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In Vivo Visualization and Quantification of Optic Disc Microvasculature for Assessing Renal Dysfunction

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Objective: To assess the relationship between optic disc microvasculature and renal function in subjects with diabetes mellitus without diabetic retinopathy (DR).

Design: Prospective, cross-sectional study.

Participants: A total 1629 patients with type 2 diabetes mellitus without DR were recruited from the community of Guangzhou, China.

Methods: All subjects underwent 6 mm × 6 mm OCT angiography (OCTA) centered on the optic nerve head. Four state-of-the-art microcirculation parameters, including peripapillary vessel density (PVD) in the radial peripapillary capillaries (RPC), superficial capillary plexus, deep capillary plexus (DCP), and a choriocapillaris flow void density percentage (CC FVD%) were assessed via swept-source OCTA.

Primary Outcomes: Renal function was assessed by levels of microalbuminuria (MAU) and estimated glomerular filtration rate (eGFR).

Results: Compared with non-chronic kidney disease (CKD) participants, PVD was significantly lower in subjects in the CKD group and worsened as eGFR declined. After adjustment for covariates, higher eGFR was significantly associated with higher PVD in the RPC ($\beta = 0.01$; 95% confidence interval [CI], 0.01−0.02; $P < 0.001$), in the superficial capillary plexus ($\beta = 0.010$; 95% CI, 0.002−0.019; $P = 0.020$), in the DCP ($\beta = 0.02$; 95% CI, 0.01−0.03; $P < 0.001$), and lower CC FVD% ($\beta = -0.01$; 95% CI, −0.03 to −0.001; $P = 0.040$) in the entire images. After they were fully adjusted, the parameters in the inner ring of the RPC, DCP, and CC FVD% were significantly associated with MAU ($P < 0.05$).

Conclusion: Decrease in retinal and choroidal microcirculation in the optic nerve head was independently associated with renal dysfunction. Further longitudinal studies are needed to clarify the peripapillary vessel changes during CKD progression.

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The most common microvascular complications of diabetes mellitus are diabetic retinopathy (DR) and kidney disease.[1] Currently, DR can be easily detected via retinal fundus photography.[2] However, chronic kidney disease (CKD) often remains asymptomatic in its early stages, leading to a low rate of early diagnosis.[3] The development of DR and CKD have common pathologies including alterations in microvascular structure and function, and altered blood flow regulation mechanisms. This implies that the microvasculature is impaired in both diseases, and retinal microcirculation can serve as a noninvasive "window" for kidney microvascular abnormalities.[4–6]

Previously, emerging evidence has suggested that abnormal blood flow in the optic nerve head may serve as an early marker for CKD.[7] At an anatomical level, due to the convergence of all retinal vessels at the optic disc, any abnormal perfusion of the retinal vessels may cause peripapillary microvascular changes. Furthermore, correlational analyses have confirmed a bidirectional association between CKD and glaucoma, with diabetes being a potential underlying cause.[7] Alterations in the microcirculation of optic nerve head are considered a key shared characteristic between these 2 ocular diseases.[8] Previous studies that investigated this hypothesis have reported a close relationship between the vessel caliber around the disc and renal function using fundus photography. Although informative, this technique can only quantify large retinal vessels and cannot assess the

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retinal and choroidal microvasculature, which is a more robust representative of damage caused by hyperglycemia in smaller vessels.[9]

The emergence of OCT angiography (OCTA) has made it possible to visualize and quantify the microvasculature in each plexus layer.[10] Quantitative analysis of the peripapillary vessel density (PVD) and choriocapillaris flow void density percentage (CC FVD%) via swept-source OCTA can be achieved with excellent repeatability and reproducibility.[10,11] However, the relationship between PVD, CC FVD%, and renal function has yet to be investigated. Therefore, the aim of this study was to assess the association between OCTA-derived PVD, CC FVD%, and renal function in a large cohort of Chinese subjects with no DR.

Methods

Participants

This cross-sectional analysis was an integral part of the ongoing prospective Guanzhou Diabetic Eye Study (ISRCTN registry identifier: 15853192), which was conducted at Zhongshan Ophthalmic Centre, Sun Yat-sen University, Guangzhou, China. The study protocol was approved by the ethics committee of the Zhongshan Ophthalmic Centre (2017KYPJ094). The study was performed according to the principles of the Declaration of Helsinki. All participants provide a written informed consent. The overall framework of this study is presented in Figure 1.

Type 2 diabetes subjects with no DR from the communities of Guangzhou were included. The exclusion criteria were: (1) the presence of ocular pathologies, such as DR, myopic maculopathy, glaucoma, or vitreous hemorrhage; this was verified using 7-field retinal photography and OCT imaging; (2) a history of ocular treatment, such as refractive surgery, cataract/lens surgery, or retinal laser surgery; (3) best-corrected visual acuity $\leq$ 20/200; (4) spherical degree ≤ -6.0 and/or cylinder degree $\geq$ 3.0 diopter; (5) axis length $\geq$ 26.00 mm; (6) a history of systemic diseases other than diabetes, such as uncontrollable hypertension, nephrotic syndrome, nephritis, or dialysis; (7) the inability to cooperate with questionnaires and examinations, such as the presence of a mental illness; (8) the presence of severe pterygium or cataracts that precluded retinal imaging; and (9) inadequate quality on the part of fundus or OCTA images.

Anthropological and Laboratory Parameters

Demographics were collected via standardized questionnaires. Anthropological parameters, such as height, waist circumference, and blood pressure (BP), were measured based on standardized procedures. Fasting blood and midstream urine samples were collected and analyzed. The Chronic Kidney Disease Epidemiology Collaboration formula was used to calculate estimated glomerular filtration rate (eGFR), with eGFR $\geq$ 90 ml/min indicating no CKD, 60 ml/min $\leq$ eGFR $<$ 90 ml/min indicating mild CKD, and 30 ml/min $\leq$ eGFR $<$ 60 ml/min indicating moderate-to-severe CKD.

Comprehensive Eye Examinations

Each participant received complete eye examinations, including subjective and objective refraction, slit-lamp examination of the anterior and posterior segment, ocular biometry measurements, intraocular pressure, fundus photography, OCT, and OCTA. The pupil was fully dilated with compound tropicamide (Santen Pharmaceutical), followed by standard 7-field fundus photography according to ETDRS criteria. The DR grading was performed according to the modified Airlie House Classification system.[8]

Swept-Source OCTA Angiogram Acquisition and Analysis

All participants were asked to refrain from consuming caffeine and alcohol within 24 hours of the examination. All OCTA images were obtained via the Topcon SS-OCT device (Triton, Topcon), which adopts a swept-source light of a wavelength of 1050 nm (axial resolution of 8 microns, lateral resolution of 20 microns). The device scanned at a speed of 10 Hz/sec. The Angio Disc 6 x 6 mm^2 mode centered on the optic disc (320 $\times$ 320 A-scan), and was recorded for both eyes. The instrument's built-in artefact-removal algorithm and eye tracker system were used to ensure the removal of motion and projection artifacts during OCTA imaging. *En face* images of the radial peripapillary capillary plexus (RPC), the superficial capillary plexus (SCP), the deep capillary plexus (DCP), and the peripapillary choriocapillaris (PCC) were automatically segmented by IMAGEnet 6 software and manually adjusted if there were segmentation errors (Fig 2). Poor quality images with any following conditions were excluded from further analysis: image quality scores $<$ 60, decentration, measurement errors, artifacts.

The images were exported to Image J for further processing. First, the OCTA image acquired was adjusted according to the equation of Littman and Bennett for the AL value and then cropped to 1024 $\times$ 1024 pixels.[12] Second, image binarization of each layer was performed. Otsu's (cluster variance maximization) thresholding method was used to binarize the retinal layer images; Phansalkar's local thresholding algorithm (window radius of 15 pixels) was used to binarize the choriocapillaris (CC) layer image.[13] Third, the areas covered by large retinal vessels were excluded. Fourth, the average inner circle (1.0 to 3.0 mm) and outer circle (3.0 to 6.0 mm) measurements and PVD of each retinal layer, as well as the CC FVD% values were obtained (Fig 2). Specifically, CC FVD% was defined as the percentage of the total area of no blood flow or blood flow rate less than the lowest detection threshold to the study area (excluding the area of projection artefact), reflecting CC perfusion defects. Peripapillary vessel density was defined as the percentage of white pixels (vessels/blood flow) to total pixels in the image centered on the optic disc, reflecting the proportion of image area occupied by vessels. Therefore, higher PVD and lower CC FVD% indicates higher microvascular perfusion of eye.

Statistical Analysis

Data for the right eye were selected for further analysis. Statistical analyses were performed using Stata software (version 17.0). The Shapiro-Wilk test was used to test the normal distribution, and the chi-square test was used for categorical variables. Categorical variables were expressed as numbers (percentages), and normally distributed continuous variables were expressed as means $\pm$ standard deviations. Analysis of variance was used to compare the differences in PVD between various renal function categories. The relationship between renal function and PVD was assessed using univariate and multivariate linear regression models (Fig 1). Confounding factors that may affect PVD and PCC FVD% were fully corrected for in multivariate model, as described in previous literature. These included age, sex, AL, systolic BP, diabetes mellitus duration, cholesterol level, and glycated hemoglobin level. A P-value $<$ 0.05 was considered statistically significant.

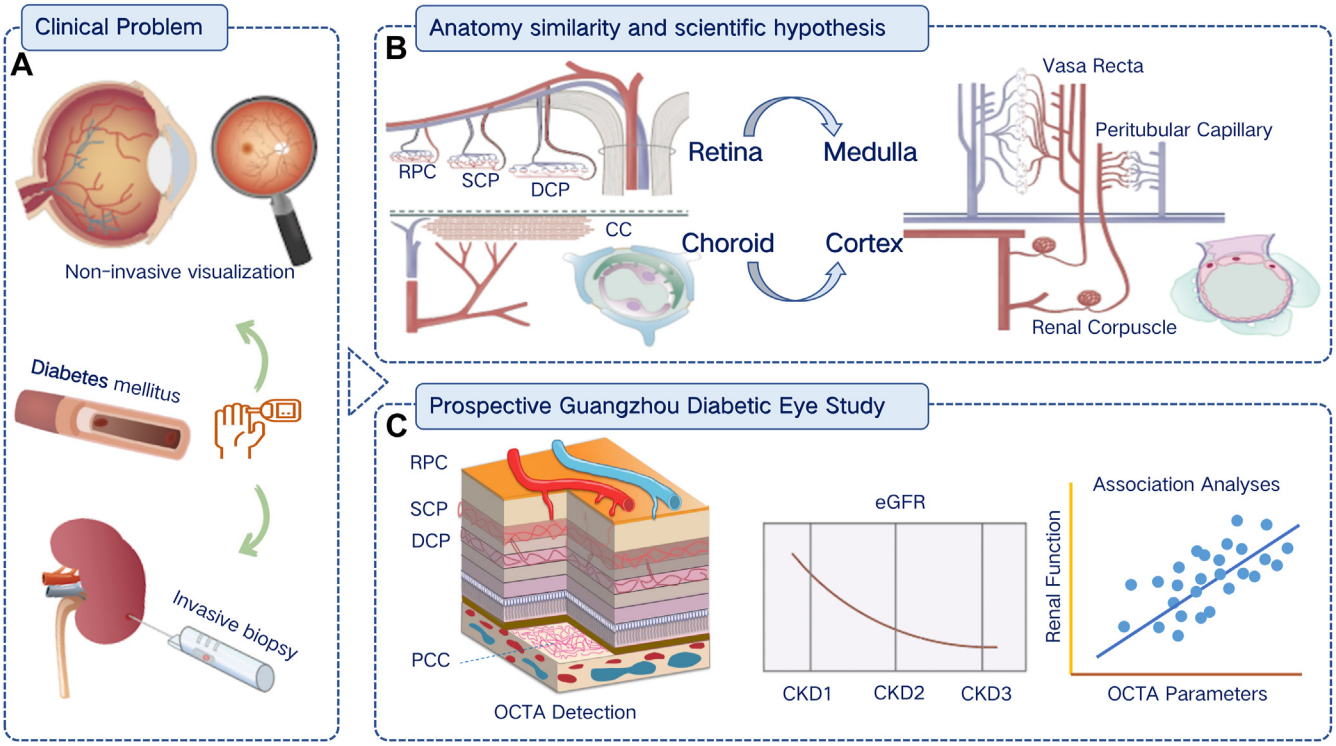

Figure 1. Overall design of the study. **A,** Clinical challenge: diabetic retinopathy (DR) and chronic kidney disease (CKD) are the most common microvascular complications of diabetes mellitus subjects. Clinically, DR can be easily detected via retinal fundus photography; however, the diagnosis of CKD largely relies on the invasive biopsy specimens. **B,** Scientific hypothesis: peripapillary chorioretinal microcirculation sharing substantial similarity in vascular structure and common blood flow regulation mechanism within the kidney microcirculation, which implied retinal microcirculation may serve as a noninvasive "window" for kidney microvascular abnormalities. **C,** Cross-sectional analyses: in a large sample of subjects with type 2 mellitus, this study evaluated the relationship between OCT angiography (OCTA)-derived peripapillary vessel density in each layer of optic nerve head and the renal function in diabetic subjects without retinopathy. CC = choriocapillaris; DCP = deep capillary plexus; eGFR = estimated glomerular filtration rate; PCC = peripapillary choriocapillaris; RPC = radial peripapillary capillary plexus; SCP = superficial capillary plexus.

Results

Demographic and Clinical Characteristics

A total of 2011 individuals underwent screening for eligibility. Among them, 382 were excluded due to missing data, low image quality, or a diagnosis of DR. Finally, 1629 (81.0%) individuals with type 2 diabetes were included in the statistical analysis, of which 1148 (70.47%) had normal renal function, 426 (26.15%) had mild CKD, and 55 (3.38%) had moderate-to-severe CKD (Table 1). The average age was 65.22 ± 7.47 years, 57.95% of participants were women, and the mean duration of diabetes for the included participants was 9.14 ± 6.91 years. Participants with renal dysfunction were likely to be older and to have higher systolic BP, AL, serum creatinine, and microalbuminuria (MAU) values, as well as lower total cholesterol, low-density lipoprotein cholesterol, and best-corrected visual acuity ($P < 0.05$). There were no statistically significant differences in body mass index, diastolic BP, intraocular pressure, levels of glycated hemoglobin, triglycerides, high-density lipoprotein cholesterol, or C-reactive protein among the different categories of CKD ($P > 0.05$).

Distribution of Peripapillary Microvascular Parameters Among Study Groups

Figure 3 shows peripapillary microvascular metrics stratified by categories of CKD. The PVD of a retinal layer decreased as renal function deteriorated. In contrast, CC FVD% increased as renal function deteriorated (Fig 3, Table 2). Significant differences were observed among study groups in the entire image of the SCP (26.11% ± 3.04% vs. 25.32% ± 3.22% vs. 24.37% ± 3.63%; $P < 0.001$), the inner ring (29.29% ± 3.60% vs. 28.78% ± 3.85% vs. 26.92% ± 4.83%; $P < 0.001$), and the outer ring (29.29% ± 3.60% vs. 28.78% ± 3.85% vs. 26.92% ± 4.83%; $P < 0.001$). Similar results were obtained within the DCP as well as the RPC. In addition, subjects with renal function loss showed increased CC FVD% in the inner ring region of the PCC (38.22 ± 6.07 vs. 39.06 ± 6.48 vs. 40.27 ± 7.60; $P = 0.006$).

Correlation Analysis between eGFR and Peripapillary Mircrovascular Parameters

Figure 4 shows the relationship between peripapillary microcirculation and eGFR. The eGFR was positively

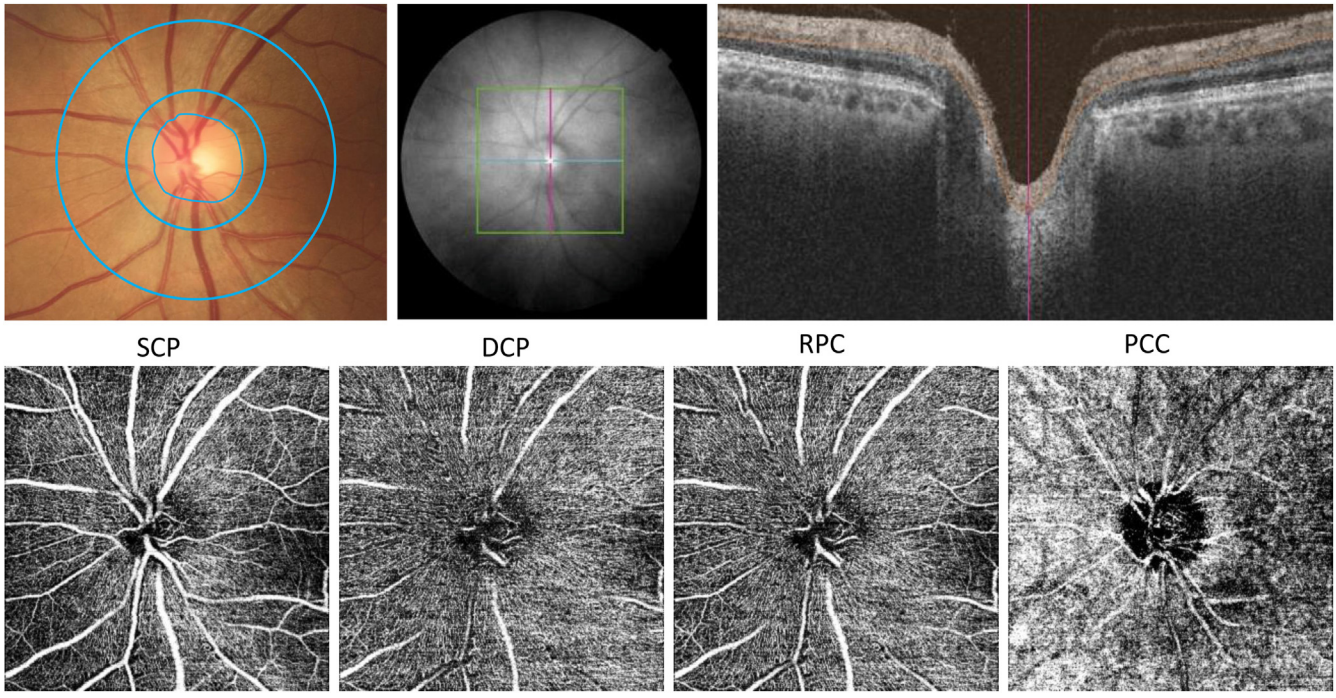

Figure 2. Illustrations of en face swept-source OCT angiography angiograms stratified by 4 layers. DCP = deep capillary plexus; PCC = peripapillary choriocapillaris; RPC = radial peripapillary capillaries; SCP = superficial capillary plexus.

correlated with the PVD of the SCP and the DCP and was negatively correlated with CC FVD% (Table 3). After adjusting for other factors, all the correlations were statistically significant, including PVD, in the entire image of the RPC (β = 0.01; 95% confidence interval [CI], 0.01−0.02; $P < 0.001$), SCP (β = 0.010; 95% CI,

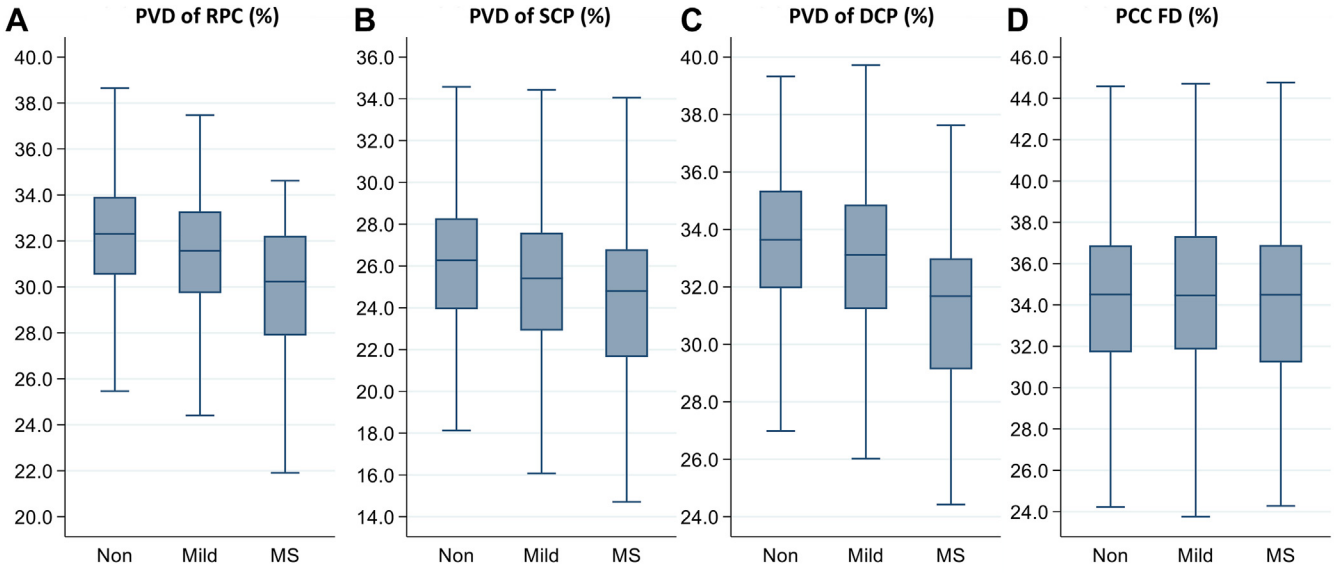

Figure 3. Scattering plots demonstrating linear relationship between peripapillary vessel density (PVD) and estimated glomerular filtration rate (eGFR). **A,** The average PVD of the radial peripapillary capillaries (RPC) versus eGFR. **B,** The average PVD of the superficial capillary plexus (SCP) versus eGFR. **C,** The average PVD of the deep capillary plexus (DCP) versus eGFR. **D,** The average peripapillary choriocapillaris flow void density percentage (PCC FVD%) versus eGFR. MS = moderate-to-severe.

Table 1. Demographic and Clinical Characteristics of Study Participants

Characteristics	Total*	Normal	Mild CKD	MS-CKD	P value†
Number of subjects, %	1629	1148 (70.47)	426 (26.15)	55 (3.38)	-
Age, yrs	65.22 ± 7.47	63.70 ± 7.36	68.51 ± 6.45	71.36 ± 5.75	< 0.001
Female, %	944 (57.95)	708 (61.67)	208 (48.83)	28 (50.91)	< 0.001
Body mass index, kg/m^2	24.73 ± 3.47	24.59 ± 3.41	25.01 ± 3.63	25.68 ± 3.25	0.012
Systolic blood pressure, mmHg	133.33 ± 17.78	131.95 ± 17.58	136.42 ± 17.58	138.59 ± 19.75	< 0.001
Diastolic blood pressure, mmHg	69.32 ± 10.06	69.36 ± 10.06	69.31 ± 9.92	68.46 ± 11.22	0.813
Duration of diabetes, yrs	9.14 ± 6.91	8.67 ± 6.63	9.93 ± 7.40	12.14 ± 7.17	< 0.001
Best-corrected visual acuity, ETDRS	80.22 ± 5.92	80.74 ± 5.60	79.26 ± 6.16	76.27 ± 8.15	< 0.001
Intraocular pressure, mmHg	15.97 ± 2.47	16.01 ± 2.44	15.90 ± 2.54	15.52 ± 2.59	0.299
Axial length, mm	23.41 ± 0.88	23.37 ± 0.87	23.51 ± 0.89	23.42 ± 0.98	0.02
HbA1c, %	7.26 ± 1.36	7.25 ± 1.36	7.27 ± 1.35	7.34 ± 1.60	0.871
Triglycerides, mmol/L	2.48 ± 1.67	2.51 ± 1.74	2.38 ± 1.41	2.61 ± 1.87	0.323
Total cholesterol, mmol/L	4.91 ± 1.11	4.97 ± 1.12	4.76 ± 1.09	4.74 ± 1.02	0.002
LDL-c, mmol/L	3.00 ± 0.99	3.06 ± 1.00	2.89 ± 0.95	2.74 ± 0.84	0.001
HDL-c, mmol/L	1.25 ± 0.38	1.25 ± 0.38	1.23 ± 0.36	1.23 ± 0.46	0.407
Microalbuminuria, mg/ml	3.36 ± 9.22	2.37 ± 6.25	4.73 ± 12.07	13.45 ± 21.25	< 0.001
C-reactive protein, mg/L	2.37 ± 3.77	2.35 ± 3.92	2.39 ± 3.53	2.50 ± 2.21	0.947

CKD = chronic kidney disease; LDL-c = low-density lipoprotein cholesterol; HbA1c = glycated hemoglobin; HDL-c = high-density lipoprotein cholesterol; MS-CKD = moderate-to-severe CKD.
*Estimated glomerular filtration rate (eGFR) ≥ 90 ml/min was defined as normal, 60 ml/min less than or equal to eGFR < 90 ml/min was defined as mild CKD, and 30 ml/min less than or equal to eGFR < 60 ml/min was defined as MS-CKD.
†Analysis of variance or chi-square tests.

0.002−0.019; $P = 0.020$), DCP (β = 0.02; 95% CI, 0.01−0.03; $P < 0.001$) and CC FVD% of the PCC (β = −0.01; 95% CI, −0.03 to −0.001; $P = 0.040$).

Correlation Analysis between Peripapillary Microvascular Parameters and MAU

In the univariate analysis, lower PVD for the SCP, DCP, and RPC was associated with MAU (Table 4). Furthermore, higher FVD in the inner ring of the PCC was associated with MAU (β = 0.05; 95% CI, 0.02−0.09; $P = 0.001$). After adjusting for potential confounding factors, lower DCP (β = −0.03; 95% CI, −0.05 to −0.01; $P < 0.001$), lower RPC PVD (β = −0.03; 95% CI, −0.05 to −0.02; $P < 0.001$), and higher PCC (β = 0.04; 95% CI, 0.01−0.07; $P = 0.019$) in the inner ring were significantly associated with MAU. In addition, Tables S5 and S6 (available at www.ophthalmologyscience.org) provide a

Table 2. Distribution of Peripapillary Vessel Density in Different Degrees of Kidney Function

	Normal	Mild Impaired	MS-CKD	P value*
RPC, %				
Whole image	32.09 ± 2.50	31.35 ± 2.82	29.57 ± 3.17	< 0.001
Inner circle	32.98 ± 3.11	32.24 ± 3.50	29.64 ± 4.14	< 0.001
Outer circle	33.69 ± 2.49	32.95 ± 2.85	31.21 ± 3.68	< 0.001
SCP, %				
Whole image	26.11 ± 3.04	25.32 ± 3.22	24.37 ± 3.63	< 0.001
Inner circle	29.29 ± 3.60	28.78 ± 3.85	26.92 ± 4.83	< 0.001
Outer circle	28.13 ± 3.21	27.27 ± 3.41	26.43 ± 4.43	< 0.001
DCP, %				
Whole image	33.60 ± 2.40	32.94 ± 2.72	30.99 ± 3.35	< 0.001
Inner circle	33.03 ± 3.35	32.44 ± 3.63	29.90 ± 4.15	< 0.001
Outer circle	34.99 ± 2.58	34.32 ± 2.92	32.35 ± 3.68	< 0.001
PCC, %				
Whole image	34.18 ± 4.12	34.30 ± 4.09	34.02 ± 4.18	0.823
Inner circle	38.22 ± 6.07	39.06 ± 6.48	40.27 ± 7.60	0.006
Outer circle	33.58 ± 5.09	33.81 ± 5.36	33.49 ± 5.30	0.721

CKD = chronic kidney disease; DCP = deep retinal capillary plexus; DM = diabetes mellitus; MS-CKD = moderate-to-severe CKD; PCC = peripapillary choriocapillaris; RPC = radial peripapillary capillary; SCP = superficial retinal capillary plexus.
*Analysis of variance tests.

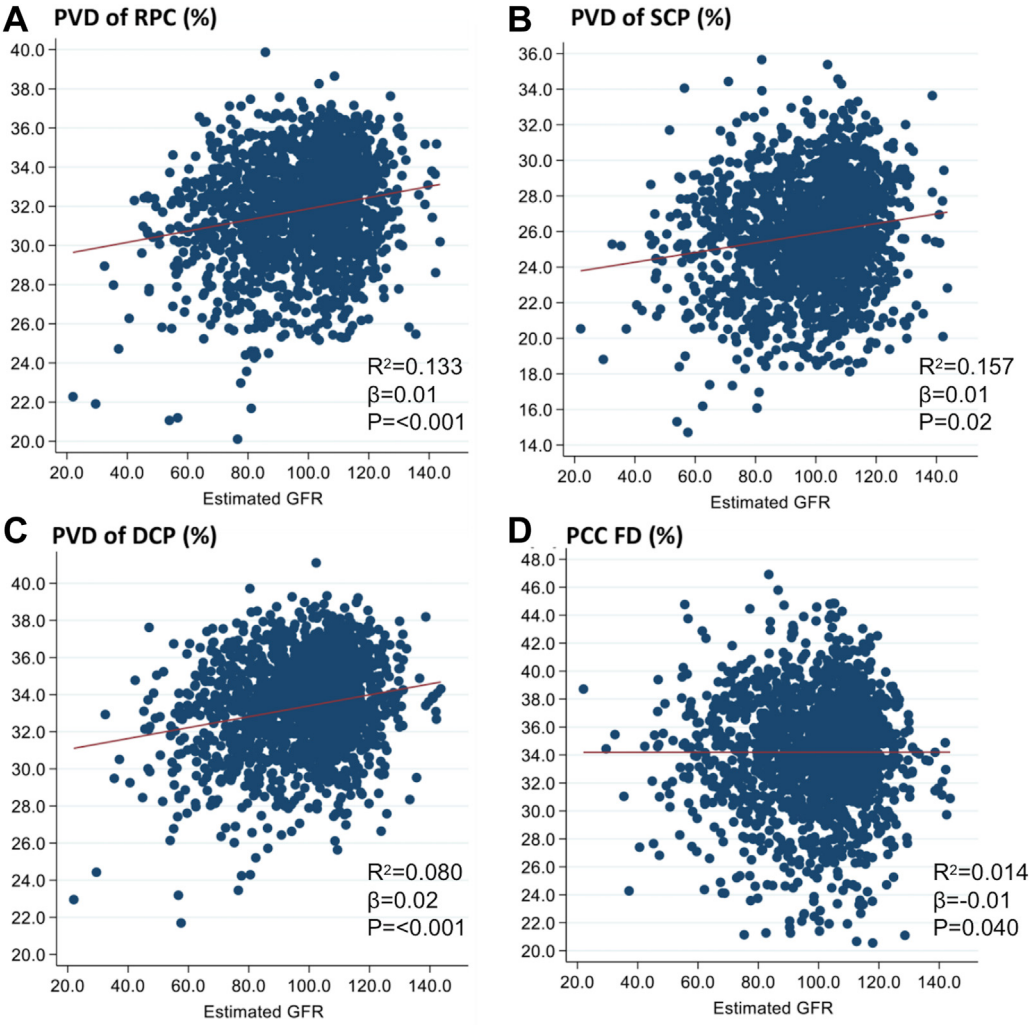

Figure 4. Boxplots demonstrating the distribution of peripapillary vessel density (PVD) among the different categories of chronic kidney disease. **A,** The average PVD of the radial peripapillary capillaries (RPC) by renal function groups. **B,** The average PVD of the superficial capillary plexus (SCP) by renal function groups. **C,** The average PVD of the deep capillary plexus (DCP) by renal function groups. **D,** The average PVD of the peripapillary choriocapillaris (PCC) by renal function groups. FD% = flow void density percentage; GFR = glomerular filtration rate.

detailed analysis of the correlation between macular microvascular parameters (vessel density [VD] and CC FVD%) and 2 specific factors: eGFR and MAU.

Discussion

This study evaluates the association between peripapillary microvascular perfusion and renal function in subjects with diabetes without diabetic retinopathy (NDR). The study had 3 essential findings: (1) peripapillary microvascular perfusion decreased as renal function worsened; (2) eGFR was positively correlated with PVD and negatively correlated with CC FVD%, independent of age and other potential confounding factors; and (3) MAU was positively correlated with peripapillary microvascular perfusion in the inner ring of the RPC, DCP, and PCC. These findings confirmed the relationship between VD decrease and renal dysfunction, thereby underlining the potential value of OCTA to detect microvascular damage in the kidney due to diabetic nephropathy.

In this study, peripapillary microvascular changes were found to be more closely associated with the severity of CKD than macular region. Our previous work has demonstrated that VD of SCP in macular region decreased in DR patients with renal function dysfunction.[14] However, the specific retinal regions and OCTA parameters associated with the severity of CKD in NDR patients remain unclear, which is crucial for early detection of renal function changes in diabetic individuals.[15] In this study, we compared the 2 regions and found no significant correlations between VD of the macular retinal layer and CKD severity. Nevertheless, PVD has attracted substantial interest because studies observed associative changes between PVD and other conditions, including subjects with diabetes, glaucoma, DR, and high myopia.[16–19] Focusing on the peripapillary microvasculature, we further

Table 3. Linear Regression Analysis of the Associations between Peripapillary OCTA Metrics and eGFR

	Univariable Model		Multivariable Model	
	β (95%CI)	P value	β (95%CI)	P value
Radial peripapillary capillary (%)				
Whole image	0.03 (0.02−0.04)	< 0.001	0.01 (0.01−0.02)	< 0.001
Inner circle	0.03 (0.03−0.04)	< 0.001	0.02 (0.01−0.03)	< 0.001
Outer circle	0.03 (0.02−0.04)	< 0.001	0.02 (0.01−0.02)	< 0.001
Superficial retinal capillary plexus (%)				
Whole image	0.03 (0.02−0.04)	< 0.001	0.01 (0.002−0.019)	0.020
Inner circle	0.03 (0.02−0.04)	< 0.001	0.009 (−0.002−0.019)	0.118
Outer circle	0.03 (0.02−0.04)	< 0.001	0.012 (0.002−0.021)	0.013
Deep retinal capillary plexus (%)				
Whole image	0.03 (0.02−0.04)	< 0.001	0.02 (0.01−0.03)	< 0.001
Inner circle	0.03 (0.02−0.04)	< 0.001	0.02 (0.01−0.03)	< 0.001
Outer circle	0.03 (0.02−0.04)	< 0.001	0.02 (0.01−0.03)	< 0.001
Peripapillary choriocapillaris (%)				
Whole image	0.0001 (−0.0111−0.0127)	0.985	−0.01 (−0.03 to −0.001)	0.040
Inner circle	−0.03 (−0.05−0.02)	< 0.001	−0.01 (−0.03 to −0.001)	< 0.001
Outer circle	0.0001 (−0.0139−0.0142)	0.985	−0.01 (−0.02−0.001)	0.985

CI = confidence interval; eGFR = estimated glomerular filtration rate; OCTA = OCT angiography.
The multivariable model was adjusted for age, sex, axial length, degree of diabetes, duration of diabetes, systolic blood pressure, and glycated hemoglobin.

demonstrated a correlation between decreased eGFR and impaired retinal perfusion in diabetic patients. The mechanisms underlying these observations are still unclear. It may be associated with the compensatory mechanisms for preserving visual function. It is well-known that the foveal region has the highest density of cone photoreceptors and oxygen consumption.[20,21] Therefore, in the early stages, there may be a compensatory sacrifice of peripheral regions to maintain central flow, which might explain the lack of observed synchronous blood flow impairment between the eye and the kidneys.

Our finding that peripapillary microvascular dropout was independently associated with poor renal function in diabetes mellitus subjects is novel and suggests peripapillary perfusion of the kidneys may be simultaneously impacted. Some well-described pathophysiologic mechanisms may explain this association. First, the excessive activation of the renin-angiotensin system is an important pathogenic mechanism of nephropathy associated with impaired blood flow regulation.[22] Similar to its the effect on the kidney, angiotensin II causes vasoconstriction around the disc through angiotensin II type 1 receptor in the eye, which

Table 4. Linear regression Analysis of the Associations between Peripapillary OCTA Metrics and MAU

	Univariable Model		Multivariable Model	
	β (95%CI)	P value	β (95%CI)	P value
Radial peripapillary capillary (%)				
Whole image	−0.03 (−0.04 to −0.01)	< 0.001	−0.01 (−0.03 to 0.001)	0.073
Inner circle	−0.05 (−0.07 to −0.03)	< 0.001	−0.03 (−0.05 to −0.02)	< 0.001
Outer circle	−0.03 (−0.04 to −0.01)	< 0.001	−0.01 (−0.03 to 0.001)	0.093
Superficial retinal capillary plexus (%)				
Whole image	−0.03 (−0.04 to −0.01)	0.003	−0.01 (−0.02 to 0.01)	0.492
Inner circle	−0.04 (−0.06 to −0.02)	< 0.001	−0.02 (−0.04 to 0.001)	0.090
Outer circle	−0.03 (−0.04 to −0.01)	0.004	−0.01 (−0.02 to 0.01)	0.546
Deep retinal capillary plexus (%)				
Whole image	−0.03 (−0.04 to −0.01)	< 0.001	−0.02 (−0.03 to −0.001)	0.013
Inner circle	−0.04 (−0.06 to −0.03)	< 0.001	−0.03 (−0.05 to −0.01)	< 0.001
Outer circle	−0.03 (−0.04 to −0.01)	< 0.001	−0.02 (−0.03 to −0.001)	0.019
Peripapillary choriocapillaris (%)				
Whole image	0.001 (−0.021 to 0.023)	0.915	0.01 (−0.01 to 0.04)	0.213
Inner circle	0.05 (0.02 to 0.09)	0.001	0.04 (0.01 to 0.07)	0.019
Outer circle	0.003 (−0.023 to 0.031)	0.795	0.02 (−0.01 to 0.04)	0.295

CI = confidence interval; MAU = microalbuminuria; OCTA = OCT angiography.
The multivariable model was adjusted for age, sex, axial length, degree of diabetes, duration of diabetes, systolic blood pressure, and glycated hemoglobin.

corresponds to the decreased perfusion density we observed in the present analysis.[23] Second, chronic hyperglycemia leads to glycosylated vessel walls which mediate endothelial inflammation, dysfunction, and cell apoptosis in the entire vasculature, but more significantly in the microvasculature, which leads to decompensation in the kidney and the optic disc.[24] These both ultimately lead to lower perfusion of the microvasculature, explaining reduced PVD. The poorer correlative values between PVD and MAU were expected considering eGFR was more reliable for evaluating renal dysfunction. A mismatch between MAU and eGFR levels may have led to this difference, and it has been reported that approximately one third to one half of subjects with type 2 diabetes have decreased levels of eGFR but not MAU.[14] Further studies are needed to confirm this phenomenon.

The results of this study may have important clinical, scientific, and public health implications. First, our study results further support the theory that microvascular screening of the ocular has potential value for detecting microvascular damage in the kidney due to diabetic nephropathy. Second, previous studies on the value of PVD to identify early microvascular damage have produced conflicting results, and it is clear now that kidney function may be a confounding variable. Triolo et al[25] noted the excellent power of the PVD of the RPC for diagnosing glaucoma, but Chung et al[26] reported that the PVD has limited diagnostic value for early-stage glaucoma. In addition, Rolle et al[27] reported that the VD of the RPC was similar between preperimetric glaucoma and healthy eyes. Not adjusting for renal function in these studies may have contributed to these discrepancies. This study underscores a significant association between renal function and PVD, emphasizing the need for future studies to consider this relationship. This can be achieved by excluding individuals with abnormal renal function during the enrollment phase and fully adjusting for renal function in the statistical analysis process. Third, our research provides a direction for CKD biomarker research. We found that the PVD of the DCP progressively declined with the aggravation of CKD, but there was no significant difference in SCP. This is consistent with the observation that changes in the VD of the DCP, but not the SCP, are reduced when DR increases with severity, indicating that abnormal perfusion of the DCP may be a sensitive biomarker for the progression of DR and CKD.[28]

Advantages of this study include its exclusion of subjects with ocular treatments and DR, its relatively large-sample size, and adjustment for several potential confounding factors. Despite this, some limitations must be acknowledged. First, as a cross-sectional study, no causal inferences can be drawn from this analysis. Second, as all subjects were Chinese, it needs to be verified whether the findings can be applied to other ethnic groups. Third, a single measurement of eGFR is not sufficient to reliably classify renal function, so classifications of CKD types may be inaccurate. Fourth, given the detection threshold for OCTA, below which current OCTA technology cannot detect flow, there may be a lack of ground truth for retinal vasculature and VD quantification.[11] Additionally, despite several strategies that were employed to reduce projection artifacts and to minimize decorrelation tails in the present study images, it is possible that the projection artifacts were not entirely removed.[20] Previous studies have shown that threshold and binarization methods may affect the results of CC FVD%. Therefore, other methods need to be used for further verification when measuring choroid images in the future, which will benefit the reliability of published CC-related studies.[13] Although the study variables have established significant links, the strength of the associations is relatively weak. Thus, this association requires prospective research to consider a potential for assessing peripapillary perfusion for monitoring of renal status in persons with diabetes.

In conclusion, we found that PVD and CC FVD% were independently correlated with renal function in Chinese subjects with type 2 diabetes. These findings confirmed the relationship between VD decrease and renal dysfunction. Further longitudinal studies are needed to clarify the peripapillary vessel changes during CKD progression.

Footnotes and Disclosures

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Abbreviations and acronyms:
AL = axial length; **BP** = blood pressure; **CC** = choriocapillaris; **CC FVD %** = choriocapillaris flow void density percentage; **CI** = confidence interval; **CKD** = chronic kidney disease; **DCP** = deep capillary plexus; **DR** = diabetic retinopathy; **eGFR** = estimated glomerular filtration rate; **MAU** = microalbuminuria; **OCTA** = OCT angiography; **PCC** = peripapillary choriocapillaris; **PVD** = peripapillary vessel density; **RPC** = radial peripapillary capillary plexus; **SCP** = superior capillary plexus; **VD** = vessel density.

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