Diabetes, Metabolic Syndrome and Obesity

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Nonlinear Association Between Serum Uric Acid and Femoral Neck Bone Mineral Density in Male Patients with Metabolic Dysfunction-Associated Fatty Liver Disease

Juan Tan[1,*], Lin Wang[1,*], Hong Li[2], Honggang Wang[3], Xiaozhong Yang[3]

[1]Department of General Practice, The Affiliated Huai 'an No. 1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu, People's Republic of China; [2]Department of Health Management Center, The Affiliated Huai 'an No. 1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu, People's Republic of China; [3]Department of Gastroenterology, The Affiliated Huai 'an No. 1 People's Hospital of Nanjing Medical University, Huai'an, Jiangsu, People's Republic of China

*These authors contributed equally to this work

Correspondence: Honggang Wang; Xiaozhong Yang, Email hayy_wanghg@163.com; hayy_yxzh@163.com

Purpose: To investigate the relationship between serum uric acid (SUA) levels and femoral neck bone mineral density (BMD) in patients with metabolic dysfunction-associated fatty liver disease (MAFLD).

Patients and Methods: This cross-sectional study included 597 adult inpatients with type 2 diabetes mellitus and ultrasonography-confirmed fatty liver disease. Participants were stratified into tertiles based on femoral neck BMD. Gender-stratified linear regression analyses were performed to assess the relationship between SUA and femoral neck BMD. Nonlinear associations were explored using generalized additive models and two-piece linear regression.

Results: No significant linear association was observed between SUA and femoral neck BMD in either gender (all $P > 0.05$). However, after adjusting for confounders, a nonlinear relationship was identified in male patients, with a threshold at 388 μmol/L. The effect sizes for SUA levels below and above this threshold were 0.001 (95% *CI*: 0.000 to 0.002, $P = 0.008$) and −0.000 (95% *CI*: −0.002 to 0.000, $P = 0.117$), respectively. No nonlinear relationship was observed in female patients.

Conclusion: In male MAFLD patients, SUA levels exhibit a nonlinear relationship with femoral neck BMD, with a positive association observed between 300 μmol/L and 388 μmol/L. This relationship was not observed in female patients, suggesting gender-specific effects of SUA on bone health in MAFLD.

Keywords: metabolic dysfunction-associated fatty liver disease, type 2 diabetes, serum uric acid, bone mineral density

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a prevalent metabolic liver disorder, with a global prevalence of approximately 25%, largely attributed to the increasing incidence of type 2 diabetes mellitus (T2DM) and obesity.[1] In 2020, an international expert panel proposed renaming NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD) to better reflect its underlying pathogenesis. Subsequently, in 2023, a joint statement led by the American Association for the Study of Liver Diseases recommended further renaming it to metabolic dysfunction-associated steatotic liver disease (MASLD).[2,3] These terminology changes underscore the metabolic aspects of NAFLD and demonstrate the evolving understanding of its pathophysiology.

Serum uric acid (SUA) is the end product of purine metabolism in humans, and hyperuricemia is one of the most common metabolic disturbances. In recent years, researchers have increasingly focused on the close relationship between MAFLD and SUA, and multiple studies have shown that SUA is an independent risk factor for MAFLD.[4–6] A recent Mendelian randomization study demonstrated a causal effect of MAFLD on increased SUA levels. However, it failed to

Received: 7 September 2024
Accepted: 28 December 2024
Published: 17 January 2025

establish a causal link between elevated uric acid and MAFLD risk, highlighting the complex bidirectional relationship between these two conditions.[7] Consequently, managing SUA levels may be a crucial aspect of MAFLD treatment.

Osteoporosis (OP) is a common metabolic bone disease characterized by reduced bone mineral density (BMD) and bone mass, along with deterioration of bone microarchitecture, leading to increased bone fragility and fracture risk.[8] The pathogenesis of OP is multifactorial, encompassing sex hormone deficiency, pro-inflammatory states, vitamin D deficiency, cellular senescence, intestinal flora disorders, and reduced mechanical stimulation.[9–13] Increasing evidence indicates that oxidative stress may also contribute to age-related bone loss by enhancing osteoclast-mediated bone resorption.[14,15] The relationship between SUA levels and bone metabolism has emerged as a subject of intense scientific inquiry, though current evidence presents a complex and sometimes contradictory picture.[16–20] While numerous studies suggest a potential bone-protective effect of physiological SUA levels, the underlying mechanisms and population-specific variations remain subjects of ongoing investigation. A comprehensive analysis of 2981 participants from the Qatar Biobank demonstrated significant positive correlations between SUA levels and BMD across multiple skeletal sites, with these associations persisting after adjustment for conventional confounders including age, gender, and body mass index.[21] These findings were further substantiated by a Korean study of 2,991 men aged ≥50 years, which revealed independent associations between elevated SUA levels and increased BMD, particularly at the femoral neck and lumbar spine.[22] However, the relationship between SUA and bone health appears to be modulated by specific clinical contexts and comorbidities. In a cross-sectional study of obese subjects, researchers observed an inverse correlation between lumbar spine BMD and hyperuricemia, though this association was gender-specific, being present only in males. Notably, no significant correlation was found between hip BMD and hyperuricemia in this population.[20] Furthermore, investigations into volumetric BMD (vBMD) and bone microarchitecture revealed that while isolated hyperuricemia was associated with higher cortical bone density and thickness, the presence of comorbid psoriasis reversed this relationship, resulting in lower mean and trabecular bone density.[18] These discrepancies in findings may be attributed to heterogeneity across study populations, including variations in genetic background, age distribution, sex ratio, obesity status, comorbid conditions, and medication history. Additionally, differences in the confounding factors adjusted for in these studies may contribute to the inconsistent results. Given these complexities, future research should focus on elucidating the mechanisms underlying the SUA-BMD relationship in specific population subgroups, while accounting for relevant comorbidities and confounding factors. Such investigations may help reconcile current discrepancies and inform more targeted therapeutic approaches for bone health management.

MAFLD has emerged as a significant public health concern. Recent evidence suggests a potential link between MAFLD and bone health. A five-year prospective cohort study of 1,064 Chinese adults with initially normal BMD found that ultrasonography-diagnosed NAFLD was associated with a 2.3-fold increased risk of developing low BMD.[23] This finding was further corroborated by a cross-sectional investigation conducted in Upper Egypt, which demonstrated that NAFLD patients exhibited significantly decreased BMD values and an increased predisposition to osteoporosis.[24] Notably, a Mendelian randomization analysis using genome-wide association studies data demonstrated a causal relationship between MAFLD and reduced femoral neck BMD.[25] However, studies exploring the association between SUA levels and BMD in MAFLD patients are scarce.

This study aims to investigate the correlation between SUA levels and BMD in MAFLD populations, with the ultimate goal of reducing the risk of osteoporosis and osteoporotic fractures in MAFLD patients through appropriate management of SUA levels.

Methods

Study Participants

This study included patients with T2DM hospitalized at the Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University between September 2019 and September 2021. Inclusion criteria were: (1) fatty liver diagnosis by abdominal ultrasonography; (2) age 20–85 years; and (3) complete dual-energy X-ray absorptiometry (DXA) bone density results. Exclusion criteria encompassed: (1) excessive alcohol consumption (>210g/week for men, >140g/week for women in the past 12 months); (2) viral hepatitis, autoimmune hepatitis, drug-induced liver injury, or malignancy; (3) use of bone metabolism-affecting medications (eg, glucocorticoids, bisphosphonates, sex hormones, calcitonin); (4) secondary osteoporosis (eg, hyperparathyroidism, rheumatic diseases, hyperthyroidism); (5) gout or use of uric acid-lowering drugs within 6 months prior to

admission; (6) renal insufficiency (eGFR <60mL/min/1.73m2); and (7) underweight (BMI <18kg/m2). This cross-sectional study was approved by the Ethics Committee of Huai'an First People's Hospital, Affiliated to Nanjing Medical University. The requirement for informed consent was waived by the Ethics Committee due to the retrospective nature of the study, which involved only data analysis without any identifiable personal information. Data were collected retrospectively through the hospital's electronic medical record system. This research was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and its subsequent amendments.

A total of 1,524 T2DM patients were initially identified. After applying inclusion and exclusion criteria, 927 patients were excluded: 212 due to incomplete data, 109 for excessive alcohol consumption, 73 with viral hepatitis, 27 with drug-induced liver injury, 78 with secondary osteoporosis, 31 with underweight, 93 who had used bone metabolism-affecting medications, 153 diagnosed with gout or taking uric acid-lowering drugs, and 151 with renal insufficiency. Consequently, 597 T2DM patients were included in the final analysis (as depicted in Figure 1). This study was approved by the Ethics Committee of the Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University (approval number: KY-2024-186-01).

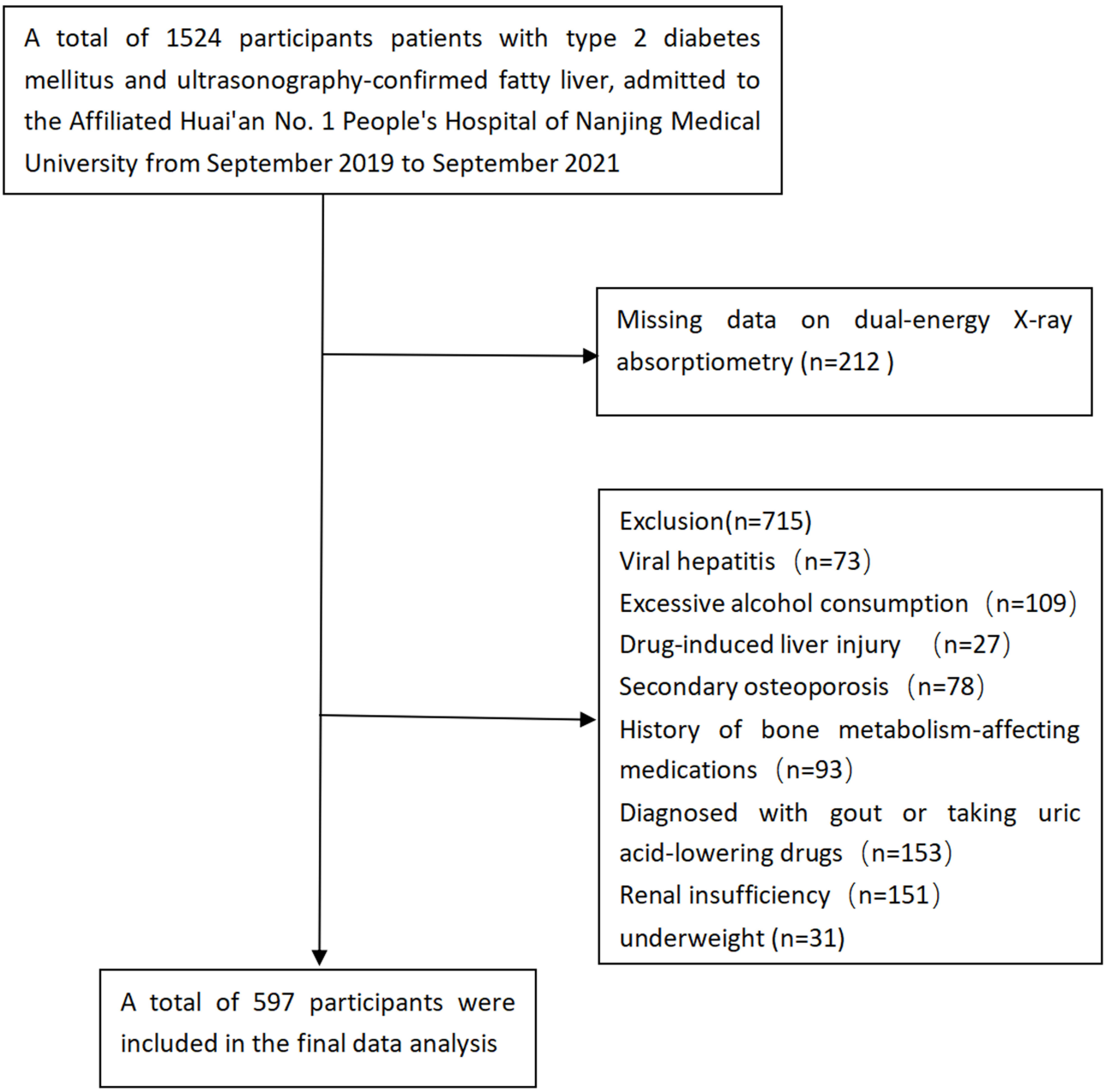

Figure 1 Participant selection and study flow diagram.

https://doi.org/10.2147/DMSO.S492060

Demographic Characteristics, Laboratory Parameters, and Bone Mineral Density

Demographic and Clinical Data: Age, sex, height, weight, diabetes duration, blood pressure, and medication history were recorded for all participants. Body Mass Index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Laboratory Measurements: Fasting blood samples were collected to assess fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), serum uric acid (UA), serum creatinine (scr), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula. Insulin resistance was evaluated using the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR).

Bone Mineral Density Assessment: Femoral neck BMD was measured using dual-energy X-ray absorptiometry (DXA) with a Hologic densitometer (Hologic Inc., USA).

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation, while non-normally distributed variables were presented as median (interquartile range). Categorical variables were reported as frequencies (percentages). Differences among femoral neck BMD tertiles were compared using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis *H*-test for non-normally distributed continuous variables, and chi-square test for categorical variables. The relationship between SUA and femoral neck BMD was initially assessed using univariate linear regression. Sensitivity analysis was performed by treating SUA as a categorical variable. A generalized additive model was employed to evaluate potential non-linear relationships. If non-linearity was detected, a two-piecewise linear regression model was used to analyze the threshold effect of SUA on BMD. The inflection point was determined by recursive algorithm, maximizing the likelihood value. Likelihood ratio tests were used to compare the one-line linear regression model with the two-piecewise linear regression model. All statistical analyses were performed using R software version 3.4.3 (http://www.R-project.org) and EmpowerStats (http://www.empowerstats.net/en/). A two-sided P-value < 0.05 was considered statistically significant.

Results

Clinical Characteristics by Femoral Neck BMD Tertiles in MAFLD Patients

The study included 597 patients with MAFLD (mean age: 57.74 ± 11.07 years; 45.39% female). The mean SUA level was 297.29 ± 81.63 μmol/L, and the average femoral neck BMD was 0.767 ± 0.149 g/cm². Patients were stratified into tertiles based on femoral neck BMD. Significant differences were observed across the tertiles in age, sex, body mass index, HbA1c, triglycerides, HDL-C, SUA, HOMA-IR, and prevalence of hypertension (all P<0.05). However, diabetes duration, total cholesterol, LDL-C, and eGFR did not differ significantly among the groups (all P>0.05) (Table 1).

Association Between Femoral Neck BMD and Risk Factors in Patients with MAFLD

Univariate analysis (Table 2) revealed significant negative associations between femoral neck BMD and age, female sex, diabetes duration, and HDL-C levels (all P<0.001). Conversely, BMI, serum uric acid, and eGFR showed significant positive correlations with femoral neck BMD (all P<0.001). No significant associations were observed between femoral neck BMD and HbA1c, total cholesterol, triglycerides, LDL-C, HOMA-IR, or presence of hypertension (all P>0.05).

Association Between SUA Levels and Femoral Neck BMD in Patients with MAFLD

We employed univariate linear regression models to analyze the relationship between serum uric acid levels and femoral neck BMD. Table 3 presents both unadjusted and adjusted models. In the overall study population, the unadjusted model revealed a significant association between serum uric acid levels and femoral neck BMD (β=0.003, 95% CI: 0.002–0.005, P<0.001). This association remained statistically significant after adjusting for age, BMI, and eGFR (β=0.002, 95% CI: 0.000–0.003, P=0.010). However, stratification by sex revealed no statistically significant associations between serum UA levels and femoral neck BMD in either males or females, in both unadjusted and adjusted models (all P>0.05).

Table 1 Clinical Characteristics of MAFLD Patients Stratified by Femoral Neck BMD Tertiles

Characteristic	Low BMD (n=196)	Medium BMD (n=195)	High BMD (n=196)	*P*-value
Age (years)	60.38 ±10.29	56.79±11.19	56.12±11.42	<0.001
Male, n (%)	32.14%	57.44%	73.98%	<0.001
BMI (kg/m²)	25.82±3.36	26.93±3.47	27.23±3.23	<0.001
Diabetes duration (years)*	7.00 (1.75–11.25)	6.00 (2.00–10.00)	5.00 (2.00–10.00)	0.403
HbA1c (%)	9.35±1.92	8.90± 1.97	8.62±1.89	0.001
Total cholesterol (mmol/L)	4.26±1.11	4.33±1.07	4.44±1.21	0.300
Triglycerides (mmol/L)*	1.52 (1.15–2.28)	1.78 (1.27–2.61)	2.18 (1.49–3.25)	<0.001
LDL-C (mmol/L))	2.57±0.94	2.67±0.92	2.60±0.93	0.549
HDL-C (mmol/L)	1.11±0.29	1.07±0.24	1.02±0.28	0.006
Uric acid (μmol/L)	212.36±36.41	292.78 ±19.65	386.72±54.82	<0.001
HOMA-IR*	2.97 (2.04–5.30)	3.93 (2.39–5.63)	4.03 (2.62–7.02)	0.019
Hypertension, n (%)	52.55%	57.95%	65.82%	0.027
eGFR (mL/min/1.73m²)	100.66±12.80	102.06±24.0	97.61±21.56	0.081

Note: Data are presented as mean ± SD, n (%), or median (interquartile range). *Variables with skewed distribution are presented as median (interquartile range).

Abbreviations: BMD, Bone Mineral Density; BMI, Body Mass Index; HbA1c, Glycated Hemoglobin; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; eGFR, estimated Glomerular Filtration Rate.

Table 2 Univariate Analysis of Risk Factors Associated with Femoral Neck Bone Mineral Density in Patients with Metabolic Dysfunction-Associated Fatty Liver

Variable	Overall (N=597)	Effect Size (*β*)	95% *CI*	*P*-value
Age (years)	57.74 ± 11.07	−0.006	−0.007~ −0.005	<0.001
Sex, n (%)				
Male	326 (54.61%)		Ref	
Female	271 (45.39%)	−0.122	−0.14 ~ −0.100	<0.001
BMI (kg/m²)	26.63 ± 3.41	0.010	0.007 ~ 0.014	<0.001
Diabetes duration (years)*	6.000 (2.000–10.000)	−0.004	−0.006 ~ −0.002	<0.001
HbA1c (%)	8.99 ± 1.99	0.001	−0.005 ~ 0.008	0.650
Total cholesterol (mmol/L)	4.34 ± 1.13	0.002	−0.008 ~ 0.013	0.700
Triglycerides (mmol/L)*	1.79 (1.29–2.69)	0.005	−0.001 ~ 0.011	0.104
LDL-C (mmol/L)	2.61 ± 0.94	0.001	−0.012 ~ 0.015	0.825
HDL-C (mmol/L)	1.07 ± 0.27	−0.086	−0.130 ~ −0.041	<0.001
Uric acid (μmol/L)	297.29 ± 81.63	0.000	0.000 ~ 0.000	<0.001
HOMA-IR*	3.70 (2.30–6.13)	−0.001	−0.002 ~ 0.001	0.597
Hypertension, n (%)				
No	247 (41.37%)		Ref	
Yes	350 (58.63%)	−0.019	−0.043 ~ 0.006	0.131
eGFR (mL/min/1.73m²)	100.10 ± 20.09	0.002	0.001 ~ 0.003	<0.001

Note: Data are presented as mean ± SD, n (%), or median (interquartile range). *Variables with skewed distribution are presented as median (interquartile range).

Abbreviations: BMI, Body Mass Index; HbA1c, Glycated Hemoglobin; LDL-C, Low-Density Lipoprotein Cholesterol; HDL-C, High-Density Lipoprotein Cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; eGFR, estimated Glomerular Filtration Rate; CI, Confidence Interval; Ref: Reference category.

To assess the robustness of our findings, we conducted a sensitivity analysis treating serum uric acid levels as a categorical variable (≤420 μmol/L vs >420 μmol/L). This analysis showed no statistically significant associations between categorized uric acid levels and femoral neck BMD in the overall population, or in sex-stratified subgroups, for both unadjusted and adjusted models (all $P>0.05$).

Table 3 Regression Analysis of Serum Uric Acid Levels and Femoral Neck Bone Mineral Density in Patients with Metabolic Dysfunction-Associated Fatty Liver Disease

Group	Unadjusted *β* (95% *CI*)	*P*-value	Adjusted *β* (95% *CI*)†	*P*-value
Overall				
Uric acid per 10 μmol/L	0.003 (0.002, 0.005)	<0.001	0.002 (0.000, 0.003)	0.010
Uric acid, μmol/L		0.562		0.486
≤420umol/L	Ref		Ref	
>420umol/L	0.014 (−0.033, 0.061)		0.015 (−0.027, 0.056)	
Females				
Uric acid per 10 μmol/L	0.000 (−0.002, 0.002)	0.761	−0.000 (−0.002, 0.002)	0.948
Uric acid, μmol/L		0.104		0.518
≤420umol/L	Ref		Ref	
>420umol/L	−0.068 (−0.150, 0.014)		−0.022 (−0.088, 0.044)	
Males				
Uric acid per 10 μmol/L	0.002 (−0.000, 0.004)	0.138	0.001 (−0.001, 0.003)	0.432
Uric acid, μmol/L		0.694		0.600
≤420umol/L	Ref		Ref	
>420umol/L	0.010 (−0.040, 0.060)		0.013 (−0.035, 0.061)	

Note: † Adjusted for age, BMI, and eGFR.
Abbreviations: CI, Confidence Interval; Ref, Reference category; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate.

Nonlinear Association Between Serum UA Levels and Femoral Neck BMD in Patients with MAFLD

Figure 2 illustrates the nonlinear relationship between serum uric acid levels and femoral neck BMD after adjusting for age, BMI, and eGFR. Using a two-segment linear regression model, we identified a threshold at 421 μmol/L. To the left

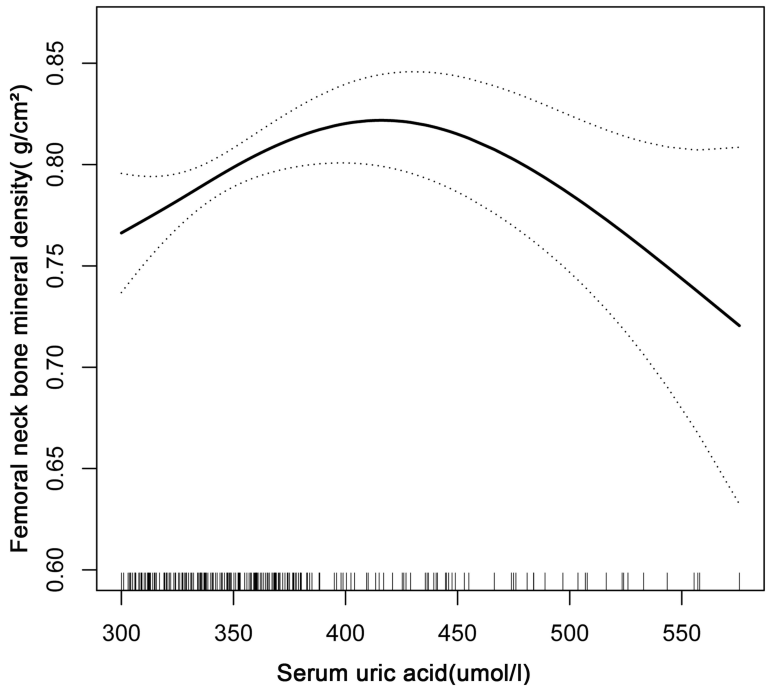

Figure 2 Nonlinear Association between serum uric acid levels and femoral neck bone mineral density in patients with metabolic dysfunction-associated fatty liver. This graph illustrates a nonlinear relationship between serum uric acid (SUA) levels and femoral neck bone mineral density (BMD) in patients with metabolic dysfunction-associated fatty liver disease. The x-axis represents serum uric acid levels (SUA) ranging from approximately 300 to 550 (μmol/L), while the y-axis shows the femoral neck BMD ranging from about 0.60 to 0.85 (g/cm²).

of this threshold, serum uric acid levels showed a positive association with femoral neck BMD (β = 0.001, 95% *CI*: 0.000 to 0.001, *P* = 0.003). Conversely, to the right of the threshold, we observed a negative association between serum uric acid levels and femoral neck BMD (β = −0.001, 95% *CI*: −0.002 to −0.000, *P* = 0.004) (Table 3).

We conducted a stratified analysis by gender to further explore potential differences in the nonlinear relationship between serum uric acid levels and femoral neck BMD. As illustrated in Figure 3, male patients exhibited a nonlinear relationship between serum uric acid levels and femoral neck BMD. In contrast, for female patients, a likelihood ratio test comparing linear and segmented regression models yielded a *P*-value > 0.05, suggesting the absence of a nonlinear relationship.

Further analysis of the male subgroup using a two-segment linear regression model revealed a trend consistent with the overall population. We identified a threshold at 388 μmol/L. To the left of this threshold, serum uric acid levels showed a positive association with femoral neck BMD (β = 0.001, 95% *CI*: 0.000 to 0.002, *P* = 0.008). To the right of the threshold, although a negative trend was observed between serum uric acid levels and femoral neck BMD, it did not reach statistical significance (β = −0.000, 95% *CI*: −0.002 to 0.000, *P* = 0.117) (Table 4).

Discussion

This study investigated the relationship between SUA levels and femoral neck BMD in 597 hospitalized patients with MAFLD. In male MAFLD patients, an inverted U-shaped association was observed between SUA levels and femoral neck BMD. The inflection point of SUA was identified at 388 μmol/L. SUA levels between 300–388 μmol/L were positively associated with femoral neck BMD, suggesting a potential protective effect. Conversely, SUA levels ≥388 μmol/L showed a trend towards adverse effects on femoral neck BMD, although this association did not reach statistical significance. In female MAFLD patients, no statistically significant non-linear relationship was observed between SUA levels and femoral neck BMD.

Although studies have explored the association between SUA and BMD, their relationship remains debated. A cross-sectional study of 6,704 healthy American adult males found no correlation between SUA levels and lumbar spine

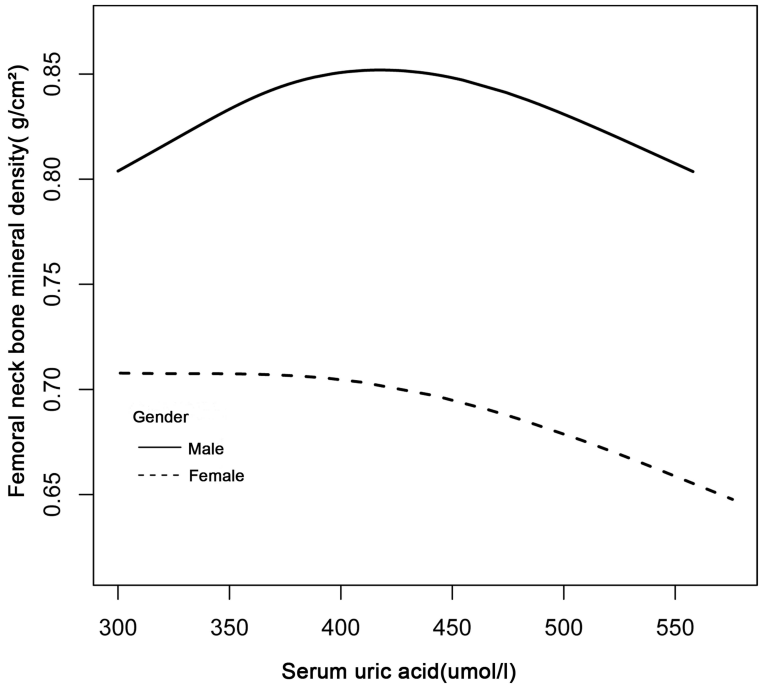

Figure 3 Nonlinear association between serum uric acid levels and femoral neck bone mineral density in patients with metabolic dysfunction-associated fatty liver stratified by gender. This graph illustrates the nonlinear relationship between serum uric acid (UA) levels and femoral neck bone mineral density (BMD) in patients with metabolic dysfunction-associated fatty liver disease, separated by gender. The x-axis represents serum uric acid levels (UA) ranging from 300 to 550 μmol/L, while the y-axis shows the femoral neck BMD ranging from about 0.65 to 0.85 g/cm².

https://doi.org/10.2147/DMSO.S492060

Table 4 Threshold Effect of Serum UA on Femoral Neck Bone Mineral Density In Patients with Metabolic Dysfunction-Associated Fatty Liver Disease

Group	Effect Size (*β*)	95% *CI*	*P*-value
Overall			
Uric acid threshold (μmol/L)			
< 421	0.001	0.000 ~ 0.001	0.003
≥ 421	−0.001	−0.002 ~ −0.000	0.004
Females			
Uric acid threshold (μmol/L)			
< 306	−0.036	−0.073 ~0.001	0.063
≥306	−0.000	−0.001 ~ 0.000	0.578
Males			
Uric acid threshold (μmol/L)			
< 388	0.001	0.000 ~ 0.002	0.008
≥388	−0.000	−0.001~ 0.000	0.117

Note: Adjusted for age, BMI, and eGFR.
Abbreviations: CI, Confidence Interval; BMI, Body Mass Index; eGFR, estimated Glomerular Filtration Rate.

BMD.[16] This study differed from ours in its focus on healthy individuals, examination of lumbar spine BMD, and lack of consideration for BMI effects on BMD.A retrospective cohort study of 1,423 healthy Mexican individuals revealed a negative correlation between SUA levels and total hip, femoral neck, and lumbar spine BMD in women, with no such association in men.[26] Unlike our study, this research focused on healthy individuals and used linear regression analysis without exploring non-linear relationships in males. Furthermore, a study based on the National Health and Nutrition Examination Survey demonstrated an inverted U-shaped relationship between SUA levels and femoral neck BMD in hypertensive males, but not in females.[27] While these findings align with our results, the study utilized publicly available data without considering medications affecting BMD, chronic kidney disease status, or BMI. Additionally, it did not perform threshold effect analysis to determine the inflection point of the non-linear relationship.

Our study extended the investigation to MAFLD patients, with careful consideration of potential confounding factors including chronic kidney disease, low body weight, and medications affecting BMD. We observed a non-linear relationship between SUA levels and femoral neck BMD in male MAFLD patients. Specifically, femoral neck BMD increased with rising SUA levels within the physiological range of 300–388 μmol/L. This positive correlation may be attributed to uric acid's antioxidant properties at physiological levels, potentially protecting bone metabolism by scavenging free radicals.[28] Furthermore, previous studies in male T2DM patients have demonstrated significant negative correlations between SUA and bone turnover markers, including osteocalcin, procollagen type I N-terminal propeptide, and C-terminal telopeptide of type I collagen, suggesting SUA's potential role in modulating bone turnover and reducing bone loss in this population.[29] Notably, recent evidence has revealed that elevated SUA levels correlate positively with preserved muscle mass and enhanced grip strength, potentially offering a protective mechanism against sarcopenia progression.[30] This observation gains particular significance in the context of MAFLD, given the established genetic and pathophysiological links between MAFLD and sarcopenia, with sarcopenia prevalence showing a linear increase corresponding to liver fibrosis severity.[31] While sarcopenia is conventionally defined as an age-related decline in skeletal muscle mass and function, its multifaceted etiology and heterogeneous clinical manifestations have posed significant challenges in establishing standardized diagnostic criteria.[32] We hypothesize that sarcopenia may function as a critical mediating factor in the SUA-BMD relationship, particularly in MAFLD populations. However, elucidating the precise molecular mechanisms underlying these complex interactions and their clinical implications for skeletal health necessitates robust longitudinal investigations with standardized methodological approaches.

Our study revealed a negative correlation between SUA levels and femoral neck BMD in male MAFLD patients when SUA levels exceeded 388 μmol/L. Several potential mechanisms may explain this observation. Hyperuricemia has

been associated with lower testosterone levels,[33] potentially increasing the risk of osteoporosis due to testosterone deficiency.[34] Additionally, elevated SUA levels may induce inflammatory factor accumulation, leading to increased oxidative stress. This can inhibit osteoblast-mediated bone formation and promote osteoclast-mediated bone resorption, thereby increasing fracture risk.[35] Furthermore, uric acid may suppress the expression of 1-α-hydroxylase in proximal tubules, resulting in secondary hyperparathyroidism. This can exacerbate bone loss, impede bone remodeling, and increase fracture risk.[28]

In female MAFLD patients, we observed a negative trend between SUA levels and femoral neck BMD. This association may be related to estrogen's role in bone metabolism regulation. Estrogen is a key regulator of bone metabolism, and its deficiency can lead to decreased BMD in postmenopausal women. We noted lower SUA levels in females compared to males, possibly due to estrogen's promotion of uric acid clearance in the kidneys.[36] Therefore, we hypothesize that low estrogen levels may contribute to the negative correlation between SUA levels and femoral neck BMD in females. However, direct evidence linking estrogen to both SUA levels and BMD is currently lacking, warranting further investigation. Future studies should aim to elucidate the precise mechanisms underlying the sex-specific differences in the relationship between SUA levels and BMD in MAFLD patients.

To our knowledge, this is the first study to investigate the relationship between SUA levels and BMD in patients with MAFLD. Our findings suggest that moderate reduction of SUA levels may have a protective effect on femoral neck BMD in male MAFLD patients, providing new insights for clinical management of this population. However, several limitations of this study should be acknowledged.

First, the cross-sectional design precludes the establishment of causal relationships between SUA and BMD, necessitating further longitudinal studies for validation. Second, while our strict inclusion/exclusion criteria enhanced internal validity by controlling for confounders (excluding conditions affecting uric acid metabolism and bone density), they limit the generalizability of our findings to the broader MAFLD population. Our results primarily apply to previously untreated primary MAFLD patients without significant comorbidities. Third, we were unable to collect data on potentially important metabolic parameters, such as vitamin D levels and sex hormones, which should be addressed in future research. Fourth, we did not assess sarcopenia parameters, which might mediate the SUA-BMD relationship in MAFLD patients. Future studies should include comprehensive evaluation of muscle mass and function. Finally, as a single-center study in adult MAFLD patients, our findings may not be representative of different geographical regions and age groups. Multi-center studies with diverse populations are needed to validate these results. These limitations underscore the need for large-scale prospective studies incorporating comprehensive metabolic parameters to confirm our findings and explore underlying mechanisms.

Conclusion

In conclusion, our study demonstrates a non-linear relationship between SUA levels and femoral neck BMD in MAFLD patients, with this association observed only in males. These findings underscore the need for further research to elucidate the causal relationships and underlying mechanisms, which could significantly impact the clinical management of MAFLD patients. Future studies should aim to address the limitations of the current research and explore potential sex-specific interventions for optimizing bone health in this patient population.

Acknowledgments

The authors would like to express their sincere gratitude to all colleagues who contributed to this study. Special thanks are extended to the staff of the Medical Records Department and the Health Management Center for their invaluable assistance in data collection and management.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by two research grants: (1) the Jiangsu Province Geriatric Health Research Project (Grant No. LKM2022069), and (2) the Research and Innovation Team Project of The Affiliated Huai'an No. 1 People's Hospital of Nanjing Medical University (Contract No. YCT202305). Additionally, this work received support from the Jiangsu Province Cadre Health Research Project (Contract No. BJ24045).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Stefan N, Cusi K. A global view of the interplay between non-alcoholic fatty liver disease and diabetes. *Lancet Diabetes Endocrinol*. 2022;10(4):284–296. doi:10.1016/S2213-8587(22)00003-1
2. Eslam M, Sanyal AJ, George J. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. *Gastroenterology*. 2020;158(7):1999–2014.e1991. doi:10.1053/j.gastro.2019.11.312
3. Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. *J Hepatol*. 2023;79(6):1542–1556. doi:10.1016/j.jhep.2023.06.003
4. Di Bonito P, Valerio G, Licenziati MR, et al. Uric acid versus metabolic syndrome as markers of fatty liver disease in young people with overweight/obesity. *Diabetes/Metab Res Rev*. 2022;38(7):e3559. doi:10.1002/dmrr.3559
5. Lee JM, Kim HW, Heo SY, et al. Associations of serum uric acid level with liver enzymes, nonalcoholic fatty liver disease, and liver fibrosis in Korean men and women: a cross-sectional study using nationally representative data. *J Korean Med Sci*. 2023;38(34):e267. doi:10.3346/jkms.2023.38.e267
6. He J, Ye J, Sun Y, Feng S, Chen Y, Zhong B. The additive values of the classification of higher serum uric acid levels as a diagnostic criteria for metabolic-associated fatty liver disease. *Nutrients*. 2022;14(17):3587. doi:10.3390/nu14173587
7. Li S, Fu Y, Liu Y, et al. Serum uric acid levels and nonalcoholic fatty liver disease: a 2-sample bidirectional Mendelian randomization study. *J Clin Endocrinol Metab*. 2022;107(8):e3497–e3503. doi:10.1210/clinem/dgac190
8. Reid IR, Billington EO. Drug therapy for osteoporosis in older adults. *Lancet*. 2022;399(10329):1080–1092. doi:10.1016/S0140-6736(21)02646-5
9. Curtis EM, Moon RJ, Dennison EM, Harvey NC, Cooper C. Recent advances in the pathogenesis and treatment of osteoporosis. *Clin Med*. 2015;15(Suppl 6):s92–96. doi:10.7861/clinmedicine.15-6-s92
10. Khosla S, Monroe DG. Regulation of bone metabolism by sex steroids. *Cold Spring Harbor Perspect Med*. 2018;8(1):a031211. doi:10.1101/cshperspect.a031211
11. Locantore P, Del Gatto V, Gelli S, Paragliola RM, Pontecorvi A. The interplay between immune system and microbiota in osteoporosis. *Mediators Inflammation*. 2020;2020:3686749. doi:10.1155/2020/3686749
12. Li CJ, Xiao Y, Sun YC, et al. Senescent immune cells release grancalcin to promote skeletal aging. *Cell Metab*. 2021;33(10):1957–1973.e1956. doi:10.1016/j.cmet.2021.08.009
13. Farr JN, Khosla S. Cellular senescence in bone. *Bone*. 2019;121:121–133. doi:10.1016/j.bone.2019.01.015
14. Kimball JS, Johnson JP, Carlson DA. Oxidative stress and osteoporosis. *J Bone Joint Surg Am Vol*. 2021;103(15):1451–1461. doi:10.2106/JBJS.20.00989
15. Lu J, Zhang Y, Liang J, Diao J, Liu P, Zhao H. Role of exosomal microRNAs and their crosstalk with oxidative stress in the pathogenesis of osteoporosis. *Oxid Med Cell Longev*. 2021;2021:6301433. doi:10.1155/2021/6301433
16. Li X, Li L, Yang L, Yang J, Lu H. No association between serum uric acid and lumbar spine bone mineral density in US adult males: a cross sectional study. *Sci Rep*. 2021;11(1):15588. doi:10.1038/s41598-021-95207-z
17. Ma C, Yu R, Li J, et al. Association of serum uric acid levels with bone mineral density and the presence of osteoporosis in Chinese patients with Parkinson's disease: a cross-sectional study. *J Bone Min Metabolism*. 2023;41(5):714–726. doi:10.1007/s00774-023-01446-7
18. Simon D, Haschka J, Muschitz C, et al. Bone microstructure and volumetric bone mineral density in patients with hyperuricemia with and without psoriasis. *Osteoporos Int*. 2020;31(5):931–939. doi:10.1007/s00198-019-05160-x
19. Karimi F, Dabbaghmanesh MH, Omrani GR. Association between serum uric acid and bone health in adolescents. *Osteoporosis Int*. 2019;30(10):2057–2064. doi:10.1007/s00198-019-05072-w
20. Zhang Y, Tan M, Liu B, et al. Relationship between bone mineral density and hyperuricemia in obesity: a cross-sectional study. *Front Endocrinol*. 2023;14:1108475. doi:10.3389/fendo.2023.1108475
21. Ibrahim WN, Younes N, Shi Z, Abu-Madi MA. Serum uric acid level is positively associated with higher bone mineral density at multiple skeletal sites among healthy Qataris. *Front Endocrinol*. 2021;12:653685. doi:10.3389/fendo.2021.653685
22. Kim S, Lee S, Kwon H. Association between serum uric acid level and bone mineral density in men more than 50 years of age. *Front Endocrinol*. 2023;14:1259077. doi:10.3389/fendo.2023.1259077
23. Shen Z, Cen L, Chen X, et al. Increased risk of low bone mineral density in patients with non-alcoholic fatty liver disease: a cohort study. *Eur J Endocrinol*. 2020;182(2):157–164. doi:10.1530/EJE-19-0699
24. Hassan AM, Haridy MA, Shoaeir MZ, et al. Non-alcoholic fatty liver disease is associated with decreased bone mineral density in upper Egyptian patients. *Sci Rep*. 2023;13(1):4353. doi:10.1038/s41598-023-31256-w

25. Pei X, Jiang W, Li L, et al. Mendelian-randomization study revealed causal relationship between nonalcoholic fatty liver disease and osteoporosis/fractures. *J Gastroenterol Hepatol*. 2024;39(5):847–857. doi:10.1111/jgh.16448
26. Robles-Rivera K, Argoty-Pantoja AD, Hidalgo-Bravo A, et al. Uric acid levels are associated with bone mineral density in Mexican populations: a longitudinal study. *Nutrients*. 2022;14(20):4245. doi:10.3390/nu14204245
27. Su Y, Ding N, Zhou Y, Yang G, Chai X. The relationship between uric acid and total femur bone mineral density in hypertensive and non-hypertensive populations. *Front Endocrinol*. 2022;13:1022031. doi:10.3389/fendo.2022.1022031
28. Lin KM, Lu CL, Hung KC, et al. The paradoxical role of uric acid in osteoporosis. *Nutrients*. 2019;11(9):2111. doi:10.3390/nu11092111
29. Wu Y, Xiang S, Jiang X, Wang L, Wang K, Hua F. Relationship of bone status with serum uric acid and bilirubin in men with type 2 diabetes: a cross-sectional study. *Med Sci Monit*. 2021;27:e930410. doi:10.12659/MSM.930410
30. Liu X, Chen X, Hu F, et al. Higher uric acid serum levels are associated with sarcopenia in west China: a cross-sectional study. *BMC Geriatr*. 2022;22(1):121. doi:10.1186/s12877-022-02817-x
31. Yuan J, Zhang J, Luo Q, Peng L. Effects of nonalcoholic fatty liver disease on sarcopenia: evidence from genetic methods. *Sci Rep*. 2024;14(1):2709. doi:10.1038/s41598-024-53112-1
32. Coletta G, Phillips SM. An elusive consensus definition of sarcopenia impedes research and clinical treatment: a narrative review. *Ageing Res Rev*. 2023;86:101883. doi:10.1016/j.arr.2023.101883
33. Han Y, Zhang Y, Cao Y, et al. Exploration of the association between serum uric acid and testosterone in adult males: NHANES 2011–2016. *Transl Androlo Urol*. 2021;10(1):272–282. doi:10.21037/tau-20-1114
34. Golds G, Houdek D, Arnason T. Male hypogonadism and osteoporosis: the effects, clinical consequences, and treatment of testosterone deficiency in bone health. *Int J Endocrinol*. 2017;2017:4602129. doi:10.1155/2017/4602129
35. Xu R, Lian D, Xie Y, et al. Relationship between serum uric acid levels and osteoporosis. *Endocr Connections*. 2023;12(11). doi:10.1530/EC-23-0040
36. Halperin Kuhns VL, Woodward OM. Sex differences in urate handling. *Int J Mol Sci*. 2020;21(12):4269. doi:10.3390/ijms21124269