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ORIGINAL RESEARCH

Association Between Uric Acid to HDL-C Ratio and Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes Mellitus: A Cross-Sectional Study

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Background: Patients with type 2 diabetes mellitus (T2DM) exhibit an elevated risk of developing metabolic dysfunction-associated steatotic liver disease (MASLD). The uric acid to high-density lipoprotein cholesterol ratio (UHR) has emerged as a novel metabolic biomarker implicated in MASLD pathogenesis. This study aimed to evaluate the association between UHR and MASLD in a T2DM population.

Methods: In this cross-sectional study, we analyzed clinical data from 1081 T2DM patients (464 without MASLD, 617 with MASLD). Physiological and biochemical parameters were collected and analyzed. UHR was calculated as [uric acid (mg/dL)/HDL-C (mg/dL)] × 100%. Univariate and multivariate logistic regression analyses were performed to examine the association between UHR and MASLD.

Results: T2DM patients with MASLD had significantly higher UHR levels than those without MASLD (12.12[9.06–16.83] vs 10.36 [7.65–14.08], $p<0.001$). UHR showed a strong positive correlation with TG/HDL ($r=0.673$, $p < 0.001$), moderate correlations with TG ($r = 0.516$, $p < 0.001$) and TC/HDL ($r=0.548$, $p < 0.001$), weak but significant associations with BMI ($r = 0.330$), WHR ($r = 0.289$), HOMA-IR ($r = 0.121$), ALT ($r = 0.123$), and GGT ($r = 0.267$) (all $p < 0.05$). Multivariate logistic regression showed that elevated UHR levels were significantly associated with increased MASLD risk (adjusted OR = 1.057, 95% CI: 1.016–1.100, $p = 0.006$), after adjusting for age, diabetes duration, BMI, blood pressure, and biochemical confounders.

Conclusion: Elevated UHR is independently associated with MASLD in T2DM patients, suggesting its clinical relevance in MASLD screening among this high-risk population.

Keywords: type 2 diabetes mellitus, metabolic dysfunction-associated steatotic liver disease, uric acid to high-density lipoprotein ratio, metabolic syndrome

Background

Type 2 diabetes mellitus (T2DM) is a major global health challenge, affecting an estimated 1.31 billion individuals worldwide.[1,2] In addition to its characteristic glucose dysregulation, T2DM drives systemic metabolic disturbances, particularly in lipid metabolism, which contributes to multi-organ dysfunction.[1] Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD),[3–5] represents one of the most prevalent comorbidities, affecting 30% of adults globally,[6] with prevalence projected to rise to 55% by 2040.[7] Notably,

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epidemiological studies demonstrate a striking overlap between T2DM and MASLD, with 60–70% of T2DM patients exhibiting MASLD in clinical cohorts,[8,9] and biopsy-based studies reporting prevalence exceeding 90%.[10,11]

This bidirectional relationship arises from shared pathophysiological mechanisms, including insulin resistance, chronic inflammation, and dysregulated lipid metabolism.[12,13] The interplay exacerbates disease progression: MASLD increases the risk of T2DM onset by impairing hepatic insulin sensitivity, while T2DM accelerates the progression of MASLD to more severe stages, such as steatohepatitis and hepatocellular carcinoma.[14,15] Importantly, concomitant T2DM and MASLD synergistically increase the risk of hepatic fibrosis, cardiovascular events, and chronic kidney disease compared to either condition alone.[16–18] Despite clinical guidelines recommending routine MASLD screening in T2DM populations, current diagnostic tools, including conventional metabolic parameters (eg, triglycerides, BMI, liver enzymes),[19,20] non-invasive scoring systems (FLI, NLFS, FIB-4),[21,22] and imaging modalities (ultrasound, FibroScan) are limited by variable accuracy, high cost, and accessibility challenges.

Recent research has explored novel biomarkers to improve the early detection and risk stratification of MASLD. Among these, serum uric acid (UA) has gained attention due to its association with oxidative stress, inflammation, and metabolic dysregulation, all of which are implicated in MASLD pathogenesis.[23,24] Furthermore, the UA to high-density lipoprotein (HDL-C) ratio (UHR) has emerged as a potential inflammatory and metabolic marker. UHR has been linked to metabolic syndrome, insulin resistance, and cardiovascular risk, and preliminary studies suggest its utility in predicting MASLD.[25,26] However, despite these advances, the independent association between UHR and MASLD in T2DM patients remains poorly understood, particularly in comparison to established markers. This study aims to address this gap by systematically investigating the association between UHR and MASLD in a large cohort of T2DM patients.

Methods

Study Design

This cross-sectional study consecutively recruited individuals with T2DM who were admitted to the Endocrinology Department of Southeast University Affiliated Zhongda Hospital between March 2022 and September 2024.

Study Setting and Participants

A total of 1081 participants (aged 18–80 years) diagnosed with T2DM were enrolled based on the diagnostic criteria outlined in the American Diabetes Association guidelines.[27] MASLD was defined based on: (1) imaging-confirmed hepatic steatosis, (2) absence of significant alcohol consumption (<40 g/day for men, <20 g/day for women), and (3) ≥1 metabolic risk factor per international guidelines.[28] Exclusion criteria included: (1) type 1 diabetes, gestational diabetes, or other specific types of diabetes; (2) acute infection or diabetic ketoacidosis within the past two weeks; (3) use of medications affecting UA or HDL-C levels; (4) presence of severe diseases potentially impacting study outcomes. The study was approved by the Ethics Committees at Zhongda Hospital (Approval Number: 2022ZDSYLL318-P01), and conducted in compliance with the Helsinki Declaration.

Clinical Data Collection

Anthropometric, clinical, and medical history data were obtained from participants' electronic medical records in the Endocrinology Department. Collected variables included sex, age, history of hypertension, and alcohol consumption, height, weight, waist and hip circumferences, and blood pressure.

Fasting blood samples were collected after an 8-hour overnight fast. Laboratory analyses were performed using standardized methods. Hemoglobin A1c (HbA1c) was measured using high-performance liquid chromatography. Fasting blood glucose (FBG) and 2-hour blood glucose (2hBG) levels were determined using the glucose oxidase method. Liver function tests, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), were measured using standardized enzymatic assays. UA levels were determined using the uricase method. Lipid profiles, including HDL-C, triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), were measured using enzymatic colorimetric assays. Gamma-Glutamyl Transferase (GGT) was measured using a standardized enzymatic

method. All assays followed manufacturer protocols, with stringent quality control measures to ensure accuracy and reproducibility.

Definition of Index

UHR was calculated as [UA (mg/dL) / HDL-C (mg/dL)] × 100%. Urine albumin to urine Cr ratio (UACR) was calculated as urine albumin (mg/L) / urine Cr (mg/dL). The homeostatic model assessment of insulin resistance (HOMA-IR) value was calculated using the following formula: HOMA-IR= FBG (mmol/L) × fasting insulin (FINS, mU/L)/22.5. TG/HDL Ratio was calculated as triglycerides (mg/dL) divided by HDL-C (mg/dL). TC/HDL Ratio was calculated as total cholesterol (mg/dL) divided by HDL-C (mg/dL). WHR was calculated as waist circumference (cm) divided by hip circumference (cm). AST/ALT Ratio: was calculated as aspartate aminotransferase (U/L) divided by alanine aminotransferase (U/L).

Statistical Analysis

Quantitative variables were analyzed based on their distribution. Data following a normal distribution were represented as mean ± standard deviation ($\bar{\chi} \pm SD$) and analyzed using a *t*-test for group comparisons; non-normally distributed data were presented as medians (interquartile range) and analyzed using the Wilcoxon rank-sum test; categorical variables were analyzed using the chi-square test. Correlations between variables were evaluated using either Spearman's rank correlation test or Pearson's correlation test, as appropriate. Univariate and multivariate logistic regression analysis were conducted to identify factors associated with the dependent variable. All statistical analyses were performed using SPSS 25.0 software version. A p-value of < 0.05 was considered statistically significant.

Results

Participant Characteristics

The characteristics of T2DM patients with (n = 617) and without MASLD (n = 464) are presented in Table 1. The UHR was significantly elevated in in patients with MASLD compared to those without (12.12 [9.06–16.83] vs 10.36 [7.65–14.08], $p < 0.001$). The groups differed significantly in key metabolic parameters, including BMI, lipid profiles, and liver enzymes (all $p < 0.05$, Table 1).

Table 1 Comparison of General Data and Laboratory-Related Indicators in Type 2 Diabetes Mellitus Patients

Parameters	T2DM Patients		Z /t/χ^2	*p*-value
	Non-MASLD (n = 464)	MASLD (n = 617)		
Age (years)	60 (53, 68)	58 (49, 66)	−3.583	<0.001
Sex (n,%)				
Male	294 (63.36%)	362 (58.67%)	2.443	0.118
Duration of DM (years)	10.00 (4, 15)	6 (1, 12)	−4.596	<0.001
BMI (kg/m^2)	22.83 (21.22, 24.72)	25.76 (23.62, 27.78)	−14.257	<0.001
WHR	0.92 (0.88, 0.96)	0.95 (0.91, 0.98)	−5.075	<0.001
SBP (mmHg)	132.15 (20.30)	136.37 (18.12)	2.513	0.113
DBP (mmHg)	78.40 (12.02)	81.31 (12.00)	0.129	0.791
Smoking (n, %)	106 (22.84)	123 (19.94)	1.289	0.525

(*Continued*)

Table 1 (Continued).

Parameters	T2DM Patients		Z /t/χ^2	*p*-value
	Non-MASLD (n = 464)	MASLD (n = 617)		
FBG (mmol/l)	7.50 (5.86, 9.76)	7.84 (6.40, 10.13)	−2.531	0.011
2hBG (mmol/l)	18.00 (5.02)	17.81 (4.76)	−1.093	0.274
C-peptide (nmol/l)	0.55 (0.29, 1.10)	0.71 (0.41, 1.17)	−3.517	<0.001
2h C-peptide (nmol/l)	1.51 (0.82, 3.79)	2.10 (1.20, 3.63)	−3.906	<0.001
HOMA-IR	2.28 (0.77, 4.11)	2.54(0.91, 5.23)	−1.842	0.065
HbA1c (%)	9.20 (7.30, 11.10)	8.65 (7.30, 10.50)	−1.794	0. 073
TG (mmol/l)	1.19 (0.89, 1.81)	1.68 (1.15, 2.66)	−8.701	<0.001
TC (mmol/l)	4.36 (3.54,5.06)	4.29 (3.66,5.00)	−0.004	0.997
LDL-C (mmol/l)	2.36 (1.82,3.03)	2.39 (1.86,3.03)	−0.835	0. 404
HDL-C (mmol/l)	1.23 (1.00, 1.51)	1.10 (0.93, 1.34)	−5.372	<0.001
GGT (U/L)	20.00(14.00,32.48)	28.00(17.85,46.48)	−7.261	<0.001
TC/HDL	3.39(2.75,4.21)	3.85(3.08,4.87)	−5.417	<0.001
TG/HDL	0.98(0.63,1.69)	1.49(0.88,2.62)	−8.704	<0.001
ALT (U/L)	16.00 (12.00, 22.00)	21.00 (15.00, 33.00)	−7.818	<0.001
AST (U/L)	17.00 (14.00, 21.20)	19.00 (15.03, 27.00)	−5.526	<0.001
AST/ALT	1.05(0.83,1.31)	0.91(0.70,1.13)	−6.324	<0.001
UA (umol/L)	287.00 (235.75, 351.83)	313.00 (258.20, 382.00)	−4.812	<0.001
BUN (mmol/L)	6.20 (4.91, 7.30)	5.89 (4.74, 7.00)	−2.387	0.017
Cr (umol/L)	60.90 (51.10, 74.00)	62.00 (51.00, 73.60)	−0.972	0.331
UACR	18.36 (8.53, 66.02)	17.22 (8.69, 42.27)	−1.327	0.185
UHR	10.36 (7.65, 14.08)	12.12 (9.06, 16.83)	−6.337	<0.001

Notes: Data are presented as mean ± standard deviation (SD), median (interquartile range, IQR), or number (%). *t*-test (for normal distribution) and Wilcoxon rank sum test (for skewed distribution) with different samples were adopted for comparison between groups. $p < 0.05$ was considered statistically significant.

Abbreviations: BMI, Body mass index; WHR, waist-to-hip ratio; SBP, systolic pressure; DBP, diastolic pressure; FBG, fasting blood glucose; 2hBG, postprandial 2h blood glucose; HOMA-IR, insulin resistance index; HbA1c, Hemoglobin A1c; TC, total cholesterol; HDL-C, high-density lipoprotein; LDL-C, low-density lipoprotein; GGT, gamma-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate transferase; UA, uric acid; BUN, blood urea nitrogen; Cr, creatinine; UACR, urinary albumin-to-creatinine ratio; UHR, uric acid to HDL cholesterol ratio.

Correlations Between UHR and Metabolic Parameters

Correlations between UHR and various metabolic parameters are shown in Table 2. UHR showed strong correlations with TG/HDL (r =0.673, $p < 0.001$); moderate correlations with TG (r = 0.516, $p < 0.001$) and TC/HDL (r =0.548, $p < 0.001$); weak but significant correlations with BMI (r = 0.330), WHR (r = 0.289), HOMA-IR (r = 0.121), ALT (r = 0.123), and GGT (r = 0.267) (all $p < 0.05$).

Logistic Regression Analysis of UHR and MASLD Risk

Binary logistic regression models were constructed to evaluate the association between UHR and MASLD risk in T2DM patients (Table 3). Sex, age, diabetes duration, blood pressure, BMI, liver enzymes, and lipid profile, glycemic control

Table 2 The Correlation Between UHR and Indicators in Patients with Type 2 Diabetes Mellitus

Variable	r	*p*-value	Variable	r	*p*-value
Age	−0.168	<0.001	HOMA-IR	0.121	0.005
BMI	0.330	<0.001	TG	0.516	<0.001
WHR	0.289	<0.001	TC	−0.120	<0.001
SBP	0.043	0.169	TG/HDL	0.673	<0.001
DBP	0.073	0.021	TC/HDL	0.548	<0.001
Diabetes duration	−0.102	0.002	ALT	0.123	<0.001
HbA1c	−0.067	0.030	AST	0.029	0.377
FBG	0.040	0.221	AST/ALT	−0.175	<0.001
2hBG	−0.083	0.017	GGT	0.267	<0.001

Note: $p < 0.05$ was considered statistically significant.

Table 3 Results of Univariate and Multivariate Regression Analyses of UHR on Type 2 Diabetes with MASLD

Variable	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
UHR	1.085 (1.059,1.111)	<0.001	1.057 (1.016, 1.100)	0.006
Sex	0.821 (0.641,1.052)	0.118	-	-
Age	0.979 (0.969,0.989)	<0.001	1.020 (1.000, 1.040)	0.040
Diabetes duration	0.969 (0.952,0.986)	<0.001	0.984 (0.957, 1.012)	0.262
BMI	1.381 (1.312,1.452)	<0.001	1.371 (1.270, 1.479)	<0.001
SBP	1.012 (1.005,1.019)	<0.001	1.007 (0.994, 1.021)	0.263
DBP	1.021 (1.010,1.032)	<0.001	0.999 (0.978, 1.019)	0.893
HbA1c	0.931 (0.883,0.982)	0.009	0.882 (0.807, 0.964)	0.006
FBG	1.056 (1.014,1.100)	0.008	1.086 (1.018, 1.159)	0.012
2hBG	0.992 (0.964,1.021)	0.709	-	-
AST	1.022 (1.011,1.034)	<0.001	0.991 (0.969, 1.013)	0.415
ALT	1.019 (1.011,1.026)	<0.001	1.005 (0.992, 1.018)	0.447
GGT	1.004(1.001,1.007)	0.008	1.000 (0.996, 1.004)	0.953

Notes: $p < 0.05$ was considered statistically significant.
Abbreviations: OR, odds ratio; CI, confidence interval.

markers and UHR were included as independent variables, while MASLD were considered as dependent variables in logistic regression analysis. In the multivariate-adjusted model, UHR remained independently associated with MASLD risk (adjusted OR = 1.057, 95% CI: 1.016–1.100; $p = 0.006$). This association corresponds to a 5.7% increase in the odds of MASLD for each unit increment in UHR levels.

Discussion

This study demonstrates that elevated UHR is independently associated with MASLD in patients with T2DM, even after adjusting for metabolic confounders. The strong correlation between UHR and TG/HDL ratio particularly highlights its value in capturing dyslipidemia, a hallmark of MASLD pathophysiology.

The biological plausibility of our findings is supported by UHR's unique integration of two opposing metabolic pathways: pro-inflammatory UA and atheroprotective HDL-C.[29,30] Elevated UA levels contribute to hepatic lipid accumulation through multiple mechanisms, including the generation of oxidative stress, promotion of inflammatory cascades, and impairment of insulin signaling pathways.[31,32] Conversely, HDL-C improves insulin sensitivity by enhancing glucose uptake and reducing inflammation.[33] This dual-pathway mechanism accounts for UHR's superior performance in our multivariate analysis, where it maintained significant association (adjusted OR=1.057, 95% CI:1.016–1.100, $p = 0.006$) while traditional hepatic markers like AST and ALT became non-significant after adjustment. Notably, the correlation between UHR and HOMA-IR further supports its role in reflecting insulin resistance, a key pathophysiological driver common to both T2DM and MASLD progression.

Current evidence regarding the association between the UHR and MASLD in T2DM populations remains limited. While Cui et al demonstrated UHR's predictive value in a selected cohort of 343 non-obese T2DM patients,[34] our study provides novel evidence that elevated UHR is strongly and independently associated with increased MASLD risk across the entire T2DM population spectrum (n=1081). Clinically, UHR offers practical advantages for MASLD screening in T2DM patients. First, its calculation requires only routinely measured biochemical parameters, eliminating the need for specialized testing. Second, the cost-effectiveness and wide availability of UHR components make it particularly valuable for resource-limited settings where advanced diagnostic modalities like transient elastography are inaccessible. These attributes position UHR as a potential biomarker that could facilitate earlier identification of high-risk T2DM patients, enabling timely implementation of preventive strategies that may alter disease trajectory.

Several study limitations warrant consideration. First, the cross-sectional design restricts the ability to establish causality, as it captures data at a single time point rather than longitudinally. As a result, temporal changes in the relationship between MASLD and UHR remain unexplored. Second, the single-center nature of the study may introduce selection bias, limiting the generalizability of the findings to other populations with diverse demographics and clinical characteristics. Although exclusion criteria were applied to minimize confounding, residual confounding due to unmeasured factors affecting liver function cannot be entirely excluded. Additionally, although we used standard imaging criteria for MASLD diagnosis, the absence of liver biopsy data prevents assessment of histological severity. Future studies should focus on addressing these limitations by conducting larger, multicenter investigations with longitudinal designs and incorporating liver biopsy data.

In conclusion, this study demonstrates that elevated UHR is independently associated with MASLD risk in patients with T2DM. The observed correlations between UHR and key lipid markers suggest its potential as a metabolic indicator in this population. While these findings highlight the clinical relevance of UHR in T2DM patients with MASLD, further prospective studies are needed to definitively establish its predictive value for MASLD incidence and progression, and to evaluate its potential incorporation into clinical decision-making pathways for T2DM management.

Abbreviations

T2DM, Type 2 diabetes mellitus; MASLD, Metabolic dysfunction-associated steatotic liver disease; UHR, Uric acid to high-density lipoprotein cholesterol ratio; NAFLD, Non-alcoholic fatty liver disease; BMI, Body mass index; WHR, Waist-to-hip ratio; UA, Uric acid; HDL-C, HDL cholesterol; HbA1c, Hemoglobin A1c; FBG, Fasting blood glucose; 2hBG, 2-hour blood glucose; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma-Glutamyl Transferase; TG, Triglycerides; TC, Total cholesterol; LDL-C, Low-density lipoprotein cholesterol; UACR, Urine albumin to urine Cr ratio; HOMA-IR, Homeostatic model assessment of insulin resistance; FINS, Fasting insulin; SD, Standard deviation; CI, Confidence Interval.

Data Sharing Statement

The data underlying this article is available from the corresponding author under reasonable request.

Ethics Approval and Consent to Participate

The study was reviewed and approved by the Ethics Committees at Zhongda Hospital, Southeast University and was in compliance with the Helsinki Declaration. Patients' informed consent was waived by Ethics Committees at Zhongda Hospital Southeast University, because the study data were collected retrospectively. The study confirmed that participants' privacy was strictly protected.

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. Xiangyun Zhu, Han Yin and Jing Han are co-first authors.

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Disclosure

The authors declare that they have no competing interests.

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