



Hyperuricemia Predicts the Progression of Type 2 Diabetic Kidney Disease in Chinese Patients

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ABSTRACT

Introduction: Diabetic kidney disease (DKD) has a high global disease burden and substantially increases the risk of end-stage renal disease and cardiovascular events. High levels of serum uric acid (SUA), or hyperuricemia, may indicate patients with type 2 diabetes (T2D) at risk for kidney disease.

Methods: This study explored the association between SUA levels and progression of kidney disease among patients with T2D. A cross-sectional study of 993 Chinese patients aged 20–75 years with T2D and DKD was conducted.

Patients were stratified by progression risk of kidney disease based on estimated glomerular filtration rate and ratio of urinary albumin to creatinine, according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria. Ordinal logistic regression was used to assess associations between SUA and different KDIGO risk categories.

Results: Among 768 patients in the final analysis, those with hyperuricemia and higher SUA were more likely to be assigned to higher KDIGO risk categories. Patients with SUA > 420 $\mu\text{mol/L}$ were ninefold more likely to be in a higher KDIGO risk category than those with SUA < 300 $\mu\text{mol/L}$ (odds risk 9.74, 95% confidence interval 5.47–17.33, $P < 0.001$).

Conclusions: Hyperuricemia may be associated with higher risk of DKD progression in individuals with T2D.

Keywords: Diabetic kidney disease; Type 2 diabetes; Hyperuricemia; KDIGO risk categories

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Key Summary Points

Why carry out this study?

Diabetic kidney disease (DKD) occurs in approximately 40% of people with type 2 diabetes (T2D) and is the leading cause of end-stage renal disease (ESRD).

High levels of serum uric acid (SUA), or hyperuricemia, may indicate patients with T2D at risk for kidney disease.

What was learned from the study?

This study explored the association between SUA levels and progression of kidney disease among patients with T2D.

Our investigation indicated that hyperuricemia may be associated with higher risk of DKD progression in individuals with T2D.

INTRODUCTION

Diabetic kidney disease (DKD) occurs in approximately 40% of people with type 2 diabetes (T2D) and this number is only going to increase given the rising global incidence of T2D [1, 2]. DKD is characterized by an elevated ratio of urinary albumin to creatinine (UACR) and decreased glomerular filtration rate (GFR), which together increase the risk of end-stage renal disease (ESRD), cardiovascular events and all-cause mortality [3–5]. Hyperglycemia, hypertension and dyslipidemia are risk factors for DKD, but therapies targeting these factors are not curative. Thus, the search for other modifiable risk factors is critical for the development of new therapeutics to block DKD progression.

Animal and clinical studies suggest that elevated serum uric acid (SUA) may predict DKD [6]. Several cohort studies involving individuals with type 1 diabetes have linked higher levels of SUA, even those within the normal range, to

albuminuria, early decline in GFR and greater risk of cardiovascular events and mortality [6–8]. A prospective cohort study of Japanese individuals with T2D revealed that higher SUA levels correlate with albuminuria progression, but not with a decline in estimated GFR (eGFR) [9]. On the other hand, another historical cohort study based on a Japanese hospital records linked higher SUA levels to worse renal function in patients with T2D with preserved kidney function [10]. These divergent results illustrate how the link between SUA and risk of DKD remains controversial.

One reason why studies have failed to resolve this controversy may be that they have focused on changes in GFR or albuminuria separately as indicators of kidney disease progression, but never on the two indicators together. However, both eGFR and UACR should be used to predict risk of adverse cardiovascular and kidney outcomes according to the “Kidney Disease: Improving Global Outcomes” (KDIGO) classification of chronic kidney disease factors [11].

Therefore, the present study applied the KDIGO approach to explore the relationship between SUA levels and risk of progression of kidney progression in Chinese patients with T2D.

METHODS

Participants

This study was approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2019NL-I09-02). Written informed consent was obtained from each participant prior to their enrollment. This study was conducted in accordance with Helsinki Declaration of 1964 and its later amendments. This study was registered in the Chinese Clinical Trial Registration Center (ChiCTR2000028949).

In this cross-sectional study, 993 Chinese patients aged 20–75 years with T2D and DKD were recruited from March 2019 to June 2020 in the Diabetes Clinic of the Department of Endocrinology at the Affiliated Hospital of Nanjing University of Chinese Medicine.

Patients with persistently elevated urine albumin excretion (UACR ≥ 30 mg/g), persistently reduced eGFR (< 60 mL/min/1.73 m²) or both were considered eligible for inclusion in the study. Individuals were excluded if they were missing pre-baseline UACR data ($n = 95$); if they had UACR < 30 mg/g within 6 months prior to baseline measurement ($n = 47$); if they had diabetic ketoacidosis ($n = 3$); if they were diagnosed with an urinary tract infection, hematuria or other kidney disease ($n = 71$); or if they had a history of cancer ($n = 9$).

Data Collection and Procedures

Demographic parameters were collected, and glucose and lipids metabolic index were measured. Data on diabetes duration, body mass index (BMI), systolic and diastolic blood pressure, medications, hyperuricemia and hypertension were also collected systematically. All biochemical indexes were measured in our clinical laboratory with ISO15189 certification. SUA and serum creatinine was measured on a Beckman automatic biochemical analyzer (Beckman Coulter Inc., Brea, CA, USA) in fresh blood samples obtained from the fasting subjects between 8:00 and 9:00 a.m. Urinary albumin was measured by an immunonephelometric method on an early morning spot sample and expressed as the albumin-to-creatinine ratio.

Definitions

Type 2 diabetes-associated kidney disease was diagnosed as described in [12]. The eGFR was calculated using the equation developed by the Chronic Kidney Disease Epidemiology Collaboration [13]. Hyperuricemia was defined as SUA > 420 μ mol/L (7 mg/dL) [14], and hypertension was defined as either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg. Normal blood pressure was defined as 130/80 mmHg [12]. The target value of glycosylated hemoglobin A1c (HbA1c) was defined for each patient based on eGFR, macrovascular complications, comorbidities, life expectancy, awareness of hypoglycemia,

resources available for hypoglycemia management and risk that treatment would cause hypoglycemia [1]. Target values ranged from $< 6.5\%$ to $< 8.0\%$.

KDIGO Classification of Chronic Kidney Disease

Participants were categorized into four risk categories according to the KDIGO classification system, based on eGFR and UACR values at baseline [11]: (1) low risk: eGFR ≥ 60 mL/min/1.73 m² and UACR < 30 mg/g; (2) moderate risk: eGFR ≥ 45 but < 60 mL/min/1.73 m² and UACR < 30 mg/g, OR eGFR ≥ 60 mL/min/1.73 m² and UACR 30–300 mg/g; (3) high risk: eGFR ≥ 30 but < 45 mL/min/1.73 m² and UACR < 30 mg/g, OR eGFR 45 to < 60 mL/min/1.73 m² and UACR 30–300 mg/g, OR eGFR ≥ 60 mL/min/1.73 m² and UACR > 300 mg/g; (4) very high risk: eGFR < 30 mL/min/1.73 m² with any UACR, OR eGFR at ≥ 30 but < 45 mL/min/1.73 m² and UACR ≥ 30 mg/g, OR eGFR ≥ 45 but < 60 mL/min/1.73 m² and UACR > 300 mg/g.

None of the patients in our study was classified as low risk because we enrolled only participants with UACR ≥ 30 mg/g and/or eGFR < 60 mL/min/1.73 m².

Statistical Analysis

Continuous variables with normal distribution were reported as the mean \pm standard deviation (SD), while continuous variables with skewed distribution were logarithmically transformed and reported as the median with the interquartile range. Categorical variables were presented as a number with the percentage. Participants were stratified according to KDIGO risk categories, then differences in baseline characteristics among groups were compared using one-way analysis of variance. Ordinal regression was performed to explore the association of hyperuricemia and progression of DKD with KDIGO risk categories.

Participants were further stratified according to SUA levels based on National Institute for Health and Care Excellence (NICE) guidelines for

the diagnosis and management of gout [15]: (1) reference value: $< 300 \mu\text{mol/L}$ (5 mg/dL); (2) low: $300\text{--}360 \mu\text{mol/L}$ (6 mg/dL); (3) moderate: $360\text{--}420 \mu\text{mol/L}$ (7 mg/dL); (4) high $> 420 \mu\text{mol/L}$. Multivariate adjusted regression was used to model the influence of SUA level on KDIGO risk category. Model 1 was an unadjusted model; model 2 controlled for sex and age; and model 3 controlled for diabetes duration, the use of anti-diabetic and antihypertensive agents, BMI, systolic and diastolic blood pressure, fasting plasma glucose (FPG), HbA1c and lipid profile.

A sensitivity analysis was used to verify whether SUA level could predict risk of progression of DKD. Risk factors associated with KDIGO risk categories and kidney disease progression were assessed in terms of odds ratios and corresponding 95% confidence intervals (CIs).

All statistical analyses were conducted using SPSS 26.0 (SPSS-IBM, Armonk, NY, USA). All tests were two-tailed, and differences associated with $P < 0.05$ were considered statistically significant.

RESULTS

Characteristics of the Study Participants

A total of 768 patients (mean $[\pm \text{SD}]$ age 58.4 ± 12.5 years; median duration of diabetes

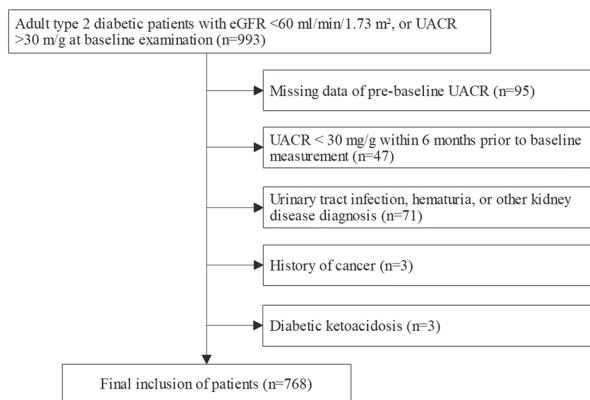


Fig. 1 Flow chart of patient enrollment. *eGFR* Estimated glomerular filtration rate, *UACR* ratio of urinary albumin to creatinine

10 years) were included in this study (Fig. 1). Participants were divided into KDIGO categories as follows: 422 (54.9%, 95% CI 0.513–0.584) were classified with moderate risk, 194 (25.3%, 95% CI 0.222–0.283) were classified with high risk and 152 (19.8%, 95% CI 0.169–0.226) were classified with very high risk (Table 1). In moving from lower to higher KDIGO risk categories, patients became older, had T2D longer, were more likely to attain their target blood glucose level because of greater insulin use and were more likely to have hypertension and hyperuricemia (all $P < 0.001$); conversely, patients had lower HbA1c levels ($P < 0.001$). Fewer than half of patients in each KDIGO risk group were using blockers of the renin-angiotensin system at baseline. Target blood pressure was achieved by significantly fewer patients in the high and very high KDIGO risk categories than in lower risk categories ($P < 0.01$).

Associations of Hyperuricemia with Progression of DKD

In contrast to patients without hyperuricemia, most patients with hyperuricemia were in the very high risk (42.2%) or high risk (30.1%) KDIGO categories (Fig. 2). Specifically, among patients in the very high KDIGO risk category, threefold more patients had hyperuricemia compared to those who without hyperuricemia (42.2% vs. 13.6%). Conversely, among patients categorized with moderate KDIGO risk, more than twice as many patients did not have hyperuricemia compared to those with hyperuricemia (62.5% vs. 27.7%).

Ordinal regression identified the following risk factors for progression of DKD (Table 2): hyperuricemia, diabetes duration, systolic blood pressure and total cholesterol. However, HbA1c level was negatively associated with progression of DKD. There was also a positive relationship between higher SUA stage and more severe KDIGO risk in unadjusted and adjusted models (all $P \leq 0.001$, Table 3). After controlling for sex and age (model 2), $\text{SUA} > 420 \mu\text{mol/L}$ (7 mg/dL) was associated with nearly an eightfold higher risk of belonging in a higher KDIGO risk

Table 1 Clinicodemographic and drug-use characteristics of patients with type 2 diabetes kidney disease, stratified by the Kidney Disease: Improving Global Outcomes risk

Characteristic	Moderate risk (<i>n</i> = 422)	High risk (<i>n</i> = 194)	Very high risk (<i>n</i> = 152)	Total (<i>n</i> = 768)	<i>P</i> ^a
Clinical					
Age, years	55.8 ± 12.3	59.8 ± 12.3	63.9 ± 12.0	58.4 ± 12.5	< 0.001
Male sex	255 (60.4)	136 (70.1)	90 (59.2)	481 (62.6)	0.70
Diabetes duration, years	9 (3–14)	13.5 (8–18)	16 (10–20)	10 (5–18)	< 0.001
Body mass index, kg/m ²	25.6 ± 3.8	25.1 ± 4.1	25.4 ± 3.7	25.4 ± 3.9	0.32
Systolic blood pressure, mmHg	140.4 ± 19.7	149.1 ± 23.2	147.3 ± 23.0	143.9 ± 21.7	0.004
Diastolic blood pressure, mmHg	81.1 ± 12.8	81.6 ± 12.1	77.0 ± 12.0	80.4 ± 12.6	0.018
Hypertension	320 (75.8)	164 (84.5)	147 (96.7)	631 (82.2)	< 0.001
Hyperuricemia	46 (10.9)	50 (25.8)	70 (46.4)	166 (21.6)	< 0.001
Biochemical					
Serum uric acid, μmol/L	304 ± 94	354 ± 111	421 ± 121	340 ± 113	< 0.001
Fasting plasma glucose, mmol/L	8.5 (6.5–11.3)	8.1 (6.3–10.5)	7.0 (5.8–9.1)	8.0 (6.2–10.8)	0.001
Glycosylated hemoglobin A1c, %	9.2 (7.6–10.6)	8.9 (7.4–10.7)	7.9 (6.7–9.7)	8.8 (7.4–10.5)	< 0.001
Total cholesterol, mmol/L	4.71 ± 1.39	4.73 ± 1.35	4.82 ± 1.42	4.74 ± 1.39	0.60
Triglycerides, mmol/L	2.48 ± 2.96	2.15 ± 2.13	2.36 ± 2.89	2.40 ± 2.79	0.46
HDL cholesterol, mmol/L	1.24 ± 0.38	1.25 ± 0.34	1.25 ± 0.39	1.24 ± 0.37	0.85
LDL cholesterol, mmol/L	2.93 ± 0.92	2.82 ± 1.04	2.85 ± 1.16	2.89 ± 1.00	0.37
Drug therapy					
Insulin	228 (54.0)	134 (69.1)	111 (73.0)	473 (61.6)	< 0.001
Sulfonylurea	101 (23.9)	50 (25.8)	17 (11.2)	168 (21.9)	0.006
Metformin	144 (34.1)	48 (24.7)	18 (11.8)	210 (27.3)	< 0.001
RAAS inhibitor	125 (29.6)	95 (49.0)	56 (36.8)	276 (35.9)	0.008
Calcium channel blocker	119 (28.2)	96 (49.5)	82 (53.9)	297 (38.7)	< 0.001
Diuretic	25 (5.9)	23 (11.9)	19 (12.5)	67 (8.7)	0.005
Attainment of target blood glucose	48 (12.3)	33 (18.3)	61 (43.9)	142 (20.0)	< 0.001

Table 1 continued

Characteristic	Moderate risk (<i>n</i> = 422)	High risk (<i>n</i> = 194)	Very high risk (<i>n</i> = 152)	Total (<i>n</i> = 768)	<i>P</i> ^a
Attainment of target blood pressure	198 (46.9)	69 (35.6)	54 (35.5)	321 (41.8)	0.004

Values in table are the mean \pm standard deviation (SD) or *n* (%), unless otherwise indicated

HDL-cholesterol high-density lipoprotein cholesterol, *KDIGO* Kidney Disease: Improving Global Outcomes, *LDL-cholesterol* low-density lipoprotein cholesterol, *RAAS inhibitor* renin–angiotensin–aldosterone system inhibitor

^aComparison among the moderate risk, high risk and the very high risk groups stratified by Kidney Disease: Improving Global Outcomes (KDIGO) risk by one-way analysis of variance (ANOVA)

category, relative to SUA levels < 300 μ mol/L (5 mg/dL). The difference increased to ninefold after adjusting for diabetes duration, use of anti-diabetic and antihypertensive agents, BMI, systolic and diastolic blood pressure, FPG, HbA1c and lipid profile (model 3).

Sensitivity Analysis

Sensitivity analysis confirmed that SUA levels predicted KDIGO severity of DKD as accurately as hyperuricemia did (Table 4).

DISCUSSION

To the best of our knowledge, this study is the first to evaluate the relationship between SUA level and progression of DKD in a large Chinese cohort with T2D, based on the comprehensive KDIGO system. We found that hyperuricemia and increased SUA levels were predictors of progression of DKD, even after adjusting for confounding factors.

The association between SUA and T2D-associated kidney disease is controversial [16–19]. A study involving a 2-year follow-up of 2518 Japanese patients with T2D found a positive relationship between SUA level and progression from micro- to macro-albuminuria, but not with changes in eGFR [9]. The results of a single-center retrospective cohort study involving a 12-year follow-up of 7703 Japanese patients with T2D showed that higher SUA levels are a prognostic factor for kidney function decline in patients with T2D with preserved kidney

function [10]. These conflicting results could be due to differences in eGFR at baseline and the duration of follow-up. In contrast to these and other studies, in present study, we incorporated both eGFR and UACR together as stipulated in the KDIGO classification system. Our findings strengthen the case that higher SUA increases the risk of DKD progression.

However, we were unable to determine based on the results of our observational study whether higher SUA levels are simply associated with progression, or actually contribute to it [17, 20, 21]. Nevertheless, the fact that we observed the association even after adjusting for numerous confounding factors suggests that SUA may indeed contribute to progression. Further work should explore this possibility, and it should also examine whether high SUA levels indirectly contribute to progression through their close association with established risk factors, such as older age, poor glycemic control, hypertension and dyslipidemia.

Whatever the mechanisms underlying the association between SUA levels and DKD progression [22–26], lowering SUA in individuals with T2D can improve eGFR and albuminuria [27–29]. A 3-year randomized open parallel-controlled trial with allopurinol in Chinese persons with T2D and asymptomatic hyperuricemia found that long-term effective control of SUA can decrease UACR, increase GFR and may exert kidney protection effects [30]. A post hoc analysis of a 3-year randomized placebo-controlled trial of losartan in individuals with T2D and chronic kidney disease (RENAAL) demonstrated that individuals experiencing a

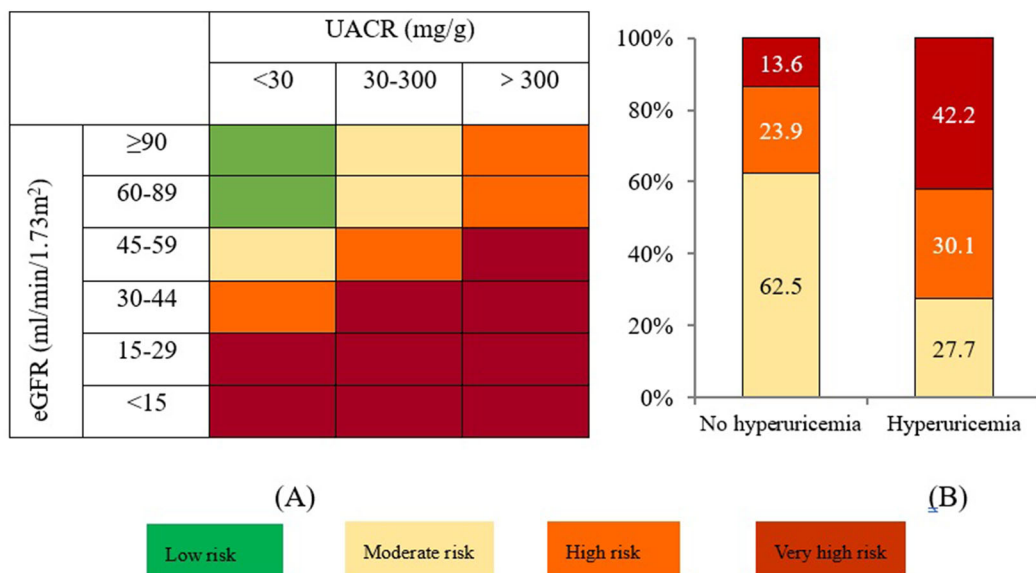


Fig. 2 Frequency of patients with hyperuricemia stratified by the KDIGO classification. **a** KDIGO risk classification of chronic kidney disease, based on eGFR and UACR [1]. **b** Proportions of participants with T2D kidney disease

with or without hyperuricemia, stratified by KDIGO risk category. *KDIGO* Kidney Disease: Improving Global Outcomes, *T2D* type 2 diabetes

Table 2 Ordinal regression analysis to identify factors independently associated with higher KDIGO risk

Factor	OR (95% CI)	P
Hyperuricemia	4.99 (3.15–7.93)	< 0.001
Age, years	1.01 (0.99–1.03)	0.354
Log-transformed diabetes duration, per 1 year	1.09 (1.05–1.12)	< 0.001
Systolic blood pressure, per 1 mmHg	1.03 (1.01–1.04)	< 0.001
Glycosylated hemoglobin A1c, per 1%	0.88 (0.80–0.97)	0.007
Total cholesterol, per 1 mmol/L	1.50 (1.06–2.13)	0.022

CI Confidence interval, OR odds ratio

SUA reduction in the first 6 months after randomization to losartan had a substantially reduced risk of renal events (doubling of serum creatinine and ESRD) compared with patients where SUA did not decrease [30]. Therefore, the therapeutic potential of lowering SUA should be explored in larger, more diverse clinical populations.

We found that patients with SUA levels > 420 μmol/L (7 mg/dL) were ninefold more likely to suffer from progression of DKD than patients with levels < 300 μmol/L. This is consistent with

current clinical guidelines of the Chinese Endocrinology Society, which recommend SUA < 360 μmol/L for patients with T2D-associated kidney disease and recommend pharmacological treatment for patients with DKD and asymptomatic hyperuricemia only if SUA levels are persistently >e 480 μmol/L (8 mg/dL) [31]. Our findings also suggest that SUA levels < 300 μmol/L are associated with lower risk of DKD progression. It is possible that cut-off SUA values for therapeutic intervention may be more restrictive for patients with DKD than for

Table 4 Sensitivity analysis to identify factors independently associated with higher KDIGO risk

Factor	OR (95% CI)	P
SUA, per 1 $\mu\text{mol/L}$	1.008 (1.006–1.010)	< 0.001
Age	1.02 (0.99–1.04)	0.142
Log-transformed diabetes duration, per 1 year	1.09 (1.06–1.13)	< 0.001
Systolic blood pressure, per 1 mmHg	1.03 (1.01–1.04)	< 0.001
Glycosylated hemoglobin A1c, per 1%	0.92 (0.84–1.02)	0.103
Total cholesterol, per 1 mmol/L	1.412 (1.002–1.989)	0.049

SUA serum uric acid

non-diabetic patients with kidney disease, just as cut-off blood pressure values for intervention are more restrictive for those with diabetes than for those without diabetes [32]. This possibility should be explored in future work.

The present study showed an association between low levels of glucose and higher KDIGO risk category. Glucose levels in patients with advanced DKD can fall because of decreased appetite, altered glycemia homeostasis, increased use of insulin, and reduced renal excretion of anti-hyperglycemic drugs [33]. Our study also indirectly suggests that intensive glycemic control provides significant but incomplete renal protection. A large cohort study of Canadian patients with diabetes mellitus reported that poor glycemic control did not affect risk of ESRD in patients with advanced DKD [34], even if it is helpful for determining the need for intervention in patients with early-stage disease.

The results of our study suggest that hypertension is an independent risk factor for the progression of T2D-associated kidney disease, consistent with the findings of a 10-year population based cohort study in China involving 141,516 patients with T2D [35]. Fewer than 50% of participants in our study were treated with blockers of the renin-angiotensin system, and those with more severe kidney disease typically had blood pressure levels outside of the ideal target range. These observations suggest that greater effort is needed to control blood

Table 3 Multi-regression analysis of risk that an individual would be classified in a higher KDIGO risk category based on serum uric acid level

Model	< 300 $\mu\text{mol/L}$ (Reference)	SUA 300–360 $\mu\text{mol/L}$		SUA 360–420 $\mu\text{mol/L}$		SUA > 420 $\mu\text{mol/L}$	
		OR	P	OR	P	OR	P
Model 1 ^a	1	1.32 (0.81–2.15)	0.27	3.71 (2.29–6.02)	< 0.001	5.84 (3.70–9.22)	< 0.001
Model 2 ^b	1	1.52 (0.91–2.53)	0.112	5.23 (3.13–8.74)	< 0.001	7.96 (4.86–13.04)	< 0.001
Model 3 ^c	1	1.39 (0.78–2.49)	0.268	5.49 (2.99–9.92)	< 0.001	9.74 (5.47–17.33)	< 0.001

SUA Serum uric acid

^aModel 1 was an unadjusted model

^bModel 2 was adjusted for sex and age

^cModel 3 was adjusted for sex, age, diabetes duration, body mass index, systolic blood pressure, diastolic blood pressure, fasting plasma glucose, glycosylated hemoglobin A1c, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, insulin, sulfonylurea, metformin, renin-angiotensin-aldosterone system inhibitor, calcium channel blocker, diuretic agent

pressure in patients with T2D-associated kidney disease.

Our study has a number of limitations. First, its cross-sectional design means that we cannot analyze the potentially causal relationship between SUA level and progression of T2D-associated kidney disease. Second, our patients came from a single center, so further work is needed to establish the generalizability of our findings. Third, we did not have data on our patients' use of uric acid-lowering drugs or of novel anti-diabetic drugs, including sodium-dependent glucose transporters 2 inhibitors or glucagon like peptide-1 receptor agonists. Use of these medications may have affected our results.

Despite these limitations, our findings link higher SUA levels with increased risk of progression of DKD in patients with T2D, independently of conventional risk factors, diabetes-related variables and prescribed medication. If our findings can be verified in additional studies, they suggest targeting hyperuricemia as a strategy to treat T2D-associated kidney disease.

CONCLUSION

Despite the limitations of our study, our findings link higher SUA levels with increased risk of progression of DKD in T2D individuals, independently of conventional risk factors, diabetes-related variables and prescribed medication. If our findings can be verified in additional studies, they suggest targeting hyperuricemia as a way to treat T2D-associated kidney disease.

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Author Contributions. Xiaofei An and Jiangyi Yu were responsible for the conception and design of the study. Xuening Wang, Jiaying Sun and Qi Qian collected patients information and performed physical examination. Lin Zhu performed the data analysis and drafted the manuscript. Xiaofei An, Lin Zhu and Jiangyi Yu reviewed the results and revised the manuscript. All authors read and approved the final manuscript.

Disclosures. Lin Zhu, Xuening Wang, Jiaying Sun, Qi Qian, Jiangyi Yu and Xiaofei An have nothing to disclose.

Compliance with Ethics Guidelines. This study was approved by the Ethics Committee of the Affiliated Hospital of Nanjing University of Chinese Medicine (2019NL-I09-02). Written informed consent was obtained from each participant prior to their enrollment. This study was conducted in accordance with Helsinki Declaration of 1964 and its later amendments.

Data Availability. All the datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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