

Retinal Microvascular Diameters are Associated with Diabetic Kidney Disease in Patients with Type 2 Diabetes Mellitus

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Objective: To investigate the association between retinal microvascular diameters and diabetic kidney disease (DKD) in patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 690 patients with T2DM were included in this retrospective study. Patients were divided into DKD and non-DKD groups according to urine microalbumin/creatinine ratio and estimated glomerular filtration rate. Retinal microvascular diameters were measured by the automated retinal image analysis system. Multivariate logistic regression analysis and restricted cubic splines were used to assess the relationships between the retinal microvascular diameters and DKD in patients with T2DM.

Results: Multivariate logistic regression showed that widened diameters of retinal venules and narrowed diameters of retinal arterioles were associated with DKD after adjusting for potential confounding variables. There was a significant linear trend between the diameters of superior temporal retinal venula (P for trend < 0.001 , P for non-linearity = 0.080), inferior temporal retinal venula (P for trend < 0.001 , P for non-linearity = 0.111) and central retinal venular equivalent (CRVE) (P for trend < 0.001 , P for non-linearity = 0.392) and risk of DKD in patients with T2DM. The restricted cubic splines showed that narrowed retinal arteriolar diameters, superior and inferior nasal retinal venules were associated with the risk of DKD in a non-linear fashion (all P for non-linearity < 0.001).

Conclusion: Wider retinal venular diameters and narrower retinal arteriolar diameters were associated with an increased risk of DKD in patients with T2DM. Widened retinal venular diameters, especially CRVE, superior and inferior temporal retinal venula, were positively associated with an increased risk of DKD in a linear fashion. In contrast, narrowed retinal arteriolar diameters were associated with the risk of DKD in a non-linear fashion.

Keywords: diabetic kidney disease, type 2 diabetes mellitus, retinal venules, retinal arterioles, diameter

Introduction

Type 2 diabetes mellitus (T2DM) and its complications are a growing global public health problem.¹ Approximately 537 million adults around the world have diabetes, and this number is expected to increase to a staggering 783 million by 2045.^{1,2} Diabetic kidney disease (DKD), a common and serious microvascular complication of diabetes, affects about 40% of people with diabetes.^{3,4} DKD is the leading cause of chronic kidney disease and end-stage renal disease and increases the risk of cardiovascular disease and mortality.^{3,5} Although the pathogenesis of DKD remains incompletely understood, damage to microvascular components, such as endothelial cells and podocytes, seems to be a pivotal factor.^{3,6}

Researchers are working to reduce the global burden of DKD - a goal that depends on early detection of the disease.⁷ However, as the onset of DKD is asymptomatic and poor available biomarkers, early diagnosis is challenging.^{7,8} Like

DKD, diabetic retinopathy (DR) is a primary microvascular complication of T2DM.^{9,10} The co-occurrence of DR and DKD suggests that the same risk factors and mechanisms, such as microvascular damage, may underlie the development of ocular and renal complications of T2DM.^{11–13} Moreover, as the eye shares strikingly similar structural, functional, developmental and genetic pathways with the kidney,¹³ DKD and DR may be closely related. Retinal microvascular visualization offers the possibility to study the systemic microvasculature in a non-invasive way. Retinal microvascular diameters are the most commonly and easily observed retinal microvascular parameters and may be early predictors of a microvascular disease.¹⁴

A meta-analysis has suggested that retinal microvascular diameters may predict future risk for chronic kidney disease development and progression.¹⁵ However, few studies have explored the relationship between retinal microvascular diameters and DKD. Therefore, this study aimed to explore the association of retinal microvascular diameters and DKD and to evaluate whether retinal microvascular diameter is a potential biomarker for the early detection of DKD in patients with T2DM.

Materials and Methods

Participants

The retrospective study included 690 eligible patients with T2DM who were admitted to Hebei General Hospital from January 2020 to December 2021. DKD was defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² and/or urine microalbumin/creatinine ratio (UACR) ≥30 mg/g based on American Diabetes Association criteria.¹⁶ Inclusion criteria were as follows: diagnosis of T2DM based on World Health Organization criteria¹⁷ and completed more than one colour fundus photography in which the four main retinal venular or arteriolar trunks at the optic disc could be clearly defined. We excluded those with glaucoma, ametropia, uveitis, macular degeneration, cataract, diabetic ketoacidosis, diabetic hyperglycemic hyperosmolar state, acute cardiovascular and cerebrovascular diseases and end-stage renal disease. The process for patient selection is shown in Figure 1.

Clinical and Laboratory Assessments

Demographic characteristics (age, sex and body mass index) and medical history (hypertension and duration of T2DM) were collected from electronic databases or by interviewing patients. Systolic blood pressure (SBP) and diastolic blood

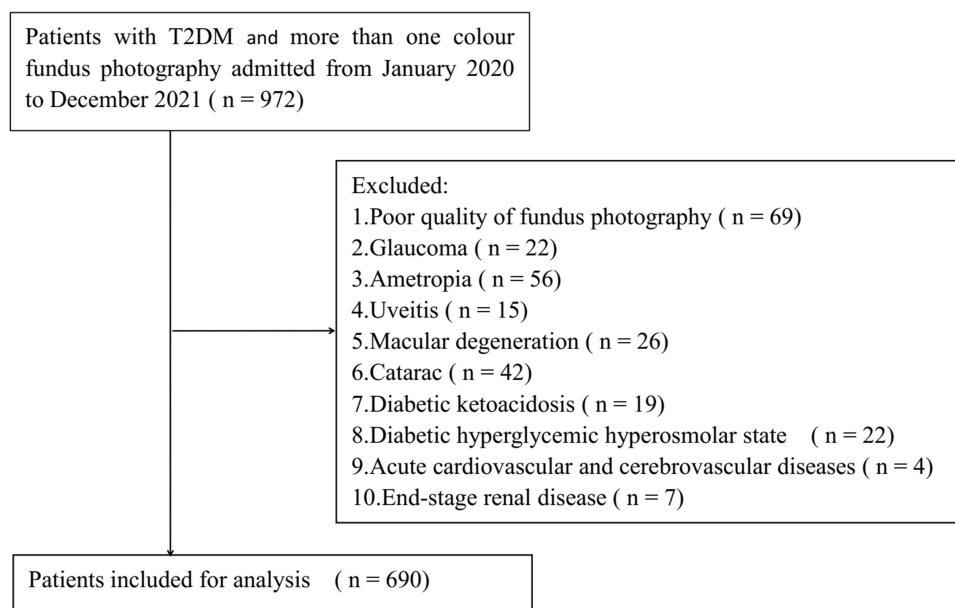


Figure 1 Flow chart of patient selection.

Abbreviation: T2DM, type 2 diabetes mellitus.

pressure (DBP) were measured in a quiet environment. Hypertension was defined as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, previous diagnosis of hypertension or antihypertensive treatment. Fasting plasma glucose (FPG), blood urea nitrogen (BUN), serum creatinine (Scr), uric acid (UA), urine microalbumin, urine creatinine, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and glycosylated haemoglobin (HbA1c) were measured in all patients after 8 hours of overnight fasting within two days of admission.

Measurement of Retinal Microvascular Diameters

A 45°Colour fundus photograph centred on the optic disc was taken in both eyes of all patients using a digital retinal camera (Canon CR-2 AF, Japan). Retinal microvascular diameters were measured from a fundus photograph of the right eye of each patient using an automated retinal image analyser (ARIA 1.0). The left eye was measured if the photograph of the right eye was ungradable. ARIA is software designed for the automated detection and measurement of retinal blood vessels. Retinal microvascular diameters were measured between one optic disc diameters and two optic disc diameter away from the central optic disc by two trained researchers who were blinded to the study. The diameters of the superior and inferior temporal retinal arterioles, superior and inferior nasal retinal arterioles, superior and inferior temporal retinal venules, and superior and inferior nasal retinal venules were recorded. Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were calculated using the modified Knudtson-Parr-Hubbard formula.^{18,19}

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 (IBM Corporation, Armonk, NY) and R, version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria). Continuous variables were expressed as mean \pm standard deviation or median (interquartile range), as appropriate. Categorical variables were expressed as the number of cases (percentage). Shapiro–Wilk test was used to test whether the variables were normally distributed. *t*-tests, Mann–Whitney *U*-tests, or chi-squared tests were used for different variables, as appropriate. Multivariate binary logistic regression models were used to investigate the association between retinal microvascular diameter and DKD in patients with T2DM. Tests for trend were conducted with using the quartiles of the retinal microvascular diameters as continuous variables by assigning the median values of the quartiles to the variable. The restricted cubic splines with four knot were used to test for possible non-linear relationships between the retinal microvascular diameters and DKD. $P < 0.05$ was considered to be statistically significant.

Results

Participant Characteristics

A total of 690 eligible participants (435 males and 255 females) were included in this retrospective study. The median age of the enrolled participants was 57 years. All participants were stratified into two groups in accordance with the American Diabetes Association criteria:¹⁶ non-DKD group ($n = 424$) and DKD group ($n = 266$).

Table 1 shows the clinical and laboratory characteristics of participants between non-DKD group and DKD group. Participants in the DKD group had significantly longer duration of T2DM and more frequent hypertension than those in the non-DKD group ($P < 0.05$). The DKD group presented higher SBP, body mass index, BUN, Scr, UA, and TG levels, but lower HDL-C than the non-DKD group ($P < 0.05$).

Retinal Venular Diameters and DKD

Participants with DKD showed significantly wider retinal venular diameters at the temporal superior, temporal inferior, nasal superior, nasal inferior and CRVE compared to the participants without DKD ($P < 0.001$) (Table 2). In univariate analysis, the widened diameters of all four retinal venules and CRVE were associated with DKD (odds ratio [OR]: 1.023, 95% confidence interval [CI]: 1.015 to 1.031, $P < 0.001$; OR: 1.037, 95% CI: 1.028 to 1.046, $P < 0.001$; OR: 1.038, 95% CI: 1.027 to 1.050, $P < 0.001$; OR: 1.030, 95% CI: 1.019 to 1.041, $P < 0.001$; OR: 1.041, 95% CI: 1.032 to 1.051, $P < 0.001$;

Table 1 Clinical and Laboratory Characteristics of Participants Between Non-DKD Group and DKD Group

Variable	Total (n=690)	Non-DKD Group (n=424)	DKD Group (n=266)	P value
Age, median (IQR), year	57 (47, 67)	57 (47, 66)	57 (46, 67)	0.401
Sex (male), n (%)	435 (63.0)	264 (62.3)	171 (64.3)	0.592
Hypertension, n (%)	332 (48.1)	168 (39.6)	164 (61.7)	<0.001*
SBP, median (IQR), mmHg	138 (123, 158)	130 (119, 142)	158 (138.75, 170)	<0.001*
DBP, median (IQR), mmHg	80 (72, 88)	81 (74, 88)	80 (70, 87)	0.075
Duration of T2DM, median (IQR), year	7 (1, 13)	5 (1, 10.8)	10 (2, 16)	<0.001*
Body mass index, median (IQR), kg/m ²	26.22 (23.73, 28.82)	25.90 (23.50, 28.40)	27.00 (24.20, 29.20)	0.022*
HbA _{1c} , median (IQR), %	9.20 (7.60, 10.90)	9.10 (7.43, 10.90)	9.30 (7.90, 10.70)	0.411
FPG, median (IQR), mmol/L	8.51 (6.52, 11.70)	8.18 (6.60, 11.62)	8.83 (6.37, 11.89)	0.878
BUN, median (IQR), mmol/L	5.30 (4.40, 6.60)	5.20 (4.30, 6.30)	5.40 (4.60, 7.13)	0.001*
Scr, median (IQR), μmol/L	61.9 (53.28, 72.33)	61.00 (52.95, 68.30)	65.15 (54.53, 80.00)	<0.001*
UA, median (IQR), μmol/L	314.85 (254.38, 383.63)	306.10 (250.68, 375.53)	331.40 (270.40, 399.73)	0.003*
TC, median (IQR), mmol/L	4.73 (3.83, 5.63)	4.77 (3.85, 5.60)	4.60 (3.75, 5.67)	0.480
TG, median (IQR), mmol/L	1.58 (1.03, 2.45)	1.49 (0.98, 2.32)	1.67 (1.11, 2.63)	0.007*
LDL-C, median (IQR), mmol/L	3.10 (2.39, 3.76)	3.14 (2.41, 3.76)	2.97 (2.36, 3.75)	0.368
HDL-C, median (IQR), mmol/L	1.07 (0.91, 1.28)	1.10 (0.94, 1.28)	1.05 (0.89, 1.24)	0.031*

Note: *Denotes significance at a *P* value of <0.05.

Abbreviations: DKD, diabetic kidney disease; IQR, interquartile range; SBP, systolic blood pressure; DBP, diastolic blood pressure; T2DM, type 2 diabetes mellitus; HbA_{1c}, glycosylated hemoglobin; FPG, fasting plasma glucose; BUN, blood urea nitrogen; Scr, serum creatinine; UA, uric acid; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

Table 2 Comparison of the Retinal Microvascular Diameters Between Non-DKD Group and DKD Group

Variable	Total (n=690)	Non-DKD Group (n=424)	DKD Group (n=266)	P value
Venule				
Temporal superior, median (IQR), μm	154.16 (138.58, 167.28)	149.24 (134.48, 164.82)	160.72 (148.42, 169.74)	<0.001*
Temporal inferior, median (IQR), μm	159.90 (141.04, 170.56)	151.70 (136.12, 166.46)	165.64 (157.24, 175.69)	<0.001*
Nasal superior, median (IQR), μm	112.75 (102.50, 123.82)	108.24 (99.22, 118.90)	119.72 (111.52, 127.10)	<0.001*
Nasal inferior, median (IQR), μm	113.16 (103.12, 122.18)	108.24 (100.04, 119.72)	118.08 (111.52, 123.82)	<0.001*
CRVE, median (IQR), μm	187.25 (170.65, 199.03)	180.78 (165.25, 193.67)	195.35 (186.03, 202.45)	<0.001*
Arteriole				
Temporal superior, median (IQR), μm	104.96 (96.76, 114.19)	109.06 (100.04, 116.44)	99.22 (94.30, 105.78)	<0.001*
Temporal inferior, median (IQR), μm	105.37 (96.76, 114.80)	108.24 (100.86, 117.26)	100.04 (92.66, 107.42)	<0.001*
Nasal superior, median (IQR), μm	86.10 (77.85, 95.12)	89.38 (82.00, 97.58)	81.68 (74.87, 88.77)	<0.001*
Nasal inferior, median (IQR), μm	85.28 (77.24, 95.12)	89.38 (82.00, 97.58)	80.98 (74.84, 86.31)	<0.001*
CRAE, median (IQR), μm	120.49 (111.47, 129.46)	124.65 (117.40, 131.00)	112.32 (108.26, 121.11)	<0.001*

Note: *Denotes significance at a *P* value of <0.05.

Abbreviations: CRVE, central retinal venular equivalent; CRAE, central retinal arteriolar equivalent.

respectively) (Table 3). This trend remained statistically significant after adjusting for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA (temporal superior OR: 1.026, 95% CI: 1.016 to 1.036, *P*<0.001; temporal inferior OR: 1.034, 95% CI: 1.023 to 1.045, *P*<0.001; nasal superior OR: 1.029, 95% CI: 1.016 to 1.042, *P*<0.001; nasal inferior OR: 1.024, 95% CI: 1.012 to 1.038, *P*<0.001; CRVE OR: 1.038, 95% CI: 1.026 to 1.050, *P*<0.001) (Table 3).

There was a significant linear trend between the diameters of superior temporal retinal venula (*P* for trend < 0.001, *P* for non-linearity = 0.080), inferior temporal retinal venula (*P* for trend < 0.001, *P* for non-linearity = 0.111) and CRVE (*P* for trend < 0.001, *P* for non-linearity = 0.392) and risk of DKD in patients with T2DM after adjusting for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA (Table 4 and Figure 2). The ORs of DKD of the

Table 3 The Logistic Regression Analyses Between Retinal Venular Diameters and DKD

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Temporal superior	1.023 (1.015 to 1.031)	<0.001	1.025 (1.016 to 1.033)	<0.001	1.026 (1.016 to 1.036)	<0.001
Temporal inferior	1.037 (1.028 to 1.046)	<0.001	1.038 (1.029 to 1.048)	<0.001	1.034 (1.023 to 1.045)	<0.001
Nasal superior	1.038 (1.027 to 1.050)	<0.001	1.039 (1.028 to 1.051)	<0.001	1.029 (1.016 to 1.042)	<0.001
Nasal inferior	1.030 (1.019 to 1.041)	<0.001	1.030 (1.019 to 1.042)	<0.001	1.024 (1.012 to 1.038)	<0.001
CRVE	1.041 (1.032 to 1.051)	<0.001	1.044 (1.033 to 1.054)	<0.001	1.038 (1.026 to 1.050)	<0.001

Notes: Model 1: Unadjusted. Model 2: Adjusted for duration of T2DM and hypertension. Model 3: Model 2 plus additional adjustments for SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA.

Table 4 ORs (and 95% CIs) of DKD According to Quartiles of Retinal Venular Diameter Levels^a

Variable	Quartiles of Retinal Venular Diameters, μm				P value for Trend ^b
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Temporal superior	1.00 (reference)	1.772 (0.984 to 3.190)	4.465 (2.504 to 7.961)	3.831 (2.131 to 6.884)	<0.001
Temporal inferior	1.00 (reference)	4.300 (2.342 to 7.894)	5.038 (2.727 to 9.308)	6.936 (3.704 to 12.987)	<0.001
Nasal superior	1.00 (reference)	0.763 (0.416 to 1.399)	3.049 (1.717 to 5.413)	3.240 (1.836 to 5.718)	<0.001
Nasal inferior	1.00 (reference)	1.079 (0.600 to 1.941)	4.200 (2.357 to 7.484)	2.976 (1.690 to 5.242)	<0.001
CRVE	1.00 (reference)	4.031 (2.139 to 7.597)	7.525 (3.960 to 14.299)	8.367 (4.379 to 15.988)	<0.001

Notes: ^aORs and 95% CIs were calculated with the use of binary logistic regression model adjusted for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA. ^bTests for trend were conducted by treating the quartiles as a continuous variable and assigning the median for each quartile.

highest quartile of superior temporal retinal venula, inferior temporal retinal venula and CRVE compared with the lowest were 3.831 (95% CI: 2.131 to 6.884), 6.936 (95% CI: 3.704 to 12.987) and 8.367 (95% CI: 4.379 to 15.988), respectively (Table 4). Figure 2C and D shows there was a nonlinear association between superior or inferior nasal retinal venulas and risk of DKD (P for non-linearity < 0.001). The ORs of DKD increased rapidly between around 113 and 134 μm of the diameters of superior nasal retinal venula and then plateaued thereafter (Figure 2C). The ORs of DKD increased rapidly between around 113 and 128 μm of the diameters of inferior nasal retinal venula and then decreased thereafter (Figure 2D).

Retinal Arteriolar Diameters and DKD

Participants with DKD had narrower retinal arteriolar diameters at the temporal superior, temporal inferior, nasal superior, nasal inferior and CRAE than participants without DKD ($P < 0.001$) (Table 2). In unadjusted logistic regression analysis, the narrowed diameters of all four retinal arterioles and CRAE were associated with DKD ($P < 0.001$) (Table 5). This trend remained statistically significant after adjusting for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA (temporal superior OR: 0.984, 95% CI: 0.972 to 0.997, $P = 0.015$; temporal inferior OR: 0.986, 95% CI: 0.974 to 0.999, $P = 0.035$; nasal superior OR: 0.978, 95% CI: 0.964 to 0.993, $P = 0.005$; nasal inferior OR: 0.966, 95% CI: 0.951 to 0.981, $P < 0.001$; CRAE OR: 0.971, 95% CI: 0.956 to 0.986, $P < 0.001$) (Table 5).

Table 6 and Figure 3 show the association between retinal arteriolar diameters and DKD. The multivariable adjusted models showed the U-shaped relation between retinal arteriolar diameters (all P for non-linearity < 0.001) and DKD after adjusting for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA. The risk of DKD was increased when the diameters of superior nasal retinal arteriole was less than 105 μm after adjustment of potential confounders (Figure 3A). A similar nonlinear shape was also seen for the inferior temporal retinal arteriole (less than 105 μm , Figure 3B), superior nasal retinal arteriole (less than 86 μm , Figure 3C), inferior nasal retinal arteriole (less than 85 μm , Figure 3D) and CRAE (less than 120 μm , Figure 3E) association.

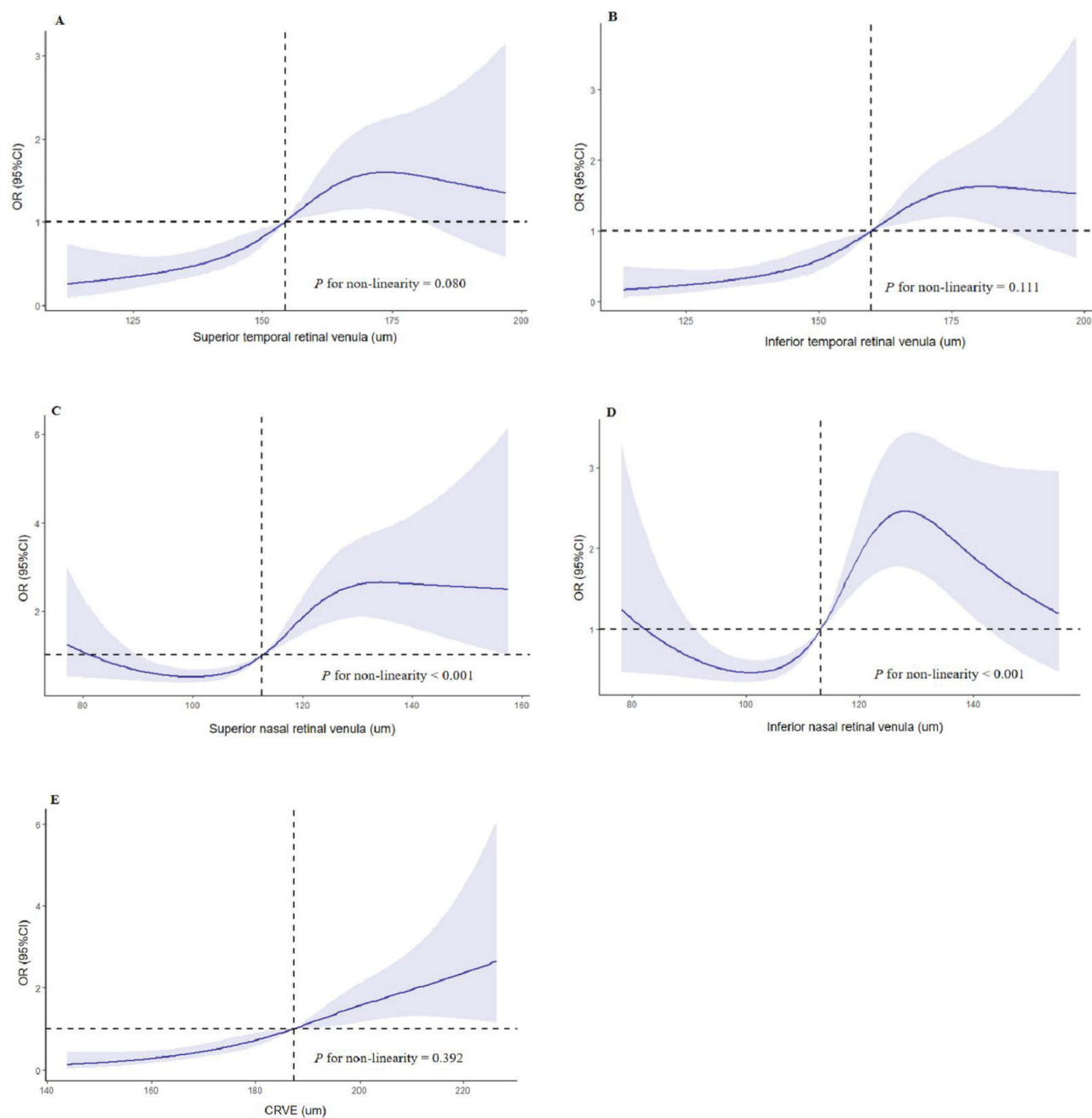


Figure 2 Restricted cubic splines for the association between retinal venular diameters and DKD. OR of DKD by the diameters of superior temporal retinal venula (**A**), inferior temporal retinal venula (**B**), superior nasal retinal venula (**C**), inferior nasal retinal venula (**D**) and CRVE (**E**) with the use of restricted cubic splines. The analysis was adjusted for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA.

Abbreviation: CRVE, central retinal venular equivalent.

Discussion

In this study, we investigated the association between retinal microvascular diameters and DKD in patients with T2DM. We found that wider retinal venular diameters and narrower retinal arteriolar diameters were associated with an increased risk of DKD. After adjustment for potential confounders, these associations remained significant. Furthermore, widened diameters of the superior temporal retinal venula, inferior temporal retinal venula and CRVE were positively associated with the risk of DKD in a linear manner. In contrast, narrowed retinal arteriolar diameters were associated with the risk of

Table 5 The Logistic Regression Analyses Between Retinal Arteriolar Diameters and DKD

Variable	Model 1		Model 2		Model 3	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Temporal superior	0.969 (0.958 to 0.980)	<0.001	0.971 (0.960 to 0.982)	<0.001	0.984 (0.972 to 0.997)	0.015
Temporal inferior	0.970 (0.960 to 0.981)	<0.001	0.973 (0.962 to 0.984)	<0.001	0.986 (0.974 to 0.999)	0.035
Nasal superior	0.964 (0.952 to 0.976)	<0.001	0.966 (0.954 to 0.979)	<0.001	0.978 (0.964 to 0.993)	0.005
Nasal inferior	0.954 (0.942 to 0.967)	<0.001	0.956 (0.944 to 0.969)	<0.001	0.966 (0.951 to 0.981)	<0.001
CRAE	0.946 (0.933 to 0.959)	<0.001	0.949 (0.935 to 0.962)	<0.001	0.971 (0.956 to 0.986)	<0.001

Notes: Model 1: Unadjusted. Model 2: Adjusted for duration of T2DM and hypertension. Model 3: Model 2 plus additional adjustments for SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA.

Table 6 ORs (and 95% CIs) of DKD According to Quartiles of Retinal Arteriolar Diameter Levels^a

Variable	Quartiles of Retinal Arteriolar Diameters, μm				P value for Trend ^b
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Temporal superior	1.932 (1.116 to 3.345)	2.347 (1.321 to 4.169)	0.480 (0.258 to 0.892)	1.00 (reference)	<0.001
Temporal inferior	2.142 (1.230 to 3.731)	1.212 (0.668 to 2.202)	0.500 (0.276 to 0.905)	1.00 (reference)	<0.001
Nasal superior	2.260 (1.282 to 3.985)	1.515 (0.853 to 2.692)	0.762 (0.425 to 1.368)	1.00 (reference)	0.001
Nasal inferior	3.310 (1.827 to 5.999)	3.348 (1.849 to 6.061)	1.278 (0.695 to 2.350)	1.00 (reference)	<0.001
CRAE	2.758 (1.565 to 4.860)	1.086 (0.620 to 1.902)	0.305 (0.164 to 0.570)	1.00 (reference)	<0.001

Notes: ^aORs and 95% CIs were calculated with the use of binary logistic regression model adjusted for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA. ^bTests for trend were conducted by treating the quartiles as a continuous variable and assigning the median for each quartile.

DKD in a non-linear manner, such that an exposure-response association was observed within a range of relatively small retinal arteriolar diameters.

Endothelial dysfunction is a key event in the pathogenesis of DKD.^{3,20} Exposure of endothelial cells to high glucose can activate the deleterious pathways, such as the polyol pathway, the protein kinase C pathway and the hexosamine pathway, leading to overproduction of endogenous reactive oxygen species and a worsening vicious cycle of inflammation, which play a direct role in DKD.^{3,20–22} It seems obvious to assess endothelial function in an accessible part of the microcirculation, as 90% of endothelial cells are located in the microcirculation.¹⁴ Importantly, the retina provides a unique window to non-invasively monitor microcirculation in vivo and is easy to visualize noninvasively.^{23,24} Changes in retinal microvascular diameter may be quantified as a subclinical marker of microvascular remodelling and dysfunction before clinical manifestation of DKD, as the retinal and renal microvasculature share similar anatomic and physiologic features.^{13,25}

Retinal venular widening is a marker of retinal ischemia²⁶ and may be mediated by endothelial dysfunction²⁷ and increased inflammatory stress.^{28,29} Previous studies have suggested that wider CRVE was associated with incident chronic kidney disease^{30,31} and DKD.^{32,33} However, the population-based prospective study (BDES) found that chronic kidney disease was associated with a greater decrease rather than an increase in CRVE over time.³⁴ Similarly, in another study, the CRVE was found to be negatively correlated with kidney function in a population without chronic kidney disease.³⁵ In addition, some reported that CRVE were not associated with CKD.^{36–38} In our study, we found that wider CRVE was associated with an increased risk of DKD in patients with T2DM, consistent with a population-based prospective study.³² Moreover, we found a stronger association in the highest quartile of CRVE levels compared with the lowest and the levels of CRVE were positively associated with DKD in a linear manner, which suggested that increased diameter of the CRVE may accelerate the progression of DKD.

Retinal arteriolar narrowing is an indicator of microvascular dysfunction caused by aging, T2DM, hypertension, inflammation and other processes.^{39,40} Histopathologically, it is characterised by intimal thickening, medial hyperplasia, hyalinisation and sclerosis.⁴¹ The association between retinal arteriolar diameter and kidney disease is controversial. A prospective population-based study indicated that CRVE, but not CRAE, was associated with 14-year incidence of

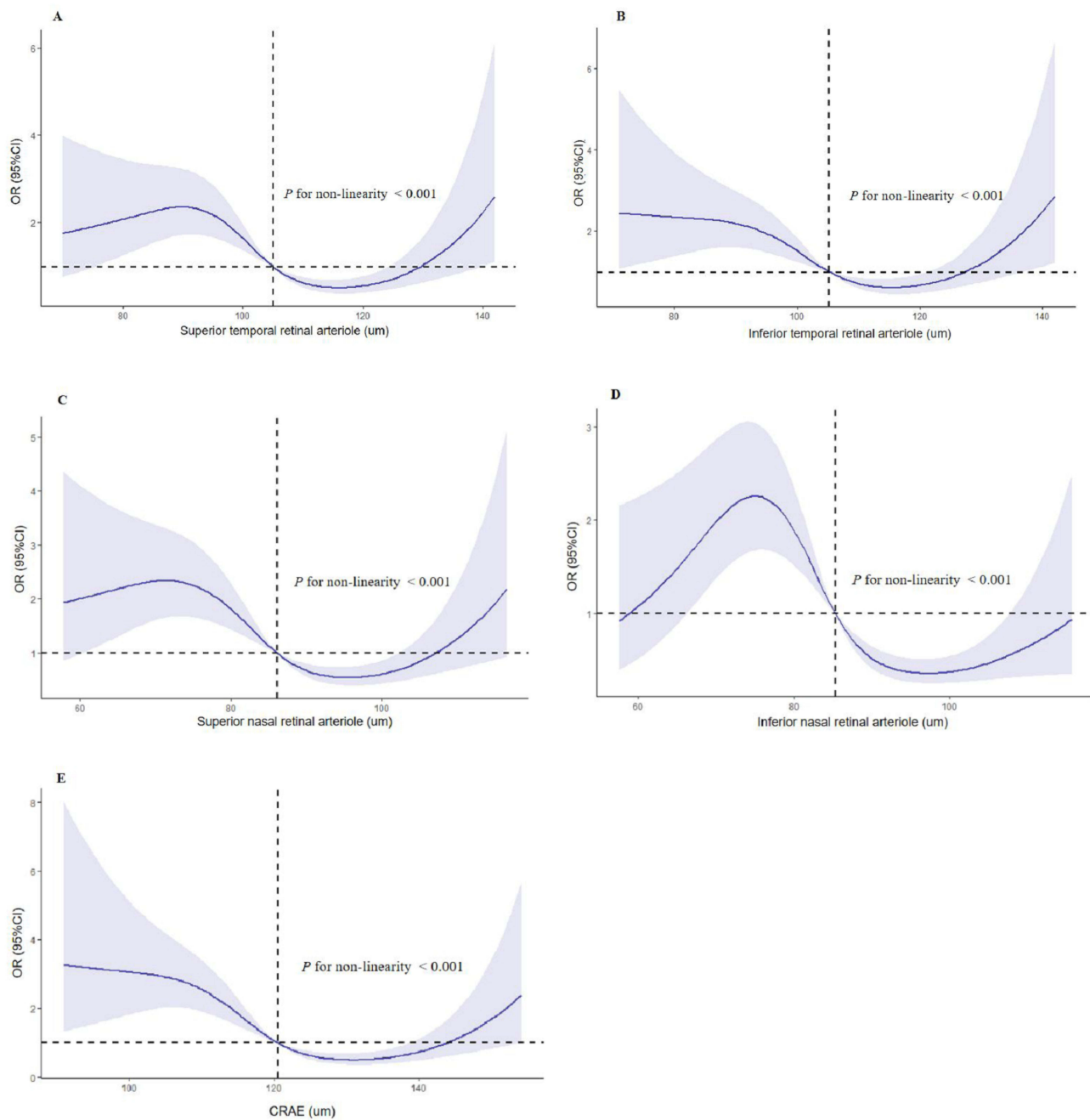


Figure 3 Restricted cubic splines for the association between retinal arteriolar diameters and DKD. OR of DKD by the diameters of superior temporal retinal arteriole (**A**), inferior temporal retinal arteriole (**B**), superior nasal retinal arteriole (**C**), inferior nasal retinal arteriole (**D**) and CRAE (**E**) with the use of restricted cubic splines. The analysis was adjusted for duration of T2DM, hypertension, SBP, DBP, BMI, TG, HDL-C, BUN, Scr and UA.

Abbreviation: CRAE, central retinal arteriolar equivalent.

DKD.³² In contrast, a population-based study suggested that reduced CRAE, but not CRVE, was associated with chronic kidney disease.³⁷ In addition, a recent meta-analysis found CRAE was associated with chronic kidney disease (OR: 1.41, 95% CI: 1.09 to 1.82).¹⁵ However, a risk estimation in previous studies depends on the assumption of a linear association. In our study, we observed that the OR for DKD was 2.758 for the lowest quartile of CRAE levels, but 0.305 for the third quartile compared with the highest. This observed pattern was further confirmed by our analysis of the association shape, which showed a U-shaped relation between CRAE levels and DKD. The result suggested that only the

lower level of CRAE (less than 120 μm) was associated with an increased risk of DKD in patients with T2DM, which may partly explain the heterogeneity of previous studies.

Another major strength of our study, in comparison with previous studies, was the evaluation of the relationship between retinal branch microvascular diameter and the risk of DKD in patients with T2DM. To our knowledge, few studies have done this. In our study, we found that similar to CRVE, superior and inferior temporal retinal venular diameters were positively associated with the DKD in a linear manner, whereas superior and inferior nasal retinal venules were associated with the DKD in a non-linear manner. Similar to CRAE, we found that a U-shaped relationship between four retinal branch arteriolar diameters and DKD. The results suggested that the smaller level of inferior temporal retinal arteriole (less than 105 μm), inferior temporal retinal arteriole (less than 105 μm), superior nasal retinal arteriole (less than 86 μm) and inferior nasal retinal arteriole (less than 85 μm) were associated with an increased risk of DKD in patients with T2DM. In conclusion, changes in retinal branch microvascular diameter may have potential clinical relevance for the risk of DKD.

The strength of our study is that we used retinal photography, a convenient and non-invasive technique, to explore the association between retinal microvascular diameters (including branch vessels) and DKD in patients with T2DM. There are several limitations in our study. First, it is a retrospective analysis. A cause-effect relationship could not be established. Longitudinal follow-up is desirable in the future to better understand the pathophysiological mechanisms of the early stages of DKD. Second, vascular geometry, such as arteriolar and venular fractal dimensions and vessel tortuosity, was not considered. However, the aim of this study is to evaluate whether retinal microvascular diameter is a potential biomarker for the detection of DKD in patients with T2DM. Third, the single-center design of our study may lead to a source of potential selection bias due to differences in ethnic factors. Large-scale longitudinal studies of retinal vessel diameter and DKD are warranted to address these issues.

Conclusions

In summary, our study demonstrated that widened retinal venular diameters, especially CRVE, superior and inferior temporal retinal venula, were positively associated with an increased risk of DKD in a linear fashion. In contrast, narrowed retinal arteriolar diameters are associated with the risk of DKD in a non-linear fashion, suggesting that only the lower level of retinal arteriolar diameters was associated with an increased risk of DKD in patients with T2DM. Our study supports that changes in retinal microvascular diameters (including branch vessels) were potential biomarkers for DKD in patients with T2DM. Retinal imaging may provide a non-invasive tool to identify patients with T2DM at risk for DKD.

Ethical Approval

The study followed the principles in the Declaration of Helsinki and was approved by the Ethical Committees of Hebei General Hospital (No.2022131). We promised that the data of the participants were anonymized or maintained with confidentiality, and the rights or interests of participants were not invaded. Therefore, the requirement for informed consent in this study was waived in accordance with the national legislation and the institutional requirements.

Disclosure

The authors report no conflicts of interest in this work.

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