Relationship of Bone Status with Serum Uric Acid and Bilirubin in Men with Type 2 Diabetes: A Cross-Sectional Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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This work was supported by research grants from Changzhou High-Level Medical Talents Training Project (No: 2016ZCLJ020) and "Six talent peaks" high-level talents found of Jiangsu province (WSN-044)

Background: Accumulating evidence has shown that serum uric acid and bilirubin are associated with some chronic diseases, owing to their antioxidant capacity, but the previous research produced discrepant results regarding the relation between uric acid, as well as bilirubin, and bone health. This study was designed to assess the relationship of serum uric acid and total bilirubin with bone mineral density and bone turnover markers in men with type 2 diabetes.

Material/Methods: In total, 631 male patients with type 2 diabetes were included. Data of patients' medical history, biochemical index, bone mineral density of the lumbar vertebra, femoral neck, and total hip, and bone turnover markers including osteocalcin (OC), amino-terminal propeptide of type I procollagen (PINP), type I collagen carboxy-terminal peptide (CTX), and parathyroid hormone were collected and retrospectively analyzed.

Results: Both serum uric acid and total bilirubin were positively related to bone mineral density of the lumbar vertebra (β=0.179, p<0.001; β=0.095, p=0.030), femoral neck (β=0.133, p=0.002; β=0.089, p=0.029), and total hip (β=0.142, p=0.001; β=0.087, p=0.032), respectively. Serum uric acid concentration was negatively related to bone turnover markers (OC: r=-0.148, p=0.037; PINP: r=-0.139, p=0005; CTX: r=-0.200, p=0.005). Each unit increase of serum uric acid and total bilirubin was associated with a 0.4% and 5.6% lower risk of osteoporosis or osteopenia (OR=0.996, 95% CI=0.994-0.998; OR=0.944, 95% CI=0.899-0.992), respectively. The risk of osteoporosis and osteopenia in patients with low-tertile concentrations of serum uric acid and total bilirubin was increased (OR=3.486, 95% CI=1.535-7.913).

Conclusions: In men with type 2 diabetes, serum uric acid level and total bilirubin were significantly associated with bone mineral density and were protective factors against osteoporosis and osteopenia.

Keywords: Bilirubin • Bone Density • Diabetes Mellitus, Type 2 • Uric Acid

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/930410

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Background

Osteoporosis is a common bone disease characterized by impaired bone mass, compromised bone strength, and increased risk of fracture. Because of atypical symptoms in the early stages, people are often unaware about the occurrence of osteoporosis until severe problems arise, such as pain or fracture.

The pathogenesis of osteoporosis is complex. Accumulating studies have shown that oxidative stress has detrimental effects that are involved in the development of osteoporosis, such as inhibiting the differentiation of osteoblasts and stimulation of osteoclastogenesis [1]. In recent years, the antioxidant capacity of several metabolites, such as uric acid (UA) and bilirubin, has been demonstrated [2,3]. UA is the end-product of purine catabolism. Although elevated serum UA level has been suggested to be strongly associated with atherosclerotic diseases [4], a potential protective role of UA was reported against neurologic diseases owing to its antioxidant ability [5-7]. With regard to the association between UA and bone health, clinical research has produced discrepant results. Some researchers have found UA is associated with higher bone mineral density (BMD) [8-10], while others have not found any correlation between UA and BMD or bone turnover markers (BTMs) [11]. Bilirubin, the end-product of heme catabolism, was generally known as a neurotoxin until 1987, when Ames et al revealed its beneficial role as a physiological antioxidant at low concentrations in vitro [3]. Past research had controversial results regarding the relationship between bilirubin and bone status. Some studies have shown that bilirubin is a risk factor for osteoporosis in patients with liver disease [12,13], some studies found bilirubin inversely associated with the prevalence of osteoporosis in patients without liver disease [14,15], and other studies have not found any correlation between bilirubin and bone metabolism [16]. Whether UA or bilirubin, most previous research has been based on data analysis of postmenopausal women, with few studies conducted among men.

The increasing prevalence of type 2 diabetes mellitus (T2DM) has become a worldwide health problem. Although BMD of patients with T2DM is similar to or even higher than that of patients without T2DM, the risk of fragility fracture is increased owing to impaired bone quality and strength [17,18]. It has been reported that the concentration of endogenous antioxidants is changed in patients with T2DM. However, few studies have evaluated the relationship of bone status with UA and bilirubin in men with T2DM. Recent epidemiological data show that in older Chinese men, the prevalence of osteoporosis and osteopenia is 6.46% and 55%, respectively [19]. Therefore, further study is needed to identify the influence of UA and bilirubin on the bone health of men with T2DM.

Material and Methods

Study population

We retrospectively reviewed the data of 631 men with T2DM hospitalized in the Department of Endocrinology of the Third Affiliated Hospital of Soochow University from December 2018 to October 2020. All patients were diagnosed with T2DM and were admitted to the hospital for adjustment of their hypoglycemic treatment and comprehensive assessment of chronic diabetic complications. **Figure 1** shows the screening process of participants. This study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University.
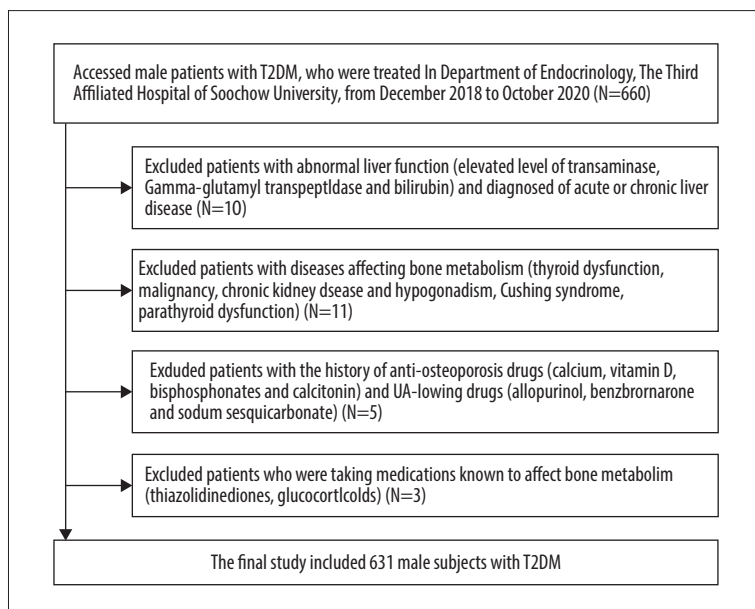
Figure 1. Process of patient screening.

Accessed male patients with T2DM, who were treated In Department of Endocrinology, The Third Affiliated Hospital of Soochow University, from December 2018 to October 2020 (N=660)

Excluded patients with abnormal liver function (elevated level of transaminase, Gamma-glutamyl transpeptldase and bilirubin) and diagnosed of acute or chronic liver disease (N=10)

Excluded patients with diseases affecting bone metabolism (thyroid dysfunction, malignancy, chronic kidney dsease and hypogonadism, Cushing syndrome, parathyroid dysfunction) (N=11)

Exduded patients with the history of anti-osteoporosis drugs (calcium, vitamin D, bisphosphonates and calcitonin) and UA-lowing drugs (allopurinol, benzbrornarone and sodium sesquicarbonate) (N=5)

Excluded patients who were taking medications known to affect bone metabolim (thiazolidinediones, glucocortlcolds) (N=3)

The final study included 631 male subjects with T2DM

Biochemical measurements

Blood samples were taken the morning after participants had fasted overnight for at least 10 hours. The concentrations of serum total bilirubin (TBIL), gamma-glutamyl transpeptidase, albumin, UA, creatinine (Cr), urea nitrogen, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), calcium, and phosphorus were measured using an automated AU-5800 analyzer (Beckman Coulter, Brea, CA, USA). Fasting levels of BTMs (osteocalcin [OC], amino-terminal propeptide of type I procollagen [PINP], type I collagen carboxy-terminal peptide [CTX], parathyroid hormone [PTH]) and 25-hydroxy vitamin D (25(OH)D3) were analyzed on Cobas E601 (Roche Diagnostics, Mannheim, Germany). Glycated hemoglobin (HbA1c) was tested using an automated glycosylated hemoglobin analyzer (Bio-Rad, Hercules, CA, USA).

BMD measurement

BMD was assessed at the lumbar vertebra (LV), femoral neck (FN), and total hip (TH) using dual-energy X-ray absorptiometry (DEXA; Hologic Discovery Wi, Ontario, Canada). The T-score is the difference in standard deviation between the BMD value of each individual and that of healthy reference adults. As defined by the World Health Organization, osteoporosis is diagnosed with T-score -2.5 or below; osteopenia is diagnosed with T-score -1.0 to -2.5. In this study, osteoporosis/osteopenia was defined as a T-score below -1.

Statistical Analysis

We used SPSS version 19.0 software for the statistical analysis (IBM Corp., Armonk, NY, USA). Continuous variables with a normal distribution and categorical variables are reported as mean±standard deviation (SD) and percentage using the *t* test and chi-square analysis. A Mann-Whitney U test was used if the data were non-normally distributed. The correlations among serum UA, serum TBIL, BMD, and BTMs were analyzed with Spearman correlation. Multiple linear regression analysis was used to determine the influence of serum UA and TBIL on BMD. Binary logistic regression was performed to obtain the odds ratio (OR) (95% confidence interval [CI]) of osteoporosis and osteopenia. The tertiles of UA and TBIL were combined to calculate the OR (95% CI) for the prevalence of osteoporosis and osteopenia using logistic regression analysis. Statistical significance was defined as p<0.05.

Results

Participant characteristics

The baseline characteristics of participants in this study are presented in **Table 1**. We divided the 631 male participants with T2DM into 2 groups, according to BMD T-scores: the normal BMD group (T-score ≥-1) and osteoporosis/osteopenia group (T-score <-1). The average age of all participants was 57.3±12.0 years. The mean duration of T2DM was 8.4±7.8 years and participants' mean level of HbA1c was 9.7±2.4%. The average BMD of the LV, FN, and TH was -0.8±1.3, -1.1±0.9, -0.5±0.8 g/cm^2, respectively. Participants with T-scores <-1 had significantly lower serum concentrations of UA, Cr, and BMI than those with T-scores ≥-1. The 2 groups showed no significant differences in the duration of T2DM; level of HbA1c; fasting blood glucose, TC, TG, HDL, LDL, and 25(OH)D3; history of hypertension; smoking; alcohol intake; and use of insulin/analogs.

Associations Among UA, TBIL, BMD, and BTMs

We calculated the associations of UA and TBIL with BMD and BTMs using Spearman correlation analysis. Serum UA level was positively correlated with BMD of the LV, FN, and TH and inversely correlated with BTMs (OC, PINP, CTX). The level of serum TBIL was also positively related to BMD of the LV, FN, and TH (**Table 2**).

To determine the relationship of serum UA and TBIL with BMD and BTMs in male patients with T2DM, we used multiple linear regression analysis. Variables including BMI and Cr were adjusted in Model I. In Model II, we adjusted variables including age, BMI, duration of T2DM, history of hypertension, and insulin/analog use, smoking, drinking, and levels of HbA1c, FBG, Cr, albumin, TC, TG, HDL, LDL, and 25(OH)D3. The results suggested that UA was associated with BMD of the LV, FN, and TH (β=0.179, p<0.001; β=0.133, p=0.002; β=0.142, p=0.001, respectively) and was also associated with BTMs including OC, PINP, and CTX (β=-0.193, p=<0.001; β=-0.185, p<0.001; β=-0.233, p<0.001, respectively). UA was not associated with PTH. TBIL was associated with BMD of the LV, FN, and TH (β=0.095, p=0.030; β=0.089, p=0.029; β=0.087, p=0.032, respectively). TBIL and BTMs presented no significant association (**Table 3**).

Influencing Factors Associated with the Prevalence of Osteoporosis and Osteopenia

To clarify the contributions made by serum UA and TBIL in the prevalence of osteoporosis and osteopenia, we performed binary logistic regression analysis. The OR (95% CI) of osteoporosis and osteopenia was 0.996 (0.994, 0.998), 0.944 (0.899, 0.992), and 0.862 (0.808, 0.919) for UA, TBIL, and BMI, respectively, in the multivariable-adjusted model, indicating that each unit increase of UA, TBIL, and BMI was associated with a 0.4%, 5.6%, and 13.8% lower risk of osteoporosis and osteopenia, respectively (**Table 4**). A forest plot showed that UA, TBIL, and BMI were protective factors against osteoporosis and osteopenia (**Figure 2**).

Table 1. Characteristics of the participants.

Characteristics	All (n=631)		T-score ≥-1 (n=257)		T-score <-1 (n=374)		P
Age (years)	57.3±12.0		56.6±11.9		57.8±12.1		0.217
BMI (kg/m²)	24.9±3.6		26.0±4.0		24.2±3.1		0.000
Diabetes duration (years)	8.4±7.8		8.4±7.5		8.4±8.1		0.996
HbA1c (%)	9.7±2.4		9.6±2.2		9.7±2.5		0.611
FBG (mmoL/L)	9.1±3.2		9.1±3.2		9.1±3.3		0.968
Insulin or analog use, n (%)	235	(37.2)	102	(16.2)	133	(21.1)	0.475
Hypertension, (n%)	371	(58.8)	163	(25.8)	208	(33.0)	0.050
Current smoker, n (%)	296	(46.9)	112	(17.7)	184	(29.2)	0.165
Drinking habits, n (%)	211	(33.4)	93	(14.7)	118	(18.7)	0.378
Total cholesterol (nmoL/L)	4.5±1.2		4.5±1.3		4.4±1.1		0.434
Triglycerides (nmoL/L)	2.4±2.4		2.4±2.2		2.3±2.4		0.633
HDL (nmoL/L)	1.0±0.2		1.0±0.2		1.0±0.2		0.928
LDL (nmoL/L)	2.6±0.9		2.6±0.8		2.5±0.8		0.943
Albumin	39.7±4.9		39.8±4.0		39.6±5.5		0.611
Creatinine (μmoL/L)	76.4±14.7		77.8±14.1		75.4±15.1		0.043
Uric acid (μmoL/)	323.7±84.4		339.9±86.9		312.7±80.9		0.000
TBIL (mmol/l)	11.7±3.9		12.1±4.1		11.5±3.8		0.079
25(OH) D3 (ng/ml)	18.6±7.9		19.4±8.2		18.1±7.7		0.146
Calcium (mmol/l)	2.3±0.1		2.3±0.1		2.3±0.1		0.336
Phosphorus (mmol/l)	1.2±0.2		1.2±0.2		1.2±0.2		0.445
TH BMD	-0.5±0.8		0.1±0.6		-0.9±0.7		0.000
FN BMD	-1.1±0.9		-0.5±0.7		-1.5±0.7		0.000
LV BMD	-0.8±1,3		0.2±0.9		-1.5±1.0		0.000
OC (ng/ml)	11.4±4.4		10.6±3.7		12.0±4.7		0.000
PINP (ng/ml)	37.8±15.2		35.1±13.6		39.7±16.0		0.000
CTX (pg/ml)	415.0±224.1		366.8±198.7		448.1±234.6		0.000
PTH (pg/ml)	36.5±14.1		36.6±14.6		36.5±13.8		0.913

BMI – body index; HbA1c – glycosylated hemoglobin; FBG – fasting blood glucose; HDL – high-density lipoprotein; LDL – low-density lipoprotein; TBIL – total bilirubin; TH – total hip; FN – femoral neck; LV – lumbar vertebral; BMD – bone mineral density; OC – osteocalcin; PINP – amino-terminal propeptide of type I procollagen; CTX – type I collagen carboxy-terminal peptide; PTH – parathyroid hormone.

To identify the influence of serum UA and TBIL at different concentrations on the prevalence of osteoporosis and osteopenia, these were divided into 3 groups according to tertiles. The prevalence of osteoporosis and osteopenia in each combination was compared. **Table 5** and **Figure 3** show that individuals with lower serum UA combined with lower serum TBIL had 3.49 times the prevalence of osteoporosis and osteopenia as compared with individuals who had higher serum UA combined with higher serum TBIL, after multivariable adjustment.

Table 2. Spearman correlations of serum UA and TBIL with BMD and BTMs.

	UA (r(p))	TBIL (r(p))
TH BMD	0.203 (0.000)	0.101 (0.011)
LV BMD	0.173 (0.000)	0.085 (0.033)
FN BMD	0.183 (0.000)	0.081 (0.041)
OC	-0.148 (0.037)	0.009 (0.835)
PINP	-0.139 (0.005)	0.036 (0.370)
CTX	-0.200 (0.005)	0.074 (0.065)
PTH	-0.025 (0.537)	0.055 (0.180)

UA – uric acid; TBIL – total bilirubin; FN – femoral neck;
LV – lumbar vertebral; TH – total hip; BMD – bone mineral
density; OC – osteocalcin; PINP – amino-terminal propeptide
of type I procollagen; CTX – type I collagen carboxy-terminal
peptide; PTH – parathyroid hormone.

Discussion

The present study focused on male patients with T2DM who were at risk of osteoporosis and osteopenia. It has been reported that mortality after osteoporotic fractures is significantly higher in men than in women [20]. However, less attention has always been paid to the bone health of men. We investigated the association between endogenous antioxidants and bone status in male patients with T2DM to provide additional evidence in this area. The current study suggested a positive relationship among the levels of UA, TBIL, and BMD of the LV, FN, and TH. The level of UA was negatively associated with BTMs including OC, PINP, and CTX. Each unit increase in the concentration of serum UA and TBIL was related to a 0.4% and 5.6% lower risk of osteoporosis/osteopenia. The prevalence of osteoporosis and osteopenia in individuals with low tertiles of UA and TBIL was 3.49 times that of individuals with high tertiles of UA and TBIL.

Table 3. Multiple linear regression analysis showing the association of serum UA and TBIL with BMD and BTMs.

	TH BMD			LV BMD		
	Unadjusted	Model I	Model II	Unadjusted	Model I	Model II
	β (p)			β (p)		
UA	0.210 (0.000)	0.116 (0.003)	0.142 (0.001)	0.182 (0.000)	0.116 (0.005)	0.179 (0.000)
TBIL	0.104 (0.009)	0.088 (0.014)	0.087 (0.032)	0.075 (0.059)	0.068 (0.047)	0.095 (0.030)
	FN BMD			OC		
	Unadjusted	Model I	Model II	Unadjusted	Model I	Model II
	β (p)			β (p)		
UA	0.204 (0.000)	0.001 (0.131)	0.133 (0.002)	-0.153 (0.000)	-0.157 (0.001)	-0.193 (0.000)
TBIL	0.093 (0.019)	0.078 (0.035)	0.089 (0.029)	0.004 (0.921)	0.007 (0.877)	-0.032 (0.508)
	PINP			CTX		
	Unadjusted	Model I	Model II	Unadjusted	Model I	Model II
	β (p)			β (p)		
UA	-0.142 (0.000)	-0.149 (0.000)	-0.185 (0.000)	-0.173 (0.000)	-0.189 (0.000)	-0.233 (0.000)
TBIL	0.025 (0.533)	0.023 (0.566)	0.013 (0.761)	0.097 (0.066)	0.098 (0.075)	0.042 (0.336)
	PTH					
	Unadjusted	Model I	Model II			
UA	0.006 (0.885)	-0.042 (0.335)	-0.013 (0.612)			
TBIL	0.036 (0.377)	0.027 (0.501)	0.064 (0.163)			

UA – uric acid; TBIL – total bilirubin; FN – femoral neck; LV – lumbar vertebral; TH – total hip; BMD – bone mineral density;
OC – osteocalcin; PINP – amino-terminal propeptide of type I procollagen; CTX – type I collagen carboxy-terminal peptide;
PTH – parathyroid hormone.

Table 4. The influence of the change in serum UA and TBIL on the prevalence of osteoporosis and osteopenia in male patients with T2DM.

	UA		TBIL	
	OR (95% CI)	p	OR (95% CI)	p
Unadjusted	0.996 (0.994, 0.998)	0.000	0.965 (0.926, 1.004)	0.080
MV adjusted	0.996 (0.994, 0.998)	0.001	0.944 (0.899, 0.992)	0.023

MV included: age, BMI, duration of T2DM, smoking habit, alcohol intake, history of hypertension, use of insulin or analogs, HbA1c, FBG, albumin, creatinine, total cholesterol, triglyceride, HDL, LDL, 25(OH)D3. UA – uric acid; TBIL – total bilirubin; MV – multiple variables; BMI – body index; T2DM – type 2 diabetes mellitus; HbA1c – glycosylated hemoglobin; FBG – fasting blood glucose; HDL – high-density lipoprotein; LDL – low-density lipoprotein.
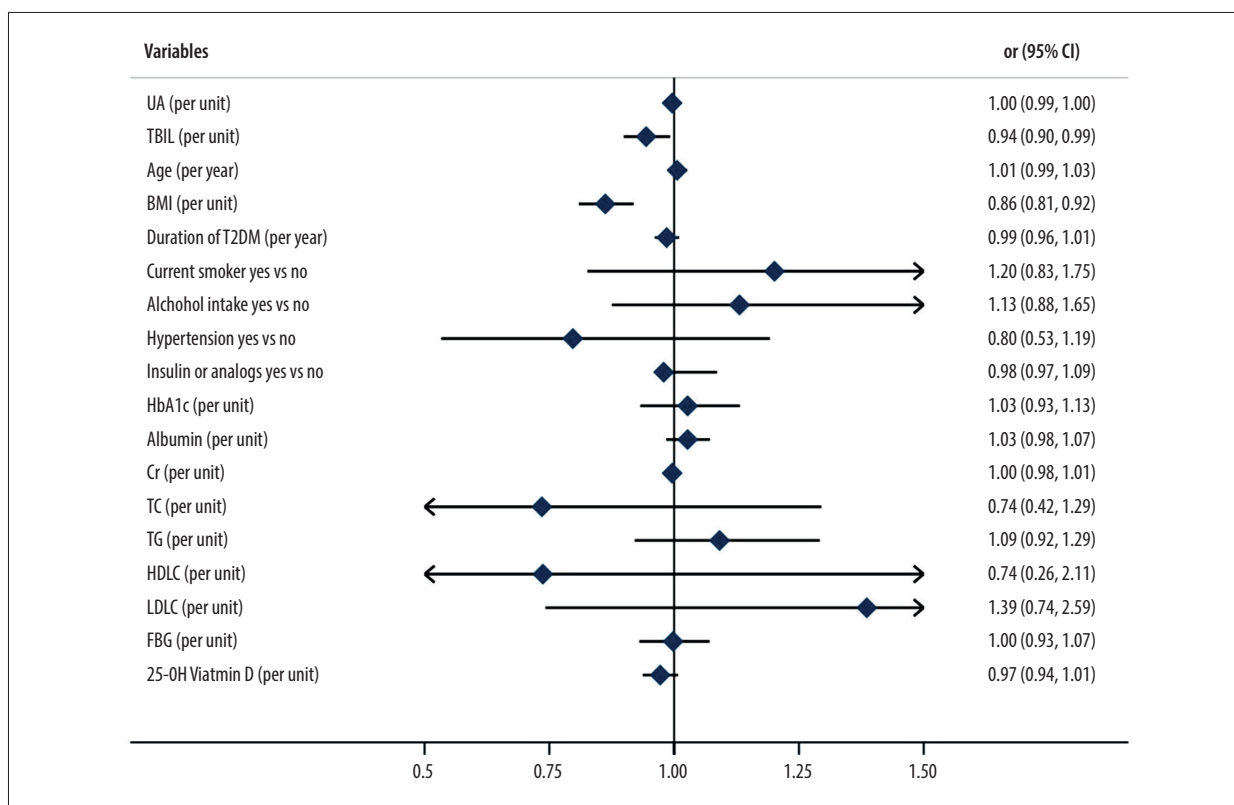

Variables	or (95% CI)
UA (per unit)	1.00 (0.99, 1.00)
TBIL (per unit)	0.94 (0.90, 0.99)
Age (per year)	1.01 (0.99, 1.03)
BMI (per unit)	0.86 (0.81, 0.92)
Duration of T2DM (per year)	0.99 (0.96, 1.01)
Current smoker yes vs no	1.20 (0.83, 1.75)
Alchohol intake yes vs no	1.13 (0.88, 1.65)
Hypertension yes vs no	0.80 (0.53, 1.19)
Insulin or analogs yes vs no	0.98 (0.97, 1.09)
HbA1c (per unit)	1.03 (0.93, 1.13)
Albumin (per unit)	1.03 (0.98, 1.07)
Cr (per unit)	1.00 (0.98, 1.01)
TC (per unit)	0.74 (0.42, 1.29)
TG (per unit)	1.09 (0.92, 1.29)
HDLC (per unit)	0.74 (0.26, 2.11)
LDLC (per unit)	1.39 (0.74, 2.59)
FBG (per unit)	1.00 (0.93, 1.07)
25-0H Viatmin D (per unit)	0.97 (0.94, 1.01)

Figure 2. Forest plot of the ORs (95% CI) for factors influencing osteoporosis and osteopenia in male patients with T2DM.

Concerning the relationship between UA concentration and BMD, our findings were consistent with those of several existing studies showing that serum UA was positively related to BMD of the LV, FN, and TH [8-10]. These past studies were mostly based on data analysis of individuals without diabetes, especially postmenopausal women. Studies on male patients with T2DM are limited. A recent study performed among Chinese men with T2DM had results similar to ours, but the researchers had not explored the relationship between serum UA and BTMs [10]. BTMs are sensitive indicators of the bone turnover process. OC and PINP are bone formation markers, reflecting the activity of osteoblasts. CTX is a marker of bone resorption, reflecting the activity of osteoclasts. The dynamic balance between bone formation and resorption plays an important role in the maintenance of bone mass. In this study, we found that serum UA was negatively associated with OC, PINP, and CTX, indicating the inhibitory effect of serum UA on the bone turnover process of men with T2DM. It has been reported that reactive oxygen species could activate the differentiation of pre-osteoclasts into osteoclasts. Bone formation is tightly coupled with bone resorption. In this study, the positive influence of serum UA on BMD was probably associated with the inhibitory effect of serum UA on the bone turnover process owing to its antioxidant ability. In vitro studies have provided evidence that the genesis of osteoclasts is inhibited by UA in a dose-dependent manner and the formation of reactive

Table 5. ORs (95% CI) for the prevalence of osteoporosis and osteopenia in different combinations of serum UA and TBIL level in male patients with T2DM.

TBIL tertiles	UA tertiles		
	<282.8 µmol/L	282.8–356.3 (µmol/L	≥356.3µmol/L
<9.7mmol/L			
Osteoporosis/osteopenia, n (%)	57 (9.0)	32 (5.1)	37 (5.9)
OR (95% CI) unadjusted	3.098 (1.548, 6.200)	1.905 (0.907, 3.999)	1.186 (0.607, 2.318)
OR (95% CI) adjusted	3.486 (1.535, 7.913)	2.033 (0.869, 4.757)	1.519 (0.713, 3.236)
9.7–13.1 mmol/L			
Osteoporosis/osteopenia, n (%)	42 (6.7)	49 (7.8)	42 (6.7)
OR (95% CI) unadjusted	2.625 (1.267, 5.438)	2.356 (1.184, 4.687)	1.750 (0.884, 3.465)
OR (95% CI) adjusted	2.391 (1.032, 5.538)	2.161 (0.994, 4.695)	1.989 (0.917, 4.317)
≥13.1 mmol/L			
Osteoporosis/osteopenia, n (%)	42 (6.7)	45 (7.1)	28 (4.4)
OR (95% CI) unadjusted	2.019 (1.005, 4.055)	1.520 (0.785, 2.943)	Reference
OR (95% CI) adjusted	2.152 (0.955, 4.847)	1.610 (0.767, 3.376)	Reference

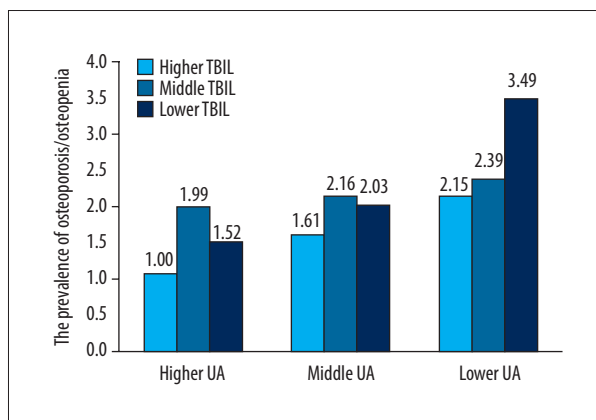UA – uric acid; TBIL – total bilirubin.

Figure 3. The prevalence of osteoporosis and osteopenia in each combination of the tertiles of serum UA and TBIL.

oxygen species is also reduced in osteoclast precursors, providing laboratory support for clinical findings [21]. However, some recent studies have suggested that serum UA is not associated with BMD and BTMs in men, including a study conducted in men with T2DM by Tanaka et al [11]. Participants in that study were elderly men with a relatively long duration of diabetes. The difference in the basic characteristics of study participants could be the reason for the discrepant results.

Clinical studies have yielded controversial results regarding the association between serum TBIL levels and bone metabolism; most of these studies were conducted among participants without diabetes [12-16]. Recently, Yan et al found that higher TBIL levels are linked to a higher BMD and lower risk of developing osteoporosis in Chinese patients with T2DM; however,

those authors did not evaluate the relationship of serum TBIL with BTMs [22]. In the present study, we found that increased levels of serum TBIL contributed to the reduced prevalence of osteoporosis and osteopenia, which is in accordance with several previous studies. However, the concentration of TBIL was not found to be associated with BTMs. Similar to the present study, a case-control study showed that patients with Gilbert syndrome characterized by hyperbilirubinemia in the absence of hepatocellular disease or hemolysis showed no difference in PTH, CTX, or OC levels compared with controls [16]. Another study among patients with chronic liver disease suggested that the change in OC was not connected with serum bilirubin levels [23]. However, only limited laboratory data concerning the influence of physiological concentrations of bilirubin on bone metabolism are available. Considering the complex regulation factors involved in the process of bone turnover, we cannot rule out the possibility that there are confounding factors that were not taken into account and that affected the association between serum TBIL and BTMs in the present study.

Although both UA and TBIL are endogenous antioxidants, whether their protective effect on BMD is decreased with lower levels of UA combined with lower TBIL levels remains unclear. In the present study, we found a significantly higher prevalence of osteoporosis/osteopenia among men with T2DM who had low tertiles of UA and TBIL, compared with other combinations, which perhaps indicates that physicians should pay greater attention to the bone health of these patients, for early detection of osteoporosis and osteopenia in clinical practice.

Our study had several limitations. First, as a cross-sectional study, the change in BMD and BTMs and the occurrence of osteoporotic fractures over time could not be evaluated without long-term follow-up. Therefore, we could not explore the exact mechanism and infer a causal relationship. Second, although we attempted to consider as many confounding factors as possible, the existence of additional potential confounders cannot be completely ruled out. Third, the sample size was not sufficiently large to conduct subgroup analysis for more detailed results. Finally, we reviewed the data from hospitalized patients, who might not represent all patients with T2DM owing to a possibly more severe state of disease compared with the general population who have T2DM.

Conclusions

Both serum UA and TBIL were found to be related to BMD in men with T2DM. Longitudinal clinical studies are needed to clarify whether higher levels of serum UA and TBIL could be protective factors against fracture in patients with T2DM.

Acknowledgments

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