Higher Serum Uric Acid Levels Are Associated With an Increased Risk of Vision-Threatening Diabetic Retinopathy in Type 2 Diabetes Patients

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Purpose. To investigate the association between serum uric acid (SUA) levels and vision-threatening diabetic retinopathy (VTDR) in patients with type 2 diabetes.

Methods. This cross-sectional study evaluated 3481 patients with type 2 diabetes from four communities in China between 2016 and 2019. VTDR was defined as severe nonproliferative, proliferative diabetic retinopathy, or clinically significant macular edema evaluated by fundus photography and optical coherence tomography. Potential association between SUA and VTDR was examined using multivariable logistic regression. Sub-group analyses based on sex were constructed.

Results. A total of 305 participants had VTDR. Both higher SUA (odds ratio [OR], 1.22 per 100 µmol/L; 95% confidence interval [CI], 1.04–1.44; $P = 0.013$) and hyperuricemia (OR, 1.47; 95% CI, 1.07–2.04; $P = 0.019$) were positively associated with VTDR after adjustment for relevant covariates. Compared with those in the lowest SUA quartile, participants in the third (OR, 1.60; 95% CI, 1.07–2.39; $P = 0.022$) and fourth (OR, 2.05; 95% CI, 1.37–3.08; $P = 0.001$) sex-specific SUA quartiles showed a significantly increased risk of VTDR after adjustment. No sex-related difference was observed.

Conclusions. Higher SUA levels were associated with an increased risk of VTDR in patients with type 2 diabetes in both sexes, although females seemed to be more sensitive to high SUA than males. Prospective cohort studies are needed to verify SUA as a biomarker for predicting the risk of VTDR. Whether decreased SUA levels could decrease the risk of VTDR also requires further investigation.

Keywords: serum uric acid, diabetic retinopathy, vision-threatening diabetic retinopathy

The incidence of hyperuricemia and associated gout is increasing worldwide, especially in high-income countries and economically developing countries with a Western lifestyle.[1] Growing evidence suggests that hyperuricemia is correlated with various metabolic and cardiovascular diseases.[2] For instance, elevated serum uric acid (SUA) is increasingly recognized as an important risk factor for diabetes mellitus and chronic complications of diabetes such as diabetic retinopathy (DR).[3,4]

DR is a common diabetic microvascular complication and a leading cause of visual impairment in working-age adults worldwide.[5] In a meta-analysis of 35 studies performed worldwide, researchers estimated an overall prevalence of 34.6% for any DR and 10.2% for vision-threatening DR (VTDR) among people with diabetes.[6] According to the Eye Diseases Prevalence Research Group definition, VTDR is defined as the presence of severe nonproliferative DR (NPDR), proliferative DR (PDR), and/or clinically significant macular edema.[5]

Cross-sectional and prospective studies have suggested an association between SUA and DR.[7–10] In patients with type 1 diabetes, a nationwide cross-sectional study conducted in Brazil revealed that SUA is positively associated with VTDR.[11] In patients with type 2 diabetes (T2D), a prospective study in Taiwan revealed that SUA levels were associated with a worsening in the severity of DR.[12] Further, our previous experimental results demonstrated that UA displays proinflammatory and proapoptotic activities through the Notch pathway in DR pathogenesis.[13] However, to our knowledge, the association between SUA and VTDR in patients with T2D remains largely unknown.

Compared to type 1 diabetes, T2D comprises a larger proportion of the disease burden in patients with visual impairment from retinopathy owing to the disproportionately large number of patients in this group. Therefore, in the current study, we aimed to investigate the association between SUA levels and VTDR in a multicenter and cross-sectional population of patients with T2D.

Methods

Study Participants

This is a cross-sectional, observational study. Patients who met the T2D criteria according to the 2006 American Diabetes Association guidelines between 2016 and 2019 were included. The exclusion criteria were as follows: (1) advanced renal failure, defined as an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m^2 and (2) other severe diseases, including thyroid problems, obstructive liver disease, heart diseases, urinary tract infection, lung infection, cerebrovascular accident, or tuberculosis. In total, 3481 patients were included in this analysis from four communities: Shanghai General Hospital (n = 1570), Shanghai 10th People's Hospital (n = 710), PLA Navy Anqing Hospital (n = 601), and Shanghai TCM-INTEGRATED Hospital (n = 600).

The study was performed following the guidelines of the World Medical Association Declaration of Helsinki and was approved by the Institutional Review Board of the Shanghai General Hospital, Shanghai Jiao Tong University. Written informed consent was obtained from all patients or their legal guardians in the respective centers where patients were recruited.

Baseline Data Collection

Diabetes duration was calculated as the difference between self-reported age of diabetes diagnosis and age at baseline examination. Anthropometric variables (height, weight, waist, and hip circumference) were measured while each subject was in the standing position. Body mass index (BMI) was calculated as weight (kg)/height^2 (m), and waist and hip measurements were conducted to determine waist-to-hip ratio. Systolic blood pressure and diastolic blood pressure values were measured (to the nearest mm Hg), while each subject was in a sitting position. Serum biochemical variables (SUA, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, and glycated hemoglobin) were measured using a conventional automated blood analyzer. The eGFR was calculated using the Modification of Diet in Renal Disease equation.[14] Hyperuricemia was defined as SUA levels of ≥420 µmol/L for males and ≥360 µmol/L for females. Chronic kidney disease was defined as an eGFR of <60 ml/min/1.73 m^2. Hypertension was defined as a systolic blood pressure of >140 mm Hg, a diastolic blood pressure of >90 mm Hg, or having a self-reported diagnosis of or treatment for hypertension. A single 24-hour urine sample was collected during the period of hospitalization, and urinary UA excretion (UUAE) was determined by enzymatic methods using a single 24-hour urine collection.

DR Evaluation

Each participant underwent a standardized clinical eye examination performed by experienced ophthalmologists, including a review of ophthalmologic history, measurement of visual acuity and IOP, slit lamp examination, and dilated fundus examination. The two -field (macular and optic disc), 45° digital retinal photography was undertaken after pupil dilation by a digital retinal camera (Carl Zeiss Meditec AG, Jena, Germany) using a standardized protocol.[15] Optical coherence tomography was obtained by Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany). The severity of DR was graded according to the Early Treatment Diabetic Retinopathy Study system for the worse eye.[16] Clinically significant macular edema was defined as edema within 500 mm of the foveal center or presence of focal laser photocoagulation scars in the macular area. VTDR was defined as severe NPDR, PDR, or clinically significant macular edema.

Table 1. Baseline Characteristics of the Study Population

Variable	Non-VTDR (n = 3176)	VTDR (n = 305)	P Value
Serum uric acid (µmol/L)	320.4 ± 87.8	334.8 ± 84.1	0.006
Hyperuricemia*	584 (18.4)	77 (25.2)	0.005
Male sex	1823 (57.4)	164 (53.8)	0.221
Age (y)	56.7 ± 11.3	59.1 ± 9.1	<0.001
Diabetes duration (y)	7 (3, 12)	14 (8, 18)	<0.001
BMI (kg/m^2)	25.2 ± 3.5	24.9 ± 3.4	0.211
Waist-to-hip ratio	0.92 ± 0.07	0.93 ± 0.07	0.163
Hypertension	1396 (44.0)	164 (53.8)	0.001
SBP (mm Hg)	131.1 ± 16.4	138.4 ± 20.2	<0.001
DBP (mm Hg)	80.5 ± 9.2	81.3 ± 10.2	0.174
Fasting blood glucose (mmol/L)	8.2 ± 2.9	8.0 ± 2.8	0.150
HbA1c (%)	8.9 ± 2.2	9.2 ± 2.2	0.022
Total cholesterol (mmol/L)	4.80 ± 1.16	5.03 ± 1.40	0.006
Triglycerides (mmol/L)	1.49 (1.02, 2.16)	1.47 (0.97, 2.05)	0.112
HDL-C (mmol/L)	1.10 ± 0.30	1.15 ± 0.34	0.014
LDL-C (mmol/L)	3.07 ± 0.94	3.18 ± 1.10	0.094
eGFR (mL/min/1.73 m^2)	99.4 ± 23.7	87.1 ± 27.6	<0.001
Urinary uric acid excretion (mmol/24 h)	3082.6 ± 1267.9	2613.6 ± 1019.1	<0.001
Chronic kidney disease	128 (4.0)	44 (15.3)	<0.001

Data are reported as the mean ± standard deviation, median (interquartile ranges) or n (%). P values indicate the difference in the diabetic retinopathy severity categories, based on either t test, Mann-Whitney U test, or χ^2 test, as appropriate.

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; VTDR, vision-threatening diabetic retinopathy.

* Hyperuricemia: defined as serum uric acid levels of ≥420 µmol/L for males and ≥360 µmol/L for females.

Table 2. Associations of Hyperuricemia and Serum Uric Acid Levels With the Presence of Vision-Threatening Diabetic Retinopathy

	Hyperuricemia			Serum Uric Acid (Per 100 µmol/L)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Model 1	1.50	1.14–1.97	0.004	1.20	1.05–1.36	0.006
Model 2 + age, sex	1.48	1.13–1.95	0.005	1.24	1.09–1.42	0.001
Model 3 + diabetes duration, hypertension, SBP, BMI	1.48	1.10–2.00	0.010	1.24	1.07–1.44	0.004
Model 4 + HbA1c, total cholesterol, HDL-C, LDL-C	1.55	1.14–2.10	0.005	1.28	1.10–1.49	0.001
Model 5 + urinary uric acid excretion, chronic kidney disease	1.47	1.07–2.04	0.019	1.22	1.04–1.44	0.013

CI, confidence interval; BMI, body mass index; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure.

Statistical Analysis

All analyses were performed by SPSS software (version 24.0, IBM, Armonk, NY). Data are reported as the mean ± standard deviation or medians (interquartile ranges) and number (%) for the description of continuous and categorical variables, respectively. Baseline characteristics of the participants were compared by using either the *t* test, Mann–Whitney U test, or χ^2 test, depending on the variable distribution.

Correlations between SUA and other clinical variables were tested with Spearman rank correlation tests (Supplementary Table S1). A strong correlation was defined as a correlation coefficient greater than 0.4 and a *P* value of less than 0.01. Logistic regression models were used to examine the relationships between SUA or hyperuricemia and the VTDR outcome. Variables with a *P* value of less than 0.1 in univariate regression were included in the multivariate logistic regression models. *P* values for the multiplicative interaction of sex with SUA or hyperuricemia as a continuous variable were obtained by adding the multiplicative term to a multivariate logistic model, and *P* values for the addictive interaction of sex with hyperuricemia were calculated using the procedure proposed by Andersson et al.[17] To test whether the relationship between SUA and VTDR outcome differed by sex, the analysis was performed separately for males and females. The results for each sex are presented. All tests were two sided, and a *P* value of less than 0.05 was considered statistically significant.

Results

Characteristics of the Study Subjects

Table 1 reports the characteristics of the 3481 participants included in the analysis, including 305 participants diagnosed with VTDR (8.8%). The mean SUA at baseline was 321.6 µmol/L, with 19.0% of participants found to have hyperuricemia. Compared with those without VTDR, participants with VTDR had greater baseline SUA (334.8 µmol/L vs. 320.4 µmol/L; $P = 0.006$) and hyperuricemia prevalence (25.2% vs. 18.4%; $P = 0.005$). In addition, VTDR participants had lower UUAE (2613.6 mmol/24 hours vs. 3082.6 mmol/24 hours; $P < 0.001$) than participants without VTDR. No significant sex difference was observed in the two groups ($P = 0.221$). The SUA levels were similar in patients with no DR and patients with sub-VTDR (321.1 ± 88.3 µmol/L vs. 317.0 ± 85.9 µmol/L; $P = 0.294$), and there was no significant difference in hyperuricemia ($P = 0.171$).

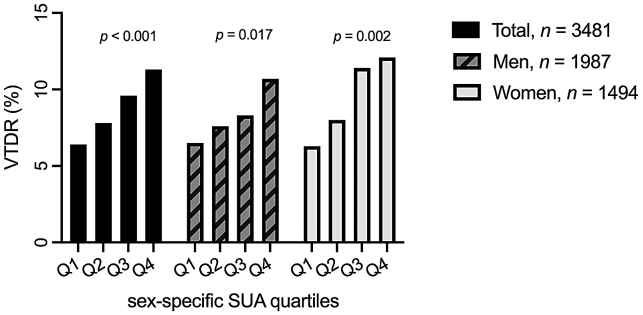

Figure. The percent of vision-threatening diabetic retinopathy (VTDR) in diabetic participants with varying serum uric acid (SUA) levels, stratified by sex. Sex-specific SUA quartiles cut-off values are found in the Results (Q1: men or women with lowest 25% SUA). *P* values were calculated using the χ^2 test for trend. The percent of VTDR increased with increasing SUA quartiles in both men and women participants.

Correlations of SUA With Other Clinical Characteristics

A correlation analysis (Supplemental Table S1) showed that, after adjustment for sex, age, and duration of diabetes, SUA was more closely associated with BMI and eGFR than with other clinical characteristics; there was a moderate positive relationship between SUA and BMI (partial correlation coefficient = 0.271; $P < 0.001$). No significant correlation was observed between SUA and UUAE (partial correlation coefficient = 0.012; $P = 0.526$).

Associations of SUA and Hyperuricemia With VTDR

Logistic regression analyses were constructed. VTDR was associated with higher SUA (odds ratio [OR] per 100 µmol/L, 1.28; $P = 0.001$) as well as hyperuricemia (OR, 1.55; $P = 0.005$) after adjustment for relevant covariates (Table 2, model 4). After additionally adjusting for UUAE and chronic kidney disease, the relationship persisted.

We also grouped SUA levels into four categories using sex-specific quartiles: <280 µmol/L in the first quartile; 280–332 µmol/L in the second quartile; 333–393 µmol/L in the third quartile; and ≥394 µmol/L in the fourth quartile for males; and <242 µmol/L in the first quartile, 242–288 µmol/L in the second quartile, 288–345 µmol/L in the third quartile, and ≥346 µmol/L in the fourth quartile for females. The prevalence of VTDR increased with increasing SUA quartiles (*P* for trend < 0.001; Fig). In multivariate logistic regression analysis (Table 3), participants in the third and fourth

Table 3. Associations of Sex-Specific Serum Uric Acid Quartiles With the Presence of VTDR

	Prevalence of VTDR	Univariate			Multivariate		
Sex-specific Quartiles	***n* (%)**	**OR**	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Total							
Q1	57 (6.4)	Reference		<0.001*	Reference		<0.001*
Q2	68 (7.8)	1.23	0.85–1.77	0.275	1.33	0.89–1.98	0.161
Q3	83 (9.6)	1.55	1.09–2.20	0.015	1.60	1.07–2.39	0.022
Q4	97 (11.3)	1.85	1.31–2.60	<0.001	2.05	1.37–3.08	0.001
Male							
Q1 (<280)	33 (6.5)	Reference		0.018*	Reference		0.013*
Q2 (280–332)	38 (7.6)	1.19	0.73–1.93	0.488	1.41	0.84–2.37	0.198
Q3 (333–393)	41 (8.3)	1.30	0.81–2.09	0.284	1.19	0.69–2.06	0.536
Q4 (≥394)	52 (10.7)	1.72	1.09–2.71	0.020	2.01	1.18–3.41	0.010
Female							
Q1 (<242)	24 (6.3)	Reference		0.002*	Reference		0.005*
Q2 (242–288)	30 (8.0)	1.28	0.73–2.23	0.387	1.31	0.71–2.43	0.384
Q3 (289–345)	42 (11.4)	1.91	1.13–3.22	0.016	2.10	1.17–3.78	0.013
Q4 (≥346)	45 (12.1)	2.02	1.21–3.40	0.008	2.17	1.20–3.92	0.010

Sex-specific quartiles are shown in the table (µmol/L).

The multivariate logistic regression model was adjusted for age, sex (only in the total population), BMI, hypertension, SBP, diabetes duration, HbA1c, chronic kidney disease, total cholesterol, HDL-C, LDL-C, and urinary uric acid excretion.

BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; VTDR, vision-threatening diabetic retinopathy.

* *P* for trend.

Table 4. Associations of Hyperuricemia and Serum Uric Acid Levels With the Presence of Vision-threatening Diabetic Retinopathy Stratified by Sex

	Hyperuricemia			Serum Uric Acid (Per 100 µmol/L)		
	OR	**95% CI**	***P* Value**	**OR**	**95% CI**	***P* Value**
Male						
Univariate	1.57	1.08–2.30	0.018	1.13	0.95–1.35	0.158
Multivariate	1.66	1.05–2.64	0.032	1.12	0.91–1.39	0.277
Female						
Univariate	1.40	0.94–2.09	0.097	1.42	1.15–1.75	0.001
Multivariate	1.34	0.85–2.12	0.208	1.44	1.14–1.83	0.002

The multivariate logistic regression model was adjusted for age, BMI, hypertension, SBP, diabetes duration, HbA1c, chronic kidney disease, total cholesterol, HDL-C, LDL-C, and urinary uric acid excretion.

BMI, body mass index; CI, confidence interval; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SBP, systolic blood pressure; VTDR, vision-threatening diabetic retinopathy.

SUA quartiles showed a significantly increased risk for VTDR compared with that of those in the lowest SUA quartile (adjusted OR, 1.60 and 2.05; $P = 0.022$ and $P = 0.001$, respectively).

Subgroup Analyses Based on Sex

Considering the potential different impacts of SUA on VTDR according to sex, the analysis was stratified by sex. The baseline characteristics stratified by sex are reported in Supplemental Table S2. The prevalence of VTDR increased with increasing SUA quartiles in both male and female subjects (P for trend = 0.017 and 0.002, respectively; Fig). In female subjects, the subjects in the third and fourth SUA quartiles were more likely to have VTDR than those in the lowest SUA quartile (adjusted OR, 2.10 and 2.17; $P = 0.013$ and $P = 0.010$, respectively; Table 3). In contrast, only male subjects in the highest SUA quartile showed a significant increase in VTDR compared with those in the lowest SUA quartile (adjusted OR, 2.01; $P = 0.010$; Table 3). In female subjects, SUA levels were positively associated with VTDR risk without any evidence of a threshold (Table 4). In contrast, in male subjects, we observed a positive association only between hyperuricemia and VTDR (Table 4). For further confirmation, the interaction of sex with SUA or hyperuricemia was analyzed. However, neither multiplicative nor additive interaction was observed between SUA or hyperuricemia and sex (data not shown) in multivariable logistic analysis.

Interestingly, we found that BMI as a continuous variable had an inverse association with VTDR only in males (adjusted OR, 0.94; 95% confidence interval [CI], 0.88–1.00; $P = 0.047$) but not in females (OR, 0.99; 95% CI, 0.94–1.05; $P = 0.780$). Moreover, we observed a multiplicative interaction of BMI with hyperuricemia in male subjects (OR, 0.98; 95% CI, 0.95–1.00; $P = 0.072$).

Discussion

To the best of our knowledge, this large-scale cross-sectional study is the first to show that higher SUA levels were associated with a higher risk of VTDR in T2D patients. No sex-specific association between SUA and VTDR was observed in this study, although females seemed to be more sensitive than males to high SUA levels.

Extensive research has also focused on the role of SUA in the pathophysiology of DR; however, the role of SUA in the process of DR development is controversial. To date, many studies have reported positive associations,[7] inverse associations,[8,9] no associations,[18,19] or sex-dependent associations[10] between SUA and DR development. A study with 652 patients with T1D showed that SUA was predicted to be associated with increased odds of developing DR.[7] A study in Japan revealed that higher SUA levels were associated with a high risk of newly developed DR in male patients[10]; however, this association was not found in female patients. However, one study analyzing 15-year medical records of male patients showed that low SUA levels precede DR incidence.[8] In addition, in a cross-sectional study of 1749 diabetic participants in Beijing, a higher SUA level was an independent protective factor for DR.[9] Moreover, a meta-analysis of nine studies and a recent study conducted in China did not demonstrate a strong association between SUA levels and DR.[18,19] Another study showed a poor correlation of SUA with retinal nerve fiber layer and macular thickness among T2D patients without DR or with NPDR.[20] In their study, the SUA levels of NPDR participants were significantly lower than those of participants without DR.[20] In our study sample, however, no significant difference was observed in SUA levels between patients with sub-VTDR and no DR.

In contrast, the results regarding the association between SUA and PDR have been consistent. In patients with T2D, patients with PDR have higher levels of SUA than those without DR or with NPDR.[21,22] Furthermore, a large-scale prospective study of 749 patients with T2D revealed that SUA levels were associated with a worsening in the severity of DR in Taiwan.[12] Moreover, intravitreal levels of UA were significantly higher in diabetic patients with macular edema than in nondiabetic control subjects.[23,24] Taken together, these studies suggest that SUA seems to be involved in more advanced retinopathy in T2D. Consistently, in our T2D sample, we found that SUA levels were significantly higher in patients with VTDR than in those without VTDR.

SUA levels are also regulated by the excretion of UA. Of total UA excretion, 70% is mediated by the kidney. Li et al.[25] reported that decreased UUAE is associated with DR in hospitalized patients with T2D. Hence, we were careful to include UUAE in our model. Consistently in this study, decreased UUAE was also independently associated with an increased risk of VTDR. It is speculated that, as UUAE decreases, an increased amount of SUA passes through the dysfunctional blood–retinal barrier and accumulates in the vitreous, causing retinal vascular damage, which in turn promotes the development of VTDR.

However, the underlying physiological mechanism is not yet known. Various studies have shown that UA can result in endothelial dysfunction, which can lead to vascular disease.[26] Several possible mechanisms can be considered. UA, the product of purine metabolism, usually acts as an antioxidant. However, paradoxically, it can also act as a pro-oxidant because reactive oxygen species are generated during its production. In parallel, previous experimental studies suggest that higher levels of UA can activate the NLRP3 inflammasome and stimulate the production of inflammatory cytokines.[27–29] Our previous research also reported that UA displays proinflammatory and proapoptotic activities through the Notch pathway in DR pathogenesis.[13] In addition, hyperuricemia could inhibit the production of endothelial nitric oxide and activate the serum-angiotensin system.[30] Given these findings, UA could play a role in VTDR development.

Contrary to expectations, in this study, no sex-dependent difference was observed in the association between SUA and VTDR. Women's serum urate levels remain relatively low throughout most of their adult lives because of the uricosuric effect of oestrogens.[31] The study in Japan discussed elsewhere in this article reported a prospective association between baseline SUA levels and developed DR only in males.[10] Other studies reported that an increase in SUA can be more detrimental to females than males. Although hyperuricemia increases the overall risk for T2D in individuals of either sex, females with hyperuricemia are much more likely to develop diabetes than males with hyperuricemia.[31] In this study, although no such difference was identified in the sex-stratified analysis, we noticed that females seemed to be more sensitive to elevated SUA than males. Age, sex, or cohort differences may explain the discrepancy. More research is still required.

Surprisingly, we observed a multiplicative interaction of BMI with hyperuricemia in male subjects. In this study, we observed a positive correlation between BMI and SUA and an inverse association between BMI and VTDR in male subjects. This result is consistent with previous studies showing that BMI is positively associated with SUA levels[32,33] and is inversely associated with DR presence and severity in Asian populations.[34–37] However, no association between BMI and VTDR was observed in female subjects. This discrepancy might be explained partly by differences in study methodology and population.

Our findings must be considered in light of the study limitations. The principle limitation of this study is related to the study's observational cross-sectional nature, which prevents conclusions concerning the predictive value of SUA for VTDR development. Our analysis also has some important strengths. To our knowledge, this study was the first that incorporated UUAE into analyses of SUA and retinopathy risk, thereby enhancing the potential aetiologic understanding. Other strengths include its multicenter design, large sample size, and sex-stratified analyses.

In conclusion, higher SUA levels were associated with an increased risk of VTDR in T2D patients of both sexes, independent of UUAE. Females seem to be more sensitive to elevated SUA than males. Prospective cohort studies are needed to verify SUA as a predictor of the risk of VTDR. Whether UA-targeted care can reduce the risk of VTDR also requires further investigation.

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