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Associations of serum uric acid to eGFR ratio with diabetic retinopathy in individuals with type 2 diabetes

Chenyu Nie[1,2], Qiaofeng Ma[1,2], Chunyao Liu[1,2], Li Chen[1,2], Chuan Wang[1,2]✉ & Xinguo Hou[1,2]✉

Serum uric acid (SUA) is closely associated with diabetes and its complications. The relationship between SUA and diabetic retinopathy (DR) remains unclear, with conflicting results from current studies on SUA in DR Patients. Since uric acid is primarily excreted by the kidneys, the ratio of SUA to eGFR (SUA/eGFR) serves as a renal function-corrected indicator of SUA levels. We tested whether SUA/eGFR might be involved in the pathogenesis and progression of DR. We collected data from 1,399 patients with type 2 diabetes mellitus (T2DM) who were hospitalized between January 2023 and April 2024. They were divided into diabetes without DR (nondiabetic retinopathy, NDR) group (*N* = 438), non-proliferative diabetic retinopathy (NPDR) group (*N* = 902) and proliferative diabetic retinopathy (PDR) group (*N* = 59). Univariate and multivariate logistic regression analyses were used to analyze the relationship between SUA/eGFR and DR and its severity. The SUA/eGFR levels increased with the severity of DR (*P*<0.05). In the multinomial logistic regression model using patients without DR as the reference, SUA/eGFR was significantly linked with PDR (*OR* = 1.07, *95%CI* 1.00-1.14; *P* = 0.036), while NPDR group showed no significant difference (*P*>0.05). In T2DM patients younger than 60 years, SUA/eGFR was positively associated with an increased risk of DR (*OR* = 1.20, *95%CI* 1.05–1.38, *P* = 0.01). Among T2DM patients with HbA1c > 7%, higher SUA/eGFR levels were linked to a greater risk of DR(*OR* = 1.10, *95%CI* 1.00-1.20, *P* = 0.045). Stratified analysis by age showed that in T2DM patients younger than 60 years, SUA/eGFR was positively correlated with the severity of DR (NPDR:*OR* = 1.20, *95%CI* 1.04–1.38, *P* = 0.01; PDR: *OR* = 1.20, *95%CI* 1.04–1.38, *P* = 0.012). Additionally, stratified analysis by HbA1c levels indicated that among T2DM patients with HbA1c > 7%, those with higher SUA/eGFR levels had an increased risk of DR severity (NPDR:*OR* = 1.09, *95%CI* 1.00-1.19, *P* = 0.049; PDR: *OR* = 1.10, *95%CI* 1.01–1.20, *P* = 0.037). Our study reported a positive association between SUA/eGFR and DR and its severity in younger T2DM patients with poorly controlled blood glucose levels. T2DM patients with higher SUA levels had an increased risk of more severe DR (progressing from NPDR to PDR). However, more prospective and high-quality clinical evidence is needed to confirm these current findings.

Keywords Serum uric acid, Diabetic retinopathy, Proliferative diabetic retinopathy

Type 2 diabetes mellitus (T2DM) is the most common metabolic disease, characterized by abnormally high blood glucose levels, often accompanied by glucose and lipid metabolism disorders. As the disease progresses, T2DM can cause chronic progressive lesions in many tissues and organs, such as eyes, kidneys, nerves, heart and blood vessels, eventually leading to their functional decline or even failure[1,2].

Diabetic retinopathy (DR) is a common microvascular complication of T2DM, which can be divided into proliferative diabetic retinopathy (PDR) and non-proliferative diabetic retinopathy (NPDR)[3]. Duration of diabetes and blood glucose level are two major factors in the development and progression of DR[4]. Clinical

[1]Department of Endocrinology and Metabolism, Qilu Hospital of Shandong University, Cheeloo College of Medicine, Shandong University, Jinan 250012, Shandong, People's Republic of China. [2]Shandong Provincial Key Laboratory of Spatiotemporal Regulation and Precision Intervention in Endocrine and Metabolic Diseases, Shandong Provincial Engineering research center for advanced Technologies in Prevention and Treatment of Chronic Metabolic Diseases, Institute of Endocrine and Metabolic Diseases of Shandong University, Jinan 250012, Shandong, China. ✉email: wangchuan@email.sdu.edu.cn; houxinguo@sdu.edu.cn

findings showed that even if the above factors were strictly controlled, the progression of DR could not be completely prevented, indicating that there may be other factors involved in the pathogenesis of DR[5,6]. Identifying clinical markers associated with the severity of DR may help in the early detection and management of DR.

Uric acid (UA), the final product of purine metabolism, is an independent risk factor for cardiovascular diseases. It is closely related to obesity, diabetes and its complications, dyslipidemia and other metabolic syndrome[7,8]. Currently, there are few studies on UA and DR, and the association between the two is unclear. Some studies have found a link between greater serum uric acid (SUA) levels and an increased risk of DR[8–12], while others have found no association[13,14] or even the opposite[15]. A Meta-analysis of 21 studies found that PDR patients had higher UA levels than the diabetic control group, but this difference was not significant in NPDR[7]. UA can activate the NLRP3/NALP3 inflammasome and increase the expression of inflammatory factors, which have been shown to be involved in the pathogenesis of DR. High levels of UA can promote retinal inflammation and enhance the activity of the Notch signaling pathway based on high glucose[16]. Since SUA levels are related to renal function and most previous studies have not considered the effect of renal function on SUA levels, it is necessary to consider the effect of renal function when assessing the association between SUA and DR. Using SUA/eGFR can correct for the influence of renal function on SUA levels, providing a more accurate reflection of UA metabolism. It also overcomes the limitations of serum creatinine related to age and sex, offering a more reliable basis for risk stratification and individualized treatment[17].

Therefore, the present study aimed to evaluate the association between SUA/eGFR levels and the occurrence and severity of DR in patients with T2DM.

Methods

Study population

Individuals diagnosed with T2DM and hospitalized in the endocrinology department of Shandong University QILU Hospital from January 2023 to April 2024 were included in this study. After that, patients who did not meet the requirements were excluded according to our inclusion and exclusion criteria. Finally, 1399 people were included based on the inclusion and exclusion criteria described.

Exclusion criteria: acute complications of diabetes, such as diabetic ketoacidosis; Cataract, glaucoma, history of eye surgery and other eye diseases; Medications taken 8 weeks before admission and during hospitalization that may affect the level of SUA; Significant mental or physical illness, including chronic kidney disease, malignant tumors, severe organ dysfunction, and mental disorders.

The Ethics Committee of Shandong University QILU Hospital gave its approval to the study protocol. The protocol was approved in advance by the relevant institutional review committee and complied with the ethical standards of the 1975 Declaration of Helsinki. All participants fully satisfied the patient's right to know and signed informed consent before participating in the study.

Definition

The diagnostic criteria for T2DM in this study were based on the 2019 WHO diagnostic criteria. According to the Clinical Guidelines for diabetic retinopathy of the American Academy of Ophthalmology[18], the enrolled T2DM patients were divided into three groups. Including non-diabetic retinopathy (NDR) group, NPDR group, and PDR group.

Clinical, anthropometric and laboratory measurements

Demographic, clinical, and laboratory data were collected and recorded from our case retrieval system. Record Gender, age, smoking history, drinking history, family history, duration of diabetes, other past medical history, height, weight, blood pressure and patients' laboratory measurements, including hemoglobin, total bilirubin, hemoglobin A1c (HbA1c), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), SUA, fasting insulin, fasting C-peptide, thyrotropin(TSH), vitamin D level, serum calcium.etc. Body mass index(BMI) was calculated by dividing weight in kilograms(kg) by the square of height in meters(m). The patient's blood pressure was taken twice and averaged after they had rested for at least five minutes.

Following an 8–12 h overnight fast and a 15-minute break, the blood biochemical indices were measured using an automated analyzer (Cobas8000 c701, Roche Diagnostics GmbH, Germany). Blood samples were centrifuged for 15 min after being kept between 4 and 15℃. The Chronic Kidney Disease Epidemiology Collaboration Equation (CKD-EPI) was used to determine eGFR[19]. All samples were tested and reported by the Clinical Laboratory Department of Qilu Hospital of Shandong University, and reference ranges for positive standards were set according to internal quality control.

Fundus examination

DR was diagnosed and graded by color fundus photography or optical coherence tomography angiography (OCTA) and was further classified into NPDR and PDR according to Evidence-based guidelines for diagnosis and treatment of diabetic retinopathy in China (2022). Following pupil dilation, a digital retina camera (CR-2 AF, CANON, Japanese) is utilized to capture high-quality fundus photographs for both eyes. OCTA images were captured utilizing a commercial wide-field OCTA apparatus from SVision Imaging, which has a 1050 nm wavelength and a scanning rate of 200,000 A-scans/s. Fundus fluorescein angiography was performed if required. Fundus examination was carried out by two seasoned deputy chief ophthalmologists who had received training in retina and DR screening. In cases of differing diagnosis, the lead ophthalmologist was consulted to obtain an agreement.

Statistical analysis

Data were analyzed using IBM SPSS version 25 statistical software (IBM Corp., Armonk, NY, USA). P-values < 0.05 indicated significance (two-sided). Continuous data are reported as mean ± standard deviation (SD), whereas categorical variables are expressed as percentages (%) where applicable. The Kruskal-Wallis test was used to determine the normality of the data. Median and interquartile ranges were used for non-normally distributed data, and non-parametric tests were used for comparison. To compare qualitative variables, the Chi-squared test or Fisher's exact test were used as needed. To investigate the relationships between DR and risk factors, we used univariate and multivariate logistic regression. Potential confounders were adjusted for in the multivariate logistic regression analysis, including gender, smoking history, alcohol history, diabetes duration, hemoglobin, total bilirubin, HbA1c, fasting C-peptide, and serum calcium.

Results

Baseline characteristics by study group

This study recruited 1399 patients with T2D, including 566 women (40.5%) and 833 men (59.5%). According to the severity of diabetic retinopathy, these diabetic patients were divided into NDR group ($n = 438$), NPDR group ($n = 902$) and PDR group ($n = 59$). There were no significant differences in age, blood pressure, BMI, prevalence of coronary heart disease and hypertension, prevalence of antihypertensive and lipid-lowering drug use among the three groups. The three groups differed significantly in terms of gender, history of drinking, and history of smoking ($P<0.05$).

The clinical characteristics of the three groups of diabetic patients are summarized in the Table 1. There were no significant differences in blood pressure, BMI, ESR, Platelet count, Urea creatinine ratio, Blood lipid, Fasting insulin, TSH or Vitamin D among the three groups. Compared with the diabetic patients in the NDR group, the diabetic patients in the NPDR and PDR groups had a longer duration of diabetes, and the levels of hemoglobin, total bilirubin, Serum calcium and eGFR were significantly decreased ($P < 0.05$). Patients in the NPDR group had higher HbA1c levels and lower fasting C-peptide levels than the other two groups.

Correlation between diabetic retinopathy and risk factors

Univariate analysis showed that SUA/eGFR were positively correlated with the occurrence of DR (*OR* = 1.08, *95%CI* 1.02–1.14, $P = 0.008$). Multivariate regression analysis showed that SUA/eGFR level was not correlated with the occurrence of DR as shown in Table 2(*OR* = 1.06, *95%CI* 1.00-1.13, $P = 0.060$).

As shown in Table 2, we performed a subgroup analysis by stratifying patients into two groups. In patients aged < 60 years, each 1-unit increase in SUA/eGFR was associated with a 1.20-fold higher risk of DR (*OR* = 1.20, *95% CI*: 1.05–1.38, $P = 0.01$). However, this association was not observed in patients aged ≥ 60 years.

We further divided the patients into two groups based on HbA1c levels for analysis. In patients with HbA1c ≥ 7%, each 1-unit increase in SUA/eGFR was associated with a 1.10-fold increased risk of DR (*OR* = 1.10, *95% CI*: 1.00-1.20, $P = 0.045$). In contrast, this association was not observed in patients with HbA1c < 7%.

Association between sSUA/eGFR and DR severity grading

We then classified all of the patients into three groups: NDR, NPDR and PDR. The level of SUA/eGFR was significantly higher in the PDR (6.19 ± 11.33 versus 3.23 ± 1.71, $P < 0.01$) and NPDR (4.1 ± 11.86 versus 3.23 ± 1.71, $P < 0.05$) group, compared with the NDR, as shown in Fig. 1.

In the multinomial logistic regression model with NDR as reference, SUA/eGFR levels were significantly associated with PDR (*OR* = 1.07, *95%CI* 1.00-1.14; $P = 0.036$) compared to the T2DM control group, while this association was not found in NPDR patients ($P > 0.05$).(Table 3).

Stratified analysis(Table 3) revealed a positive correlation between SUA/eGFR levels and DR severity in patients aged < 60 years (NPDR:*OR* = 1.20, *95%CI* 1.04–1.38, $P = 0.010$; PDR: *OR* = 1.20, *95%CI* 1.04–1.38, $P = 0.012$). Stratified analysis according to HbA1c levels indicated that in patients with HbA1c ≥ 7%, SUA/eGFR levels were positively correlated with the severity of DR (NPDR:*OR* = 1.09, *95%CI* 1.00-1.19, $P = 0.049$; PDR: *OR* = 1.10, *95%CI* 1.01–1.20, $P = 0.037$).

Discussion

This is the first study to investigate the association of SUA with DR using SUA normalized by renal function. In this cross-sectional investigation, we discovered that elevated SUA/eGFR levels can increase the risk of progression from NPDR to PDR in patients with T2DM. A high level of SUA/eGFR level was an independent factor related with DR and its severity among individuals with T2DM who are aged < 60 years or have an HbA1c level ≥ 7%.

Previous findings on the role of SUA concentration in DR have been inconsistent. Multiple studies have found that SUA is an independent risk factor for DR in DM patients, and elevated SUA levels may predict the occurrence of DR[20,21]. Both of the studies were performed with a relatively small number of patients. But a meta-analysis of nine studies and two recent studies conducted in China did not show a strong association between SUA levels and DR[22–24]. Other studies have come to the opposite conclusion, analyzing the risk factors of DR in a cohort of 17,985 people from China, and found that high UA was an independent protective factor for DR (*OR* 0.997, *95%CI* 0.995–0.999, $P = 0.018$)[25]. The type of diabetes among the included patients was not specified. Additionally, the study did not account for potential confounders such as renal function, HbA1c, and fasting C-peptide, which may have affected the results. The conflicting results among these studies may also be related to the complex pro- and antioxidant properties of UA. UA exists in two forms in the body: soluble UA and UA crystals. The role of soluble UA depends on its surrounding environment, whereas UA crystals act as pro-oxidants[26]. Further exploration of the relationship between the state of UA and its oxidative effects will help us

Variable		Total($N=1399$)	NDR group ($N=438$)	NPDR group ($N=902$)	PDR group ($N=59$)	*P* value
Gender (subjects/%)	Female	566(40.50%)	200(45.70%)	345(38.20%)	21(35.60%)	**0.006**
	Male	833(59.50%)	238(54.30%)	557(61.80%)	38(64.40%)	
Coronary heart disease(subjects/%)	No	1052(75.20%)	332(75.80%)	676(74.90%)	44(74.60%)	0.051
	Yes	347(24.80%)	106(24.20%)	226(25.10%)	15(25.40%)	
Hypertension(subjects/%)	No	708(50.60%)	232(53.00%)	449(49.80%)	27(45.80%)	0.26
	Yes	691(49.40%)	206(47.00%)	453(50.20%)	32(54.20%)	
Smoking history(subjects/%)	No	942(67.30%)	318(72.60%)	583(64.60%)	41(69.50%)	**0.002**
	Yes	457(32.70%)	120(27.40%)	319(35.40%)	18(30.50%)	
History of drinking(subjects/%)	No	949(67.80%)	322(73.50%)	586(65.00%)	41(69.50%)	**0.001**
Use of antihypertensive drugs(subjects/%)	No	696(49.7%)	224(51.1%)	446(49.4%)	26(44.1%)	0.184
	Yes	703(50.3%)	214(48.9%)	456(50.6%)	33(55.9%)	
Use of lipid-lowering drugs(subjects/%)	No	1053(75.3%)	338(77.20%)	674(74.7%)	41(69.50%)	0.095
	Yes	346(24.70%)	100(22.80%)	228(25.30%)	18(30.50%)	
	Yes	450(32.20%)	116(26.50%)	316(35.00%)	18(30.50%)	
Age(subjects/%)	< 60	729(52.10%)	242(55.30%)	460(51.00%)	27(45.80%)	0.212
	≥ 60	670(47.90%)	196(44.70%)	442(49.00%)	32(54.20%)	
Age (years)		57.72 ± 12.51	56.33 ± 14.06	58.31 ± 11.7	59.02 ± 11.83	0.103
Diabetes duration (years)		11.82 ± 7.95	9.9 ± 7.71	12.69 ± 7.82	12.72 ± 9.2	**<0.001**
SBP		135.95 ± 18.42	135.58 ± 18.6	135.87 ± 18.32	139.98 ± 18.55	0.218
DBP		79.27 ± 11.83	79.56 ± 11.65	78.99 ± 11.9	81.27 ± 12.28	0.25
BMI (kg/m2)		25.6 ± 3.94	25.91 ± 4.03	25.41 ± 3.83	26.2 ± 4.82	0.086
Hemoglobin		134.59 ± 20.39	136.51 ± 23.28	134.08 ± 18.31	128.25 ± 25.79	**<0.001**
ESR		20.33 ± 16.15	18.59 ± 12.71	21.05 ± 17.56	22.22 ± 15.79	0.135
Platelet count		221.1 ± 55.51	220.5 ± 52.6	220.66 ± 57.16	232.37 ± 50.98	0.221
Total bilirubin		10.44 ± 5.16	10.8 ± 5.21	10.35 ± 5.17	9.24 ± 4.37	**0.027**
SUA (μmol/L)		307.41 ± 85.62	310.2 ± 86.35	304.52 ± 84.11	331 ± 99.94	0.14
eGFR		99.29 ± 23.31	102.51 ± 20.04	98.4 ± 24.15	88.95 ± 28.76	**0.002**
Urea creatinine ratio		90.46 ± 27.14	90.07 ± 26.87	90.88 ± 27.36	87.07 ± 25.95	0.505
TC		4.43 ± 1.16	4.4 ± 1.13	4.45 ± 1.18	4.36 ± 1.05	0.863
HDL		1.13 ± 0.29	1.13 ± 0.29	1.14 ± 0.3	1.12 ± 0.25	0.832
LDL-c (mmol/L)		2.65 ± 0.89	2.62 ± 0.89	2.67 ± 0.89	2.64 ± 0.83	0.588
TG		1.83 ± 1.42	1.92 ± 1.66	1.8 ± 1.32	1.6 ± 0.94	0.366
Free fatty acids		54.8 ± 23.61	56.08 ± 23.78	54.16 ± 23.43	55.08 ± 25.37	0.45
Mean blood glucose concentration		12.44 ± 3.57	12.06 ± 3.64	12.64 ± 3.56	12.12 ± 2.91	**0.01**
HbA1c		8.79 ± 1.87	8.6 ± 1.9	8.9 ± 1.86	8.63 ± 1.52	**0.01**
Fasting C-peptide		1.72 ± 1.21	1.78 ± 0.97	1.67 ± 1.26	1.98 ± 1.9	**0.003**
Fasting insulin		15.55 ± 13.92	14.45 ± 11.8	15.97 ± 14.76	17.23 ± 14.96	0.275
TSH		2.24 ± 2.56	2.17 ± 1.75	2.21 ± 1.9	3.28 ± 8.85	0.596
Vitamin D		19.93 ± 7.26	19.85 ± 6.06	20.09 ± 7.6	18.03 ± 9.66	0.093
Serum calcium		2.28 ± 0.1	2.3 ± 0.1	2.28 ± 0.09	2.26 ± 0.19	**0.011**
SUA/eGFR		3.91 ± 9.86	3.23 ± 1.71	4.1 ± 11.86	6.19 ± 11.33	**0.022**

Table 1. Comparison of clinical characteristics between groups. SBP: systolic blood pressure, DBP: diastolic blood pressure, ESR: erythrocyte sedimentation rate, SUA: serum uric acid, eGFR: glomerular filtration rate, TC: total cholesterol, HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, HbA1c: hemoglobin A1c, TSH: thyrotropin, sSUA/eGFR: serum uric acid to eGFR ratio; P value represents the comparison of NDR group, NPDR group and PDR group.

better understand the association between SUA and DR. Logistic regression after adjusting for gender, history of drinking and smoking, hemoglobin, total bilirubin, fasting C-peptide, serum calcium, we found that SUA/eGFR levels were not involved in the onset of DR. However, after stratified analysis, we found that in T2DM patients who are aged < 60 years or have an HbA1c level ≥ 7%, a high SUA/eGFR ratio is a risk factor for DR.

Multiple clinical studies in T2DM patients have found that high SUA levels are associated with the severity of DR[9,12,27]. Other studies have pointed to a significant inverse association between urinary uric acid excretion and the presence of DR in T2DM[28]. Hyperuricemia may be secondary to renal disease because of reduced SUA excretion (inadequate SUA excretion), so the use of SUA levels normalized for renal function is necessary. In our study, 1399 T2DM patients were divided into NDR, NPDR, and PDR groups according to the severity of DR. Compared with patients in the NDR and NPDR groups, those in the PDR group had significantly

	NDR group	DR group	*P* value
Model 1 OR crude (95% CI)	Ref	1.08(1.02–1.14)	**0.008**
Model 2 OR adjusted (95% CI)	Ref	1.06(1.00-1.13)	0.06
Age-stratified Model 2 OR adjusted (95% CI)			
≥60	Ref	1.02(0.96–1.09)	0.556
<60	Ref	1.20(1.05–1.38)	**0.01**
HbA1c-stratified Model 2 OR adjusted (95% CI)			
HbA1c≥7%	Ref	1.10(1.00-1.20)	**0.045**
HbA1c<7%	Ref	1.04(0.95–1.14)	0.387

Table 2. Association between SUA/eGFR and DR. Model 1: a univariable analysis; Model 2: adjusted for gender, smoking history, alcohol history, diabetes duration, hemoglobin, total bilirubin, HbA1c, fasting C-peptide, and serum calcium.

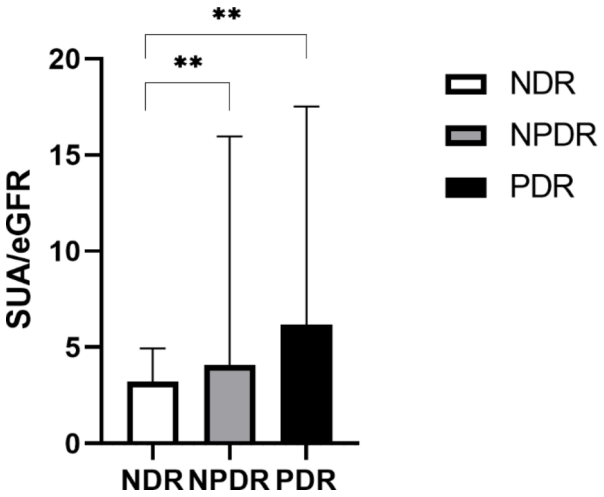

Fig. 1. The SUA/eGFR values among the three DR groups. *:$P<0.05$;**:$P<0.01$;***:$P<0.001$.

	NDR group	NPDR group		PDR group	
		OR(95% CI)	P value	OR(95% CI)	P value
Model 1 OR crude	Ref	1.08(1.02–1.14)	**0.008**	1.09(1.03–1.15)	**0.005**
Model 2 OR adjusted	Ref	1.06(1.00-1.13)	0.065	1.07(1.00-1.14)	**0.036**
Age-stratified Model 2 OR adjusted					
≥60	Ref	1.01(0.94–1.09)	0.779	1.08(0.99–1.18)	0.087
<60	Ref	1.20(1.04–1.38)	**0.010**	1.20(1.04–1.38)	**0.012**
HbA1c-stratified Model 2 OR adjusted					
HbA1c≥7%	Ref	1.09(1.00-1.19)	**0.049**	1.10(1.01–1.20)	**0.037**
HbA1c<7%	Ref	1.05(0.96–1.15)	0.327	0.91(0.62–1.32)	0.611

Table 3. Association between SUA/eGFR and DR severity grading. Model 1: a univariable analysis; Model 2: adjusted for gender, smoking history, alcohol history, diabetes duration, hemoglobin, total bilirubin, HbA1c, fasting C-peptide, and serum calcium.

higher levels of SUA/eGFR. Multivariate logistic regression analysis revealed a positive correlation between SUA/eGFR and PDR, but not with NPDR, which aligns with previous research[7]. This phenomenon may be attributed to the cumulative effect of SUA/eGFR. NPDR represents the initial phase of DR, characterized by relatively mild pathology primarily driven by microvascular damage and leakage due to chronic hyperglycemia. During this stage, the increase in SUA/eGFR may not yet reach a threshold that significantly impacts disease progression, hence its minimal effect on the risk of NPDR development. Conversely, PDR denotes the advanced stage of DR, marked by more severe pathology involving complex mechanisms such as neovascularization and fibrovascular proliferation. Prolonged high levels of SUA/eGFR could lead to the accumulation of oxidative stress, inflammatory responses, and vascular endothelial damage, ultimately propelling the progression from

NPDR to PDR. Additionally, for T2DM patients who were aged < 60 years or had an HbA1c level ≥ 7%, a high SUA/eGFR ratio was identified as a risk factor for the severity of DR.

UA is primarily excreted by the kidneys, and SUA levels are inversely related to renal function. Most patients with hyperuricemia exhibit varying degrees of renal insufficiency. Whether SUA plays an independent role in the occurrence and progression of DR or is merely a marker of deteriorating renal function remains a controversial issue. SUA have not been standardized by renal function in previous clinical studies. Therefore, this study used SUA normalized for renal function for analysis.

Our study indicates that SUA/eGFR levels are linked to DR and its severity in young patients(age <60), but not in the elderly. Younger patients have a higher metabolic rate, and the dynamic balance between uric acid production and excretion is more susceptible to influences such as diet, exercise, and stress, leading to greater fluctuations in SUA levels. Sharp fluctuations in SUA levels may trigger more intense oxidative stress and inflammatory responses[29], accelerating the progression of DR. The study also found that SUA was associated with DR in patients with HbA1c levels ≥ 7%, but no such association was observed in those with HbA1c < 7%. This phenomenon may be attributed to the synergistic pro-oxidative stress effect of SUA with hyperglycemia. In vitro models have demonstrated that elevated UA levels can exacerbate retinal inflammation under hyperglycemic conditions[30]. For patients with well-controlled blood glucose, the vascular microenvironment remains relatively stable, and SUA alone is insufficient to induce significant damage.

SUA plays a significant role in the pathogenesis and progression of DR. UA can activate the NLRP3/NALP3 inflammasome and upregulate the expression of inflammatory mediators, such as TNF-α, IL-6, and C-reactive protein[31]. These inflammatory factors have been shown to induce vascular dilation, retinal edema, platelet aggregation, and other pathological changes during the onset of DR. Zhu et al. reported that elevated uric acid can promote retinal inflammation and enhance the activity of the Notch signaling pathway in the context of hyperglycemia[30]. UA contributes to endothelial dysfunction by inhibiting endothelial cell migration and proliferation, reducing NO bioavailability, disrupting endothelial secretory function, and upregulating VEGF expression, thereby promoting the development and progression of DR in DM patients[32].

However, there are some limitations to our study. Our study was a cross-sectional survey, so we could only analyze the correlation between SUA/eGFR and DR, but could not investigate the causal relationship between them. SUA changes dynamically in the human body. This study is a cross-sectional study, and the data of SUA are only replaced by the data of one examination of the patient, which cannot represent the SUA changes of the patient throughout the progression of the disease. Although our analysis revealed a certain correlation between SUA/eGFR and DR, the effect size was small, with the confidence interval close to 1. This may be related to the insufficient sample size of PDR, which limited our ability to detect a larger effect. Future studies may consider increasing the sample size to more accurately assess this relationship. Therefore, more studies with larger sample sizes or with people from different regions are still needed to validate our findings.

Conclusion

Elevated SUA/eGFR in patients with T2DM is a risk factor for the progression from NPDR to PDR. SUA/eGFR holds significant clinical value in younger patients or those with poorly controlled blood glucose levels in T2DM. By incorporating it into DR risk assessment and intervention strategies, it may facilitate early identification, precise intervention, and improved patient prognosis. Further studies, including prospective clinical studies and experimental studies, are needed to determine the impact and potential pathophysiological role of uric acid in predicting the onset and progression of DR.

Data availability

The data in this study are available from the corresponding author upon reasonable request.

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Author contributions
All authors have made substantial contributions to the conception and design of the study. N.C., M.Q, L.C have been involved in data collection, data analysis, data interpretation, drafting the manuscript. H.X., C.L. and W.C. have been involved in revising the manuscript critically. All authors read and approved the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

Institutional review board statement
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Qilu Hospital.

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Correspondence and requests for materials should be addressed to C.W. or X.H.