is funded by the Xuanwu Hospital-level project (Serial Number: XWJL-2018010). The source of funding had no influence on the study design.

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Department of Evidence-based Medicine, Xuanwu Hospital, Capital Medical University, Xicheng district, [b] Department of Clinical Medicine, Peking Union Medical College, Dongcheng district, [c] Department of Radiology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, [d] Department of Traditional Chinese Medicine, Xuanwu Hospital, Capital Medical University, Xicheng district, [e] Beijing Xiao-Tang-Shan Hospital, Xiao-Tang-Shan Town, Changping District, Beijing, China.

[*] Correspondence: Zhao Ping, Beijing Xiao-Tang-Shan Hospital, No. 390, Hot Spring Avenue, Xiao-Tang-Shan Town, Changping District, Beijing, China (e-mail: pingzhao1959@163.com).

How to cite this article: Yang K, Miao H, Zhao R, Wu X, Liu B, Zheng S, Huang D, Ping Z. Association between serum uric acid and bone mineral density in patients with type 2 diabetes: a 6-year longitudinal study in China. Medicine 2021;100:17(e25733).

Received: 9 December 2019 / Received in final form: 15 February 2021 / Accepted: 4 April 2021

http://dx.doi.org/10.1097/MD.0000000000025733

1. Introduction

Type 2 diabetes mellitus (T2DM) has become a major clinical and public issue due to the increasing morbidity and high mortality and disability rates.[1] T2DM is a metabolic disorder characterized by chronic hyperglycemia and vascular complications,[2] and T2DM patients face bone turnover problems and present a special skeletal phenotype and aberrant structure and function, resulting in an increased risk of osteopenia, osteoporosis (OP) and fracture.[3] Diabetes can influence the bone through many mechanisms, some of which are still controversial.[4,5] Investigating the association between T2DM and osteopenia, especially the possible risk factors, is of vital importance and may provide a theoretical basis for the prevention of osteopenia-OP in T2DM patients.[6]

Osteopenia or OP is a complex, multifactorial condition characterized by a reduced bone mass and impaired micro-architectural structure with increasing fragility that predisposes the bone to fractures. The mechanism by which T2DM leads to osteoporosis is controversial.[7] Oxidative stress reactions might play a vital role in osteopenia.[8] Participating in the pathophysiological processes of bone metabolism, antioxidants might have a protective function in relation to osteopenia, and lower levels of antioxidants have detrimental effects on bone health. Serum uric acid (UA) is an oxidative stress factor and a final product of purine metabolism in humans. Excess serum UA might increase metabolic diseases such as arthritis, renal calculus, and other diseases, including cardiovascular disorders.[9] Moreover, hyperuricemia is a risk factor for the development of insulin resistance and diabetes mellitus.[10]

Several studies have concentrated on whether serum UA influences bone mineral density (BMD) in T2DM patients. Some researchers concluded that elevated serum UA concentrations were related to higher BMD and lower risk of OP in Chinese men.[11,12] After stratifying by sex and body mass index (BMI), a positive association was also observed.[13] Both studies were cross-sectionally designed, and the level of evidence was not strong and did not consider the concentrations of blood calcium and phosphate. The eventual effect of serum UA on osteopenia or OP in T2DM is still unclear.

In this longitudinal study, associations between the serum UA levels and osteopenia or OP in Chinese T2DM patients were examined, stratified by age group, sex and BMI level. Therefore, we hypothesized that

1. high serum UA levels play a protective role independent of diabetic osteopenia or OP and that
2. the cutoff value of serum UA could serve as a predictor of osteopenia or OP in T2DM patients.

2. Methods

2.1. Study population

This study was part of the Beijing Health Management Cohort study. The Beijing Health Management Cohort study is a large prospective dynamic cohort study, and its design has been described in former research.[14] The participants went to the hospital for physical examinations annually. Participants with a previous diagnosis of liver disease, renal dysfunction, hyperthyroidism, hyperparathyroidism, hypogonadism, and at least osteopenia, which could significantly affect bone metabolism, were excluded at baseline. In addition, all individuals enrolled during 2012 to 2014 were free use of drugs for at least 3 months, such as glucocorticoids, bisphosphonates, and calcitonin injection, which could significantly affect bone and calcium metabolism (see Fig. S1, http://links.lww.com/MD/G47, Supplemental Content, which illustrates the details of data collection and measurements, http://links.lww.com/MD/G49). The study was approved by the Ethics Committee of Capital Medical University (approval number: 2015SY33).

2.2. Data collection

All individuals in the study who received routine physical examinations underwent anthropometrically and laboratory tests. Interviews pertaining to sociodemographic characteristics, medication records, and any previous medical or surgical diseases were conducted by trained staff. Weight and height were measured without shoes, and the BMI was calculated as the weight (kg) divided by the squared height (m). Patients were instructed to fast for at least 10 hours before morning blood collection. Blood samples were collected from an antecubital vein into tubes containing ethylenediaminetetraacetic acid in the morning after overnight fasting. Platelets (PLT), mean platelet volume (MPV), platelet distribution width (PDW), Fasting plasma glucose, triglycerides (TG), high density lipoprotein (HDL), white blood cells (WBC), red blood cells, hemoglobin (HGB), hematocrit (HCT), and erythrocyte mean corpuscular volume were measured by an autoanalyzer (Sysmex SE-9000, Kobe, Japan). Fasting serum UA, calcium (Ca), phosphate and creatinine (Cr) levels were measured using an automatic biochemical analyzer (Modular E170, Roche, Basel, Switzerland). Glycosylated hemoglobin (HbA1c) was measured by high-performance liquid chromatography. Information on drug usage was obtained from individuals' medical history. Drugs were adjusted as covariates in the analysis. All analyses were performed in accordance with the manufacturer's recommendations. Renal function is an important factor for serum UA and osteoporosis. Modification of Diet in Renal Disease equations were used to calculate the estimated glomerular filtration rate (eGFR), which can represent the renal function.

2.3. Measurements

T2DM was diagnosed consistent with the latest update in 2019 of the WHO standard classification criteria.[15] In this paper, we defined T2DM as follows: fasting plasma glucose $\geq$7.0 mmol/L (126 mg/dL), 2-hour postload plasma glucose $\geq$11.1 mmol/L (200 mg/dL), glycosylated hemoglobin (HbA1c) $\geq$6.5% (48 mmol/mol), or random blood glucose $\geq$11.1 mmol/L (200 mg/dL) and the presence of signs and symptoms considered to indicate diabetes.

BMD was measured at the lumbar spine (L1-L4) by dual-energy X-ray absorptiometry. According to the criteria recommended by the WHO[16] and recommendations of the Epidemiology and Quality of Life Working Group of The Committee of Scientific Advisors of International Osteoporosis Foundation,[17] osteopenia was diagnosed by $-2.5 <$ T-score < -1.0 standard deviation (SD), and OP was diagnosed by T-score < -2.5 SD. In this study, T2DM patients with osteopenia or OP were defined as having "at least osteopenia (T-score < -1.0)," according to a previous study.[11]

2.4. Statistical analysis

The statistics were summarized to demonstrate the characteristics of the variables' distributions. The Shapiro–Wilk test and Q–Q plots were performed to confirm the normality. All normally

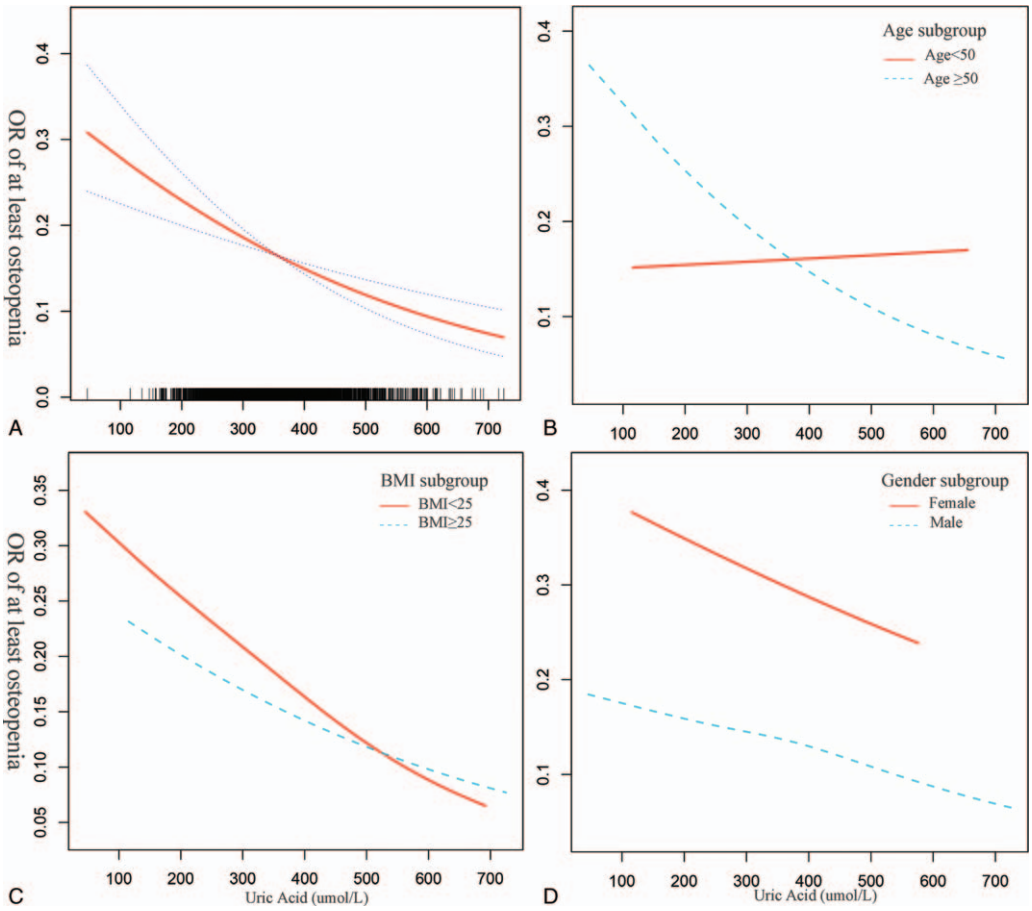

Figure 1. Nonlinear relationship between serum UA and the risk of at least osteopenia. A: the whole population, B: the age-level subgroup, C: the BMI-level subgroup, D: the sex subgroup.

distributed continuous variables were described as the mean ± SD. Analysis of variance was conducted to compare continuous variables with quantiles of serum UA, and Dunnett multiple comparison tests were performed. Pearson correlation between serum UA and BMD was calculated and visually displayed through a scatter plot using the ggplot package in the R language. A generalized additive model with spline smoothing function was used to test the nonlinear association between serum UA and at least osteopenia in Figure 1.

The original continuous serum UA was categorized into 4 levels (Q_1, Q_2, Q_3, and Q_4) using the 3 quartiles of P_{25}, P_{50}, and P_{75} as critical values, with $\leq P_{25}$ for Q_1 (<297 μmol/L, n = 862), $>P_{25}$ and $\leq P_{50}$ for Q_2 (298–350 μmol/L, n = 865), $>P_{50}$ and $\leq P_{75}$ for Q3 (351–406 μmol/L, n = 867), and $>P_{75}$ for Q4 (>407 μmol/L, n = 882).

To better examine the association between serum UA and at least osteopenia, 3 logistic regression models were estimated to adjust for confounding factors. Model 1 was a univariate model. Model 2 was adjusted for sex and BMI level. Serum Ca, serum phosphate, eGFR, TG, HGB, PLT, and glutamyl transpeptidase (GGT) were additionally adjusted for in model 3 using full-adjusted model combining with expert knowledge.

Receiver operating characteristic (ROC) analysis was conducted to determine the accuracy of serum UA concentration in distinguishing between diabetic patients with and without at least osteopenia. The area under the curve (AUC) was reported. At least osteopenia was used as an independent variable, and the probability value was calculated using logistic regression. The optimal cutoff point was determined by the maximum Youden index, which is equal to sensitivity + specificity −1.

Propensity score matching (PSM) was used to verify the correctness of the cutoff point. A propensity score (the probability of having a high serum UA level) was estimated using logistic regression based on the baseline characteristics. The dependent variables included sociodemographic characteristics and clinical indices than adjust in model 3. The cutoff value for UA classification was obtained from ROC analysis. Nearest neighborhood caliper matching[18] was used to match patients based on the logit of the propensity score using a caliper from 0.0001 to 0.1 of the SD. A 1:1 matching without replacement was used for relatively higher statistical power than other matching ratios.

Analyses were completed in SAS (Version 9.2; SAS Institute Inc., Cary, North Carolina), MedCalc (Version 12.0; Mariakerke, Belgium) and R (version 3.6.1). All P values were two-sided, and $P < .05$ indicated statistical significance.

3. Results

3.1. Baseline characteristics

The general characteristics and clinical and laboratory information of the participants are displayed in Table 1. In total, 3476 patients

Table 1

Baseline clinical characteristics according to the UA quantile.

	Total subjects (n = 3476)	Q1: < 297 μmol/L (n = 862)	Q2: 298–350 μmol/L (n = 865)	Q3: 351–406 μmol/L (n = 867)	Q4: > 407 μmol/L (n = 882)	*P* value
BMD (g/cm^2)	0.57 ± 1.20	0.49 ± 1.15	0.47 ± 1.08	0.62 ± 1.26	0.70 ± 1.27	.04
Serum UA (μmol/L)	356.43 ± 84.39	255.83 ± 34.25	324.27 ± 15.25	376.78 ± 16.17	466.31 ± 55.19	<.001
Male (n,%)	2869 (82.54%)	617 (21.51%)	702 (24.47%)	751 (26.18%)	799 (27.85%)	<.001
Age (Yr)	62.39 ± 12.90	60.54 ± 12.62	62.53 ± 12.24	62.79 ± 12.87	63.66 ± 13.62	<.001
>50 (n,%)	2898 (83.37%)	677 (23.36%)	734 (25.33%)	743 (25.64%)	744 (25.67%)	<.001
BMI (kg/m^2)	26.61 ± 3.31	25.86 ± 3.51	26.29 ± 3.14	26.76 ± 3.04	27.47 ± 3.33	<.001
>25 (n,%)	2196 (63.18%)	453 (20.63%)	529 (24.09%)	580 (26.41%)	634 (28.87%)	<.001
Serum Ca (mmol/L)	2.35 ± 0.14	2.33 ± 0.14	2.34 ± 0.14	2.36 ± 0.14	2.36 ± 0.14	<.001
Serum phosphate (mmol/L)	1.16 ± 0.15	1.14 ± 0.15	1.14 ± 0.15	1.18 ± 0.15	1.18 ± 0.16	<.001
Hb1AC (%)	6.91 ± 1.08	7.10 ± 1.33	6.96 ± 1.10	6.83 ± 1.01	6.80 ± 0.88	.001
BUN (mmol/L)	5.80 ± 1.68	5.47 ± 1.39	5.66 ± 1.60	5.80 ± 1.56	6.24 ± 2.00	<.001
Cr (μmol/L)	79.55 ± 21.34	71.61 ± 19.96	76.89 ± 18.26	80.62 ± 16.30	88.87 ± 25.72	<.001
eGFR (mL/min/1.73 m^2)	95.15 ± 43.70	80.59 ± 42.00	89.38 ± 37.72	96.94 ± 33.47	113.28 ± 52.35	<.001
TC (mmol/L)	4.65 ± 1.07	4.71 ± 1.18	4.63 ± 1.00	4.64 ± 1.01	4.63 ± 1.08	.35
TG (mmol/L)	1.93 ± 2.47	1.82 ± 3.71	1.74 ± 1.64	1.85 ± 1.51	2.28 ± 2.38	<.001
HDL (mmol/L)	1.20 ± 0.32	1.28 ± 0.33	1.23 ± 0.34	1.17 ± 0.29	1.13 ± 0.29	<.001
LDL (mmol/L)	2.93 ± 0.88	2.94 ± 0.88	2.92 ± 0.89	2.98 ± 0.88	2.87 ± 0.88	.05
AST (U/L)/ALT (U/L)	0.99 ± 0.35	1.02 ± 0.38	0.98 ± 0.32	1.00 ± 0.33	0.97 ± 0.35	.01
WBC (10^{12}/L)	6.58 ± 1.62	6.40 ± 1.68	6.56 ± 1.63	6.59 ± 1.61	6.74 ± 1.55	<.001
HGB (g/L)	147.18 ± 14.23	145.31 ± 13.88	147.86 ± 14.19	148.66 ± 14.22	146.89 ± 14.42	<.001
PLT (10^9/L)	204.79 ± 50.58	212.86 ± 50.44	201.69 ± 48.86	199.05 ± 49.66	205.58 ± 52.28	<.001
MPV (fL)	10.80 ± 0.85	10.77 ± 0.88	10.81 ± 0.82	10.83 ± 0.81	10.79 ± 0.87	.50
PDW (%)	13.00 ± 1.87	12.93 ± 1.92	13.02 ± 1.78	13.03 ± 1.79	13.01 ± 1.98	.72
RDW (%)	12.81 ± 0.72	12.75 ± 0.76	12.81 ± 0.68	12.81 ± 0.65	12.88 ± 0.80	.01
HCT (%)	43.33 ± 3.73	42.83 ± 3.62	43.54 ± 3.74	43.71 ± 3.72	43.23 ± 3.77	<.001
GGT (U/L)	33.33 ± 32.23	29.78 ± 29.82	32.18 ± 31.43	33.06 ± 25.77	38.17 ± 39.59	<.001

ALT = alanine aminotransferase (mmol/L), AST = aspartate aminotransferase (mmol/L), BMD = bone mineral density, body mass index (kg/m^2), BUN = urea nitrogen (mmol/L), Cr = creatinine (μmol/L), eGFR = estimated glomerular filtration rate, GGT = glutamyl transpeptidase (U/L), Hb1AC = glycated hemoglobin (%), HCT = red blood cell specific volume (%), HDL = high-density lipoprotein (mmol/L), HGB = hemoglobin (g/L), LDL = low-density lipoprotein (mmol/L), MPV = mean platelet volume (fL), PDW = platelet distribution width (%), PLT = blood platelet (10^9/L), RDW = red blood cell distribution width (%), TC = total cholesterol (mmol/L), TG = triglyceride (mmol/L), UA = serum uric acid, WBC = white blood cell (10^{12}/L).

diagnosed with T2DM who were free of osteopenia or OP were enrolled in 2012. The average age was 62 ± 13 years (from 23 to 93), and the mean serum UA concentration was 356.43 ± 84.39 μmol/L (ranging from 46 to 725 μmol/L). Participants with higher serum UA levels tended to be elder and had greater BMI. Comparing to those with lower serum UA levels, some laboratory index, like serum Ca, serum phosphate, blood urea nitrogen , Cr levels, eGFR, TG, WBC, HGB, PDW, HCT, and GGT were significantly higher at the highest UA level, While HbA1c, HDL, LDL, AST/ALT, and PLT were lower. BMD, TC, MPV, and PDW showed no significant differences across the 4 quantiles.

3.2. Relationship of serum UA with BMD and osteopenia-related outcomes

Correlation results between serum UA concentration and BMD were displayed through scatter plots (see Fig. S2–S6, http://links.lww.com/MD/G48, Supplemental Content, which illustrates the correlation between serum UA and BMD stratified by different stratification). Serum UA concentration was positively associated with BMD in the total sample. In the female-sex and age-younger-than-50-years subgroups, serum UA was negatively associated with BMD, while the other groups exhibited a positive association (see Table S7, http://links.lww.com/MD/G50, Supplemental Content, which shows the correlation coefficient and its significance of serum UA and BMD).

Osteopenia-related outcomes at the end of follow-up to 2018 are shown in Table 2. The incidences of patients with osteopenia, osteoporosis and at least osteopenia were 15.02% (522/3476), 1.44% (50/3476), and 16.46% (572/3476), respectively.

The nonlinear relationship between serum UA concentration and the risk of at least osteopenia is shown in Figure 1. Except for in the age-younger-than-50-years subgroup, serum UA concentration was positively associated with the risk of at least osteopenia.

After adjusting for potential confounders in multiple logistic regression analyses, serum UA was negatively associated with at least osteopenia. Setting Q_1 as the reference, the risk of at least

Table 2

Osteopenia related outcomes at the end of follow-up.

	Osteopenia	Osteoporosis	At least osteopenia	*P* value*
Total sample	522 (15.02%)	50 (1.44%)	572 (16.46%)	
Stratified factors				
Female	361 (69.16%)	22 (44.00%)	189 (31.14%)	<.001
BMI >=25	304 (58.24%)	28 (56.00%)	332 (15.12%)	.01
Elder than 50	433 (82.95%)	47 (94.00%)	480 (16.56%)	.70
UA quantile				<.001
Q1	150 (5.01%)	16 (0.53%)	171 (19.84%)	
Q2	128 (4.28%)	14 (0.47%)	146 (16.88%)	
Q3	121 (4.04%)	11 (0.37%)	144 (16.61%)	
Q4	86 (2.87%)	5 (0.17%)	111 (12.59%)	

* *P* value of the results of the comparison with the at least osteopenia group.

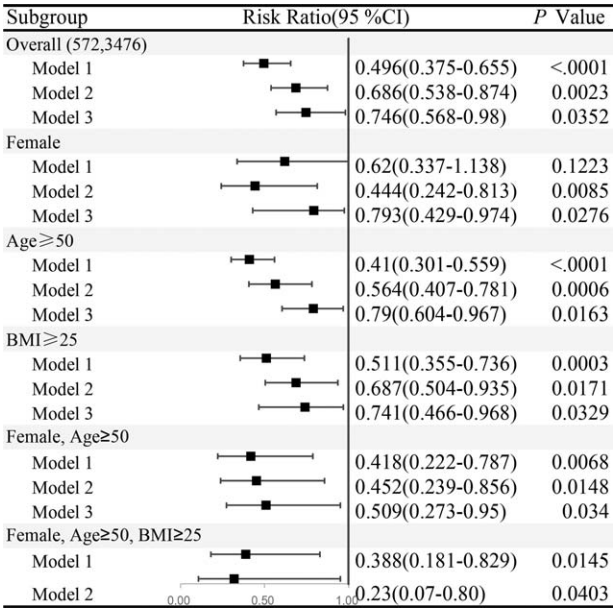

Figure 2. Stratified analysis of the relationship between serum UA and at least osteopenia.

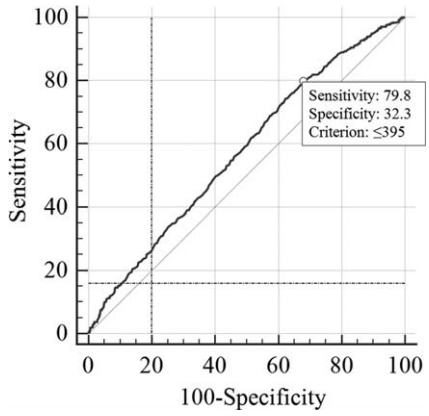

Figure 3. ROC curve of the relationship between serum UA and at least osteopenia.

osteopenia in Q_4 (odds ratio [OR] = 0.75; 95% confidence interval [CI] = 0.57–0.98; $P = .04$) was significant (see Fig. 2).

Subgroups were defined according to sex, age group and BMI levels to further explore the association between serum UA and at least osteopenia. Setting Q_1 as the reference, in the females, the risk of at least osteopenia in Q_4 (OR = 0.73; 95% CI = 0.43–0.97; $P = .03$) was statistically significant. For people older than 50 years, the risk of at least osteopenia in Q_4 (OR = 0.79; 95% CI = 0.60–0.97; $P = .02$) was significant. Among the individuals with a BMI higher than 25, the risk of at least osteopenia in Q_4 (OR = 0.74; 95% CI = 0.47–0.97; $P = .03$) was statistically significant. Among the female participants who were older than 50 years, the risk of at least osteopenia in Q_4 (OR = 0.51; 95% CI = 0.27–0.95; $P = .03$) was statistically significant. For participants who were female, older than 50 years old, and had a BMI higher than 25, the risk of at least osteopenia in Q_4 (OR = 0.23; 95% CI = 0.07, –0.80; $P = .04$) was significant. In general, when compared with the subjects in Q_1, the odds for at least osteopenia in Q_4 corresponded to a lower risk of at least osteopenia (see Table S8, http://links.lww.com/MD/G51, Supplemental Content, which displays the results of logistic regression).

3.3. The optimal cutoff point for serum UA and its validation

According to the ROC analysis and Youden index, the optimal cutoff point of the serum UA level to distinguish diabetic patients with at least osteopenia from those without at least osteopenia was 395 μmol/L, with a sensitivity of 79.8%, a specificity of 32.3%, and the highest AUC was equal to 0.58 [(0.56–0.59), $P < .001$] (see Fig. 3).

The traditional regression method and PS matching technique were used to verify the cutoff point in the dataset (see Table S9, http://links.lww.com/MD/G52, Supplemental Content, which presentations the summed results using the propensity score). In participants whose serum UA concentration was lower than 395 μmol/L, the risk of at least osteopenia was 0.75 (95% CI: 0.56, 0.99, $P = .04$) in the fully adjusted model 3 and 0.67 (95% CI: 0. 49, 0. 92, $P = .01$) after PS matching, and the results are shown in Table 3.

4. Discussion

This study identified that elevated serum UA levels were negatively associated with at least osteopenia in a hospital-based cohort of T2DM patients, and this association was independent of other possible risk factors. Furthermore, we discussed the stratified effects of sex, age, and BMI. To the best of our knowledge, this is the first study to identify a cutoff serum UA

Table 3

Multivariable analysis of the association of serum uric acid with osteoporosis.

	Estimate	Stand Error	Wald chi square	OR	95% CI		P
					Lower	Upper	
Result of traditional regression (N = 3476)							
Model 1	−0.6128	0.1154	28.2029	0.542	0.432	0.679	<.001
Model 2	−0.2761	0.1098	6.3211	0.759	0.612	0.941	.0119
Model 3	−0.2912	0.1448	4.0445	0.747	0.563	0.993	.0443
Using propensity score as a covariate*	−0.3744	0.1133	10.9120	0.688	0.551	0.859	.001
Results after PSM (n = 686)	−0.1990	0.0808	6.0622	0.672	0.489	0.922	.0138

Model 1 was a univariate model. **Model 2** was adjusted for gender and BMI. **Model 3** included the parameters of model 2 and was additionally adjusted for serum Ca, serum phosphate, eGFR, TC, HGB, PLT, and GGT.

* Indicates the results of regression using the propensity score (PS) as a covariate.

concentration of 395 μmol/L according to a ROC analysis. Moreover, we verified this result with the traditional regression method and the PSM technique. This cutoff value may be used as a potential threshold to demarcate at least osteopenia from no osteopenia in T2DM patients.

The relationship between serum UA and OP has been proposed by several researchers, but there has been no consensus regarding the relationships among serum UA, diabetes and at least osteopenia.[19] One researcher did not find a protective effect of higher serum UA on bone health.[20] Research concerning this topic has expanded from epidemiology to animal modeling with the establishment of a rat model of inducible mild hyperuricemia. Interestingly, no differences in either BMD or bone volume density were observed in hyperuricemia rats.[21] Except for these 2 studies, all the others found a positive and significant association between serum UA and bone health, especially BMD, at all skeletal sites.[11,22] Additionally, some researchers noted that high serum UA was associated with a lower risk of incident osteoporotic fracture risk.[23,24] Hyperuricemia might be independently associated with BMD and fractures,[10] indicating a protective role of serum UA in bone disorders.[25]

Similar results have been verified in our study. There are several mechanisms that can explain why serum UA is negatively associated with at least osteopenia. Serum UA is a final enzymatic product in the degradation of purine nucleosides and free bases in humans, and it accounts for approximately half of the antioxidant properties of human plasma. Its antioxidant effects might be an important source of its protective effect on osteopenia and OP.[26] Physiological concentrations of soluble serum UA were chondroprotective and anti-inflammatory. Serum UA exerted protective effects against arthritis in oxonic acid-treated mice, as these mice displayed less inflammatory cell infiltration in the synovium, less synovial hyperplasia, less cartilage damage, and less bone erosion than control mice.[9] Osteopenia is associated with increased reactive oxygen species (ROS), as ROS greatly suppress osteoblast generation, differentiation and enhance osteoclast development and activity.[27]

It is well established that osteopenia or OP and diabetes are prevalent diseases with significant associated morbidity and mortality.[28] First, the antioxidative characteristics of serum UA displayed paradoxical roles depending on blood concentration. Serum UA showed antioxidative value at the normal concentrations but served as an important risk factor for metabolic syndrome in hyperuricemia[29] Serum UA not only has several antioxidant properties, including the ability to clear oxygen radicals and participate in the chelation of metals, but also displays prooxidant features, such as the ability to reduce nitric oxide bioavailability and increase ROS production; the pro- or antioxidant features of serum UA depend on its chemical microenvironment. Thus, serum UA can have different roles in atherosclerosis depending on the chemical microenvironment. Therefore, serum UA may be differentially associated with different atherosclerotic lesions and metabolic patterns in different populations. Additionally, the differences in methodology, analysis, and study populations may also result in discrepancies among studies.

Sex was an important factor. A study that recruited 943 males and 4256 postmenopausal females showed that serum UA was negatively correlated with BMD only in females.[30] Studies have demonstrated a positive association between serum UA levels and BMD in males,[31] and the sexual dimorphism could be observed in many ways, such as bone structure, osteoporosis pathophysiology and treatment response, which might be related to the sex difference. Furthermore, a positive association between serum UA levels and BMD in postmenopausal women was detected.[32] Antioxidant function was an important mediating effect between the UA levels and BMD in the patients with T2DM.[33] Female estrogen prevents and protects against osteoporosis. Postmenopausal women constituted an estrogen-deficient[34] group vulnerable to oxidative stress associated with many molecules, including vitamin E, hydrogen peroxide and other antioxidants, a leading cause for the high risk of osteoporosis.[35,36]

This study also found that UA had a protective influence on osteopenia in the group with a BMI higher than 25, which is consistent with other studies. The BMI stratification showed that a positive association existed between serum UA and BMD at all sites in all healthy subjects and may explain approximately 1/4 of the variance in the effect of serum UA on BMD.[12] A cross-sectional study involving 17,735 normal weight and overweight individuals[37] has confirmed the protective effect of serum UA on bone health, which was significantly stronger in nonobese men than in obese men.[38] Percent body fat was negatively associated with BMD.[39] In summary, high BMI or obesity was an effect modifier to UA and BMD, consistent with the conclusions of other studies.[40]

In conclusion, there might be 2 ways to explain the protective effect of serum UA:

1. the UA-hyperglycemia association might be sex-dependent among Asian populations; and
2. the relationship might be nonlinear, and hyperglycemia could impair tubular reabsorption of serum UA according to BMI and aging.

The serum UA concentration differed between men and women, which should be carefully considered before using serum UA as an indicator of osteopenia and OP in Chinese participants. The serum UA concentration was higher in men than in women because of differences in the renal clearance rate. Additionally, a high estradiol concentration may be a reason for the lower concentration of serum UA in women, although the precise mechanism has not yet been clarified, limiting for the clinical use of serum UA as an osteoporotic marker.

This longitudinal study could provide stronger evidence than cross-sectional studies for clinical application. However, serum UA level remains a double-edged sword, because excessive UA concentration increases the risk of metabolic diseases and cardiovascular disorders. Clinicians should consider the overall condition of individual T2DM patients and maintain a moderate UA level to reduce the risk of both osteopenia and hyperuricemia. For those asymptomatic hyperuricemia T2DM patients facing a high risk of osteoporosis, both UA levels and the patient's general condition should be considered during the treatment.

4.1. Limitations

Our study has several limitations. First, genes associated with the development of osteopenia and OP and diabetes were not included in this investigation. In addition, BMD assessments with DXA were not performed at other sites of the body, such as the ribs, hands, and feet. Furthermore, details on the women's menopausal status were not available. The subjects were patients who came for voluntary health check-ups at a single tertiary hospital, causing 41% loss of enrolled participant and the bias might occur. The conclusion was limited to Chinese people, thus

more data should be collected in further analysis. This paper obtained a relatively low AUC and specificity, and attention should be paid when using this cutoff point in clinical practice.

4.2. Future directions

Animal experiments and genes-associated clinical researches are needed to explore the mechanism in the future studies.

5. Conclusion

Elevated serum UA levels were negatively related to at least osteopenia and may be a useful indicator of at least osteopenia in hospital-based T2DM patients. This finding may provide some evidence for the management of osteopenia and osteoporosis in Chinese patients with T2DM.

Acknowledgments

We sincerely express our gratitude to all staff of Xiao-Tang-Shan Hospital and we also express our gratitude to the participants in the present study for their valuable contributions.

Author contributions

Conceptualization: Kun Yang, Shuiqiao Zheng, Zhao Ping.
Data curation: Kun Yang, Shuiqiao Zheng.
Formal analysis: Kun Yang.
Funding acquisition: Zhao Ping.
Methodology: Kun Yang, Xiling Wu.
Project administration: Shuiqiao Zheng.
Resources: Zhao Ping.
Software: Bo Liu, Dan Huang.
Supervision: Zhao Ping.
Validation: Bo Liu.
Visualization: Dan Huang.
Writing – original draft: Kun Yang, Huilei Miao, Ruijie Zhao, Xiling Wu, Bo Liu, Shuiqiao Zheng, Zhao Ping.
Writing – review & editing: Kun Yang, Ruijie Zhao, Bo Liu, Dan Huang, Zhao Ping.

References

[1] Ding D, Lawson KD, Kolbe-Alexander TL, et al. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. Lancet (London, England) 2016;388:1311–24.
[2] Chatterjee S, Davies MJ. Accurate diagnosis of diabetes mellitus and new paradigms of classification. Nat Rev Endocrinol 2018;14:386–7.
[3] Compston J. Type 2 diabetes mellitus and bone. J Intern Med 2018;283:140–53.
[4] Napoli N, Chandran M, Pierroz DD, et al. Mechanisms of diabetes mellitus-induced bone fragility. Nat Rev Endocrinol 2017;13:208–19.
[5] Raška IJr, Rašková M, Zikán V, et al. Prevalence and risk factors of osteoporosis in postmenopausal women with type 2 diabetes mellitus. Cent Eur J Public Health 2017;25:3–10.
[6] Paschou SA, Dede AD, Anagnostis PG, et al. Type 2 diabetes and osteoporosis: a guide to optimal management. J Clin Endocrinol Metabol 2017;102:3621–34.
[7] Walsh JS, Vilaca T. Obesity, type 2 diabetes bone in adults. Calcif Tissue Int 2017;100:528–35.
[8] Hamada Y, Fujii H, Kitazawa R, et al. Thioredoxin-1 overexpression in transgenic mice attenuates streptozotocin-induced diabetic osteopenia: a novel role of oxidative stress and therapeutic implications. Bone 2009;44:936–41.
[9] Lai J-H, Luo S-F, Hung L-F, et al. Physiological concentrations of soluble uric acid are chondroprotective and anti-inflammatory. Sci Rep 2017;7:2359–12359.
[10] Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: a review. J Adv Res 2017;8:537–48.
[11] Zhao DD, Jiao PL, Yu JJ, et al. Higher Serum Uric Acid Is Associated with Higher Bone Mineral Density in Chinese Men with Type 2 Diabetes Mellitus. Int J Endocrinol 2016;2016:2528956. doi: 10.1155/2016/2528956.
[12] Yan P, Zhang Z, Wan Q, et al. Association of serum uric acid with bone mineral density and clinical fractures in Chinese type 2 diabetes mellitus patients: a cross-sectional study. Clin Chim Acta 2018;486:76–85.
[13] Xu M, Su J, Hao J, et al. Positive association between serum uric acid and bone mineral density in Chinese type 2 diabetes mellitus stratified by gender and BMI. J Bone Miner Metab 2018;36:609–19.
[14] Liu J, Zhao Z, Mu Y, et al. Gender differences in the association between serum uric acid and prediabetes: a six-year longitudinal cohort study. Int J Environ Res Public Health 2018;15:1560.
[15] American Diabetes AssociationDiagnosis and classification of diabetes mellitus. Diabetes Care 2014;37(Suppl 1):S81–90.
[16] Lorentzon M, Cummings SR. Osteoporosis: the evolution of a diagnosis. J Intern Med 2015;277:650–61.
[17] Kanis JA, Adachi JD, Cooper C, et al. Standardising the descriptive epidemiology of osteoporosis: recommendations from the Epidemiology and Quality of Life Working Group of IOF. Osteoporos Int 2013;24:2763–4.
[18] Wang Y, Cai H, Li C, et al. Optimal caliper width for propensity score matching of three treatment groups: a Monte Carlo study. PloS One 2013;8:e81045–181045.
[19] Lin KM, Lu CL, Hung KC, et al. The paradoxical role of uric acid in osteoporosis. Nutrients 2019;11:2111. doi: 10.3390/nu11092111.
[20] Xiong A, Yao Q, He J, et al. No causal effect of serum urate on bone-related outcomes among a population of postmenopausal women and elderly men of Chinese Han ethnicity–a Mendelian randomization study. Osteoporos Int 2016;27:1031–9.
[21] Zhang D, Bobulescu IA, Maalouf NM, et al. Relationship between serum uric acid and bone mineral density in the general population and in rats with experimental hyperuricemia. J Bone Miner ResV 30 2015;992–9.
[22] Kaushal N, Vohora D, Jalali RK, et al. Raised serum uric acid is associated with higher bone mineral density in a cross-sectional study of a healthy Indian population. Ther Clin Risk Manag 2018;14:75–82.
[23] Kim BJ, Baek S, Ahn SH, et al. Higher serum uric acid as a protective factor against incident osteoporotic fractures in Korean men: a longitudinal study using the National Claim Registry. Osteoporos Int 2014;25:1837–44.
[24] Hayashino Y, Okamura S, Tsujii S, et al. Association of serum uric acid levels with the risk of development or progression of albuminuria among Japanese patients with type 2 diabetes: a prospective cohort study [Diabetes Distress and Care Registry at Tenri (DDCRT 10)]. Acta Diabetol 2016;53:599–607.
[25] Veronese N, Carraro S, Bano G, et al. Hyperuricemia protects against low bone mineral density, osteoporosis and fractures: a systematic review and meta-analysis. Eur J Clin Invest 2016;46:920–30.
[26] Kaushal N, Vohora D, Jalali RK, et al. Review of the literature examining the association of serum uric acid with osteoporosis and mechanistic lnsights into its effect on bone metabolism. Endocr Metab Immune Disord Drug Targets 2019;19:259–73.
[27] Lee HS, Hwang JS. Impact of Type 2 Diabetes Mellitus and Antidiabetic Medications on Bone Metabolism. Curr Diab Rep 2020;20:78. doi: 10.1007/s11892-020-01361-5.
[28] Abdulameer SA, Sulaiman SA, Hassali MA, et al. Osteoporosis and type 2 diabetes mellitus: what do we know, and what we can do? Patient Prefer Adherence 2012;6:435–48.
[29] Zhang Q, Zhang C, Song X, et al. A longitudinal cohort based association study between uric acid level and metabolic syndrome in Chinese Han urban male population. BMC Public Health 2012;12:419–1419.
[30] Yan D-D, Wang J, Hou X-H, et al. Association of serum uric acid levels with osteoporosis and bone turnover markers in a Chinese population. Acta Pharmacol Sin 2018;39:626–32.
[31] Sritara C, Ongphiphadhanakul B, Chailurkit L, et al. Serum uric acid levels in relation to bone-related phenotypes in men and women. J Clin Densitom 2013;16:336–40.
[32] Ahn SH, Lee SH, Kim BJ, et al. Higher serum uric acid is associated with higher bone mass, lower bone turnover, and lower prevalence of vertebral fracture in healthy postmenopausal women. Osteoporos Int 2013;24:2961–70.

[33] Tanaka KI, Kanazawa I, Notsu M, et al. Higher serum uric acid is a risk factor of vertebral fractures in postmenopausal women with type 2 diabetes mellitus. Exp Clin Endocrinol Diabetes 2020;128:66–71.
[34] Hamidi MS, Corey PN, Cheung AM. Effects of vitamin E on bone turnover markers among US postmenopausal women. J Bone Miner Res 2012;27:1368–80.
[35] Kim HN, Ponte F, Nookaew I, et al. Estrogens decrease osteoclast number by attenuating mitochondria oxidative phosphorylation and ATP production in early osteoclast precursors. Sci Rep 2020;10:11933. doi: 10.1038/s41598-020-68890-7.
[36] Qiao W, Yu S, Sun H, et al. 1,25-Dihydroxyvitamin D insufficiency accelerates age-related bone loss by increasing oxidative stress and cell senescence. Am J Transl Res 2020;12:507–18.
[37] Lin X, Zhao C, Qin A, et al. Association between serum uric acid and bone health in general population: a large and multicentre study. Oncotarget 2015;6:35395–403.
[38] Hwang J, Hwang JH, Ryu S, et al. Higher serum uric acid is associated with higher lumbar spine bone mineral density in male health-screening examinees: a cross-sectional study. J Bone Miner Metab 2019;37: 142–51.
[39] Marin-Mio RV, Moreira LDF, Camargo M, et al. Lean mass as a determinant of bone mineral density of proximal femur in postmenopausal women. Arch Endocrinol Metab 2018;62:431–7.
[40] Kang DH, Guo LF, Guo T, et al. Association of body composition with bone mineral density in northern Chinese men by different criteria for obesity. J Endocrinol Invest 2015;38:323–31.