

# Relationship of Bone Turnover Markers with Serum Uric Acid-to-Creatinine Ratio in Men and Postmenopausal Women with Type 2 Diabetes

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**Purpose:** Accumulating evidence has shown that serum uric acid (UA) is associated with some chronic diseases owing to its antioxidant capacity; however, previous research has discrepant results regarding the relationship between UA and bone health. UA normalized by renal function can reflect endogenous UA levels more precisely than SUA levels. This study assessed the relationship between serum UA-to-creatinine (SUA/Cr) ratio and bone turnover markers (BTMs) in men and postmenopausal women with type 2 diabetes mellitus (T2DM).

**Patients and Methods:** Overall, 1691 patients (1028 males and 663 postmenopausal females) with T2DM admitted to Hebei General Hospital between January and December 2020 were selected and divided into two groups according to their SUA/Cr ratio. One-way analysis of variance was used to compare groups. The relationship between the SUA/Cr ratio and BTMs (including osteocalcin [OC], procollagen I N-terminal peptide [PINP], and  $\beta$ -isomerized type I collagen C-telopeptide breakdown products [ $\beta$ -CTX]) was analyzed using multiple linear regression. Furthermore, subgroup analyses were performed to explore the differences between men and women in the relationship between SUA/Cr and BTMs. Mediation analysis was used to explore whether insulin resistance mediated the association between SUA/Cr and BTMs.

**Results:**  $\beta$ -CTX and PNIP levels of patients with T2DM in the low SUA/Cr group were significantly higher than those in the high SUA/Cr group, and the difference between the two groups was statistically significant ( $P < 0.05$ ). Correlation analysis showed that SUA/Cr was negatively correlated with  $\beta$ -CTX and PNIP. After adjusting for confounding factors, multivariate linear regression analysis revealed that the SUA/Cr level was negatively correlated with PINP and  $\beta$ -CTX in male patients and postmenopausal women with T2DM. Stronger correlations were found in patients with  $25(\text{OH})\text{D}_3 < 20\text{ng/mL}$ , course  $\geq 5$  years,  $\text{HbA}_{1c} > 7\%$ , or  $\text{BMI} < 28 \text{ kg/m}^2$ .

**Conclusion:** SUA/Cr ratio was an independent influencing factor of BTMs in patients with T2DM.

**Keywords:** type 2 diabetes, bone turnover markers, serum uric acid to creatinine ratio

## Introduction

Globally, 463 million people are affected by diabetes, and this number is predicted to increase to 700 million by 2045.<sup>1</sup> Osteoporosis (OP), one of the most common metabolic bone diseases, is characterized by low bone mass and damage to bone microarchitecture, leading to increased bone brittleness and susceptibility to fractures.<sup>2</sup> Currently, OP is a primary public health concern in many countries because of its potential for serious fractures as well as its increasing prevalence due to our aging population.<sup>3,4</sup> Furthermore, it has been noted that a relationship could exist between diabetes (primarily type 2 diabetes mellitus [T2DM]) and OP. In China, Si et al found that the pooled prevalence of osteoporosis among patients with T2DM was 37.8%.<sup>5</sup> The Rotterdam Study (RS) revealed that compared with the general population, patients with T2DM have increased bone mineral density (BMD) of the femoral neck and lumbar spine, yet a 69% greater susceptibility to fracture.<sup>6</sup> This disparity

can be attributed to decreased bone strength.<sup>7</sup> The lack of association between higher BMD and lower incidence of fractures indicates that in T2DM, bone biomechanical properties are compromised.

Uric acid (UA) is the final product of human purine metabolism. As UA excretion is influenced by kidney function, we hypothesized that UA normalized by renal function (serum UA-to-creatinine ratio [SUA/Cr]) could accurately reflect endogenous UA levels more precisely than SUA. Studies investigating the relationship between UA levels and bone health have produced mixed results. Some studies have reported associations between UA levels and higher BMD.<sup>8–10</sup> However, multiple studies have reported the absence of a significant association between UA, bone turnover markers (BTMs), and BMD, even among patients with T2DM.<sup>11</sup> The pathophysiology of bone fragility in patients with T2DM was therefore regarded as substantially different from OP because patients with T2DM have an increased risk of bone fractures despite a normal to high BMD compared with participants without diabetes.<sup>12</sup> Thus, further investigations should be conducted on the role of UA in bone metabolism in patients with T2DM. Bone remodeling is a dynamic process that occurs throughout life, replacing old and damaged bones with new ones. Bone loss occurs during bone remodeling and has been shown to reflect this process.<sup>13</sup> Accumulating evidence suggests that osteoporosis is associated with increased inflammatory burden.<sup>14</sup> In contrast, serum UA is associated with inflammatory conditions such as T2DM<sup>15</sup> and diabetic kidney disease.<sup>16</sup> Not only uric acid but also UA-derived metabolic markers have been associated with various diseases, including hypertension,<sup>17</sup> hepatic steatosis,<sup>18</sup> thyroiditis,<sup>19</sup> metabolic syndrome,<sup>20</sup> and T2DM.<sup>21</sup> Therefore, studying the correlation between uric acid-derived markers and bone turnover markers is important. Evaluation of the relationship between SUA/Cr and BTMs, including osteocalcin (OC), procollagen I N-terminal peptide (PINP), and  $\beta$ -isomerized type I collagen C-telopeptide breakdown products ( $\beta$ -CTX), would provide significant clues to UA's role in bone metabolism. This study aimed to evaluate the associations between SUA/Cr and BTMs and explore the mediation effect of SUA/Cr on the relationship between BTMs.

## Patients and Methods

### Study Participants

This study was performed in accordance with the Helsinki Declaration and approved by the Ethics Committee of Hebei General Hospital. This study included patients admitted to Hebei General Hospital from January 1, 2020, to December 31, 2019. All participants provided written informed consent for participation in the study.

The inclusion criteria were as follows: patients who met the diagnostic criteria for T2DM of the American Diabetes Association: FPG  $\geq 7.0$  mmol/L, 2-hour plasma glucose  $\geq 11.1$  mmol/L, or random blood glucose measurement  $\geq 11.1$  mmol/L in the presence of classic symptoms such as polydipsia and polyuria.

The exclusion criteria were as follows: (1) other types of diabetes, such as type 1 diabetes, gestational diabetes, and other specific types of diabetes; (2) recent acute complications of diabetes such as diabetic ketoacidosis, diabetic hyperosmolar coma, and hypoglycemia; (3) perimenopausal and premenopausal women; (4) pregnant or nursing (lactating) women; (5) patients with a history of myocardial infarction, cerebral hemorrhage, severe hepatorenal dysfunction, infection, recent surgery, stress condition, and another severe chronic disease in the past 3 months; (6) presence of a malignant tumor; (7) recent bone fracture ( $<1$  year); (8) patients suffering from diseases that affect bone metabolism and UA (such as gout, hyperthyroidism, hyperparathyroidism, rheumatoid arthritis, kidney disease, multiple myeloma, uricases, uricosuric agents, xanthine oxidase inhibitors, etc.) or being treated with drugs that affect bone metabolism and UA (such as vitamin D, calcium, abisphosphonate, aglucocorticoid, estrogen, warfarin, or other drugs) were excluded.

## Methods

### The Laboratory and Demographic Data

Upon study enrollment, detailed history and demographics were recorded, including name, sex, date of birth, course of T2DM, past history, weight, and height. Venous blood was collected from patients on an empty stomach for at least 8 hours in the early morning of the day after admission. All laboratory tests were performed in the Clinical Detection Department of Hebei General Hospital, using the same instruments and unified reagents: UA, hemoglobin A1c (HbA1c), creatinine (Cr), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), calcium ion (Ca<sup>2+</sup>), 25-hydroxy vitamin

D (25(OH)D<sub>3</sub>), fasting plasma glucose (FPG), parathyroid hormone (PTH), OC, PINP, and  $\beta$ -CTX were measured. To ensure data extraction accuracy, the information was entered into a spreadsheet by one assessor and cross-checked by a second independent assessor.

SUA/Cr Was Defined as  $SUA/Cr = UA \text{ (mmol/l)}/Cr \text{ (umol/l)}$

#### Statistical Analysis

Statistical analysis was performed using SPSS statistical software (Version 25.0). Data were tested for homogeneity of variance and normality. Normally distributed data are shown as the mean  $\pm$  standard deviation, and an independent samples *t*-test was used to compare the groups. On-normally distributed data are presented as medians (quartiles), and nonparametric tests were used. The enumeration data were expressed as numbers (percentage) and were compared with the  $\chi^2$  test, and Spearman ('s) correlation analysis was used to assess the correlation between SUA/Cr and BTMs. To evaluate whether SUA/Cr was an independent risk factor for BTMs, multiple linear regression analysis was used. We used a false discovery rate (FDR) correction according to the Benjamini–Hochberg method to control for Type I error and conducted a subgroup analysis to assess the robustness of our results.

## Results

### Basic Clinical Characteristics of the Study Subjects

A total of 1691 patients with T2DM were included in this study (Figure 1). There were 1028 men and 663 postmenopausal women with a median age of 60 years, median T2DM duration of 10 years, median OC level of 12.74 ng/mL, median  $\beta$ -CTX level of 0.38 ng/mL, median PINP level of 38.68 ng/mL, and median SUA/Cr level of 4.19 (Table 1). Compared with the male group, the postmenopausal female group presented higher levels of age, course, HDL-C, PINP,  $\beta$ -CTX, and OC, and lower levels of BMI, 25(OH)D<sub>3</sub>. The two groups showed no statistical difference in SUA/Cr (Table 1).

### Clinical Characteristics of the Subjects Categorized According to Their SUA/Cr Levels

The patients were divided into high and low groups based on the median SUA/Cr value. Among patients with T2DM, BMI, Ca<sup>2+</sup>, TG, and FPG levels were significantly higher, and age, course, HDL-C, PINP, and  $\beta$ -CTX in the high SUA/Cr group than in the low SUA/Cr group. However, there was no significant difference in OC between the two groups (Table 2).

Male patients in the higher SUA/Cr level group had higher BMI, Ca<sup>2+</sup>, TG, and FPG levels and lower age, cholesterol, HDL-C, PINP, and  $\beta$ -CTX levels compared with those in the lower SUA/Cr level group, with statistically

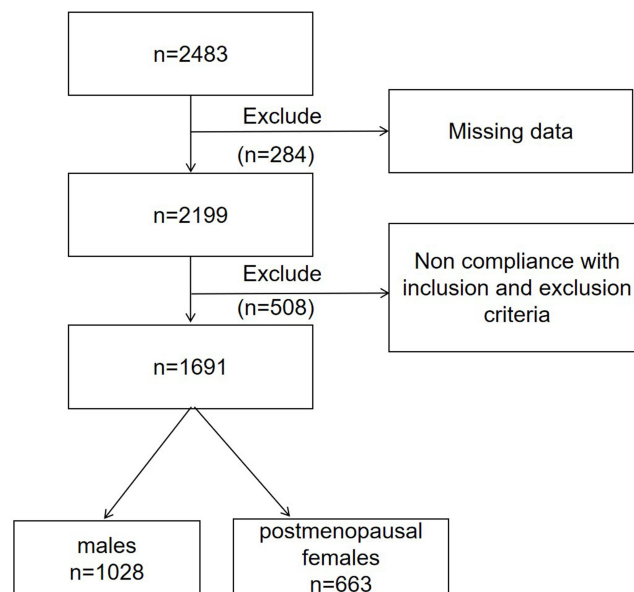


Figure 1 Flow chart.

**Table 1** Comparison of Indicators Between the Male and Postmenopausal Female Groups

	All Patients	Male Patients	Postmenopausal Female Patients	P	Adjusted P for FDR
n	1691	1028	663	–	–
Age (years)	60(52,68)	56(47,65)	65(58,72)	<0.001	0.004
BMI (kg/m <sup>2</sup> )	25.95(23.44,28.11)	26.03(23.84,28.34)	25.71(23.14,28.00)	0.006	0.029
Course(years)	10.00(3.00,17.00)	8.00(2.00,15.00)	10.00(5.00,20.00)	<0.001	0.025
Ca <sup>2+</sup> (mmol/L)	2.29(2.22,2.36)	2.29(2.21,2.36)	2.29(2.23,2.37)	0.103	0.004
TG (mmol/L)	1.38(0.99,2.09)	1.41(0.99,2.21)	1.33(1.00,1.92)	0.052	0.032
HDL-C(mmol/L)	1.10(0.92,1.35)	1.02(0.87,1.26)	1.20(1.02,1.48)	<0.001	0.036
HbA1c (%)	8.60(7.30,10.20)	8.6(7.2,10.2)	8.60(7.45,10.30)	0.417	0.046
FPG(mmol/L)	7.84(6.10,10.46)	7.85(6.15,10.55)	7.81(5.98,10.30)	0.425	0.050
PTH(pg/mL)	37.31(28.45,48.52)	37.08(28.56,46.81)	37.82(28.35,50.23)	0.183	0.039
25(OH)D3 (ng/mL)	17.28(13.43,22.27)	18.71(14.68,23.46)	15.72(12.42,19.92)	<0.001	0.004
SUA/Cr	4.19(3.29,5.09)	4.18(3.30,5.04)	4.24(3.31,5.17)	0.400	0.043
OC(ng/mL)	12.74(9.96,16.49)	11.84(9.45,14.80)	14.77(11.19,19.30)	<0.001	0.004
PINP(ng/mL)	38.68(29.29,51.63)	35.84(27.85,47.63)	44.10(32.59,58.71)	<0.001	0.004
β-CTX(ng/mL)	0.38(0.26,0.53)	0.35(0.24,0.49)	0.42(0.28,0.60)	<0.001	0.021

**Abbreviations:** BMI, body mass index; Ca<sup>2+</sup>, calcium ion; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; FPG, fasting plasma glucose; PTH, parathyroid hormone; 25(OH)D3, 25-hydroxyvitamin D3; SUA/Cr, serum UA-to-creatinine ratio; OC, osteocalcin; PINP, type I procollagen amino-terminal peptide; β-CTX, type I collagen carboxyl terminal peptide; FDR, false discovery rate.

significant differences (Table 2). Postmenopausal female patients with higher SUA/Cr levels had higher Ca<sup>2+</sup> and TG levels and lower HDL-C, OC, PINP, and β-CTX levels than those in the lower SUA/Cr level group, with statistically significant differences (Table 2).

## Correlation Analysis Results

The correlation results are shown in Figures 2 and 3. SUA/Cr was positively correlated with BMI, Ca<sup>2+</sup>, TG, and FPG and negatively correlated with age, course, HDL-C, OC, and β-CTX in all patients. SUA/Cr was positively correlated with Ca, TG, and FPG and negatively correlated with age, course, HDL-C, OC, and β-CTX in postmenopausal female patients. SUA/Cr was positively correlated with BMI, Ca<sup>2+</sup>, TG, 25(OH)D3, and FPG, and negatively correlated with age, course, HDL-C, PINP, and β-CTX in male patients.

## Multivariate Linear Regression Analysis of SUA/Cr and BTMs

### Male Patients with T2DM

After adjusting for age, BMI, course, Ca<sup>2+</sup>, TG, HDL-C, HbA1c, 25(OH)D3, PTH, and FPG (Model III), SUA/Cr was negatively associated with PINP ( $\beta = -0.829$ ,  $P = 0.027$ ) and β-CTX ( $\beta = -0.015$ ,  $P = 0.001$ ). The SUA/Cr ratio was not significantly correlated with OC ( $\beta = -0.135$ ,  $P = 0.193$ ) (Table 3).

### Postmenopausal Female Patients with T2DM

In the unadjusted model, multiple linear regression analysis demonstrated that SUA/Cr was significantly and inversely correlated with OC, PINP, and β-CTX. After adjusting for potential confounders (Model III), SUA/Cr was only inversely associated with β-CTX ( $\beta = -0.036$ ,  $P < 0.001$ ), OC ( $\beta = -0.916$ ,  $P=0.002$ ), and PINP ( $\beta = -3.1$ ,  $P = 0.002$ ) (Table 3).

## Subgroup Analysis

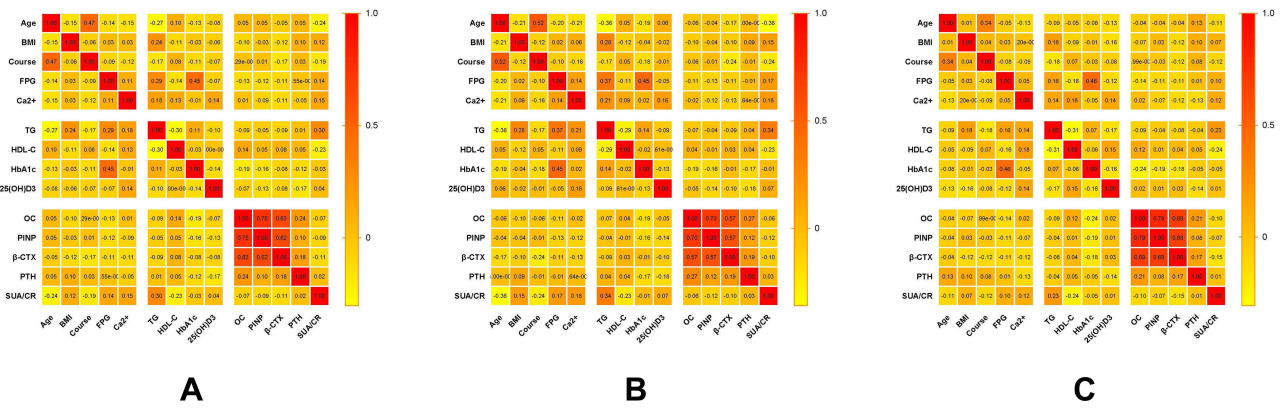
We performed subgroup analyses to determine whether the association between SUA/Cr and BTMs differed according to the presence or absence of non-alcoholic fatty liver disease (NAFLD), 25(OH)D3, course of T2DM, HbA1c, BMI, and TG (Table 4).

Multivariate regression analysis revealed that the SUA/Cr level was significantly negatively associated with BTMs in postmenopausal females with 25(OH)D3 < 20ng/mL, course  $\geq 5$  years, HbA1c > 7%, or BMI < 28 kg/m<sup>2</sup>.

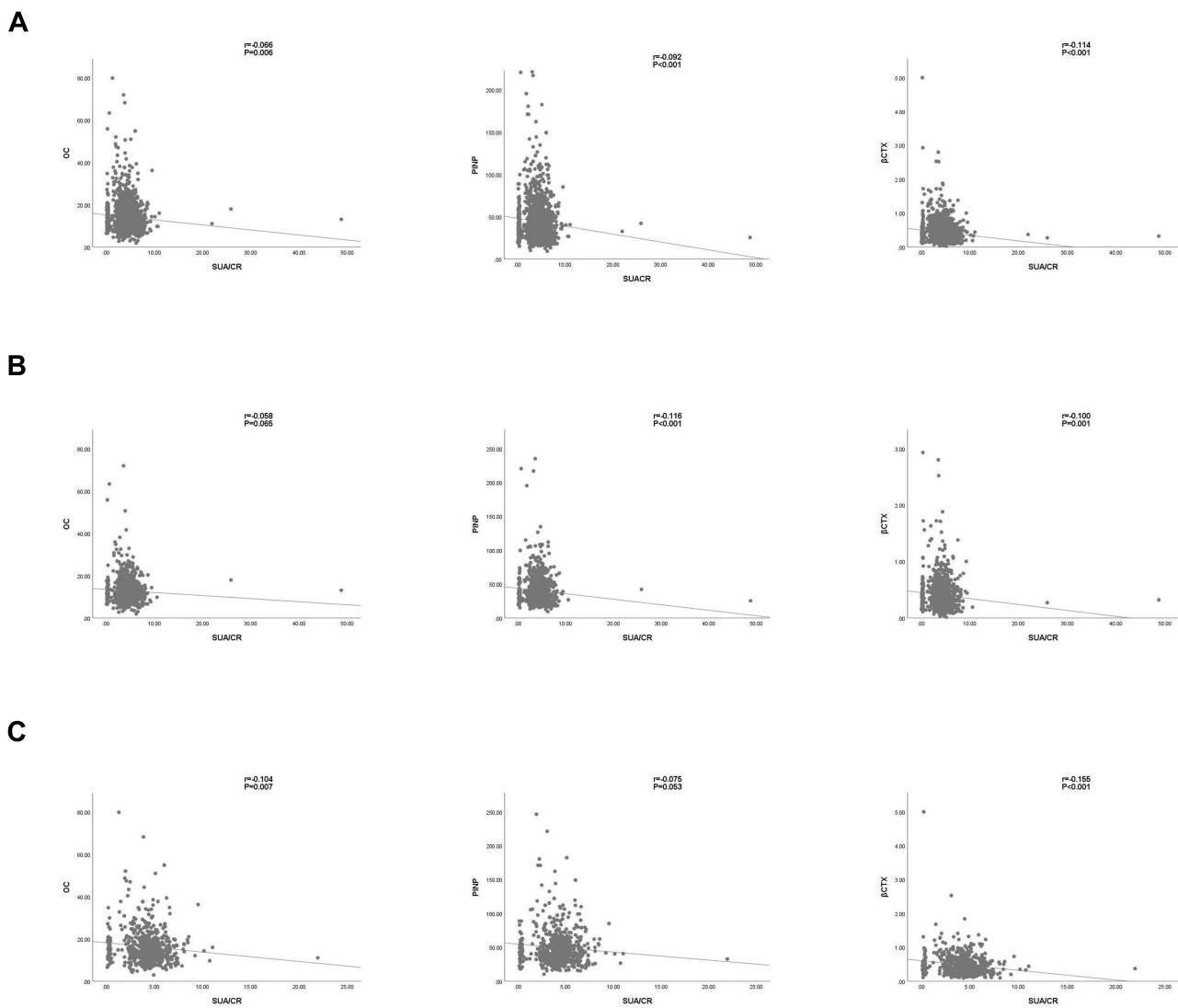
**Table 2** Comparison of Indicators Between the Low SUA/Cr and High SUA/Cr Groups

	All Patients				Male Patients				Postmenopausal Female Patients			
	Low SUA/Cr	High SUA/Cr	P	Adjusted P	Low SUA/Cr	High SUA/Cr	P	Adjusted P	Low SUA/Cr	High SUA/Cr	P	Adjusted P
n	845	846	–	–	521	507	–	–	324	339	–	
Age (years)	63.00(54.00,70.00)	57.00(49.00,66.00)	<0.001	0.011	60.00(51.00,69.00)	53.00(44.00,61.00)	<0.001	0.004	65.00(59.00,72.00)	63.00(57.00,72.00)	0.246	0.039
BMI (kg/m <sup>2</sup> )	25.65(23.19,27.68)	26.35(23.83,28.59)	<0.001	0.025	25.71(23.38,27.68)	26.56(24.22,29.01)	<0.001	0.018	25.39(23.09,27.94)	25.91(23.32,28.08)	0.312	0.043
Course(years)	10.00(5.00,19.00)	9.00(2.00,15.00)	<0.001	0.021	10.00(3.00,18.00)	7.00(2.00,12.00)	<0.001	0.021	11.00(6.00,20.00)	10.00(5.00,19.00)	0.086	0.025
Ca <sup>2+</sup> (mmol/L)	2.28(2.22,2.35)	2.31(2.24,2.37)	<0.001	0.018	2.28(2.19,2.34)	2.30(2.23,2.37)	<0.001	0.025	2.28(2.21,2.36)	2.31(2.24,2.38)	0.011	0.018
TG (mmol/L)	1.21(0.91,1.74)	1.56(1.09,2.43)	<0.001	0.004	1.2(0.89,1.76)	1.67(1.12,2.66)	<0.001	0.004	1.23(0.94,1.76)	1.45(1.05,2.08)	<0.001	0.011
HDL-C (mmol/L)	1.16(0.95,1.48)	1.05(0.89,1.26)	<0.001	0.014	1.11(0.89,1.39)	0.98(0.86,1.17)	<0.001	0.014	1.27(1.04,1.63)	1.18(0.99,1.36)	<0.001	0.007
HbA1c (%)	8.6(7.4,10.2)	8.60(7.20,10.20)	0.263	0.046	8.60(7.30,10.10)	8.70(7.10,10.20)	0.835	0.05	8.60(7.60,10.40)	8.06(7.30,10.28)	0.112	0.032
FPG(mmol/L)	7.61(5.80,10.40)	7.99(6.44,10.66)	0.001	0.032	7.62(5.80,10.10)	8.05(6.49,11.36)	0.001	0.029	7.61(5.53,10.88)	7.89(6.33,10.09)	0.234	0.036
PTH(pg/mL)	37.42(28.03,48.66)	37.17(29.38,48.13)	0.446	0.050	36.87(27.87,46.73)	37.08(29.31,46.90)	0.265	0.043	38.08(28.03,51.91)	37.36(29.40,49.27)	0.858	0.05
25(OH)D3 (ng/mL)	16.81(13.07,22.34)	17.95(13.85,22.22)	0.0570	0.039	17.84(13.79,24.18)	19.23(15.31,23.23)	0.043	0.039	15.84(12.16,19.82)	15.39(12.48,20.00)	0.678	0.046
SUA/Cr	3.29(2.53,3.79)	5.09(4.63,5.99)	<0.001	0.004	3.31(2.65,3.78)	5.05(4.61,5.87)	<0.001	0.004	3.28(2.34,3.82)	5.14(4.64,6.13)	<0.001	0.004
OC(ng/mL)	12.99(10.01,16.72)	12.52(9.94,15.98)	0.072	0.043	11.88(9.30,15.17)	11.79(9.61,14.53)	0.442	0.046	14.95(11.46,20.38)	14.08(10.89,18.38)	0.020	0.021
PINP(ng/mL)	40.33(29.78,52.83)	37.61(28.62,50.13)	0.003	0.036	37.32(28.63,49.81)	34.35(26.75,44.90)	0.004	0.032	45.54(33.04,61.01)	42.35(31.75,56.78)	0.019	0.029
β-CTX(ng/mL)	0.40(0.27,0.58)	0.36(0.25,0.50)	<0.001	0.029	0.36(0.25,0.52)	0.33(0.23,0.47)	0.013	0.036	0.45(0.31,0.65)	0.40(0.28,0.56)	0.001	0.014

**Abbreviations:** BMI, body mass index; Ca<sup>2+</sup>, calcium ion; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; FPG, fasting plasma glucose; PTH, parathyroid hormone; 25(OH)D3, 25-hydroxyvitamin D3; SUA/Cr, serum UA-to-creatinine ratio; OC, osteocalcin; PINP, type I procollagen amino-terminal peptide; β-CTX, type I collagen carboxyl terminal peptide; FDR, false discovery rate.



**Figure 2** Spearman's correlation coefficient matrix illustrating the association between SUA/CR and baseline patient characteristics in T2DM patients (A) all patients; (B) male patients; (C) postmenopausal female patients.



**Figure 3** The correlation between SUA/CR and BTMs levels in T2DM participants (A) all patients; (B) male patients; (C) postmenopausal female patients.

**Table 3** Correlation of SUA/Cr with BTMs in T2DM Patients

		Model I		Model II		Model III	
		$\beta$ (95% CI)	P	$\beta$ (95% CI)	P	$\beta$ (95% CI)	P
Male patients	OC	-0.145(-0.298,0.008)	0.063	-0.164(-0.373,0.044)	0.121	-0.135(-0.339,0.069)	0.193
	PINP	-0.813(-1.368,-0.258)	0.004	-0.965(-1.692,-0.239)	0.009	-0.829(-1.564,-0.094)	0.027
	$\beta$ -CTX	-0.011(-0.018,-0.003)	0.005	-0.015(-0.024,-0.006)	0.001	-0.015(-0.024,-0.006)	0.001
Female patients	OC	-0.443(-0.77,-0.116)	0.008	-0.953(-1.528,-0.378)	0.001	-0.916(-1.497,-0.334)	0.002
	PINP	-1.183(-2.254,-0.113)	0.030	-2.74(-4.656,-0.825)	0.005	-3.1(-5.095,-1.106)	0.002
	$\beta$ -CTX	-0.029(-0.041,-0.016)	<0.001	-0.035(-0.052,-0.017)	<0.001	-0.036(-0.053,-0.019)	<0.001

**Notes:** Model I crude model; Mode II adjusted for age, BMI, course; Model III further adjusted for Ca<sup>2+</sup>, TG, HDL-C, HbA1c, FPG, 25(OH)D3, PTH.

**Table 4** Subgroup Correlation Analysis of SUA/Cr and BTMs

		OC		PINP		$\beta$ -CTX	
		$\beta$	P	$\beta$	P	$\beta$	P
Male patients	NAFLD	-0.351	0.376	-2.872	0.016	-0.048	0.011
	Non-NAFLD	-0.324	0.481	-2.196	0.149	-0.035	0.064
	25(OH)D3<20	-0.519	0.042	-2.159	0.028	-0.036	0.002
	25(OH)D3 $\geq$ 20	-0.021	0.851	-0.460	0.196	-0.010	0.042
	Course $\leq$ 5	-0.009	0.944	-0.352	0.439	-0.006	0.354
	Course>5	-0.267	0.146	-1.684	0.013	-0.029	<0.001
	HbA1c $\leq$ 7	-0.222	0.767	-3.147	0.217	-0.065	0.032
	HbA1c>7	-0.118	0.203	-0.714	0.044	-0.013	0.002
	BMI<28	-0.175	0.362	-1.424	0.038	-0.032	<0.001
	BMI $\geq$ 28	-0.046	0.568	-0.439	0.209	-0.003	0.518
	TG<1.7	-0.281	0.153	-1.348	0.055	-0.032	<0.001
	TG $\geq$ 1.7	-0.002	0.984	-0.432	0.332	-0.006	0.249
Female patients	NAFLD	-0.88	0.06	-2.275	0.091	-0.039	0.012
	Non-NAFLD	-0.057	0.93	1.207	0.659	-0.038	0.103
	25(OH)D3<20	-1.109	0.002	-3.663	0.003	-0.037	<0.001
	25(OH)D3 $\geq$ 20	-0.378	0.386	-0.773	0.643	-0.034	0.071
	Course $\leq$ 5	-0.547	0.236	-1.477	0.352	-0.017	0.356
	Course>5	-1.053	0.005	-3.705	0.004	-0.044	<0.001
	HbA1c $\leq$ 7	-1.527	0.100	-6.639	0.044	-0.071	0.003
	HbA1c>7	-1.013	0.001	-2.808	0.006	-0.036	<0.001
	BMI<28	-0.745	0.019	-2.672	0.017	-0.029	0.004
	BMI $\geq$ 28	-1.432	0.062	-4.121	0.087	-0.061	0.001

(Continued)

**Table 4** (Continued).

		OC		PINP		β-CTX	
		β	P	β	P	β	P
	TG<1.7	-1.203	0.004	-3.428	0.015	-0.037	0.002
	TG≥1.7	-0.588	0.096	-2.889	0.046	-0.04	0.001

Notes: The model was adjusted for age, BMI, course, Ca2+, TG, HDL-C, HbA1c, FPG, 25(OH)D3, PTH.

Multivariable linear regression analysis showed that, after adjusting for potential confounders, SUA/Cr had a stronger negative relationship with β-CTX and PINP in male patients with NAFLD, 25(OH)D3 < 20ng/mL, course ≥ 5 years, HbA1c > 7%, or BMI < 28 kg/m<sup>2</sup>.

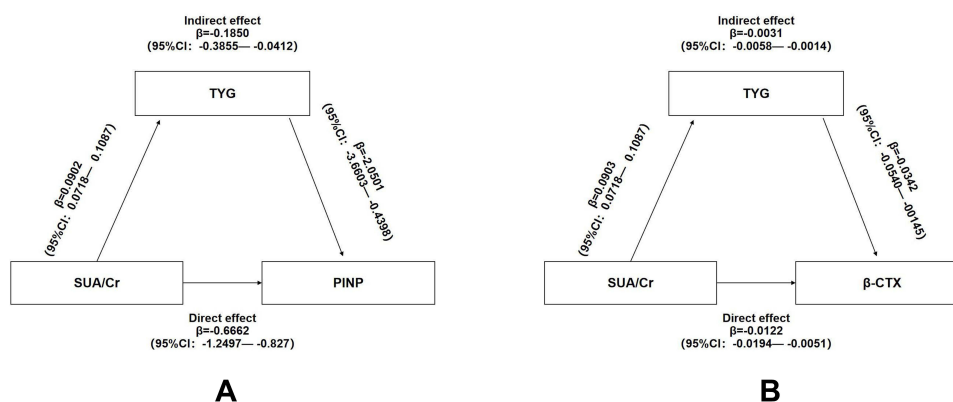
## Mediation Effect of SUA on PINP and β-CTX

Since SUA/Cr was inversely associated with PINP and β-CTX in both genders, we treated triglyceride glucose (TyG) as a mediator and further conducted the mediation analysis to explore the intermediate role of SUA/Cr in BTM association. Both SUA/Cr and TyG were negatively associated with PINP and β-CTX. Simultaneously, SUA/Cr was positively correlated with TyG, suggesting a mechanistic link between SUA/Cr and PINP ( $\beta = -0.6662$ , 95% CI: -1.2497 to 0.0827), possibly explained by TyG ( $\beta = -0.1850$ , 95% CI: -0.3855 to 0.0412). A mediated percentage of 21.84% was observed in this model (Figure 4). There were significant direct ( $\beta = -0.012$ , 95% CI: -0.0194 to 0.051) and indirect effects ( $\beta = -0.0031$ , 95% CI: -0.058 to 0.0014) between SUA/Cr and β-CTX, and TyG mediated 20.26% of this association (Figure 4).

## Discussion

Bone metabolism is regulated by a balance between the formation of new bone by osteoblasts and the resorption of old bone by osteoclasts, which are enzymes released from osteoclasts or osteoblasts during the bone remodeling process or proteins released from the bone matrix.<sup>22,23</sup> Recently, the importance of BTMs that indirectly reflect the process of bone remodeling has been increasing.<sup>24</sup> As a result, BTMs have been recognized as a promising tool for assessing bone quality and metabolism by the National Osteoporosis Foundation.<sup>25</sup> Specifically, PINP is secreted by osteoblasts during the formation of bone collagen. While OC was a protein marker of osteogenesis secreted by osteoblasts, and β-CTX was a breakdown product during the degradation of mature type I collagen secreted by osteoclasts. Therefore, β-CTX is a marker of bone resorption, whereas OC and PINP indicate bone formation.<sup>26,27</sup>

Prior studies found that patients with T2DM have a lower rate of bone turnover.<sup>28</sup> T2DM could disrupt normal osteocyte function and may affect bone formation and bone resorption to varying degrees.<sup>29</sup> Moreover, T2DM and bone



**Figure 4** Mediation of TYG on the association between SUA/Cr and BTMs (A) PINP; (B) β-CTX.



disease share many common pathophysiology and epidemiology.<sup>30</sup> In the current meta-analysis, both bone formation and resorption markers were decreased in patients with T2DM, suggesting that T2DM was the impaired state of bone metabolism.<sup>31</sup> Patients with T2DM have increased fragility fracture risk despite having similar or even higher BMD than that in nondiabetic patients, and that risk is likely increased due to impaired bone quality and strength.<sup>32,33</sup> BTMs provide useful information for clinical research on bone health and osteoporosis. Sodium-glucose transport protein 2 (SGLT2) inhibitors improve blood glucose levels by promoting urinary glucose excretion, which may affect urinary calcium excretion and bone metabolism.<sup>34</sup> As a metabolic disease, T2DM treatment is complex and requires additional clinical studies to evaluate the influence of these therapies on bone metabolism. None of the patients with diabetes included in the study were taking SGLT-2 inhibitors.

Our findings indicated that BTM levels were diminished in the high SUA/Cr group compared to the low SUA/Cr group. Our data showed that SUA/Cr was negatively associated with PINP and  $\beta$ -CTX in both male patients with T2DM and postmenopausal female patients after adjusting for confounding factors. This study showed that SUA/Cr ratio could reduce bone turnover. Consistent with our findings, Nabipour et al reported that SUA levels were inversely associated with bone absorption markers in old males.<sup>35</sup> A cross-sectional study, including 7502 healthy postmenopausal women, found that the higher the level of SUA/Cr, the lower the bone turnover.<sup>36</sup> SUA was inversely associated with OC and  $\beta$ -CTX in males, while SUA was only inversely associated with  $\beta$ -CTX in postmenopausal females.<sup>37</sup> A meta-analysis showed that PINP, OC, and  $\beta$ -CTX levels were lower among patients with T2DM.<sup>31</sup>

Previous studies suggested that elevated SUA levels are significantly associated with insulin resistance (IR).<sup>38</sup> SUA directly inhibits insulin receptor substrate 1 (IRS1) and insulin/AKT signaling, resulting in IR.<sup>39</sup> Huang et al found that IR leads to restrained bone turnover in mice.<sup>40</sup> Guo et al found that PINP and  $\beta$ -CTX levels were negatively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR).<sup>41</sup> Hyperinsulinemia can itself trigger IR, leading to a vicious cycle of hyperinsulinemia-IR, affecting osteoclasts and osteoblasts via dysfunction of the insulin-signaling cascade.<sup>42,43</sup> High insulin levels may increase osteoclast activity, which may affect the balance of bone metabolism and thus increase the risk of fracture in patients with T2DM.<sup>44</sup> Furthermore, hyperglycemia may lead to changes in bone structure because of the accumulation of advanced glycosylation end products (AGEs) through translational modification. The occurrence of these reactions in the bone matrix may cause damage to bone structure, affecting bone strength.<sup>45–48</sup> Moreover, all these reactions might have led to reduced bone strength, increased bone fragility, and fractures.<sup>49</sup> Our finding showed that TyG partly mediated the association between SUA/Cr and PINP and  $\beta$ -CTX.

PINP and  $\beta$ -CTX levels have been reported to be influenced by BMI.<sup>50</sup> This study found that among patients with T2DM with a BMI  $\geq 28$  kg/m<sup>2</sup>, SUA/Cr was negatively associated with PINP and  $\beta$ -CTX in males and inversely related to OC, PINP, and  $\beta$ -CTX in postmenopausal females. A study in postmenopausal Chinese women showed that bone metabolism differed in patients with T2DM with different BMI levels.<sup>51</sup> Some studies have shown that T2DM duration may lead to increased bone fragility and promote the development of T2DM combined with OP.<sup>52</sup> The United Kingdom Prospective Diabetes Study (UKPDS) results also showed that longer diabetes duration is associated with a worse prevalence of diabetes complications,<sup>53</sup> which would be true for bone health. Furthermore, previous studies have demonstrated that T2DM duration was associated with fracture risk.<sup>54</sup> Therefore, we performed subgroup analyses according to T2DM duration. The results showed no correlation between SUA/Cr and BTMs in patients with T2DM with a disease duration of  $\leq 5$  years. This was true for both sexes. However, among patients with longer T2DM duration, we observed that SUA/Cr was negatively associated with  $\beta$ -CTX and PINP in males and negatively associated with OC, PINP, and  $\beta$ -CTX in postmenopausal females. Du et al<sup>55</sup> showed that the NAFLD group had higher femoral neck and total hip BMD than the non-NAFLD group, suggesting that NAFLD in postmenopausal women with T2DM may reduce the risk of osteoporosis. The analysis was further conducted on subgroups based on the presence or absence of NAFLD. SUA/Cr levels were significantly associated with  $\beta$ -CTX levels in patients with NAFLD. Studies have reported that the correlation coefficients of TyG and HOMA-IR with the euglycemic-glucose clamp were similar, supporting TyG as an accessible and reliable tool for clearly reflecting IR.<sup>56,57</sup> Thus, the TyG index has shown a direct correlation with IR and has been proposed as a reliable and simple surrogate marker of IR in clinical practice.<sup>58–60</sup> The current findings highlight the mediating role of TyG in the SUA/Cr–BTM relationship. In addition, controlling TyG levels among patients with T2DM may help improve their bone turnover.

Ahn et al<sup>36</sup> also suggested that SUA was able to inhibit osteoclastogenesis in a dose-dependent manner and decrease reactive oxygen species (ROS) production of osteoclast precursors, revealing that SUA may directly contribute to the pathogenesis of osteoporosis as a consequence of its antioxidant properties. In experimental studies, oxidative stress has recently been identified as a potential mechanism for the inhibition of osteoblastic cells, resulting in the suppression of bone formation.<sup>61,62</sup> Previous studies suggested a possible association between oxidative stress and diabetes-related bone fragility.<sup>63</sup> UA stimulates inflammation through the production of p38 mitogen-activated protein kinases (MAPK), cyclooxygenase-2 (COX-2), and chemokine monocyte chemoattractant protein-1. SUA is positively associated with interleukin-18 (IL-18), interleukin-6 (IL-6), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).<sup>64,65</sup> UA was known to induce systemic inflammation.<sup>66,67</sup> It has been reported that hyperglycemia would alter the release and function of IL (especially interleukin-1 and IL-6).<sup>68,69</sup> The levels of proinflammatory cytokines associated with increased fracture risk, such as C-reactive protein (CRP) and TNF- $\alpha$ , are high in patients with T2DM.<sup>70,71</sup> The downstream target of these cytokines is nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF $\kappa$ B), which mediates certain aspects of bone physiology.<sup>72</sup>

Higher UA levels were associated with a significant decrease in tartrate-resistant acid phosphatase-5b (TRACP-5b), a new marker of bone resorption,<sup>73</sup> and urinary NTX-1, a marker of osteoclast activation.<sup>36</sup> Moreover, UA can promote osteogenic differentiation and inhibit the differentiation of human bone marrow mesenchymal stem cells into adipocytes.<sup>74</sup>

In the present study, we found a significant negative relationship between SUA/Cr and BTMs among men and postmenopausal women with T2DM, which perhaps indicates that physicians should pay greater attention to the bone health of these T2DM patients with high levels of SUA/Cr, for early detection of osteoporosis in clinical practice. The strength of our study is the large patient sample and the application of mediation analysis to explore whether IR mediated the association between SUA/Cr and BTMs. Our study has some limitations. First, the change in BTMs and the occurrence of osteoporotic fractures over time could not be evaluated without long-term follow-up. Therefore, we could not infer a causal relationship. Our cross-sectional findings need to be confirmed prospectively. Moreover, patients were only tested once with SUA/Cr and BTMs. Third, although we tried our best to control the confounding factors, the lack of drinking, smoking, fruit and vegetable consumption, physical activity and other potential confounding factors may affect the bone health. Therefore, further investigation is certainly necessary to characterize these factors. Although the limitations further influence the accuracy of the present study, it can still be considered that the bone turnover of T2DM patients with high SUA/Cr level is impaired, which means it leads to a higher risk of osteoporosis.

## Conclusions

SUA/Cr was negatively correlated with PINP and  $\beta$ -CTX in male and postmenopausal female patients with T2DM, and IR partly mediated this association.

## Data Sharing Statement

The original data can be available by email at any time (Yuling Xing: xingyl95@163.com).

## Disclosure

The authors report no conflicts of interest in this work.

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