Association between uric acid to high-density lipoprotein cholesterol ratio (UHR) and osteoporosis in type 2 diabetes with MASLD

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ABSTRACT

Background and Objectives: Uric acid to high-density lipoprotein cholesterol ratio (UHR) plays a significant role in metabolic and inflammatory responses. However, the association between UHR and osteoporosis (OP) remains unclear in type 2 diabetes mellitus (T2DM) with metabolic dysfunction-associated steatotic liver disease (MASLD). This study aims to investigate this association and identify potential biomarkers for early OP screening. **Methods and Study Design:** A total of 420 T2DM patients with MASLD aged ≥50 years were enrolled in this retrospective study. All subjects underwent dual energy X-ray absorptiometry (DXA) examination to measure bone mineral density (BMD) and were divided into three groups according to UHR tertiles, and the differences in BMD levels and OP prevalence among the three groups were compared. Logistic regression was used to analyze the relationship between UHR and OP. **Results:** Patients in the highest tertile of UHR group (UHR >363.46) had lower BMD and a higher incidence of OP than those in the lower tertiles. In the UHR >363.46 group, UHR was negatively correlated with lumbar spine, whole body, and femoral neck BMD (p <0.05). After adjusting for confounding factors, UHR >363.46 was associated with a significantly increased risk of OP compared to UHR ≤312.35 (OR=3.341, 95%CI: 1.129-9.887, p = 0.029). ROC curve indicated that UHR combined with Age, HOMA-IR and 25(OH)D had a high predictive value for OP, with an area under the curve of 0.837 (p <0.001). **Conclusions:** Increased UHR is significantly associated with higher risk of OP, suggesting that clinical monitoring of UHR is valuable for early detection of OP in T2DM with MASLD.

Key Words: uric acid to high-density lipoprotein cholesterol ratio (UHR), type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease (MASLD), bone mineral density, osteoporosis

INTRODUCTION

Type 2 diabetes mellitus (T2DM) and metabolic dysfunction-associated steatotic liver disease (MASLD) are increasingly common and interrelated diseases worldwide, and they often coexist.[1] Osteoporosis (OP) is a systemic metabolic bone disease characterized by decreased bone mass and impaired bone microarchitecture, with increased bone fragility and risk of fracture caused by unbalanced bone remodeling.[2] Notably, T2DM and MASLD are important risk factors for OP, increasing the risk of fractures in patients and the economic burden on their families.[3,4] A meta-analysis showed the prevalence of OP in T2DM ranged from 7.29%

to 53.71%.[3] Thus, early clinical identification of OP in T2DM with MASLD is particularly crucial.

Growing evidence indicates that the key pathophysiological link between T2DM, MASLD, and OP is a chronic state of low-grade inflammation and oxidative stress, driven by shared metabolic disorders such as insulin resistance (IR), adipose tissue dysfunction and lipid metabolism abnormalities.[5,6] This pro-inflammatory environment directly disrupts bone homeostasis by promoting bone resorption and damaging bone formation, leading to OP.[7,8] Moreover, these metabolic disorders also disrupt the balance of key circulating factors involved in inflammation and oxidation, such as abnormal purine metabolism.[9]

Inflammation and lipid metabolism disorders are known to adversely affect bone health. Uric acid (UA) is the end product of purine metabolism, exhibits pro-oxidative and pro-inflammatory properties that impair bone health when exceeding certain thresholds.[10] Conversely, high-density lipoprotein cholesterol (HDL-C) has anti-inflammatory and antioxidant activities that contribute to maintaining the homeostasis of bone microenvironment.[11] However, the association between UA/ HDL-C and OP remains controversial. The recently proposed uric acid to high-density lipoprotein cholesterol ratio (UHR) is a novel biomarker for evaluating metabolic function and inflammation, which can better reflect the overall balance between pro-inflammatory and anti-inflammatory/oxidative forces, and has been shown to be associated with diseases such as T2DM, MASLD, metabolic syndrome (MS), coronary heart disease and Hashimoto's thyroiditis.[12,13] However, the relationship between UHR and OP is unclear and less studied in T2DM combined with MASLD.

Therefore, the purpose of this study is to investigate the association between UHR and OP in T2DM with MASLD, in order to provide new ideas for the diagnosis and prevention of osteoporosis in this population.

MATERIALS AND METHODS

Study design and population

This study included T2DM patients combined with MASLD aged ≥50 years who were hospitalized in the Department of Endocrinology of the First Hospital of Lanzhou University from September 2023 to May 2024. A total of 420 subjects were enrolled in this study based on inclusion and exclusion criteria and divided into three groups by UHR tertiles (Figure 1). All investigations followed the ethical principles of the Declaration of Helsinki, and this study

was approved by the Ethics Committee of the First Hospital of Lanzhou University (LDYYLL-2024-746).

Inclusion criteria were as follows: (1) men and postmenopausal women aged ≥50 years; (2) diagnosis of T2DM based on the 1999 World Health Organization (WHO) classification and diagnostic criteria for diabetes; (3) diagnosis of MASLD based on 2023 Delphi Consensus.[14]

Exclusion criteria were as follows: (1) type 1 diabetes and other types of diabetes; (2) acute complications of diabetes mellitus, such as diabetic hypertonic hyperglycemic syndrome, diabetic ketoacidosis, hypoglycemia; (3) diseases affecting bone metabolism: severe heart, liver, renal insufficiency, suffering from thyroid or parathyroid diseases, rickets, immune diseases, malignant tumors and Cushing's syndrome; (4) patients treated with antiepileptic drugs, thiazolidinediones, calcium, bisphosphonates, glucocorticoids, vitamin D, diuretics and other drugs affecting bone metabolism; (5) patients with disabilities who are chronically immobile or bedridden; (6) taking medications affecting uric acid or lipid levels within the last 3 months, or having an acute attack of gout; (7) patients with incomplete information.

Data collection

General information collected including age, gender, duration of diabetes, smoking and drinking history, medication use, menstrual history and history of previous illnesses (such as rheumatoid arthritis, fracture history). Osteoporotic fractures are defined as fractures that occur during daily life or when subjected to minor external forces, and the time range of fractures in this study was 0-14 years. Systolic blood pressure (SBP), diastolic blood pressure (DBP), height and weight were measured. BMI=weight/height^2 (kg/m^2).

Blood samples were collected in the early morning after fasting for 12 h. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), fasting plasma glucose (FPG), triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), calcium (Ca), phosphorus (P) and uric acid (UA) were detected by AU5800 automatic biochemical analyzer and matching reagents (Beckman Coulter Diagnostics, California, USA). Glycated hemoglobin A (HbA1c) was determined by high-performance liquid chromatography (Bio-Rad variant turbo II analyzer). 25-hydroxyvitamin D (25(OH)D), parathyroid hormone (PTH), osteocalcin (OC), procollagen type I N-propeptide (PINP) and beta-isomer of the C-terminal telopeptide of type I collagen (β-CTx) were measured by electrochemiluminescence immunoassay (Cobas e 801 immunoassay analyzer and matching reagent, Roche Diagnostics, Basel, Switzerland). Fasting insulin (FINS) levels were assayed by chemiluminescence (DxI

800 immunoassay system and matching reagent; Beckman Coulter Diagnostics). Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) equation.[15] Homeostatic modeling assessed insulin resistance index (HOMA-IR) = FPG (mmol/L) × FINS (mIU/L)/22.5. UHR was calculated by dividing serum UA level by HDL-C level.

BMD measurement and OP diagnosis

Bone mineral density (BMD) of lumbar spine (LS), femoral neck (FN) and whole body (WB) were measured by an experienced operator using a dual-energy X-ray bone densitometer (Lunar iDXA, GE Healthcare) and the corresponding T-values were obtained. The diagnosis of osteoporosis is based on the World Health Organization (WHO) criteria, which are as follows: for postmenopausal females and males aged ≥50 years, T value ≤−2.5 was diagnosed as osteoporosis, −2.5 <T value <−1.0 as osteopenia and T value ≥−1.0 as normal bone mass.[16]

Diagnostic criteria and grouping

T2DM was diagnosed according to the 1999 WHO diagnostic criteria, one of the following: (1) patients with typical hyperglycemic symptoms and random blood glucose ≥11.1mmol/L; (2) FPG ≥7.0 mmol/L; (3) 2hPG ≥11.1mmol/L.

Diagnosis of MASLD was based on hepatic steatosis (confirmed by imaging or biopsy) and one of the following five items:14 (1) BMI ≥25kg/m^2 (≥23 kg/m^2 in Asians) or waist circumference >94cm for men and >80cm for women;(2) FPG ≥5.6mmol/L or 2hPG ≥7.8mmol/L or HbA1c level ≥5.7% or hypoglycemic therapy; (3) blood pressure ≥130/85mmHg or antihypertensive therapy;(4) plasma TG ≥1.7mmol/L or lipid-lowering therapy; (5) plasma HDL-C ≤1.0mmol/L for men and ≤1.3mmol/L for women or lipid-lowering therapy. In this study, we employed abdominal ultrasound (the most widely available and practical imaging diagnostic tool) to assess hepatic steatosis, but its accuracy may be limited, future studies should combine liver elastography or biopsy.

Hypertension was defined as SBP ≥140mmHg and/or DBP ≥90mmHg or having a history of hypertension and currently taking antihypertensive medications.

Subjects were categorized into T1 (UHR ≤312.35), T2 (312.35 <UHR ≤363.46) and T3 (UHR >363.46) groups based on UHR tertiles.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. The continuous variables in accordance with normal distribution were expressed by (mean±standard deviation), the comparison between groups was expressed by ANOVA. The continuous variables of non-normal distribution were represented by median (P25–P75), and the comparison between groups was expressed using the Kruskal-Wallis test. Categorical variables were expressed as percentages (%), and the Chi-squared test or Fisher's exact method was used for comparison between groups. Linear and logistic regression models were used to analyze the relationship between UHR and BMD and OP, respectively. Binary logistic regression was used to analyze independent risk factors associated with OP in T2DM with MASLD. The predictive value of UHR combined with relevant indicators for OP was evaluated using receiver operating characteristic curve (ROC). p <0.05 was considered statistically significant.

RESULTS

Clinical baseline data

A total of 420 T2DM patients with MASLD with an average age of (61±8) years were enrolled in this study, including 267 men and 153 postmenopausal women. All participants were divided into three groups (T1-T3) based on UHR tertiles. There were significant differences in age, BMI, SBP, FINS, HOMA-IR, TG, TC, HDL-C, ALT, UA, 25(OH)D, OC, LS BMD, FN BMD and WB BMD among the three groups (p <0.05), among which UHR >363.46 had the lowest BMD, while age, BMI, FINS, HOMA- IR, TG and UA were higher than the other two groups (p <0.05).There were no significant differences in other clinical data and laboratory tests among the three groups (p >0.05) (Tables 1 and 2).

Proportion of abnormal bone mass in different UHR levels

The results in Table 2showed that the proportion of people with normal bone mass gradually decreased with increasing UHR levels, while the proportion of people with osteopenia and OP gradually increased. Among them, the proportion of OP in the UHR ≤312.35 group (2.9%) was significantly lower than that in the UHR >363.46 group (24.3%). The proportion of OP among the three groups was statistically significant (p <0.001).

Correlation between UHR and BMD and OP by Model regression analysis

According to the UHR stratification, in UHR >363.46 group, UHR was negatively correlated with WB, LS, and FN BMD (WB, β = -0.278, p = 0.001; LS, β = -0.307, p =<0.001; FN, β = -

0.457, p =<0.001), and this relationship still persisted in regression Model 3 (WB,β=-0.244, p = 0.006; LS, β = -0.301, p = 0.001; FN, β = -0.477, p =<0.001). However, there was no correlation between UHR and BMD at any site in UHR ≤312.35 and 312.35 <UHR ≤363.46 groups (p >0.05) (Table 3). In addition, taking T1 group as the reference group, stratified logistic regression was used to analyze the risk of OP at different UHR levels (Table 4). The results showed that compared with the lowest tertile of UHR, 312.35 <UHR ≤363.46 was not associated with the risk of OP (p >0.05), while UHR>363.46 was a risk factor for OP (p <0.05). After adjusting for age, sex, duration of T2DM, HbA1c, BMI, HOMA-IR, TG, ALT and 25(OH)D, UHR>363.46 remained an independent risk factor for OP (OR = 3.341, 95%CI = 1.129-9.887, p = 0.029).

Analysis of influencing factors of OP in T2DM patients with MASLD

Binary logistic regression analysis showed that age, HOMA-IR and UHR were risk factors for OP in T2DM combined with MASLD, while 25(OH)D was a protective factor (p <0.05). For a 1-unit increase in HOMA-IR and UHR, the risk of OP was increased by 1.414-fold and 1.077-fold, respectively. The risk of OP increased 1.048-fold with each additional year of age. In addition, elevated 25(OH)D levels decreased the risk of OP (OR = 0.934,95%CI = 0.877-0.994, p = 0.032) (Table 5).

Subgroup analysis of UHR and OP based on BMI

In a subgroup analysis based on BMI, elevated UHR was a risk factor for OP in T2DM with MASLD with BMI ≥24 (OR = 1.006, 95%CI = 1.001-1.012, p = 0.031). After adjusting for age, sex, duration of T2DM, HbA1c, BMI, HOMA-IR, TG, ALT and 25(OH)D, UHR was still an independent risk factor for OP in BMI⩾24 group (OR = 1.008, 95%CI = 0.998-1.015, p = 0.037). However, there was no significant correlation between UHR and OP in BMI <24 group (p >0.05) (Table 6).

ROC curve analysis of UHR combined with other indicators for screening osteoporosis

This study constructed an OP prediction model based on comprehensive predictors, with the composite predictor (L) = −8.229 + 0.032 * Age + 0.230 * HOMA – IR − 0.066 * 25(OH)D + 0.024 * UHR. As shown in Figure 2, ROC curve analysis revealed that the area under the curve (AUC) for predicting OP using Age, HOMA-IR, 25(OH)D and UHR was 0.837

(95%CI: 0.782-0.893, p <0.001), with a sensitivity of 64.8% and specificity of 83.8%, indicating that the composite index possesses high predictive value.

DISCUSSION

The pathogenesis of OP involves the complex interaction of multiple factors, including aging, inflammation, oxidative stress and metabolic disorders.[17] It has also been reported that UA and HDL-C may be associated with OP and fracture risk. UA plays a dual role in bone metabolism. At physiological level, UA exhibits antioxidant effects, but its excessive accumulation promotes oxidative stress and inflammation, enhancing osteoclast-mediated bone resorption, resulting in bone loss and fractures.[18] A large population-based cohort study in Austria demonstrated that high serum UA levels were associated with the risk of hip fracture in people aged 50 years and older.[19] Conversely, HDL-C has also been shown to play a role in bone metabolism in addition to its anti-inflammatory, antioxidant and antithrombotic properties.[11, 20] Low HDL-C concentrations are associated with the development of an inflammatory microenvironment and increased bone marrow obesity, which inhibits osteoblast differentiation and function, leading to decreased bone mass.[21] Furthermore, a cross-sectional study examining the link between lipid metabolism and OP in elderly patients with type 2 diabetes revealed that higher HDL-C levels had a protective effect against OP.[22] More importantly, in metabolic disorders such as T2DM and MASLD, abnormal UA metabolism frequently coexists with dyslipidemia and is closely associated with oxidative stress and chronic inflammation.[9,23] These interrelated metabolic disorders may exert synergistic detrimental effects on bone homeostasis, so we hypothesize that the balance between UA and HDL-C may be associated with OP risk.

UHR is a composite marker integrating UA and HDL-C to assess overall inflammatory/metabolic disorders. Many previous studies have demonstrated its association with T2DM, MAFLD and MS diseases.[12, 24] However, there are few studies on the relationship between UHR and OP. Liu Z et al. studied 2963 healthy people ≥50 years of age and found a positive correlation between UHR and FN BMD, which was a protective factor for OP.[25] Different from the above studies, our results showed that compared to the lowest UHR tertile group, the highest UHR tertile group had the lowest BMD and the highest proportion of OP (24.3%), and that higher levels of UHR were associated with an increased risk of OP in T2DM with MASLD. This may be due to different study designs and populations, our study population was characterized by metabolic disorders and inflammatory states.

It is well known that OP is closely associated with chronic inflammation and oxidative stress. T2DM with MASLD are accompanied by low HDL-C and high UA levels, showing higher levels of UHR. At present, the mechanism of interaction between UHR and OP is unclear and may involve multiple factors. On the one hand, elevated UHR indicates increased inflammation. High levels of serum UA induce inflammation and oxidative stress responses and lead to bone loss by inhibiting osteoblast differentiation and activity through the endoplasmic reticulum kinase (ERK)-dependent NF-κB signaling pathway.[10, 26] HDL-C reduces osteoclastogenesis by blocking T cell signaling in macrophages and inhibiting the production of the pro-inflammatory factors TNF-αand IL-1β, whereas low HDL-C loses its anti-inflammatory properties and thus indirectly affects bone metabolism.[27] On the other hand, UHR may impair bone health through hormone metabolism disorders. Clinical studies have also demonstrated that increased serum UA levels lead to vitamin D insufficiency and deficiency, which adversely affects bone growth and development.[28] In addition, elevated UHR was significantly positively correlated with IR, which inhibited insulin receptor signaling pathway and reduced osteoblast activity, further aggravating UHR damage to bone.[29] The present study further demonstrated that UHR was significantly correlated with OP and negatively correlated with OC, which may mainly affect OP by reducing bone formation.

Furthermore, binary logistic regression analysis showed that UHR, HOMA-IR, age and 25(OH)D were independent influencing factors for OP, which was consistent with previous studies.[30-32] Among them, UHR level and HOMA-IR had a greater effect on OP in T2DM with MASLD, followed by age and 25(OH)D. As a composite indicator of inflammation, UHR can better reflect the overall imbalance of inflammatory oxidative stress and lipid metabolism in the body, and may increase the inhibition of bone formation by inflammatory cytokines, leading to OP.[33] Our results further confirm that an increase in UHR is significantly associated with elevated risk of OP, and the causal relationship between them requires further validation through prospective studies. Shin D et al. found that patients with higher levels of HOMA-IR had a higher odds ratio for osteoporosis.[34] In addition, with increasing age, bone cells become senescent cells that are insensitive to mechanical stimulation, disrupting bone homeostasis and leading to OP.[31] 25(OH)D promotes intestinal calcium absorption and is involved in bone growth and bone remodeling in osteoblasts and osteoclasts, and its deficiency accelerates bone conversion and bone loss.[32] Yao et al. showed in a meta-analysis of 11 observational studies that every 10ng/mL increase in serum 25(OH)D concentration reduced the risk of any fracture by 7% and hip fracture by 20%.[35]

Given that BMI was an important influencing factor driving systemic metabolic disorders and OP, we performed subgroup analysis based on BMI to further explore the impact of UHR on OP under different metabolic states. The results showed that after adjusting for age, sex, duration of T2DM, HbA1c, BMI, HOMA-IR, TG, ALT and 25(OH)D, elevated UHR was still associated with increased OP risk in T2DM combined with MASLD with BMI ≥24kg/m^2, whereas no correlation was found between UHR and the risk of OP in BMI <24 kg/m^2. This may be due to increased inflammation and fracture risk in overweight or obese patients.[36, 37]

Notably, this study found an association between higher levels of UHR and OP in T2DM with MASLD, with the highest proportion of OP in the highest UHR level group (24.3%). However, there are some limitations of our study: First of all, due to the cross-sectional design of our study, we were unable to determine a causal relationship between UHR and OP. Secondly, it is necessary to further study the mechanism of UHR on osteoblasts and osteoclasts, so as to clarify the influence of UHR on bone metabolism. Thirdly, it was a single-center study only for T2DM inpatients, the generalizability of the results may be limited, and more large-scale and multi-center studies are needed. In addition, some important potential confounding factors such as dietary habits, calcium and phosphorus micronutrient intake, sunlight exposure and exercise were not considered and measured, subsequent research should collect these data to control for confounding. Finally, the study's OP sample size was relatively small and may increase the risk of false positives.

In summary, elevated UHR levels are significantly associated with increased OP risk in T2DM with MASLD, especially among those who are overweight or obese. This study indicates that UHR may be related to the risk of OP, and it is worthy of further verification in prospective studies to explore its potential as a screening indicator. For patients with higher UHR levels, it is necessary to regularly monitor BMD to prevent OP and fracture.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Comparison of baseline data in T2DM patients with MASLD

	UHR			*p*
	T1 (≤312.35)	T2 (312.35 <UHR ≤363.46)	T3 (>363.46)	
Age(year)	58 (54,65)	59 (55,65)	61 (57, 68)	0.001
Gender (male) (%)	82 (58.6)	87 (62.1)	98 (70)	0.127
Diabetes duration (year)	7.5 (3.5, 14)	8 (4.5, 14)	10 (5, 13.5)	0.266
BMI (kg/m^2)	24.20 ± 2.79	25.59 ± 2.79	26.26 ± 2.93	<0.001
SBP (mmHg)	134.73 ± 17.27	137.35 ± 16.54	139.31 ± 15.44	0.045
DBP (mmHg)	81.75 ± 10.31	82.99 ± 11.73	84.56 ± 10.14	0.091
Hypertension (%)	66 (47.1)	75 (53.6)	83 (59.3)	0.125
Smoking (%)	29 (20.7)	35 (25)	37 (26.4)	0.508
Fragility fracture history (%)	9 (6.4)	13 (9.3)	15 (10.7)	0.436
HbA1c (%)	8.0 (7.0,9.4)	8.1 (6.9, 9.7)	8.2 (7.1, 9.6)	0.622
FPG (mmol/L)	8.53 (7.10,10.55)	8.08 (6.71, 10.35)	8.53(7.02, 10.87)	0.403
FINS (mIU/L)	6.37 (4.98,7.88)	7.02 (5.57, 8.27)	8.47 (6.95, 9.34)	<0.001
HOMA-IR	2.38 (1.99,2.91)	2.47 (2.14, 2.96)	3.16 (2.67, 3.63)	<0.001
TG (mmol/L)	1.64 (1.17,2.62)	1.86 (1.33, 2.64)	1.97 (1.41, 2.97)	0.018
TC (mmol/L)	4.62 ± 1.22	4.22 ± 1.23	4.09 ± 1.01	<0.001
HDL-C (mmol/L)	1.20 ± 0.20	1.00 ± 0.12	0.86 ± 0.11	<0.001
LDL-C (mmol/L)	2.87 ± 0.90	2.73 ± 0.84	2.82 ± 0.73	0.337
ALT (U/L)	19 (15,29)	23 (16, 35)	24 (18, 35)	0.013
AST (U/L)	20 (16,26)	22 (16, 27)	21 (17, 29)	0.554
eGFR, mL/min/1.73m^2	99.10 ± 28.38	97.92 ± 28.60	101.99 ± 30.72	0.487
UA (μmol/L)	320.72 ± 40.15	336.12 ± 39.19	354.88 ± 33.77	<0.001

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, HbA1c glycated hemoglobin A, FPG fasting plasma glucose, FINS fasting insulin, HOMA-IR insulin resistance index, TG triglyceride, TC total cholesterol, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, ALT alanine aminotransferase, AST aspartate aminotransferase, eGFR estimated glomerular filtration rate, UA uric acid, UHR uric acid to high-density lipoprotein cholesterol ratio.

Table 2. Comparison of BMD and bone metabolism markers among three groups

	UHR			*p*
	T1 (≤312.35)	T2 (312.35 <UHR ≤363.46)	T3 (>363.46)	
25(OH)D (ng/mL)	12.8 (9.5, 16.6)	10.6 (8.6, 15.1)	10.9 (8.9, 14.5)	0.017
Ca (mmol/L)	2.22 (2.14, 2.26)	2.20 (2.12, 2.27)	2.18 (2.11, 2.26)	0.119
P (mmol/L)	1.20 ± 0.18	1.18 ± 0.17	1.14 ± 0.20	0.143
ALP (U/L)	74.90 (63.05, 92.75)	70.80 (58.80, 86.80)	70.05 (61.40, 87.75)	0.189
PTH (pg/mL)	43.9 (36.8, 51.2)	41.0 (35.2, 47.9)	44.8 (37.2, 53.0)	0.077
OC (ng/mL)	15.20 (10.05, 19.25)	12.87 (9.87, 16.99)	12.50 (9.50, 16.55)	0.012
PINP (ng/mL)	39.2 (29.7, 52.3)	37.5 (30.3, 48.3)	37.7 (29.0, 44.4)	0.239
β-CTx (pg/mL)	436 (290, 568)	377 (275, 519)	383 (267, 535)	0.268
LS BMD (g/cm2)	1.12 ± 0.16	1.06 ± 0.17	0.99 ± 0.15	<0.001
FN BMD (g/cm2)	0.97 ± 0.14	0.90 ± 0.12	0.81 ± 0.13	<0.001
WB BMD (g/cm2)	1.14 ± 0.16	1.04 ± 0.14	0.99 ± 0.15	<0.001
Bone mass status				<0.001
Normal (n, %)	92 (65.7%)	72 (51.4%)	39 (27.9%)	
Osteopenia (n, %)	44 (31.4%)	53 (37.9%)	67 (47.9%)	
OP (n, %)	4 (2.9%)	15 (10.7)	34 (24.3%)	

25(OH)D 25-hydroxyvitamin D, Ca calcium, P phosphorus, ALP alkaline phosphatase, PTH parathyroid hormone, OC osteocalcin, PINP procollagen type I N-propeptide, β-CTx beta-isomer of the C-terminal telopeptide of type I collagen, BMD bone mineral density, LS lumbar spine, FN femoral neck, WB whole body, OP osteoporosis.

Table 3. Correlation between UHR level and BMD in different groups

UHR	WB BMD		LS BMD		FN BMD	
	β	*p*	β	*p*	β	*p*
T1						
Model 1†	-0.059	0.490	-0.168	0.048	-0.088	0.301
Model 2‡	-0.072	0.395	-0.145	0.086	-0.067	0.432
Model 3§	-0.055	0.516	-0.131	0.123	-0.079	0.350
T2						
Model 1†	-0.137	0.108	-0.170	0.044	-0.135	0.113
Model 2‡	-0.122	0.159	-0.152	0.075	-0.145	0.086
Model 3§	-0.134	0.116	-0.153	0.060	-0.148	0.085
T3						
Model 1†	-0.278	0.001	-0.307	<0.001	-0.457	<0.001
Model 2‡	-0.268	0.002	-0.287	0.001	-0.461	<0.001
Model 3§	-0.244	0.006	-0.301	0.001	-0.477	<0.001

†Model I: not adjusted
‡Model 2: adjusted for age, sex, duration of diabetes
§Model 3: adjusted for adjusted for age, sex, duration of diabetes, HbA1c, BMI, HOMA-IR, TG, ALT, 25(OH)D
†p<0.05 compared with Gp1; ‡p<0.05 compared with Gp2; §p<0.05 compared with Gm1; ¶p<0.05 compared with Gm2; ††p<0.05 compared with Gm3.

Table 4. Correlation between tertiles of UHR levels and OP

UHR	β	SE	Wald	*p*	OR	95% CI
T1 (ref.)	0				Ref	
T2						
Model 1†	0.436	0.473	0.851	0.356	1.547	0.612-3.909
Model 2‡	0.543	0.493	1.213	0.271	1.721	0.655-4.524
Model 3§	0.604	0.504	1.436	0.231	1.829	0.681-4.910
T3						
Model 1†	1.069	0.434	6.057	0.014	2.912	1.243-6.820
Model 2‡	1.140	0.499	5.208	0.022	3.126	1.175-8.319
Model 3§	1.206	0.554	4.748	0.029	3.341	1.129-9.887

†Model I: not adjusted
‡Model 2: adjusted for age, sex, duration of diabetes
§Model 3: adjusted for adjusted for age, sex, duration of diabetes, HbA1c, BMI, HOMA-IR, TG, ALT, 25(OH)D

Table 5. Binary logistic regression analysis of influencing factors of OP

Variables	β	SE	Wald	*p*	OR	95% CI
Age	0.046	0.019	6.262	0.012	1.048	1.010-1.086
BMI	-0.025	0.052	0.225	0.635	0.976	0.881-1.085
HbA1c	0.091	0.070	1.667	0.197	1.095	0.954-1.257
HOMA-IR	0.346	0.129	7.218	0.007	1.414	1.098-1.820
UHR	0.038	0.006	17.625	0.001	1.077	1.023-1.255
ALT	0.005	0.007	0.498	0.480	1.005	0.991-1.019
25(OH)D	-0.069	0.032	4.635	0.032	0.934	0.877-0.994

Table 6. Multivariate regression model of factors influencing OP stratified by BMI

BMI (kg/m^2)	UHR	β	SE	Wald	*p*	OR	95% CI
<24	Model 1†	0.006	0.004	2.302	0.129	1.005	0.998-1.013
	Model 2‡	0.006	0.004	1.687	0.194	1.006	0.997-1.014
	Model 3§	0.006	0.005	1.073	0.300	1.006	0.995-1.017
≥24	Model 1†	0.006	0.003	4.676	0.031	1.006	1.001-1.012
	Model 2‡	0.008	0.003	5.509	0.019	1.008	1.001-1.014
	Model 3§	0.008	0.004	4.368	0.037	1.008	0.998-1.015

†Model I: not adjusted
‡Model 2: adjusted for age, sex, duration of diabetes
§Model 3: adjusted for adjusted for age, sex, duration of diabetes, HbA1c, BMI, HOMA-IR, TG, ALT, 25(OH)D

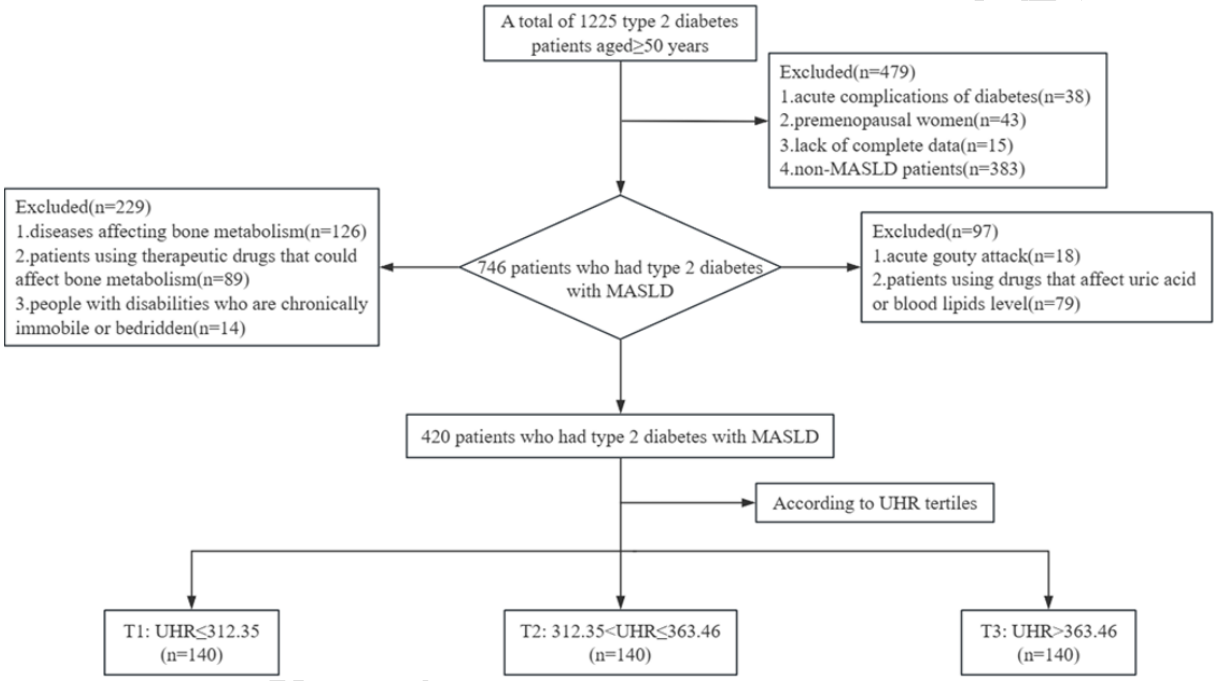

Figure 1. Flowchart of study participant selection

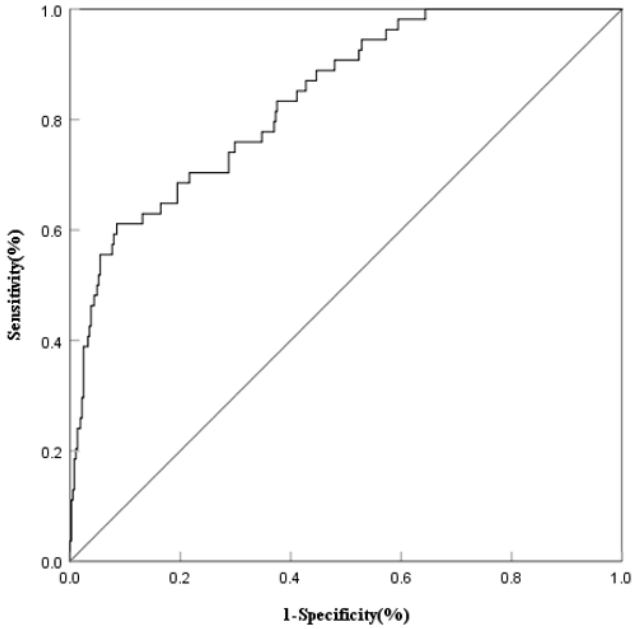

Figure 2. The predictive value of UHR combined with other indicators for OP in T2DM with MASLD