International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Serum Uric Acid to Creatinine Ratio as a Predictor of Normoalbuminuric DKD in T2DM with Normal Renal Function

Huimin Peng[1,*], Haoran Mu[1,*], Qilun Zhang[2,*], Qiang Pan[1], Yanyan Lu[3], Ying Li[1], Zhangxiang Zhu[1], Qianqian Zhang[1], Mao Zheng[4], Li Chen[1]

[1]Department of Endocrinology, The Third Affiliated Hospital of Anhui Medical University (The First People's Hospital of Hefei), Hefei, Anhui, People's Republic of China; [2]Department of Central Laboratory, The Third People's Hospital of Bengbu Affiliated to Bengbu Medical University (Bengbu Central Hospital), Bengbu, Anhui, People's Republic of China; [3]Department of Laboratory, The Third Affiliated Hospital of Anhui Medical University (The First People's Hospital of Hefei), Hefei, Anhui, People's Republic of China; [4]Department of Endocrinology, The First Affiliated Hospital of USTC, University of Science and Technology of China, Hefei, Anhui, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mao Zheng; Li Chen, Email zhengmao1999@foxmail.com; daisy1982@foxmail.com

Background: Diabetic kidney disease is a major complication of diabetes. Among its phenotypes, normoalbuminuric diabetic kidney disease (NADKD), defined as GFR decline without albuminuria, has become increasingly prevalent recently. However, reliable tools for this phenotype are still lacking.

Aim: This study aimed to evaluate whether the serum uric acid to creatinine ratio (SUA/SCr) predicts NADKD in type 2 diabetes mellitus (T2DM) patients with normal renal function.

Materials and Methods: In this retrospective analysis, we examined inpatient electronic medical records of the First People's Hospital of Hefei from 2012 to 2024. Our study included 262 eligible patients with T2DM who had experienced at least three medical encounters across different years and did not have a prior history of kidney disease. Univariate and Multivariate Cox regression models and Logistic regression model were used to assess the relationship between SUA/SCr and the risk of developing NADKD.

Results: During a median follow-up period of 8 years, a total of 17 patients (6.6%) progressed to NADKD. Compared with those who did not develop NADKD, these patients were characterized by older age, a higher proportion of females, longer duration of diabetes, and lower estimated glomerular filtration rate (eGFR) at baseline. Additionally, the NADKD group exhibited a more rapid annual decline rate of SUA/SCr and eGFR in contrast to the non-NADKD group. Logistic regression analysis revealed that a lower SUA/SCr ratio was independently associated with a reduced risk of NADKD (OR 0.408 [95% CI 0.207–0.804]; $P < 0.05$). Receiver operating characteristic curve (ROC) analysis for SUA/SCr showed the area under the curve (AUC) was 0.753 (95% CI 0.634–0.873, $P < 0.05$). In a multivariable Cox proportional hazards model adjusted for age, sex, diabetes duration, blood pressure, and glycemic control, a lower SUA/SCr was independently associated with a reduced risk of developing NADKD (HR 0.504 [95% CI 0.292–0.87]; $P < 0.05$).

Conclusion: Among individuals with type 2 diabetes and normal renal function, SUA/SCr is an important prognostic indicator for the development of NADKD.

Keywords: estimated glomerular filtration rate, diabetic kidney disease, biomarker, retrospective cohort study

Introduction

Diabetic kidney disease (DKD) is one of the most common complications of diabetes and is also the leading cause of end-stage kidney disease (ESKD).[1–3] Traditionally, most people with diabetic kidney disease (DKD) are believed to develop albuminuria prior to a decline in estimated glomerular filtration rate (eGFR).[4] However, previous studies indicate that a significant proportion of diabetes patients have kidney disease as defined by abnormal eGFR without

https://doi.org/10.2147/IJGM.S611255
Received: 25 March 2026
Accepted: 8 July 2026
Published: 17 July 2026

albuminuria.[5–9] This new phenotype is recognized as normoalbuminuric diabetic kidney disease (NADKD). Furthermore, epidemiological studies have indicated that NADKD has become increasingly prevalent in DKD, affecting 20%–60% of type 1 diabetic patients[10,11] and 10%–60% of type 2 diabetic patients with kidney disease.[12–15]

Currently, numerous studies have focused on exploring the prognosis of this increasingly common phenotype. Differences in patient cohorts, ethnicity, medication history, and study criteria have led to inconsistent clinical outcomes for NADKD patients in published studies. Studies have indicated that patients with NADKD have higher risks of cardiovascular disease (CVD), ESKD, and all-cause mortality compared to patients with general diabetes mellitus (DM).[8,9,16–20] Moreover, studies have further shown that NADKD is not only an independent risk factor for CVD in patients with type 2 diabetes mellitus (T2DM), but also a reliable predictor of all-cause mortality.[19,21] However, other studies have reported conflicting results, suggesting that patients with NADKD do not have a significantly higher risk of all-cause mortality, cardiovascular events, or renal function decline compared with other DKD phenotypes.[15,22]

First-line treatment for DKD includes four classes of drugs: renin-angiotensin system inhibitors (RASi),[23] sodium-glucose cotransporter-2 inhibitors (SGLT2i),[24] glucagon-like peptide-1 receptor agonists (GLP-1RA),[25,26] and mineralocorticoid receptor antagonists (MRA).[27] These agents act primarily by reducing proteinuria and improving glomerular hemodynamics to slow down kidney function decline. In albuminuric T2DM patients, some agents may improve cardiovascular and renal outcomes and extend survival.[28] However, for those with NADKD, it remains unclear whether these treatments have renoprotective effects.

Therefore, NADKD is a distinct phenotype within DKD, characterized by a higher incidence, heterogeneous clinical manifestations and no targeted therapies.[29] Hence, the early identification and diagnosis of NADKD in clinical settings are crucial. Given the limitations of eGFR,[30] conventional biomarkers are insufficient for NADKD management. Moreover, the cost burden of DKD and ESKD is substantial. Progression through chronic kidney disease (CKD) stages is closely associated with a stepwise increase in cost.[31] There is an urgent need for novel and low-cost diagnostic tools.[32] The serum uric acid to serum creatinine ratio (SUA/SCr) is a creatinine-normalized marker calculated from routine blood work without extra assays, offering a cost-effective and readily accessible option in clinical settings. Our prior study found that the SUA/SCr is an independent risk factor for DKD and, among T2DM patients with normal urinary albumin creatinine ratio (UACR), those with decreased eGFR had significantly lower SUA/SCr than those with normal eGFR.[33] Subsequently, our further research revealed that the SUA/SCr is an independent risk factor for NADKD.[34]

In this study, we aimed to explore whether the SUA/SCr can predict progression to NADKD in T2DM patients with normal renal function, based on the electronic medical records of the Third Affiliated Hospital of Anhui Medical University.

Research Design and Methods

Data Source and Study Population

This retrospective cohort study utilized data from the electronic medical record system of the Third Affiliated Hospital of Anhui Medical University. We collected demographic and relevant laboratory data from 2012 to 2024, including age, gender, height, weight, blood pressure, duration of diabetes, history of hypertension, past medication history, as well as SUA, SCr, serum cystatin-C (SCysc), blood urea nitrogen (BUN), glycated hemoglobin (HbA1c), and other parameters. We excluded patients with the following conditions: type 1 diabetes, gestational hyperglycemia, or other specific types of diabetes; acute or chronic infections; primary kidney disease or other factors causing acute renal impairment; loss to follow-up (including death); or incomplete data. Additionally, we excluded patients who take medications that could influence uric acid or urine protein levels, such as urate-lowering agents, RASi, SGLT2i, GLP-1RA, and MRA, and kidney-protecting traditional Chinese medicines. The final cohort consisted of 262 adult patients with type 2 diabetes. All participants had a baseline eGFR ≥60 mL/min/1.73 m^2 (calculated using the CKD-EPI[35] creatinine-cystatin C equation), normoalbuminuria (UACR <30 mg/g), and completed at least three follow-up visits. The baseline was defined as the first visit, and the study endpoint was either the occurrence of various DKD phenotypes or the final visit. Serum uric acid, creatinine, cystatin C, HbA1c, and other biomarkers were measured at baseline and each follow-up visit. New-onset DKD was defined as a sustained decline in eGFR to <60 mL/min/1.73 m^2 or the development of confirmed albuminuria

(UACR ≥30 mg/g).[3] Particularly, none of the included patients received any renal protective therapy throughout the whole follow-up period.

Outcome Measures and Grouping

The primary outcome was the incidence of NADKD. NADKD[12,36,37] was defined as having both an eGFR <60 mL/min/1.73 m^2 and a UACR <30 mg/g on at least two occasions over six months, after excluding acute kidney injury and other causes of reduced eGFR. Based on progression to NADKD during follow-up, we stratified patients into non-NADKD group (n=245) and NADKD group (n=17).

Statistical Analyses

Descriptive statistics were summarized for the study participants' baseline characteristics. Normality of continuous variables was assessed using the Kolmogorov–Smirnov test (with Lilliefors correction for sample sizes ≥50) and the Shapiro–Wilk test (for sample sizes <50). Continuous data were expressed as the mean±standard deviation (SD) if normally distributed and median (interquartile range, IQR) if nonnormally distributed. Categorical variables are expressed as percentages or proportions. Continuous variables were compared using the *t*-test for normally distributed data, or the Mann–Whitney *U*-test for non-normally distributed data. Categorical variables were compared using the chi-square test. Univariate and multivariate logistic regression analyses were employed to assess the association between SUA/SCr and the risk of developing NADKD. Multicollinearity was assessed by calculating the variance inflation factor (VIF). Receiver operating characteristic (ROC) curve analysis was conducted to evaluate the diagnostic accuracy of SUA/SCr for NADKD. The area under the curve (AUC) was calculated, and the optimal cut-off value was determined based on the Youden index, with corresponding sensitivity and specificity reported. The annual decline rates of eGFR and SUA/SCr were compared between the NADKD and non-NADKD groups to evaluate differences in disease progression. The annual decline rates for eGFR and SUA/SCr were defined as (baseline value - final value) / total follow-up time (in years). Multivariate Cox proportional hazards regression model was conducted to evaluate the association between SUA/SCr and NADKD progression and to identify independent risk factors.

SPSS 26.0 and GraphPad Prism 10 were used for all statistical analyses and graphing. $P < 0.05$ was considered statistically significant in all analyses.

Results

Summary of the Study Population

In this study, we screened 7701 diabetic patients hospitalized in the Third Affiliated Hospital of Anhui Medical University between 2010 and 2024. Of these, 7245 were diagnosed with T2DM. After a rigorous eligibility assessment (Figure 1), 262 eligible T2DM patients without pre-existing CKD were included. Finally, 17 patients progressed to NADKD, while 245 patients did not progress to NADKD. Among the 245 patients who did not progress to NADKD, 52 developed albuminuric diabetic kidney disease (ADKD).

Table 1 summarizes the baseline characteristics of patients according to NADKD development. Compared with patients without NADKD, those who developed NADKD were older (median [IQR] 64 [59, 71] vs 52 [45.5, 62], years) and included a higher proportion of females (47.1% vs 33.1%). The NADKD group had a higher prevalence of hypertension (58.8% vs 33.5%) and a lower proportion of smokers (17.6% vs 37.1%). Additionally, the NADKD group had higher SCr levels (mean± [SD] 71.82±19.0 vs 61.6±14.02, μmol/L) and lower eGFR (median [IQR] 72.0 [65.7, 95.6] vs 107.8 [92.8, 121.3], mL/min/1.73 m^2). No significant differences were observed in the remaining clinical characteristics between the two groups.

SUA/SCr as an Independent Predictor for NADKD

We performed both univariate and multivariate logistic regression analyses to identify independent factors associated with NADKD (Tables 2 and 3). Univariate analysis showed that higher BUN levels, longer duration of diabetes, and older age were associated with an increased risk of NADKD, while a higher SUA/SCr ratio was associated with

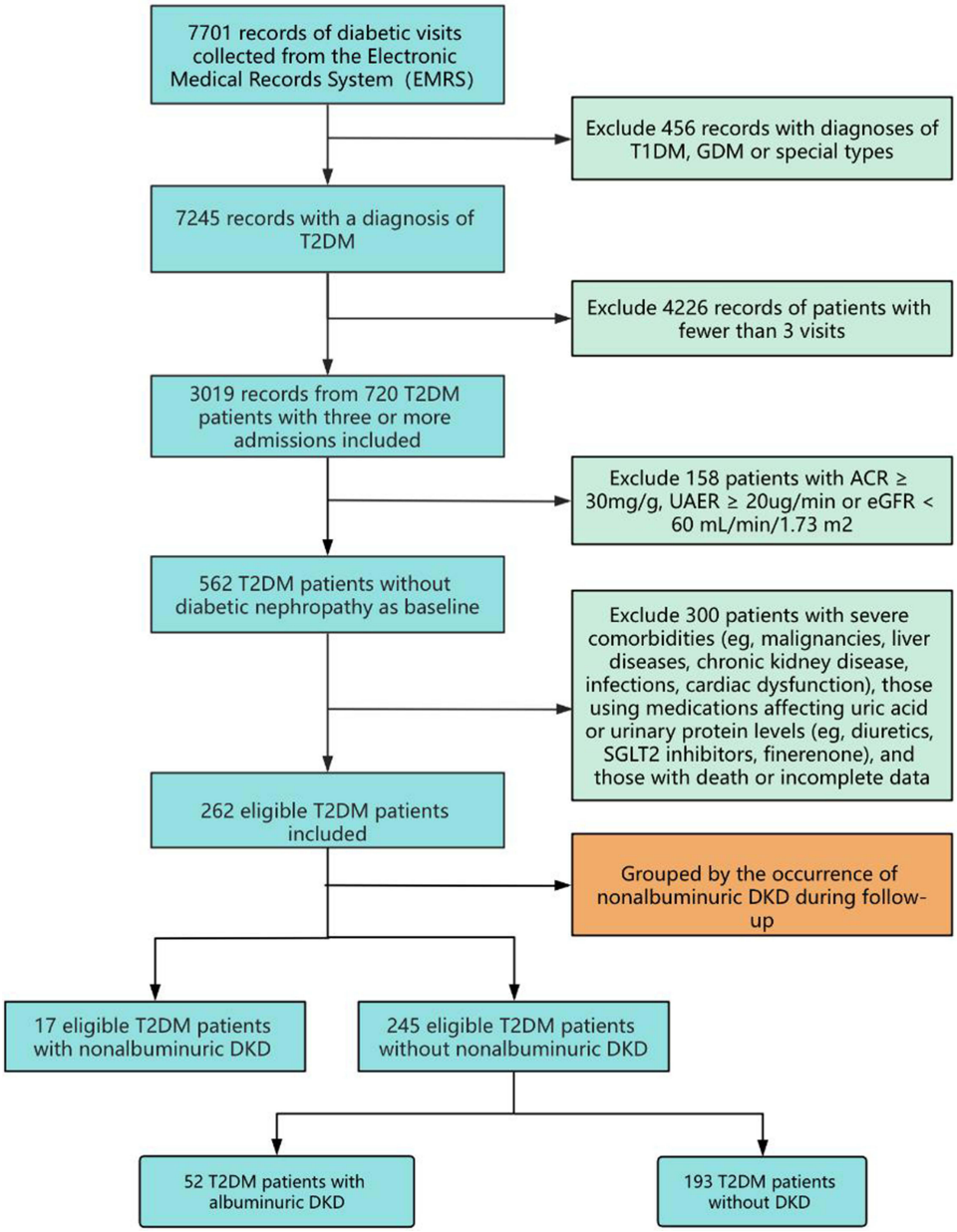

Figure 1 Flowchart for Eligibility Screening and Grouping of the Study Population.
Abbreviations: T2DM, type 2 diabetes mellitus; T1DM, type 1 diabetes mellitus; GMD gestational diabetes mellitus; DKD, diabetic kidney disease; ACR albumin-to-rreatinine ratio; UAER urinary albumin excretion rate; eGFR, estimated glomerular filtration rate; SGLT-2 sodium-glucose cotransporter 2.

a decreased risk (all $P < 0.05$). The multivariate model, including variables with $P < 0.1$ in univariate analysis, demonstrated that the SUA/SCr ratio was an independent protective factor against NADKD (odds ratio [OR] = 0.408, 95% confidence interval [CI]: 0.207–0.804; P = 0.010). In addition, BUN (OR = 1.732, 95% CI: 1.218–2.464; P = 0.002) and age (OR = 1.100, 95% CI: 1.028–1.177; P = 0.006) remained independent risk factors for NADKD. However, the associations of diastolic blood pressure (OR = 1.000, 95% CI: 0.937–1.068; P = 0.997), history of hypertension (OR = 1.552, 95% CI: 0.438–5.500; P = 0.496), and diabetes duration (OR = 1.001, 95% CI: 0.994–1.007; P = 0.858) with NADKD were no longer statistically significant after multivariate adjustment. All results of the multivariate analysis are visually presented in the forest plot (Figure 2). The diagnostic value of SUA/SCr was further evaluated by ROC analysis (Figure 3). The area under the ROC curve (AUC) for SUA/SCr in

Table 1 Baseline Clinical Characteristics of All Participants Stratified by Terminal DKD Phenotype

Variable	Overall (n =262)	Without NADKD (n = 245)	NADKD (n = 17)	p
Male, n (%)	173 (66%)	164 (66.9%)	9 (52.9%)	<0.0001
Age, years	53 (46,63)	52 (45.5, 62)	64 (59, 71)	<0.0001
Follow-up period, years	8 (5, 10)	7 (5, 10)	10 (7, 11.5)	0.049
Diabetes duration, months	60 (24,120)	60 (24, 120)	60 (18, 132)	0.694
History of Hypertension,n (%)	92 (35%)	82 (33.5%)	10 (58.8%)	<0.0001
Family history of diabetes, n (%)	121 (46.18%)	114 (46.5%)	7 (41.2%)	0.669
Smoking history, n (%)	94 (35.9%)	91 (37.1%)	3 (17.6%)	<0.0001
BMI, kg/m2	24.22 (22.48, 26.52)	24.3 (22.3, 26.5)	23.8 (23.1, 27.5)	0.629
Systolic BP, mmHg	126 (118, 138)	126 (118, 138)	130 (120 148)	0.246
Diastolic BP, mmHg	80.01 (70, 80)	80 (70, 80)	76 (70, 80)	0.203
Fasting glucose, mmol/L	8.7 (6.86, 11.22)	8.69 (6.85, 11.32)	9.06 (7.29, 10.64)	0.834
HbA1c, %	8.05 (6.8, 9.7)	8.1 (6.8, 9.7)	7.0 (6.4, 9.2)	0.226
Total-cholesterol, mg/dL	4.71±1.13	4.61 (3.94, 5.36)	4.95 (4.32, 5.59)	0.273
LDL cholesterol, mg/dL	2.78±0.93	2.74 (2.14, 3.37)	3.16 (2.63, 3.53)	0.24
HDL cholesterol, mg/dL	0.97 (0.81, 1.14)	0.96 (0.81, 1.14)	1.02 (0.86, 1.20)	0.532
Triglycerides, mg/dL	1.57 (1.1, 2.5)	1.57 (1.06, 2.57)	1.61 (1.26, 1.97)	0.657
ALT, U/L	22 (16, 30)	22 (16, 30)	19 (15.5, 23)	0.183
AST, U/L	19 (16, 23)	19 (16, 23)	21 (16.5, 23)	0.426
BUN	4.53 (3.90, 5.32)	4.51 (3.9,5.33)	4.62 (3.95, 6.06)	0.731
SUA, μmol/L	285.5 (235.8, 336.7)	284 (238.7, 333.3)	298.4 (224, 378.8)	0.49
SCr, μmol/L	62.3 ±14.57	61.6±14.02	71.82±19.0	0.03
eGFR, mL/min/1.73 m2	106.62±23.1	107.8 (92.8, 121.3)	72.0 (65.7, 95.6)	<0.0001
SUA/SCr	4.65 (3.86, 5.37)	4.66 (3.86, 5.39)	4.48 (3.58, 5.17)	0.278

Notes: Data are presented as number (%), mean (standard deviation, SD), or median (interquartile range, IQR).
Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine amino transferase; AST, aspartate transaminase; BUN, blood urea nitrogen; SUA, serum uric acid; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; SUA/SCr, serum uric acid to serum creatinine ratio.

Table 2 Univariate Logistic Analysis Associated with NADKD

Variable	Univariate Analysis	
	OR (95% CI)	P
HbA1c	0.866 (0.632–1.187)	0.372
BUN	1.851 (1.368–2.505)	0.001
SUA/SCr	0.380 (0.214–0.677)	0.001
Fasting glucose	0.895 (0.729–1.098)	0.286
BMI	1.006 (0.959–1.056)	0.807
Diabetes duration	1.006 (1.000–1.012)	0.043
Age	1.102 (1.047–1.161)	0.0001
Systolic BP	1.007 (0.980–1.035)	0.611
Diastolic BP	0.951 (0.904–1.001)	0.055
Total-cholesterol	1.082 (0.734–1.595)	0.691
LDL cholesterol	0.934 (0.541–1.610)	0.805
HDL cholesterol	0.777 (0.187–3.226)	0.729
Triglycerides	1.019 (0.849–1.222)	0.844
ALT	1.005 (0.974–1.037)	0.752
AST	0.99 (0.927–1.056)	0.75

(*Continued*)

Table 2 (Continued).

Variable	Univariate Analysis	
	OR (95% CI)	P
Family history of diabetes		
No	Reference	
Yes	0.804 (0.279–2.182)	0.669
History of Hypertension		
No	Reference	
Yes	2.486 (0.891–6.938)	0.082
Smoking history		
No	Reference	
Yes	0.944 (0.321–2.776)	0.917
Sex		
Male	Reference	
Female	1.8 (0.669–4.838)	0.244

Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine amino transferase; AST, aspartate transaminase; BUN, blood urea nitrogen; SUA/SCr, serum uric acid to serum creatinine ratio.

Table 3 Multivariate Logistic Analysis Associated with NADKD

Variable	Multivariate Analysis	
	OR (95% CI)	P
BUN	1.732 (1.218–2.464)	0.002
SUA/SCr	0.408 (0.207–0.804)	0.01
Diabetes duration	1.001 (0.994–1.007)	0.858
Age	1.1 (1.028–1.177)	0.006
Diastolic BP	1.0 (0.937–1.068)	0.997
History of Hypertension		
No		
Yes	1.552 (0.438–5.5)	0.496

Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; BP, blood pressure; BUN, blood urea nitrogen; SUA/SCr, serum uric acid to serum creatinine ratio.

detecting NADKD was 0.753 (95% CI 0.634–0.873, $P < 0.05$). At the optimal cut-off value of 0.49 (based on the Youden index), the sensitivity and specificity were 78.8% and 70.6%, respectively.

Comparison of the Annual Decline Rates of SUA/SCr and eGFR Between NADKD and Non- NADKD Groups

As summarized in Table 4, among all 262 patients, the median annual decline was –0.052/year (IQR: –0.132 to 0.043) for SUA/SCr and −1.160 mL/min/1.73 m^2/year (IQR: −2.69 to 0.317) for eGFR. Patients were stratified based on the development of NADKD for analysis. Patients was observed a significantly faster annual decline in SUA/SCr than those who did not (–0.099/year [IQR: –0.158 to –0.060/year] vs –0.044/year [IQR: –0.131 to 0.049 /year]; $P < 0.05$). A similarly accelerated decline was observed for eGFR in the NADKD group (–2.833 mL/min/1.73 m^2/year [IQR: –5.127 to –1.422 mL/min/1.73 m^2/year]) compared with the non-NADKD group (–0.967 mL/min/1.73 m^2/year [IQR: –2.549 to –0.435 mL/min/1.73 m^2/year]; $P < 0.05$).

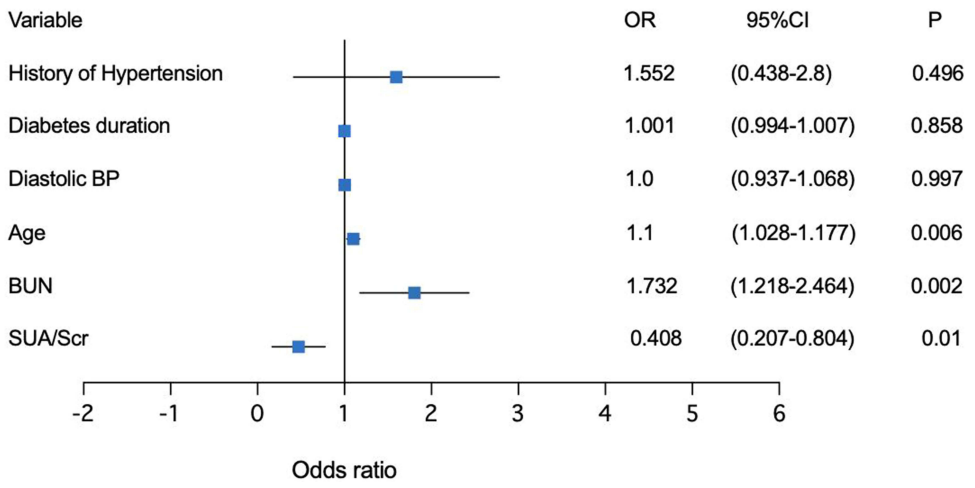

Figure 2 Forest plot of factors independently associated with NADKD. Multivariable logistic regression in 262 patients identified three independent predictors of NADKD. The forest plot shows the odds ratios (OR) and 95% confidence intervals (CI) for each variable. Diamond markers represent the point estimates, with an OR > 1 indicating increased risk.

Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; BUN, blood urea nitrogen; SUA/SCr, serum uric acid to creatinine ratio; BP, blood pressure.

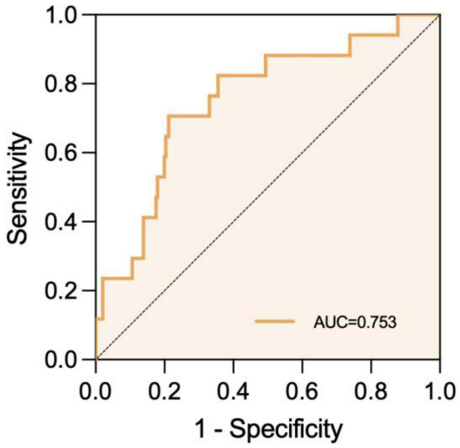

Figure 3 ROC Curve of SUA/SCr for NADKD. The area under the curve (AUC) is 0.753 (95% CI 0.634–0.873, P < 0.005); cut-off 0.49 (Youden index) gave sensitivity 78.8% and specificity 70.6%.

Univariate and Multivariable Cox Regression Analyses for Factors Associated with Incident Normoalbuminuric Diabetic Kidney Disease

Univariate Cox regression analysis (Table 5) revealed that BUN, SUA/SCr, and age were significantly correlated with the progression of NADKD (all P < 0.05). In contrast, no significant associations were observed in other clinical parameters (including HbA1c, fasting glucose, lipid profile, liver enzymes, sex, and smoking history). Multivariate analysis further

Table 4 Comparison of Annual Decline in SUA/SCr and eGFR Between NADKD and Non-NADKD Groups

HbA1c	Overall (n =262)	Without NADKD (n = 245)	NADKD (n = 17)	p
Annual decline in SUA/SCr (/year)	−0.052 (−0.132, 0.043)	−0.044 (−0.131, 0.049)	−0.099 (−0.158, 0.060)	0.027
Annual decline in eGFR (mL/min/1.73 m2/year)	−1.160 (−2.69, 0.317)	−0.967 (−2.549,0.435)	−2.833 (−5.127, −1.422)	0.001

Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; eGFR, estimated glomerular filtration rate; SUA/SCr, serum uric acid to serum creatinine ratio.

https://doi.org/10.2147/IJGM.S611255

Table 5 Univariate Cox Analysis Associated with NADKD

Variable	Univariate Analysis	
	HR (95% CI)	**P**
HbA1c	0.934 (0.688–1.268)	0.661
BUN	1.736 (1.283–2.349)	0.0001
SUA/SCr	0.433 (0.248–0.755)	0.003
Fasting glucose	0.949 (0.794–1.133)	0.562
Diabetes duration	1.003 (0.997–1.009)	0.387
Age	1.088 (1.036–1.142)	0.001
BMI	1.010 (0.969–1.053)	0.629
Systolic BP	1.011 (0.984–1.038)	0.436
Diastolic BP	0.973 (0.927–1.022)	0.273
Total-cholesterol	1.082 (0.723–1.621)	0.701
LDL cholesterol	0.882 (0.523–1.489)	0.638
HDL cholesterol	0.599 (0.128–2.804)	0.515
Triglycerides	1.064 (0.86–1.318)	0.567
ALT	1.021 (0.989–1.054)	0.201
AST	0.997 (0.93–1.069)	0.932
Family history of diabetes		
No	Reference	
Yes	0.775 (0.295–2.038)	0.606
History of Hypertension		
No	Reference	
Yes	1.682 (0.616–4.592)	0.310
Smoking history		
No	Reference	
Yes	1.41 (0.492–4.043)	0.523
Sex		
Male	Reference	
Female	1.390 (0.534–3.62)	0.5

Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine amino transferase; AST, aspartate transaminase; BUN, blood urea nitrogen; SUA/SCr, serum uric acid to serum creatinine ratio.

Table 6 Multivariate Cox Analysis Associated with NADKD

Variable	Multivariate Analysis	
	HR (95% CI)	**P**
BUN	1.551 (1.160–2.074)	0.03
SUA/SCr	0.504 (0.292–0.870)	0.014
Age	1.084 (1.031–1.139)	0.002

Abbreviations: NADKD, normoalbuminuric diabetic kidney disease; BUN, blood urea nitrogen; SUA/SCr, serum uric acid to serum creatinine ratio.

determined that increased BUN (hazard ratio [HR] = 1.551, 95% CI: 1.160–2.074; P = 0.030), increase in age (HR = 1.084, 95% CI: 1.031–1.139; P = 0.002), and decrease in SUA/SCr (HR = 0.504, 95% CI: 0.292–0.870; P = 0.014) were independent predictors of NADKD progression (Table 6).

Discussions

NADKD is a phenotype of DKD distinct from the classical proteinuric type, defined primarily by the absence of proteinuria with a significant decline in eGFR.[12,29,37] Research has predominantly focused on the epidemiology[10–15] and adverse outcomes[7,8,16,18,19,21] of NADKD, revealing a high disease burden. However, predictive strategies for disease progression to help early preventive interventions are still lacking. In this retrospective longitudinal study, we propose for the first time that the SUA/SCr serves as a strong and independent predictor of NADKD in T2DM patients with normal renal function.

The relationship between SUA and CKD remains controversial. Some studies have identified SUA as an independent risk factor for the progression of CKD to kidney failure[38] and have suggested that hyperuricemia may increase all-cause and cardiovascular mortality in patients with stage 3–4 CKD;[39] however, another study has found no significant association between SUA and eGFR in CKD patients.[40] Moreover, uric acid-lowering drugs have not demonstrated benefits for renal outcomes.[41] These differences may stem from the complex bidirectional interaction between SUA and kidney function. Kidney damage can cause hyperuricemia, which in turn can further aggravate kidney damage.[42] Due to the influence between SUA and CKD, it was difficult to distinguish their own effects on disease progression in previous studies.[43] The SUA/SCr, a renal function-adjusted metric, reflects net uric acid production and may be a better predictor of DKD progression than uncorrected SUA levels. Liubao Gu et al found that the SUA/SCr was more effective than SUA alone in predicting new-onset chronic kidney disease[44] Our prior research demonstrated that SUA/SCr is a risk factor for T2DM with albuminuria.[33]

The pathogenesis of NADKD is different from that of proteinuric DKD. To our knowledge, research on the association between SUA/SCr and NADKD remains limited, and no studies other than our own have reported this significant correlation.[34] The multivariate logistic regression analysis in this study not only confirmed this initial finding but also verified the potential of SUA/SCr as a predictive marker for NADKD. The ROC analysis demonstrated that SUA/SCr had moderate diagnostic accuracy for NADKD, with an AUC of 0.753 (95% CI: 0.634–0.873, $P < 0.05$). We observed a significantly accelerated annual decline in the SUA/SCr during the progression from T2DM to NADKD ($P < 0.05$). Multivariable Cox regression indicated that SUA/SCr is an independent predictor of NADKD ($P < 0.05$).

The predictive value of SUA/SCr for NADKD is biologically plausible. NADKD is characterized by reduced kidney size and parenchymal volume rather than glomerular damage (typically described in albuminuric DKD).[45] Its histopathological features include diffuse glomerulosclerosis, interstitial fibrosis, tubular atrophy, and arteriosclerosis, all occurring in the absence of overt albuminuria.[46,47] NADKD patients carry a higher burden of cardiovascular events.[20] Renal biopsy study has shown moderate arteriolar hyalinosis and sclerosis in T2DM patients with renal function decline, regardless of albuminuria.[48] These findings indicate that renal insufficiency in NADKD may be closely related to both macrovascular disease and intrarenal arteriosclerosis. Endothelial dysfunction impairs renal hemodynamics, limiting oxygen delivery to the interstitium, which in turn leads to interstitial fibrosis.[49] Inflammation and oxidative stress also contribute. TNF-α, NGAL, and other inflammatory markers are overexpressed in NADKD.[50] The kidney contains abundant mitochondria and maintains high metabolic activity. These features render it susceptible to ROS-induced injury, leading to the interstitium.[51] These pathological changes have direct implications for uric acid handling. After glomerular filtration, uric acid is extensively reabsorbed and secreted in the proximal tubule. When tubular atrophy and interstitial fibrosis set in, this reabsorptive capacity is compromised,[46] and SUA/SCr declines. The progressive fall in SUA/SCr from normal renal function in T2DM to NADKD therefore reflects cumulative tubulointerstitial injury more than a simple reduction in GFR. This gives SUA/SCr a solid mechanistic foundation for identifying NADKD, particularly in patients without albuminuria.

The results of our study showed that patients with NADKD exhibited a significantly faster annual eGFR decline than non-NADKD patients (–2.833 vs –0.967 mL/min/1.73 m^2/year). Given that eGFR decline is a known independent risk factor for mortality, this finding helps explain the higher mortality risk of previous study.[8,9,18–20] Additionally, the observed incidence of NADKD in our study was 6.6%, which is lower than the previously reported range of 7%–50%.[5,15,19,21,22,52,53] The differences between the results of this study and previous studies are mainly due to the following two reasons. Previous studies have covered both community and hospitalized populations, while our study

enrolled only hospitalized patients and excluded those with confounding conditions such as other renal diseases and infections. Additionally, some patients may exhibit false-negative proteinuria due to the reduction in urinary protein caused by medications such as RASi, SGLT-2i, MRA, or kidney-protective traditional Chinese medicine, leading to incorrect diagnosis as NADKD. However, our study strictly excluded patients using such agents, providing a more accurate estimate of NADKD incidence.

Our study indicated that female, age and hypertension are associated with an increased incidence of NADKD among T2DM patients. It is possible that sex hormones contribute to the higher incidence of NADKD in women. Studies have reported that progesterone therapy can reduce UACR and relieve glomerulosclerosis, as well as promote the expression of angiogenic factors.[54] Furthermore, in T2DM patients with declining renal function, the renal pathology is characterized by moderate arteriolar hyalinosis and sclerosis, irrespective of the presence of proteinuria. This suggests that sclerotic intrarenal microvascular changes are critical pathological reasons for renal decline.[48] Therefore, the reason why patients with advanced age and hypertension are more likely to develop NADKD may be related to the susceptibility of macrovascular disease and intrarenal arteriosclerosis.

Limitations

There are some limitations in this study that must be addressed. Our study is limited by a relatively small sample size due to strict inclusion criteria, which resulted in few NADKD progression events, may have affected the stability of our estimates. Additionally, previous studies have shown that muscle content is related to serum creatinine, which may affect the measurement of SUA/SCr. Interpretation should be based on body shape characteristics and exercise habits. The conclusions of this study still need to be further validated through large-scale prospective cohort studies and data on including muscle mass. Furthermore, the results of this study are limited to clinical research, and prospective research and cellular and animal studies are needed in the future to further clarify the pathogenesis of the disease and find therapeutic targets for NADKD. Despite these limitations, our findings still provide preliminary but important evidence supporting its predictive potential.

Conclusion

This study demonstrated that SUA/SCr is a reliable predictor of progression to NADKD in patients with type 2 diabetes mellitus with normal renal function. The clinical value of this indicator is the predictability of NADKD onset, providing an earlier window for clinical intervention. Moreover, this indicator can be obtained through routine blood tests and is relatively low-cost. This helps clinicians quickly identify high-risk patients and strengthen follow-up and intervention. However, the study was based on single-center retrospective data with a limited sample size, and the generalizability of the results remains to be verified. In the future, validation will be needed in larger, multi-center prospective queues.

Data Sharing Statement

All data generated and analyzed during our study are available from the corresponding author on reasonable request.All data access inquiries should be directed solely to Dr. Chen (daisy1982@foxmail.com), who serves as the designated contact for data sharing.

Ethical Statement

This research proposal has been reviewed by the Medical Ethics Committee of the Third Affiliated Hospital of Anhui Medical University (Ethics Batch No.: 2024-083-01). This study strictly follows the Declaration of Helsinki, and does not involve any therapeutic intervention or biological sample collection. After review, the Ethics Committee approved an exemption from the informed consent procedure. To protect patient privacy, all identifying information was removed from the dataset and replaced with unique study codes prior to analysis. Access to the master code list was restricted to the principal investigator. This approval covers the same patient database used in our previously published work (Mu H et al. Front Med. 2025;12:1584049). However, the two manuscripts address distinct scientific questions: the prior study focused on diagnosis, while this manuscript investigates the prediction of incident normoalbuminuric diabetic kidney disease. There is no overlap in the core findings.

Consent for Publication

This study is a retrospective analysis of anonymized clinical data, and no identifiable patient information is included in this manuscript.

Author Contributions

Huimin Peng, Haoran Mu, Qilun Zhang: Data analysis and manuscript preparation. Qiang Pan, Yanyan Lu, Ying Li, Zhangxiang Zhu, Qianqian Zhang: Collection of original data. Mao Zheng: Manuscript revision. Li Chen: Project design, supervision, and funding acquisition. 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 research was supported by the 2022 Basic and Clinical Collaborative Research Enhancement Plan of the Third Affiliated Hospital of Anhui Medical University (2022sfy005).

Disclosure

The authors declared that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Persson F, Rossing P. Diagnosis of diabetic kidney disease: state of the art and future perspective. *Kidney Int Suppl*. 2018;8(1):2–7. doi:10.1016/j.kisu.2017.10.003
2. Collaboration GCKD, Purcell CA, Levey AS. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2020;395(10225):709–733. doi:10.1016/S0140-6736(20)30045-3
3. D Care. Chronic Kidney Disease and Risk Management: standards of Care in Diabetes-2025. *Diabetes Care*. 2025;48:S239–S251.
4. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. *Diabetes*. 1983;32 Suppl 2(Supplement_2):64–78. doi:10.2337/diab.32.2.S64
5. Kramer HJ, Nguyen QD, Curhan G, Hsu CY. Renal insufficiency in the absence of albuminuria and retinopathy among adults with type 2 diabetes mellitus. *JAMA*. 2003;289(24):3273–3277. doi:10.1001/jama.289.24.3273
6. Ninomiya T, Perkovic V, de Galan BE, et al. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. *J Am Soc Nephrol*. 2009;20(8):1813–1821. doi:10.1681/ASN.2008121270
7. Packham DK, Alves TP, Dwyer JP, et al. Relative incidence of ESRD versus cardiovascular mortality in proteinuric type 2 diabetes and nephropathy: results from the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) database. *Am J Kidney Dis*. 2012;59(1):75–83. doi:10.1053/j.ajkd.2011.09.017
8. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR. Risk factors for renal dysfunction in type 2 diabetes: u.K. Prospective Diabetes Study 74. *Diabetes*. 2006;55(6):1832–1839. doi:10.2337/db05-1620
9. Thomas MC, Macisaac RJ, Jerums G, et al. Nonalbuminuric renal impairment in type 2 diabetic patients and in the general population (national evaluation of the frequency of renal impairment cO-existing with NIDDM [NEFRON] 11). *Diabetes Care*. 2009;32(8):1497–1502. doi:10.2337/dc08-2186
10. Penno G, Russo E, Garofolo M, et al. Evidence for two distinct phenotypes of chronic kidney disease in individuals with type 1 diabetes mellitus. *Diabetologia*. 2017;60(6):1102–1113. doi:10.1007/s00125-017-4251-1
11. Thorn LM, Gordin D, Harjutsalo V, et al. The Presence and Consequence of Nonalbuminuric Chronic Kidney Disease in Patients With Type 1 Diabetes. *Diabetes Care*. 2015;38(11):2128–2133. doi:10.2337/dc15-0641
12. Afkarian M, Zelnick LR, Hall YN, et al. Clinical Manifestations of Kidney Disease Among US Adults With Diabetes, 1988–2014. *JAMA*. 2016;316(6):602–610. doi:10.1001/jama.2016.10924
13. Kramer H, Boucher RE, Leehey D, et al. Increasing Mortality in Adults With Diabetes and Low Estimated Glomerular Filtration Rate in the Absence of Albuminuria. *Diabetes Care*. 2018;41(4):775–781. doi:10.2337/dc17-1954
14. Penno G, Solini A, Bonora E, et al. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. *J Hypertens*. 2011;29(9):1802–1809. doi:10.1097/HJH.0b013e3283495cd6
15. Vistisen D, Andersen GS, Hulman A, Persson F, Rossing P, Jørgensen ME. Progressive Decline in Estimated Glomerular Filtration Rate in Patients With Diabetes After Moderate Loss in Kidney Function-Even Without Albuminuria. *Diabetes Care*. 2019;42(10):1886–1894. doi:10.2337/dc19-0349
16. Di Marco M, Scilletta S, Miano N, et al. Cardiovascular risk and renal injury profile in subjects with type 2 diabetes and non-albuminuric diabetic kidney disease. *Cardiovasc Diabetol*. 2023;22(1):344. doi:10.1186/s12933-023-02065-2

17. Jin Q, Luk AO, Lau ESH, et al. Nonalbuminuric Diabetic Kidney Disease and Risk of All-Cause Mortality and Cardiovascular and Kidney Outcomes in Type 2 Diabetes: findings From the Hong Kong Diabetes Biobank. *Am J Kidney Dis*. 2022;80(2):196–206.e1. doi:10.1053/j.ajkd.2021.11.011
18. Niu J, Zhang X, Li M, et al. Risk of cardiovascular disease, death, and renal progression in diabetes according to albuminuria and estimated glomerular filtration rate. *Diabetes Metab*. 2023;49(2):101420. doi:10.1016/j.diabet.2023.101420
19. Penno G, Solini A, Orsi E, et al. Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study. *Diabetologia*. 2018;61(11):2277–2289. doi:10.1007/s00125-018-4691-2
20. Buyadaa O, Magliano DJ, Salim A, Koye DN, Shaw JE. Risk of Rapid Kidney Function Decline, All-Cause Mortality, and Major Cardiovascular Events in Nonalbuminuric Chronic Kidney Disease in Type 2 Diabetes. *Diabetes Care*. 2020;43(1):122–129. doi:10.2337/dc19-1438
21. Dai Q, Chen N, Zeng L, et al. Clinical features of and risk factors for normoalbuminuric diabetic kidney disease in hospitalized patients with type 2 diabetes mellitus: a retrospective cross-sectional study. *BMC Endocr Disord*. 2021;21(1):104. doi:10.1186/s12902-021-00769-8
22. Yokoyama H, Araki SI, Kawai K, et al. The Prognosis of Patients With Type 2 Diabetes and Nonalbuminuric Diabetic Kidney Disease Is Not Always Poor: implication of the Effects of Coexisting Macrovascular Complications (JDDM 54). *Diabetes Care*. 2020;43(5):1102–1110. doi:10.2337/dc19-2049
23. Coats AJ. Angiotensin receptor blockers – finally the evidence is coming in: IDNT and RENAAL. *Int J Cardiol*. 2001;79:99–102.
24. Herrington WG, Staplin N, Wanner C, et al. Empagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med*. 2023;388:117–127.
25. Muskiet MHA, Tonneijck L, Huang Y, et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2018;6(11):859–869. doi:10.1016/S2213-8587(18)30268-7
26. Perkovic V, Tuttle KR, Rossing P, et al. Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. *N Engl J Med*. 2024;391(2):109–121. doi:10.1056/NEJMoa2403347
27. Filippatos G, Anker SD, Agarwal R, et al. Finerenone and Cardiovascular Outcomes in Patients With Chronic Kidney Disease and Type 2 Diabetes. *Circulation*. 2021;143(6):540–552. doi:10.1161/CIRCULATIONAHA.120.051898
28. Neuen BL, Heerspink HJL, Vart P, et al. Estimated Lifetime Cardiovascular, Kidney, and Mortality Benefits of Combination Treatment With SGLT2 Inhibitors, GLP-1 Receptor Agonists, and Nonsteroidal MRA Compared With Conventional Care in Patients With Type 2 Diabetes and Albuminuria. *Circulation*. 2024;149(6):450–462. doi:10.1161/CIRCULATIONAHA.123.067584
29. Ahmadi N, Amouzegar A. Diabetic Kidney Disease Without Albuminuria: a New Entity in Diabetic Nephropathy. *Iran J Kidney Dis*. 2024;18(1):1–8. doi:10.52547/ijkd.7966
30. Deng L, Li W, Xu G. Update on pathogenesis and diagnosis flow of normoalbuminuric diabetes with renal insufficiency. *Eur J Med Res*. 2021;26(1):144. doi:10.1186/s40001-021-00612-9
31. Martinez Leon V, Aggarwal ST. Targets, and Translational Promise in Diabetic Kidney Disease. *Kidney360*. 2026;7(1):7–10. doi:10.34067/KID.0000001088
32. Villanueva AR, de Leon D, Encarnacion PJ, et al. Cost-of-illness analysis of chronic kidney disease (CKD) management in the Philippines. *J Med Econ*. 2025;28(1):494–507. doi:10.1080/13696998.2025.2481766
33. Chen L, Zhu Z, Ye S, Zheng M. The Serum Uric Acid to Serum Creatinine Ratio is an Independent Risk Factor for Diabetic Kidney Disease. *Diabetes Metab Syndr Obes*. 2022;15:3693–3703. doi:10.2147/DMSO.S387426
34. Mu H, Zhang Q, Huang W, et al. The serum uric acid to creatinine ratio as a diagnostic biomarker for normoalbuminuric diabetic kidney disease. *Front Med Lausanne*. 2025;12:1584049. doi:10.3389/fmed.2025.1584049
35. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. *N Engl J Med*. 2012;367(1):20–29. doi:10.1056/NEJMoa1114248
36. Doshi SM, Friedman AN. Diagnosis and Management of Type 2 Diabetic Kidney Disease. *Clin J Am Soc Nephrol*. 2017;12(8):1366–1373. doi:10.2215/CJN.11111016
37. Chen C, Wang C, Hu C, et al. Normoalbuminuric diabetic kidney disease. *Front Med*. 2017;11(3):310–318. doi:10.1007/s11684-017-0542-7
38. Srivastava A, Kaze AD, McMullan CJ, Isakova T, Waikar SS. Uric Acid and the Risks of Kidney Failure and Death in Individuals With CKD. *Am J Kidney Dis*. 2018;71(3):362–370. doi:10.1053/j.ajkd.2017.08.017
39. Madero M, Sarnak MJ, Wang X, et al. Uric acid and long-term outcomes in CKD. *Am J Kidney Dis*. 2009;53(5):796–803. doi:10.1053/j.ajkd.2008.12.021
40. Nacak H, van Diepen M, Qureshi AR, et al. Uric acid is not associated with decline in renal function or time to renal replacement therapy initiation in a referred cohort of patients with Stage III, IV and V chronic kidney disease. *Nephrol Dial Transplant*. 2015;30(12):2039–2045. doi:10.1093/ndt/gfv225
41. Bose B, Badve SV, Hiremath SS, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2014;29(2):406–413. doi:10.1093/ndt/gft378
42. Mazzali M, Kanellis J, Han L, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol*. 2002;282:F991–F997.
43. Nashar K, Fried LF. Hyperuricemia and the progression of chronic kidney disease: is uric acid a marker or an independent risk factor? *Adv Chronic Kidney Dis*. 2012;19(6):386–391. doi:10.1053/j.ackd.2012.05.004
44. Gu L, Huang L, Wu H, Lou Q, Bian R. Serum uric acid to creatinine ratio: a predictor of incident chronic kidney disease in type 2 diabetes mellitus patients with preserved kidney function. *Diab Vasc Dis Res*. 2017;14(3):221–225. doi:10.1177/1479164116680318
45. Garofolo M, Napoli V, Lucchesi D, et al. Type 2 diabetes albuminuric and non-albuminuric phenotypes have different morphological and functional ultrasound features of diabetic kidney disease. *Diabetes Metab Res Rev*. 2023;39(1):e3585. doi:10.1002/dmrr.3585
46. Yamanouchi M, Furuichi K, Hoshino J, et al. Nonproteinuric Versus Proteinuric Phenotypes in Diabetic Kidney Disease: a Propensity Score-Matched Analysis of a Nationwide, Biopsy-Based Cohort Study. *Diabetes Care*. 2019;42(5):891–902. doi:10.2337/dc18-1320
47. Taft JL, Nolan CJ, Yeung SP, Hewitson TD, Martin FI. Clinical and histological correlations of decline in renal function in diabetic patients with proteinuria. *Diabetes*. 1994;43(8):1046–1051. doi:10.2337/diab.43.8.1046
48. Rodríguez-Rodríguez R, Hojs R, Trevisani F, et al. The Role of Vascular Lesions in Diabetes Across a Spectrum of Clinical Kidney Disease. *Kidney Int Rep*. 2021;6(9):2392–2403. doi:10.1016/j.ekir.2021.06.001

49. Zhang H, Zhang L, Tian D, et al. CD146^{+} Endothelial Cells Facilitate Renal Interstitial Fibrosis Through Endothelial-to-Mesenchymal Transition. *Ann Transplant*. 2024;29:e945917.
50. Phanish MK, Chapman AN, Yates S, et al. Evaluation of Urinary Biomarkers of Proximal Tubular Injury, Inflammation, and Fibrosis in Patients With Albuminuric and Nonalbuminuric Diabetic Kidney Disease. *Kidney Int Rep*. 2021;6(5):1355–1367. doi:10.1016/j.ekir.2021.01.012
51. Ma X, Ma J, Leng T, et al. Advances in oxidative stress in pathogenesis of diabetic kidney disease and efficacy of TCM intervention. *Ren Fail*. 2023;45(1):2146512. doi:10.1080/0886022X.2022.2146512
52. Klimontov VV, Korbut AI. Albuminuric and non-albuminuric patterns of chronic kidney disease in type 2 diabetes. *Diabetes Metab Syndr*. 2019;13 (1):474–479. doi:10.1016/j.dsx.2018.11.014
53. Jia X, Zang L, Pang P, et al. A study on the status of normoalbuminuric renal insufficiency among type 2 diabetes mellitus patients: a multicenter study based on a Chinese population. *J Diabetes*. 2022;14(1):15–25. doi:10.1111/1753-0407.13230
54. Al-Trad B, Ashankyty IM, Alaraj M. Progesterone ameliorates diabetic nephropathy in streptozotocin-induced diabetic Rats. *Diabetol Metab Syndr*. 2015;7(1):97. doi:10.1186/s13098-015-0097-1