

The Serum Uric Acid to Serum Creatinine Ratio is an Independent Risk Factor for Diabetic Kidney Disease

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Purpose: A retrospective study was designed to evaluate whether the serum uric acid to serum creatinine ratio (SUA/SCr) can be used as an indicator of diabetic kidney disease (DKD) and macroangiopathy in patients with type 2 diabetes mellitus (T2DM).

Patients and Methods: We screened 2227 patients diagnosed with T2DM, and 450 patients were finally included. They were assigned to three groups based on the tertile of SUA/SCr (Group Tertile 1, Tertile 2, Tertile 3). Demographic information and biochemical parameters were collected from Electronic Patient Record (EPR).

Results: The estimated glomerular filtration rate (eGFR) values were lowest in Group Tertile 1 and highest in Group Tertile 3 ($P < 0.05$). There was no significant difference in urinary albumin creatinine ratio (UACR) among the three groups ($P > 0.05$). Partial correlation analyses revealed that SUA/SCr levels were significantly and positively correlated with eGFR, SUA, body mass index, gamma-glutamyl transpeptidase, alanine transaminase, triglycerides, C-peptide, high-density lipoprotein cholesterol and fatty liver, while they were negatively correlated with SCr, blood urea nitrogen, cystatin-c, age, male sex, DM duration and hypertension history ($P < 0.05$). Logistic regression analysis revealed that SUA/SCr was an independent risk factor for $eGFR < 60 \text{ mL/min/1.73 m}^2$ ($P < 0.05$). The ROC curve showed that the cutoff value of SUA/SCr for the identification of $eGFR < 60 \text{ mL/min/1.73 m}^2$ was 3.434. In patients with normal UACR, SUA/SCr levels of patients with $eGFR < 60 \text{ mL/min/1.73 m}^2$ were lower than those with $eGFR \geq 60 \text{ mL/min/1.73 m}^2$ ($P < 0.05$). Regression analysis did not show SUA/SCr associate to macrovascular disease after adjusting for confounding factors.

Conclusion: SUA/SCr is an independent risk factor for DKD in patients with T2DM and may be helpful for identifying normoalbuminuric DKD.

Keywords: diabetes mellitus, glomerular filtration rate, serum uric acid, creatinine

Introduction

Diabetic kidney disease (DKD) and diabetic macroangiopathy are major complications of diabetes mellitus (DM).^{1,2} A variety of pathophysiological mechanisms are involved in the development of DKD, including hemodynamic changes, inflammation, fibrosis and mesangial expansion, endothelial cell and podocyte injury, leading to the occurrence of proteinuria and decreased renal function.^{3,4} Epidemiological investigation shows DKD occurs in 20%–40% of DM patients.^{5,6} Patients with DKD are at higher risk of cardiovascular disease (CVD) and end-stage renal disease (ESRD), leading to a significant increase in all-cause mortality and overall medical costs.^{7,8} From 2000 to 2015, the proportion of ESRD patients with DM increased from 19.0% to 29.7%, and the annual incidence increased from 375.8 per million people to 1016 per million people.⁹ The overall prognosis of DM patients with DKD is poor and the mortality rate is high. Although there are many treatment and intervention methods, the overall prevalence of ESRD has not decreased significantly.¹⁰ Therefore, early detection, diagnosis and treatment of chronic diabetic complications, including DKD and macroangiopathy, are of great importance during the early stage of DM.

Hyperuricemia (HUA) is an increase in serum uric acid (SUA) caused by increased production or decreased urinary excretion of UA, or a combination of both. In recent decades, research on the association between SUA and chronic kidney disease (CKD)^{11–17} or macroangiopathy^{18–24} has not reached a unified consensus and has attracted extensive attention. These conflicting data may be attributed to the fact that the level of endogenous SUA depends primarily on renal clearance function, and some studies have ignored the effect of renal function. Thus, the serum uric acid to serum creatinine ratio (SUA/SCr) has emerged as a new biomarker that assesses SUA levels after standardizing the degree of renal function and it reflects the net production of UA.^{25,26} Recent studies reported SUA/SCr was relevant to the metabolic change or the preserved function of kidney.^{26,27} In the present study, we evaluated the relationship between SUA/SCr and renal function as well as macroangiopathy in patients with type 2 DM (T2DM).

Materials and Methods

Ethics Statement

This investigation was approved by the Research Ethics Committee of the Third Affiliated Hospital of Anhui Medical University (No. 2022–007-01) and adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants.

Patients

In this single-center retrospective study, 2227 patients diagnosed with T2DM²¹ from August 2019 to September 2021 in the Endocrinology Department of the Third Affiliated Hospital of Anhui Medical University were screened. After rigorous screening, 450 patients with T2DM were included in the present study (Figure 1). The exclusion criteria were as follows: patients with type 1 DM, acute complications of DM, specific types of

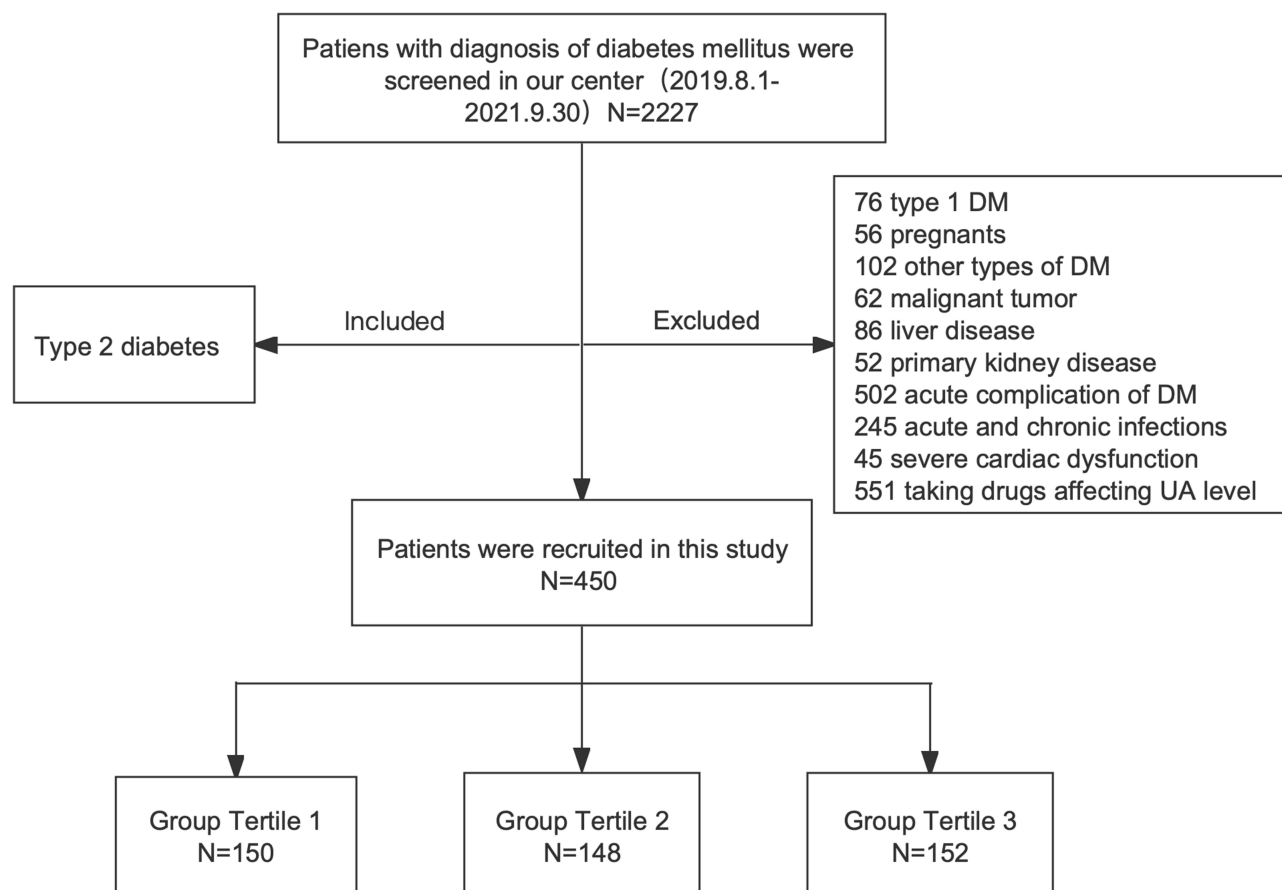


Figure 1 Flow chart of the study.

Abbreviations: DM, diabetes mellitus; UA, uric acid.

diabetes due to other causes, pregnancy, malignant tumor, liver disease, primary kidney disease, acute and chronic infections, severe cardiac dysfunction, taking drugs that affect the SUA level (such as uric acid-lowering drugs, diuretics, sodium glucose cotransporter 2 inhibitors, pyrazinamide, ethambutol, levodopa and etcetera).

Data Collection

We obtained demographic information (including age, sex, smoking history, family history of DM (at least one first-degree relative with diabetes), duration of DM, history of hypertension (HBP), and previous medication history), and biochemical parameters from Electronic Patient Record (EPR) of our hospital.

Blood samples were collected after an 8–10 hour overnight fast for biochemical tests. Blood urea nitrogen (BUN), SUA, SCr, cystatin-c (Cysc), fasting blood glucose (FBG), triglycerides, total cholesterol (TCH), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), gamma-glutamyl transpeptidase (GGT), alanine transaminase (ALT), and aspartate transaminase (AST) were measured using serum by the standard enzymatic methods (Beckman Coulter Unicel DxC800, Beckman Coulter in vitro diagnostic, Cartridge Reagents). Glycosylated hemoglobin A1c (HbA1C) was measured using whole blood with high-performance liquid chromatography (Arkray HA-1880, ARKRAY Factory, Inc. ELUENT 80A, ELUENT 80B, Hemolysis Washing Solution 80H) using whole blood. C-peptide (C-P) was performed with serum using electrochemiluminescence (ROCHE Cobase 602, Roche Diagnostics GmbH, Elecsys C-Peptide). Spot urine was collected in the morning for urinary albumin creatinine ratio (UACR) test, which was estimated using the dry immunomarker scattering quantitative method (Abbott AFINION 2, Abbott Diagnostics Technologies AS, Afinion ACR).

DKD was defined as $UACR \geq 30$ mg/g and/or $eGFR < 60$ mL/min/1.73 m² in the absence of signs or symptoms of other primary causes of kidney damage.²⁸ The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI-SCr-Cysc formula.^{29–31}

$eGFR = 135 \times \min(SCr/\kappa, 1)^\alpha \times \max(SCr/\kappa, 1)^{-0.601} \times \min(Cysc/0.8, 1)^{-0.375} \times \max(Cysc/0.8, 1)^{-0.711} \times 0.995^{\text{year}} \times 0.969$
(Female).

κ : Female: 0.7; Male: 0.9; α : Female: -0.248; Male: -0.207, min refers to the small value of both and max refers to the large value of both.

Anthropometry

The height and weight were measured by pointer mechanical height and weight scale (Tianjin Weighing Instrument Factory Co., Ltd. Xiheng, RGZ-120-RT). The scale was placed on a smooth flat ground, and zero correction was performed before use. After overnight fasting, the subject was asked to remove the shoes, bulky clothing, and hair ornaments, and unbraided hair that interferes with the measurement. Make sure the subject looking straight ahead and that the line of sight is parallel with the floor. The height and weight of the patients were measured three times by the same method, and the average value was recorded for the calculation of body mass index (BMI, kg/m²). The patients underwent a liver ultrasound examination by using high-resolution B-mode ultrasound (Philips-iu22, C5-2 probe), and fatty liver disease was defined as an excessive accumulation of fat in more than 5% of liver cells or a fat content greater than 5.6% in the liver. High-resolution B-mode ultrasound (Philips- IU22, L12-3 probe) was applied to examine the carotid arteries and lower limb arteries of each subject. Carotid artery lesions were defined as thickened or roughened walls of the common carotid artery or the formation of carotid plaques. Carotid intima-media thickness (CIMT) > 0.11 cm was defined as common carotid artery wall thickening. A lower limb atherosclerotic lesion (LLAL) was defined as an intima-media thickness of the lower extremity artery higher than 1.5 mm or a protrusion displaying a thickness 50% higher than the surrounding area.

Data Analyses

Statistical analyses were carried out using IBM SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were presented based on tertiles of SUA/SCr. Data following the normal distribution were described as the mean \pm standard deviation (SD), and t-tests or one-way analysis of variance (ANOVA) were used to compare differences among groups. Data following the

skewed distribution are described as the median and interquartile range, and the Mann–Whitney *U*-test was performed. The rates or ratios were compared using the chi-square test. Partial correlation analysis was conducted to investigate the correlation between SUA/SCr and the other parameters. Binary logistic regression analysis was performed to evaluate the association of SUA/SCr with DKD and macroangiopathy after adjusting for other covariates. Receiver operating characteristic (ROC) curve analysis of SUA/SCr was performed for predicting DKD. A *P* value < 0.05 was considered statistically significant.

Results

Characteristics of T2DM Patients According to the SUA/SCr Tertiles

Based on their tertiles of SUA/SCr, the patients were divided into three groups of Tertile 1, Tertile 2 and Tertile 3. As shown in Table 1, many parameters, including age, sex, BMI, SUA, SCr, BUN, Cysc, triglycerides, GGT, ALT and HDL-C, as well as the proportions of HBP history and fatty liver, showed significant differences among the three groups. Figure 2A demonstrates that the eGFR values were lowest in the Tertile 1 group and highest in the Tertile 3 group, accompanied by an SUA/SCr increase (86.40±25.33 versus 101.18±19.50 versus 108.23±18.43 mL/min/1.73 m², *P* < 0.05). There was no significant difference in UACR among the three groups (*P* > 0.05) (Figure 2B).

Table 1 Characteristics of T2DM Patients According to the SUA/SCr Tertiles

	Tertile 1 (SUA/SCr < 3.934)	Tertile 2 (3.934 ≤ SUA/SCr < 4.947)	Tertile 3 (SUA/SCr ≥ 4.947)	P-value
N	150	148	152	
Characteristics				
Age(year)	60.30±11.64	55.59±11.91*	54.64±12.85*	0.000
Male, N (%)	101(67.3)	106(71.6)	73(48.0)* [▲]	0.000
Duration of DM(year)	8.00(3.75,13.00)	7.50(2.25,12.00)	6.00(2.00,11.00)	0.127
BMI(kg/m ²)	23.69(21.86,25.42)	24.16(22.10,26.13)	24.80(22.83,27.18)*	0.002
DM family History, N (%)	65(43.3)	67(45.3)	73(48.0)	0.713
HBP history, N (%)	79(52.7)	59(39.9)	54(35.5)*	0.008
Smoking history, N (%)	65(43.3)	59(39.9)	48(31.6)	0.097
Parameters				
FBG(mmol/L)	7.63(6.36,9.33)	7.80(6.64,10.05)	7.56(6.37,9.49)	0.345
HbA1C(%)	8.20(6.87,9.97)	8.60(7.30,10.20)	8.15(6.90,10.00)	0.378
C-P(nmol/L)	0.56(0.38,0.70)	0.57(0.39,0.75)	0.59(0.44,0.79)	0.165
Renal function				
SCr(μmol/L)	80.30(67.93,95.93)	70.35(61.05,79.00)*	56.30(48.00,67.07)* [▲]	0.000
BUN(mmol/L)	5.25(4.40,6.48)	5.20(4.40,6.20)	4.40(3.80,5.10)* [▲]	0.000
Cysc(mg/L)	0.87(0.75,1.06)	0.79(0.68,0.90)*	0.74(0.66,0.89)*	0.000
SUA(μmol/L)	268.82±61.21	307.54±62.65*	351.86±78.04* [▲]	0.000
Hepatic function				
GGT(IU/L)	18.00(12.00,27.00)	20.00(14.25,31.00)	22.00(14.00,34.00)*	0.028
ALT(U/L)	19.00(14.00,28.00)	21.00(16.00,29.00)	22.00(17.00,31.00)*	0.026
AST(U/L)	19.00(15.00,24.00)	18.50(15.25,23.00)	20.00(17.00,23.00)	0.217
Fatty liver, N (%)	71(48)	84(57.9)	110(73.8)* [▲]	0.000
Serum lipid				
Triglycerides(mmol/L)	1.37(1.05,2.08)	1.62(1.13,2.48)	1.81(1.18,2.49)*	0.010
TCH(mmol/L)	4.35±1.00	4.33±0.94	4.55±1.02 [▲]	0.093
LDL-C(mmol/L)	2.42±0.89	2.36±0.82	2.50±0.88	0.398
HDL-C(mmol/L)	1.14(0.95,1.33)	1.02(0.88,1.23)	1.04(0.90,1.29)*	0.009

Notes: *Compared with Tertile 1 group, *P* < 0.05; [▲]Compared with Tertile 2 group, *P* < 0.05.

Abbreviations: T2DM, type 2 diabetes mellitus; SUA/SCr, serum uric acid to serum creatinine ratio; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio; DM, diabetes mellitus; BMI, body mass index; HBP, hypertension; FBG, fasting Blood Glucose; HbA1C, glycosylated hemoglobin A1c; BUN, blood urea nitrogen; Cysc, cystatin-c; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; C-P, C-peptide; TCH, total cholesterol, LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

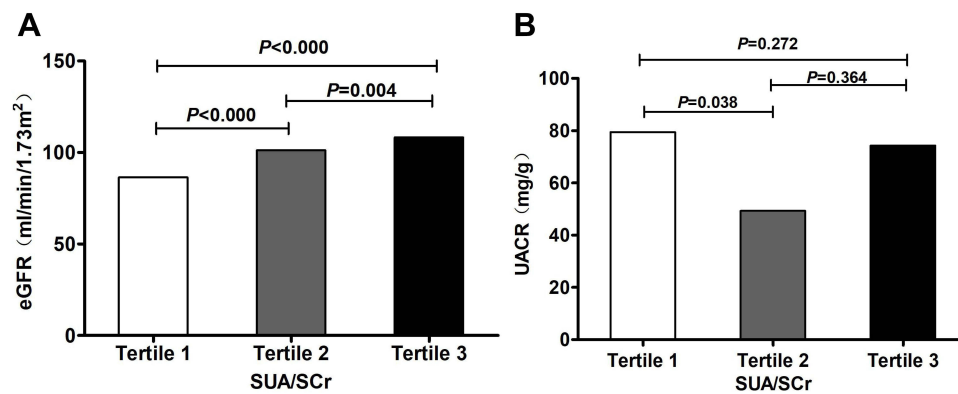


Figure 2 Prevalence of eGFR and UACR among three groups categorized by tertile of SUA/SCr. (A) Comparison of eGFR among the three groups; (B) Comparison of UACR among the three groups.

Abbreviations: SUA/SCr, serum uric acid to serum creatinine ratio; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio.

The prevalence of carotid lesions (108 (74.5%) versus 90 (62.9%) versus 88 (59.1%), $P < 0.05$) and LLAL (119 (81.5%) versus 94 (62.7%) versus 93 (62.4%), $P < 0.05$) showed significant differences among the three groups (Figure 3).

The Correlations Between SUA/SCr and Other Parameters in T2DM Patients

Partial correlation analyses were performed to evaluate the relationship between SUA/SCr and other parameters in T2DM patients. As described in Table 2, eGFR was significantly and positively correlated with SUA/SCr. No significant relationship was detected between SUA/SCr and UACR.

SUA, BMI, GGT, ALT, triglycerides, C-P, HDL-C, and fatty liver were significantly and positively correlated with SUA/SCr. SCr, BUN, Cysc, age, male sex, DM duration and HBP history were significantly and negatively correlated with SUA/SCr (Table 2).

Partial correlation analyses revealed that the prevalence of carotid lesions and LLAL was significantly and negatively correlated with SUA/SCr (Table 2).

SUA/SCr Was Independently Associated with eGFR in T2DM Patients

As shown in Table 3, regression analysis showed that the SUA/SCr was an independent risk factors for eGFR < 60 mL/min/1.73 m² before and after adjustment for potential confounding factors.

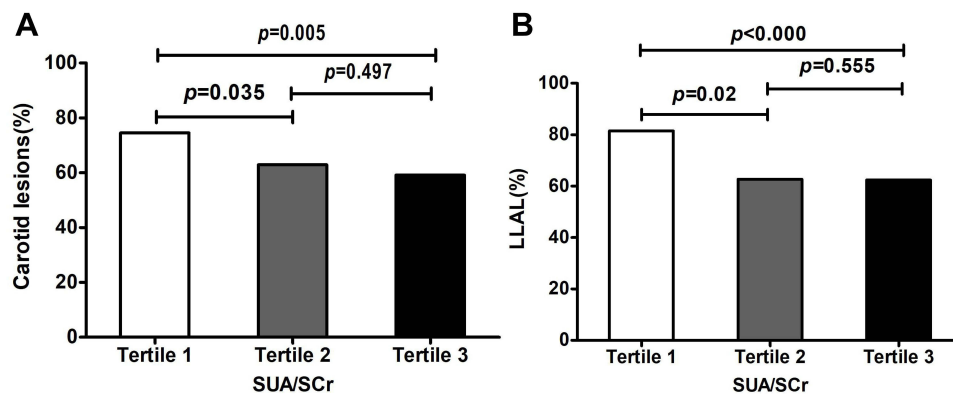


Figure 3 Prevalence of carotid lesions and LLAL among three groups categorized by tertile of SUA/SCr. (A) Comparison of the prevalence of carotid lesions among the three groups; (B) Comparison of the prevalence of LLAL among the three groups.

Abbreviations: SUA/SCr, serum uric acid to serum creatinine ratio; LLAL, lower limb atherosclerotic lesion.

Table 2 Correlation Between SUA/SCr and Other Parameters in T2DM Patients

Variables	r	P
eGFR(mL/min/1.73m ²)	0.419	0.000
UACR(mg/g)	-0.048	0.311
Age(year)	-0.199	0.000
Male	-0.166	0.000
Duration of DM(year)	-0.119	0.012
BMI(kg/m ²)	0.198	0.000
DM family history	0.043	0.365
HBP history	-0.153	0.001
Smoking history	-0.091	0.054
FBG(mmol/L)	0.021	0.662
HbA1C(%)	0.005	0.918
C-P(nmol/L)	0.111	0.019
SCr(umol/L)	-0.577	0.000
BUN(mmol/L)	-0.285	0.000
Cysc(mg/L)	-0.314	0.000
SUA(umol/L)	0.455	0.000
GGT(IU/L)	0.129	0.006
ALT(IU/L)	0.122	0.010
AST(IU/L)	0.065	0.168
Fatty liver	0.210	0.000
Triglycerides(mmol/L)	0.114	0.016
TCH(mmol/L)	0.035	0.461
LDL-C(mmol/L)	-0.020	0.677
HDL-C(mmol/L)	0.096	0.041
Carotid lesions	-0.139	0.004
LLAL	-0.155	0.001

Abbreviations: T2DM, type 2 diabetes mellitus; SUA/SCr, serum uric acid to serum creatinine ratio; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio; DM, diabetes mellitus; BMI, body mass index; HBP, hypertension; FBG, fasting Blood Glucose; HbA1C, glycosylated hemoglobin A1c; BUN, blood urea nitrogen; Cysc, cystatin-c; ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transpeptidase; C-P, C-peptide; TCH, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LLAL, Lower limb atherosclerotic lesion.

Table 3 Logistic Regression Analysis of SUA/SCr for DKD in T2DM Patients

	Regression Coefficient	SE	Wald -Value	P-value	OR(95% CI)
Model 1	1.827	0.300	36.993	0.000	6.214(3.449~11.195)
Model 2	1.713	0.327	27.361	0.000	5.544(2.918~10.532)
Model 3	2.341	0.473	24.445	0.000	10.389(4.107~26.275)
Model 4	2.456	0.497	24.467	0.000	11.66(4.406~30.856)

Notes: Model 1: no parameter was adjusted; Model 2: adjusted for age, sex; Model 3: Model 2 plus duration of DM, BMI, DM family history, HBP history, smoking history, FBG, HbA1C, C-P; Model 4: Model 3 plus hepatic function and serum lipids.

Abbreviations: T2DM, type 2 diabetes mellitus; SUA/SCr, serum uric acid to serum creatinine ratio; DM, diabetes mellitus.

SUA/SCr Was Not Associated with Macroangiopathy in T2DM Patients

As shown in Table 4, the univariate binary regression model showed that SUA/SCr was a risk factor for carotid lesions and LLAL. After adjustment for potential confounding factors, the SUA/SCr was not associated with carotid lesions or LLAL.

Table 4 Logistic Regression Analysis of SUA/SCr for Macroangiopathy in T2DM Patients

	Regression Coefficient	SE	Wald -Value	P-value	OR(95% CI)
Carotid lesion					
Model 1	-0.125	0.063	3.938	0.047	0.883(0.780~0.998)
Model 2	-0.009	0.074	0.014	0.906	0.991(0.858~1.145)
Model 3	-0.019	0.08	0.054	0.816	0.982(0.84~1.147)
Model 4	-0.02	0.083	0.059	0.807	0.98(0.833~1.153)
LLAL					
Model 1	-0.184	0.065	7.873	0.005	0.832(0.732~0.946)
Model 2	-0.077	0.076	1.043	0.307	0.926(0.798~1.074)
Model 3	-0.069	0.082	0.708	0.400	0.933(0.794~1.096)
Model 4	-0.1	0.085	1.379	0.240	0.905(0.765~1.069)

Notes: Model 1: no parameter was adjusted; Model 2: adjusted for age, sex; Model 3: Model 2 plus duration of DM, BMI, DM family history, HBP history, smoking history, FBG, HbA1C, C-P; Model 4: Model 3 plus hepatic function and serum lipids.

Abbreviations: T2DM, type 2 diabetes mellitus; SUA/SCr, serum uric acid to serum creatinine ratio; DM, diabetes mellitus; LLAL, lower limb atherosclerotic lesion.

The Accuracy of SUA/SCr for the Diagnosis of DKD in T2DM Patients

The ROC curve showed that the cutoff value of SUA/SCr for T2DM patients with $eGFR < 60 \text{ mL/min/1.73 m}^2$ was 3.434, and the corresponding area under the curve (AUC) was 0.849, with a sensitivity of 0.836 and specificity of 0.815 (Figure 4). The Youden index value of SUA/SCr for identifying DKD (evaluated by $eGFR < 60 \text{ mL/min/1.73 m}^2$) in T2DM patients was 0.651.

Comparison of SUA/SCr Between Patients with Normal UACR With or Without eGFR Decline

Patients with normal UACR were divided into a normal eGFR group ($eGFR \geq 60 \text{ mL/min/1.73 m}^2$) and a low eGFR group ($eGFR < 60 \text{ mL/min/1.73 m}^2$). As shown in Figure 5, the SUA/SCr levels of patients in the low eGFR group were lower than those in the normal eGFR group (3.33 versus 4.50, $P < 0.05$).

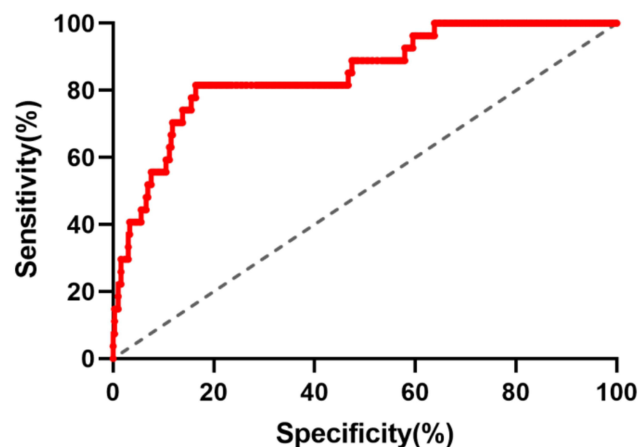


Figure 4 The ROC curves of SUA/SCr for DKD in T2DM.

Abbreviations: SUA/SCr, serum uric acid to serum creatinine ratio; T2DM, type 2 diabetes mellitus; DKD, diabetic kidney disease.

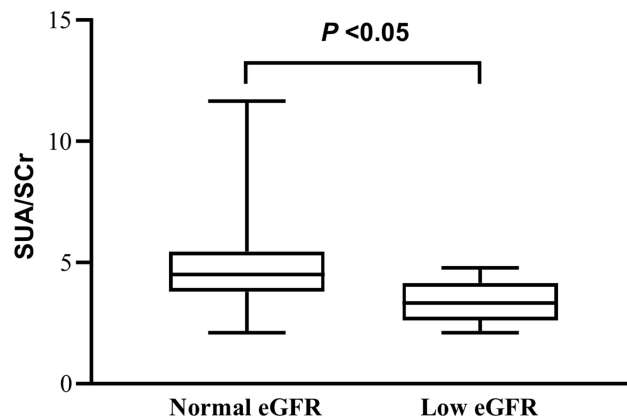


Figure 5 Comparison of SUA/SCr levels according to eGFR among patients with normal UACR.

Notes: Normal eGFR group, eGFR \geq mL/min/1.73 m²; Low eGFR group, eGFR < 60 mL/min/1.73 m².

Abbreviations: SUA/SCr, serum uric acid to serum creatinine ratio; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio.

Discussion

In this retrospective study, the main findings were as follows: SUA/SCr is an independent risk factor for DKD in patients with T2DM and may be helpful in identifying normoalbuminuric DKD. To the best of our knowledge, the present study is the first in the literature to observe an elevated SUA/SCr level in normoalbuminuric DKD.

During the past decades, T2DM and HUA have been considered two growing epidemics with an increasingly earlier age of onset. Reduced physical activity, sedentary lifestyle, and obesity are common characteristics of these two diseases.^{32–34} The prevalence of HUA among patients with T2DM is reported to be as high as 20.68%–33.8%.^{35–37} SUA levels were positively correlated with T2DM,³⁸ and the risk of T2DM was increased by 6% per 1 mg/dL increment in SUA level.³⁹ The causal relationship between SUA and CKD has been studied in different populations and remains controversial. HUA was recognized as a risk factor for the development and progression of kidney disease, including DKD, in some research.^{11–13} Zhu P et al reported that the relationship between SUA and CKD was different at various ages.¹⁴ Elevated SUA had a positive association with new-onset CKD.¹⁵ A positive association was observed between SUA and CKD among patients aged < 60 years but it vanished among those over 60 years. However, other researchers hold a different view that SUA is not associated with CKD, at least in patients with CKD stage 3–4.^{16,17}

In our retrospective study, SUA/SCr, which reflects the net production of UA, was used to evaluate renal function in patients with T2DM. We found that the eGFR level was consistent with the SUA/SCr increase, according to the SUA/SCr tertiles, which was also reported in some previous studies.^{25,27} Further analysis revealed that eGFR was significantly and positively correlated with SUA/SCr levels and that SUA/SCr was an independent risk factor for eGFR < 60 mL/min/1.73 m² in T2DM patients. However, there was no difference in UACR in stratified SUA levels, and no correlation was found between SUA/SCr and UACR.

SUA/SCr was at a low level in patients with decreased eGFR, which reflects their lesions in the glomeruli. However, we observed that the reduced filtration of SUA did not show an entirely consistent manifestation with SCr. This phenomenon may be theoretically explained by impaired renal tubules. Zhou JJ et al performed kidney biopsies in their study and found that when diffuse tubulointerstitial renal lesions occurred, the reabsorption of UA decreased, accompanied by an elevated SCr level, leading to changes in SUA/SCr.⁴⁰ Therefore, we speculated that decreased SUA/SCr could also reflect damage of the tubular interstitium to some degree.

ROC curve analysis was then performed to determine the accuracy of using SUA/SCr as a diagnostic test for DKD. The results showed that the cutoff value of SUA/SCr for T2DM patients with eGFR < 60 mL/min/1.73 m² was 3.434, and the AUC was 0.849 with high sensitivity and specificity. Therefore, SUA/SCr provides discrimination for eGFR < 60 mL/min/1.73 m², which could be used as a supplementary evaluation indicator of DKD in patients with T2DM.

In the last few decades, normoalbuminuric diabetic kidney disease (NADKD), which presents as decreased eGFR with normal UACR, was gradually recognized, and it currently accounts for 10–60% of DKD patients.^{29,41–43} The risks of ESRD, CVD and death in patients with NADKD are higher than those in DM patients without NADKD.^{29,44} To the best of our knowledge, no observation of SUA/SCr in patients with NADKD has been reported thus far. In our study, the levels of SUA/SCr in patients with NADKD were lower than those in the normal eGFR group, which indicates that a low SUA/SCr level might be a predictor of NADKD in T2DM patients.

We also discussed the relationship between SUA/SCr and macroangiopathy in T2DM. The prevalence of carotid lesions and LLAL was significantly different among the three groups of SUA/SCr tertiles. Although carotid lesions and LLAL were significantly and negatively correlated with SUA/SCr, further logistic regression analysis did not show any association between SUA/SCr and macrovascular disease after adjusting for confounding covariates. A previous study reported that higher SUA/SCr was associated with an elevated risk of CVD.⁴⁵ However, we did not find that SUA/SCr was an independent risk factor for macroangiopathy in patients with T2DM.

The indicators related to metabolic syndrome, including BMI, HBP history, triglycerides, HDL-C, GGT, ALT, C-P and fatty liver, were positively correlated with SUA/SCr in this study. Some literature has already reported SUA/SCr as a risk factor for metabolic syndrome^{25,46,47} and metabolically associated fatty liver disease.^{47,48}

There were several limitations to our study. First, our study is a single-center retrospective study that can only lead to associations but not causality, and the sample size was relatively small, which can merely represent the results of this center. Therefore, the results should be extended with caution. Second, eGFR is calculated using a formula that factors in serum creatinine. It is better to use renal biopsies or measure GFR with the golden standard technology (such as the inulin clearance rate or GFR evaluated by the nuclear medicine method). Therefore, it may make serum creatinine a potential confounder in the entire process of comparing SUA/SCr ratio and eGFR. Third, we have considered the possible effects of underlying diseases and medications influencing UA metabolism (including antihypertensive, antidyslipidemic and antidiabetic medication) in the present study, but we cannot exclude other possible effects on the present findings.

Conclusion

In summary, SUA/SCr is an independent risk factor for DKD in patients with T2DM and may be helpful in identifying NADKD. However, no association was observed between SUA/SCr and macroangiopathy in our study. Consequently, SUA/SCr may provide a practical and effective biomarker for DKD in T2DM patients, especially for primary hospitals and medical institutions in China with relatively inadequate equipment.

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Disclosure

The authors report no conflicts of interest in this work.

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