

Peripapillary Retinal and Choroidal Vasculature in Patients with Diabetes of Different Durations without Clinical Diabetic Retinopathy

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Objective: The aim of this study is to quantitatively assess peripapillary retinal and choroidal vasculature using swept-source optical coherence tomography angiography (SS-OCTA) in patients with diabetes mellitus (DM) across different disease durations but without clinical signs of diabetic retinopathy (DR).

Methods: This was a single-center, cross-sectional study conducted at General Hospital of Central Theater Command from April to September 2023. A total of 211 subjects were enrolled and categorized into four groups: non-diabetic controls (88 eyes), DM duration <5 years (135 eyes), 5–10 years (87 eyes), and ≥10 years (92 eyes). SS-OCTA was used to assess peripapillary retinal nerve fiber layer (pRNFL) thickness, ganglion cell-inner plexiform layer (pGCL-IPL) thickness, superficial capillary plexus vascular density (SCP pVD), and choroidal parameters. Linear regression analysis identified factors associated with SCP pVD.

Results: Compared with the control group, peripapillary SCP pVD in the diabetic group was significantly lower ($33.56 \pm 2.87\%$ vs $31.39 \pm 3.77\%$, $p < 0.05$). This decrease was significantly correlated with diabetes duration ($B = -0.205$, $p < 0.001$). A progressive reduction in pRNFL thickness was observed with increasing disease duration, which reached statistical significance. Differences in macular ganglion cell–inner plexiform layer (mGCL-IPL) thickness were identified across the DM groups. Peripapillary choroidal vascularity index (CVI) was significantly lower in all DM groups compared with controls. Furthermore, SCP pVD was independently associated with diabetes duration, pRNFL thickness, peripapillary choroidal thickness, and the presence of hypertension.

Conclusion: SS-OCTA can detect early progressive damage to peripapillary microvasculature and choroid in DM patients without clinical DR. These parameters (including SCP pVD, pRNFL thickness, mGCL-IPL thickness, and peripapillary CVI) may serve as early biomarkers for preclinical DR, providing a scientific basis for early screening and targeted intervention to delay the progression of diabetic retinopathy.

Keywords: diabetes mellitus, peripapillary vascular system, swept-source optical coherence tomography angiography

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder with a multifactorial etiology. According to the IDF Diabetes Atlas, 589 million adults aged 20–79 years worldwide were living with DM in 2024, and this number is projected to climb to 853 million by 2050 (International Diabetes Federation).¹ The global burden of DM continues to rise, contributing to higher mortality rates and escalating healthcare costs worldwide.² The age-standardized prevalence of diabetic retinopathy (DR), a major ocular complication of DM, is also increasing and is now one of the leading causes of moderate-to-severe vision impairment and blindness.³ A recent review study summarizing retinal photography-based DR screening data from 2017 to 2024 confirmed that the global prevalence of DR remains stable between 20% and 30%, indicating that over 117 million diabetic patients worldwide may be affected by DR in 2024.⁴ However, the progression

of DR can often be mitigated through timely detection and intervention, underscoring the importance of identifying early pathological changes that precede its onset.⁵

Both microangiopathy and neurodegeneration have been implicated in the pathogenesis of DR.^{6–11} Previous studies have reported greater retinal nerve fiber layer (RNFL) loss in individuals with diabetes, indicating a potential role for retinal neurodegeneration in the early stages of DR development.^{11,12} A recent 2-year prospective cohort study further confirmed that DM patients exhibit accelerated thinning of the choroid and ganglion cell-inner plexiform layer (GCL-IPL) compared to healthy controls, validating the progressive nature of early ocular structural damage in diabetes.¹³ The peripapillary retinal nerve fiber layer (pRNFL) receives its vascular supply primarily from the choroidal circulation.^{14,15} Multimodal imaging and histopathological analyses have provided evidence supporting the concurrent presence of diabetic choroidopathy (DC) in these patients.^{16–18} Consistent with this, recent OCTA studies have demonstrated that even in diabetic patients without clinically visible DR, choroidal thickness (CT) reduction and choroidal vascular index (CVI) decrease may already exist, suggesting that choroidal impairment is an early ocular manifestation of DM.¹⁹ Evaluation of peripapillary vascular and choroidal parameters in subclinical DR, along with the analysis of associated factors, is essential to advance preventive and therapeutic strategies.

Swept-source optical coherence tomography angiography (SS-OCTA) is a non-invasive imaging modality capable of objectively quantifying structural and perfusion-related parameters of the retina and choroid. In recent years, OCTA has been extensively used to assess pathological changes in the peripapillary vasculature in patients with DM without clinical signs of DR.^{9,20} However, the characteristics and alterations of the peripapillary choroid and its vascular components in this population remain insufficiently understood. Additionally, the incidence and severity of diabetic complications are known to be closely associated with disease duration.²¹ Most prior studies have primarily focused on binary comparisons between individuals with and without DM or DR, without considering the impact of disease duration.^{22,23}

Therefore, the aim of this study was to systematically assess and compare differences in peripapillary retinal microvascular density, pRNFL/ganglion cell complex (GCC) thickness, and key choroidal vascular parameters (including choroidal vascular volume [CVV], CT, and CVI) between non-DR diabetic patients stratified by disease duration (<5 years, 5–10 years, ≥10 years) and healthy controls using SS-OCTA. To the best of our knowledge, this is the first SS-OCTA study to synchronously and quantitatively explore the peripapillary integrated “neuro-vascular-choroid” structure in non-DR diabetic patients with strict disease duration stratification. The study intends to identify early structural biomarkers and their evolutionary patterns in the preclinical stage of DR, thereby providing important imaging evidence for early risk prediction and intervention of diabetic ocular diseases. Defining early alterations is essential for guiding preventive and therapeutic strategies.

Methods

Patients

committee approval for this retrospective cross-sectional study was obtained from the Central Theater General Hospital (Approval No.: [2024]013-01), in accordance with the ethical principles outlined in the Declaration of Helsinki.²⁴ The sample size was determined via power analysis using G*Power 3.1 software, based on the primary outcome measure of superficial capillary plexus peripapillary vessel density (SCP pVD) from previous SS-OCTA studies on diabetic retinopathy (DR).²⁵ Assuming an alpha level (α) of 0.05, power ($1-\beta$) of 0.80, and an expected effect size of 0.30, the minimum required sample size was calculated as 152 participants. Considering a potential dropout and exclusion rate of 8%, we initially planned to recruit 165 diabetic patients and 88 non-diabetic controls, which was successfully achieved through consecutive enrollment.

Inclusion criteria for the diabetic group required a confirmed diagnosis of diabetes mellitus (DM) without clinically apparent DR. Non-diabetic individuals without concurrent retinal or choroidal diseases were included in the control group, with the same exclusion criteria applied. All participants were consecutively recruited from individuals who visited the ophthalmology clinic of the Central Theater General Hospital between April 2023 and September 2023 (recruitment channel: referrals from the hospital’s endocrine department and self-referred patients for routine ophthalmic screening). Participants were categorized into four groups based on diabetes duration confirmed by hospital electronic

medical records (date of initial DM diagnosis documented in medical charts): control group (non-diabetic controls), DM group 1 (diabetes duration < 5 years), DM group 2 (5 years \leq diabetes duration < 10 years), and DM group 3 (diabetes duration \geq 10 years). The control group was frequency-matched to the diabetic groups by age (\pm 5 years) and sex ratio to minimize confounding bias.

Inclusion criteria were defined as follows: (1) Aged \geq 18 years and \leq 75 years; (2) For diabetic groups: confirmed diagnosis of type 2 DM based on the World Health Organization (WHO) diagnostic criteria (1999);²⁶ (3) For diabetic groups: no clinical signs of DR as confirmed by standardized fundus examination (detailed below); (4) For control group: no history of DM or retinal/choroidal diseases (confirmed by self-report and electronic medical records); (5) Best-corrected visual acuity (BCVA) \geq 20/40 (Snellen chart); (6) No history of other retinal diseases (eg, age-related macular degeneration, retinal vein occlusion), glaucoma, or intraocular surgery. Exclusion criteria were: (1) BCVA below 20/200; (2) Spherical equivalent less than -4 diopters (D); (3) Presence of DR or diabetic macular edema (per ICDR grading);²⁷ (4) Other ocular pathologies, such as retinal vein occlusion, glaucoma, or age-related macular degeneration; (5) Poor-quality imaging (signal strength index < 7/10), images with motion artifacts, segmentation errors, off-centered scans, or incorrect segmentation; (6) Severe systemic diseases (eg, end-stage renal disease, liver cirrhosis, malignant tumors) or pregnancy; (7) Inability to cooperate with ophthalmic examinations or data collection.

All participants underwent a comprehensive ophthalmic evaluation, including intraocular pressure (IOP) measurement using an iCare tonometer (TA01i, Icare Finland Oy, Vantaa, Finland), BCVA assessment (Snellen chart, standardized illumination), slit-lamp biomicroscopy (BX900, Haag-Streit, Bern, Switzerland), and comprehensive fundus examination after pharmacologic mydriasis with 5% tropicamide (Mydrin-P, Santen Pharmaceutical Co., Ltd., Osaka, Japan; mydriasis duration \geq 30 minutes to ensure pupil diameter \geq 6 mm). DR severity was graded strictly in accordance with the International Clinical Classification of Diabetic Retinopathy (ICDR, 2002 revision)²⁵ by two senior ophthalmologists with over 10 years of specialized experience in retinal disease diagnosis and DR grading. The two physicians performed the fundus evaluation independently in a masked manner (unaware of participants' group assignments), and any cases with ambiguous findings (eg, questionable subtle microaneurysms) or inconsistent grading results were resolved via joint consultation with a third senior retinal specialist; unresolved cases were excluded from the study. Only eyes explicitly classified as "no DR" by both evaluating physicians (ie, absence of microaneurysms, intraretinal hemorrhages, hard/soft exudates, macular edema, or other DR-specific signs on fundus examination)²⁷ were included.

Fundus fluorescein angiography (FFA) was not performed in any patient, including those in DM group 3. This decision was based on ethical and clinical feasibility considerations: FFA is an invasive procedure with well-documented potential risks (eg, contrast agent allergy, acute renal injury in patients with subclinical renal impairment).²⁸ Additionally, both the WHO guidelines²⁶ and the American Diabetes Association (ADA) 2024 Clinical Practice Recommendations²⁹ explicitly state that FFA is not recommended as a routine screening tool for patients with unremarkable fundus findings—even in those with long-duration diabetes—further supporting our approach.

In diabetic participants, fundus examination was performed following pharmacologic mydriasis (consistent with the aforementioned protocol). General data, including sex, age, duration of diabetes, insulin use, fasting blood glucose (measured via venous blood sampling after 8-hour fasting using an automatic biochemical analyzer, AU5800, Beckman Coulter, Inc., Brea, USA), glycated hemoglobin (HbA1c) levels (high-performance liquid chromatography, D-10, Bio-Rad Laboratories, Inc., Hercules, USA), presence of other systemic diseases (eg, hypertension, hyperlipidemia), height, weight, and smoking status, were obtained from the electronic medical record system and verified via participant interviews.

Swept-Source OCTA Measurements

All participants underwent SS-OCTA imaging (VG200; SVision Imaging, Luoyang, China) under standardized conditions. Participants were seated with chin and forehead stabilized on the chin rest, and eye alignment was guided by the built-in fixation target to minimize motion artifacts. All operators completed unified standardized training on device operation and image acquisition protocols before the study. The optic disc cube mode was used, with axial scans covering a 6 \times 6 mm area at 512 \times 512 pixel resolution and 100 kHz scan speed. A signal strength index (SSI) \geq 7/10 was set as the

quality control criterion. Scans with SSI < 7/10, motion artifacts, or off-centered alignment were repeated immediately; images were excluded if satisfactory quality was not achieved after 3 attempts.

CVI was calculated using the VG200 system's built-in software (version 1.32.9; SVision Imaging). The VG200D system's built-in software (version 1.32.9; SVision Imaging) was applied to measure pRNFL thickness, peripapillary ganglion cell layer-inner plexiform layer (pGCL-IPL) thickness, peripapillary superficial capillary plexus vascular density (SCP pVD), and choroid-related parameters. Ganglion cell-inner plexiform layer (GC-IPL) thickness was derived from 26×21 mm² OCTA scans. The software's automated segmentation algorithm was used to identify the SCP, deep capillary plexus (DCP), and choroidal layers; manual adjustments were performed by a senior ophthalmologist if segmentation errors (eg, misidentification of the RPE-Bruch's membrane complex) were detected.

SCP pVD, pRNFL thickness, and pGCL-IPL thickness were assessed using the optic nerve head (ONH) mode. The ONH region was defined as a 4-mm-diameter ring, including a central 2 mm circle and an annular zone from 2 to 4 mm, which was divided into eight segments according to the Garway-Heath map.¹⁸ Choroidal thickness (CT) was defined as the vertical distance from the inner border of the choroido-scleral junction to the outer margin of the RPE-Bruch's membrane complex. Choroidal vessel volume was defined as the volume of vessels within Sattler's and Haller's layers. The choroidal vessel index (CVI) was calculated as the ratio of Sattler's and Haller's layer volumes to total choroidal volume. Measurements were obtained within a 2.00–6.00 mm region centered on the ONH. Mean values and quadrant-specific values (superior [S], nasal [N], inferior [I], temporal [T]) were analyzed.

To ensure measurement reliability, all image analyses were performed by a single experienced ophthalmologist masked to participants' group assignments (diabetic vs control, and diabetes duration subgroups). Inter-observer consistency was assessed by a second independent ophthalmologist who re-analyzed 15% of randomly selected images. The intraclass correlation coefficient (ICC) for CVI measurements was > 0.92, confirming good reproducibility. Intra-observer reliability was verified by the first ophthalmologist who re-analyzed the same 15% of images after a 4-week interval. ICC values for all outcome measures (SCP pVD, pRNFL thickness, pGCL-IPL thickness, CVI) were > 0.93, ensuring measurement stability. All imaging procedures were conducted by a single trained operator to minimize inter-operator variability.

Statistical Analysis

Statistical analyses were conducted using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Independent *t*-tests or Mann–Whitney *U*-tests were applied to compare continuous variables between the control and DM groups. One-way analysis of variance was used to assess baseline demographic differences among the four groups. The chi-squared (χ^2) test was used for comparisons involving categorical variables. For comparisons among the DM subgroups, analysis of covariance was conducted to adjust for potential confounding variables, followed by post hoc testing using the least significant difference method. Univariate and multivariate linear regression analyses were carried out to determine factors associated with the vascular density of the SCP pVD. (see [Supplementary Figures 1–47](#), for the residual distribution diagram following covariance adjustment).

Results

Basic Patient Characteristics

A total of 88 eyes from 46 control participants and 314 eyes from 165 patients with DM were included in the study. Participants were categorized into four groups: 88 eyes in the control group, 135 in DM group 1, 87 in DM group 2, and 92 in DM group 3. No statistically significant differences were observed in smoking status among the groups ($p > 0.05$). Similarly, the use of insulin did not differ significantly among DM group 1, DM group 2, and DM group 3 ($p > 0.05$). However, significant differences were identified among the four groups in terms of age, BCVA, IOP, optic disc area, and body mass index (all $p < 0.05$). Fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) levels did not differ significantly among the DM subgroups ($p > 0.05$). The baseline characteristics of the study population are presented in [Table 1](#).

pRNFL and pGCL-IPL Thickness in Each Group

The pRNFL thickness across groups is presented in [Figures 1 and 2](#). The mean pRNFL thickness in the control group, DM group 1, DM group 2, and DM group 3 was $124.14 \pm 12.44 \mu\text{m}$, $127.85 \pm 15.86 \mu\text{m}$, $127.01 \pm 13.54 \mu\text{m}$, and $121.53 \pm 16.73 \mu\text{m}$, respectively. No statistically significant differences in average pRNFL or pGCL-IPL thickness were observed between the control group and the DM groups. However, a significant difference in pRNFL thickness was noted among the DM groups ($p = 0.018$). A decreasing trend in pRNFL thickness was observed with increasing duration of diabetes, with statistically significant differences identified in the superior (S), inferior (I), inferotemporal (IT), temporoinferior (TI), and superotemporal (ST) sectors ($p = 0.032, 0.019, 0.010, 0.019, \text{ and } 0.025$, respectively).

No statistically significant differences in pGCL-IPL thickness were found among the DM groups. Although macular GC-IPL thickness did not differ significantly between the diabetic and control groups, significant differences were found among the DM subgroups ($F = 7.647, p = 0.001$). Post hoc analysis indicated that GC-IPL thickness was significantly lower in DM group 3 compared to DM group 1 ($p = 0.000118$). (see [Supplementary Tables 1–4](#), for detailed group values and p-values).

SCP pVD in Each Group

OCTA images of the superficial retinal capillary plexus from representative participants in the control and DM groups are shown in [Figure 1C](#). The mean vascular density of the SCP pVD was $33.56 \pm 2.87\%$ in the control group and $31.39 \pm 3.77\%$ in the DM group, indicating a statistically significant reduction in the diabetic group. SCP pVD showed a progressive decline with increasing duration of diabetes, with significant differences observed across multiple regions.

Post hoc analysis indicated statistically significant differences in the average, temporoinferior (TI), and temporosuperior (TS) regions between DM group 1 and DM group 3 ($p = 0.000271, 0.000009, \text{ and } 0.000008$, respectively). Additionally, a significant difference was observed in the TS sector between DM group 2 and DM group 3 ($p = 0.000082$). (see [Supplementary Tables 1–4](#), for detailed values and p-values across groups).

Peripapillary Choroidal Complexes

[Figure 3](#) depicts the measurements of peripapillary choroidal thickness (pCT), peripapillary choroidal vessel volume (pCVV), and peripapillary choroidal vascularity index (pCVI) in healthy controls and among the DM groups. Within the DM groups, no statistically significant differences were observed in pCT, pCVV, or pCVI. Although a decreasing trend in

Table 1 Main Demographic and Clinical Data of the Study Subjects

Parameters	Control	DM Group 1	DM Group 2	DM Group 3	P value*
Number of subjects (n)	46	70	46	49	–
Eyes (n)	88	135	87	92	0.054
Age (years)	54.5 ± 11.4	49.2 ± 15.7	54.9 ± 14.3	65.1 ± 9.6	<0.001
Sex (female/male)	28/18	24/46	20/27	24/25	0.002
Laterality (right, %)	44 (50)	69 (51.1)	45 (51.7)	47 (51.1)	–
BMI	23.18 ± 3.14	25.26 ± 3.87	23.77 ± 4.38	25.01 ± 2.78	0.009
Smoking (n, %)	13 (14.8)	29 (21.5)	25 (28.7)	22 (23.9)	0.082
BCVA (logMAR)	0.13 ± 0.19	0.16 ± 0.19	0.18 ± 0.15	0.22 ± 0.19	0.019
IOP (mmHg)	14.77 ± 3.44	16.2 ± 3.07	15.28 ± 3.32	14.53 ± 3.08	0.003
DM duration (months)	N/A	6	84	180	–
FBG (mmol/L)	N/A	7.89 ± 3.15	7.28 ± 2.34	7.86 ± 2.75	0.523
HbA1c (%)	N/A	8.85 ± 2.67	8 ± 2.11	8.15 ± 1.62	0.114
Disc parameters					
Rim area	1.46 ± 0.31	1.46 ± 0.36	1.51 ± 0.28	1.49 ± 0.31	0.883
Disc area	2.13 ± 0.39	2.23 ± 0.41	2.32 ± 0.45	2.31 ± 0.39	0.008

Notes: DM group 1 = patients with diabetes < 5 years, DM group 2 = patients with diabetes \geq 5 years, <10 years, and DM group 3 = patients with diabetes \geq 10 years. P value* = P value among the four groups.

Abbreviations: BMI, body mass index; BCVA, best-corrected visual acuity; IOP, intraocular pressure; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1C, glycated hemoglobin.

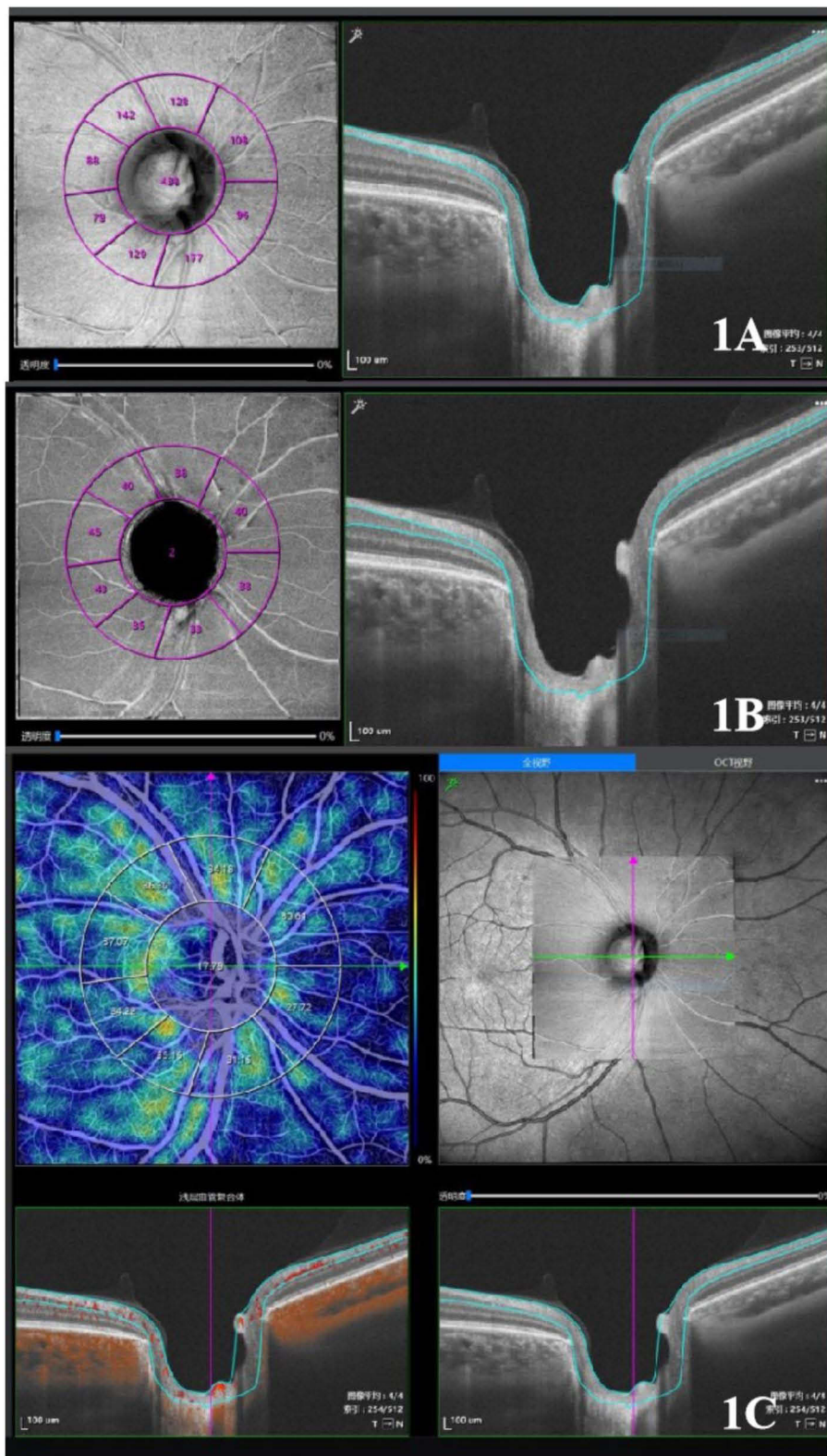


Figure 1 The OCTA images covered an area of $6 \times 6 \text{ mm}^2$ around the Optic nerve. The swept-source optical coherence tomography angiography technology and Garway-Heath map-based ONH measurement software were applied to explore the peripapillary retinal nerve fiber layer, ganglion cell layer plus inner plexiform layer thickness and superficial capillary plexus vascular density as shown in (A–C). The en-face angiograms of the peripapillary superficial capillary plexus vascular density (from ILM-5 to one-third border of GC-IPL) as shown in (C).

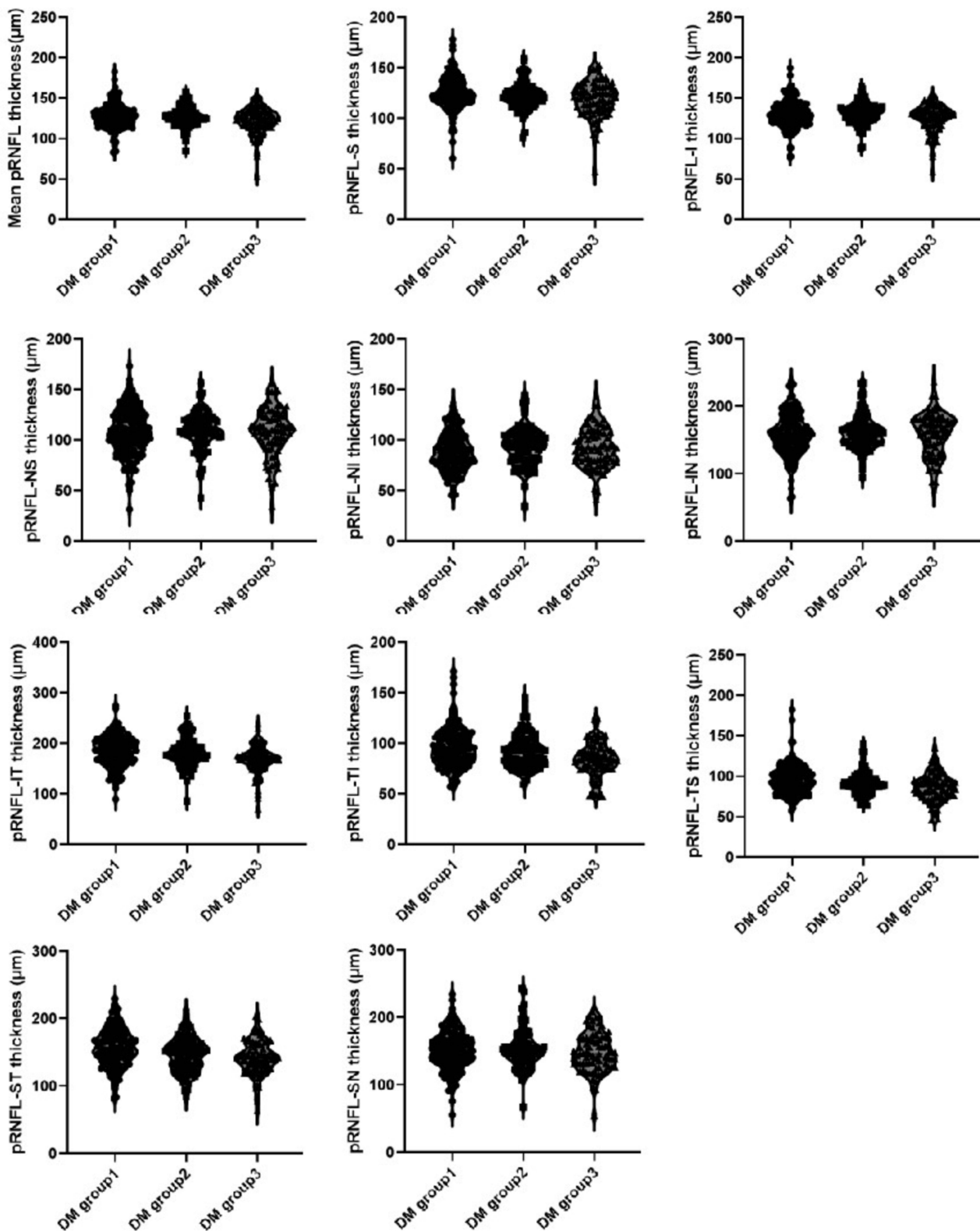


Figure 2 Peripapillary retinal nerve fiber layer (pRNFL) thickness of the diabetic subjects.

Abbreviations: S, super; I, infer; NS, nasosuper; NI, nasoinfer; IN, inferonasal; IT, inferotemporal; TI, temporoinfer; TS, temporosuper; ST, superotemporal; SN, superonasal.

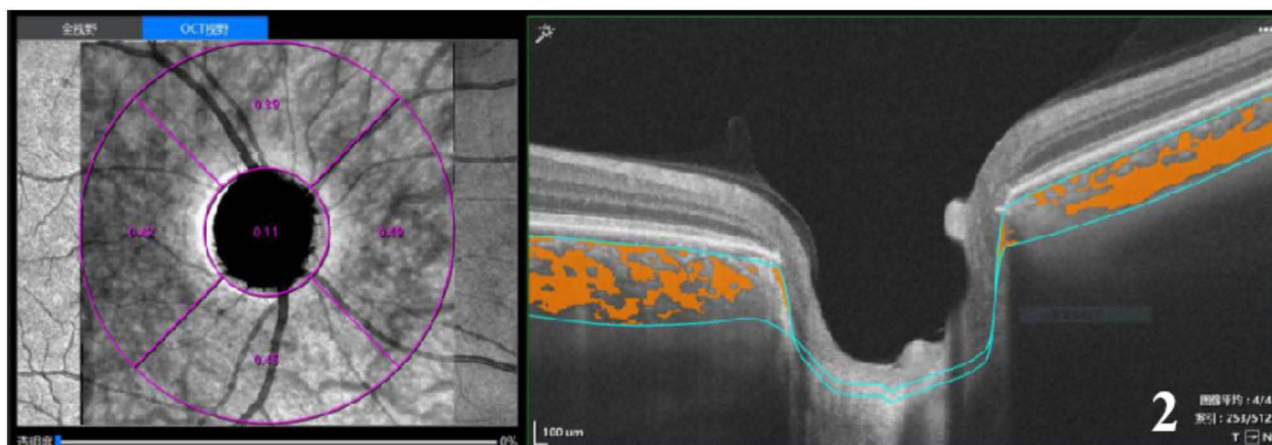


Figure 3 Illustration of extraction of choroidal lumen and calculation of three-dimensional choroidal vascularity index (3D CVI). Measurement of choroidal thickness and lumen. The superior and inferior boundary of the choroid (blue line) and choroidal vascular lumen (Orange area) were identified by deep learning. Magnified non-infrared image with 6-mm ring. The CT, CVV and CVI was calculated into four parts, including superior, inferior, nasal, and temporal.

choroidal index values was associated with longer diabetes duration, no significant differences were identified among the DM subgroups following statistical adjustment. (See [Figure 4](#) and [Supplementary Figure 48](#), for the visual representation of changes in choroid-related indices between groups; see [Supplementary Tables 1–4](#), for specific values and p-values).

Indicators Related to SCP pVD in Patients with DM

In univariate analyses, several factors were significantly associated with SCP pVD in patients with DM, including DM duration ($B = -0.016$, $p < 0.001$), hypertension (HTN) ($B = 0.190$, $p = 0.001$), renal dysfunction ($B = 0.160$, $p = 0.005$), BCVA ($B = -0.112$, $p = 0.049$), pRNFL thickness ($B = 0.280$, $p < 0.001$), GCL-IPL thickness ($B = 0.229$, $p < 0.001$), and pCT ($B = 0.245$, $p < 0.001$).

In multivariate analyses, DM duration ($B = -0.205$, $p < 0.001$), HBP ($B = 0.168$, $p = 0.001$), pRNFL thickness ($B = 0.083$, $p < 0.001$), and pCT ($B = 0.174$, $P = 0.005$) remained significantly associated with SCP pVD. (Refer to [Table 2](#) for detailed results).

Discussion

In this cross-sectional study, SS-OCT was used to assess the peripapillary retinal and choroidal vasculature in patients with DM without clinical DR. To our knowledge, this is the first investigation comparing non-diabetic patients with diabetic patients at varying disease durations based on pRNFL thickness, pGCL-IPL thickness, pCT, pCVV, and pCVI parameters obtained from SS-OCT imaging. This integrated parameter assessment fills a key gap in current research, as most prior studies have focused on isolated retinal or choroidal indices rather than synchronously evaluating the “neurovascular-choroid” complex in relation to diabetes duration.^{18,31}

Significant differences were observed in pRNFL thickness, SCP pVD, pGCL-IPL thickness, and choroid-related peripapillary indices among non-diabetic controls and diabetic groups with varying durations of disease. Although no statistically significant differences in average pRNFL thickness, pGCL-IPL thickness, or pCT were found between the control and DM groups, a progressive decrease in pRNFL thickness was noted with increasing diabetes duration, with significant reductions in the S, I, IT, TI, and ST sectors. Macular GC-IPL thickness did not differ between the diabetic and control groups, but significant differences were found among the DM subgroups.

Notably, in the diabetic groups, macular ganglion cell layer (GCL) thickness decreased with prolonged disease duration, while no statistically significant change was observed in peripapillary GCL (pGCL) thickness. This indicates that diabetes-induced early neurodegeneration exhibits spatial heterogeneity. We hypothesize that this damage pattern may be associated with functional metabolic load: macular ganglion cells are responsible for high-acuity vision, and their extremely high metabolic rate renders them more susceptible to energy crisis and oxidative stress induced by diabetes.

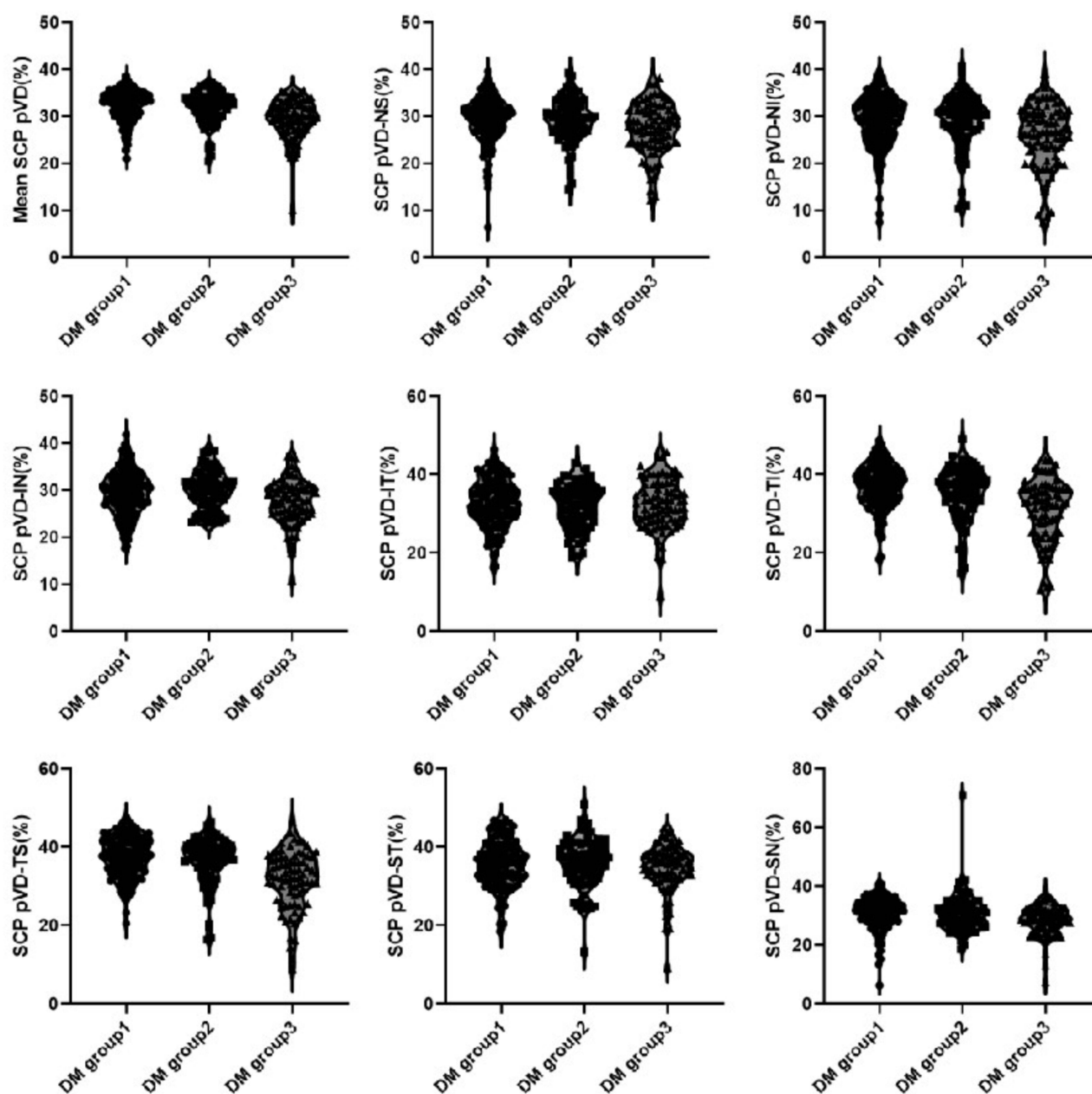


Figure 4 Peripapillary superficial capillary plexus vascular density (SCP pVD) of the diabetic subjects.

Abbreviations: NS, nasosuper; NI, nasoinfer; IN, inferonasal; IT, inferotemporal; TI, temporoinfer; TS, temporosuper; ST, superotemporal; SN, superonasal.

This finding emphasizes that macular GCL thickness is an extremely sensitive indicator for monitoring diabetic neuropathy. In clinical practice, priority should be given to monitoring morphological changes in this region to identify patients at risk of neural damage at an earlier stage.

Notably, SCP pVD was reduced in patients with diabetes without DR compared to non-diabetic controls and showed a further decline with longer disease duration. The pCVI was also reduced in the diabetic groups compared to the control group. In addition, differences in pCVV were identified among the DM subgroups. This sequential reduction of SCP pVD with disease duration, combined with the absence of significant global neural layer thinning in the overall DM cohort, supports the hypothesis that microvascular impairment may precede detectable neurodegeneration in preclinical DR.^{11,31}

There is increasing evidence supporting the involvement of retinal neurodegeneration and choroidal impairment in the early pathogenesis of DR. Thinning of the RNFL and pGCL-IPL has been identified as a potential marker of

Table 2 Univariable and Multivariable Regression Analysis to Determine the Factors Associated with SCP pVD (%)

	Univariate		Multivariate	
	B (95% CI)	P values	B (95% CI)	P values
BMI	-0.051 (-0.205 ~ 0.105)	0.523		
DM duration	-0.016 (-0.020 ~ -0.011)	<0.001	-0.205 (-0.015 ~ -0.005)	<0.001
Insulin	0.034 (-0.595 ~ 1.099)	0.558		
HBP	0.190 (0.600 ~ 2.266)	0.001	0.168 (0.496 to 2.001)	0.001
Dyslipidemia	0.062 (-0.380 ~ 1.309)	0.280		
Renal dysfunction	0.160 (0.556 ~ 3.114)	0.005	0.083 (-0.251 to 2.185)	0.119
Smoking	0.048 (-1.404 ~ 0.566)	0.403		
FBG	-0.073 (-0.315 ~ 0.123)	0.386		
HbA1c	0.002 (-0.269 ~ 0.274)	0.985		
BCVA	-0.112 (-4.350 ~ -0.009)	0.049	0.024 (-1.563 ~ 2.504)	0.649
pRNFL	0.280 (0.041 ~ 0.094)	<0.001	0.275 (0.042 ~ 0.091)	<0.001
GCL-IPL	0.229 (0.123 ~ 0.352)	<0.001	0.094 (-0.024 ~ 0.220)	0.116
pCT	0.245 (0.007 ~ 0.019)	<0.001	0.174 (0.003 ~ 0.015)	0.005

Abbreviation: CI, confidence interval.

neurodegeneration. Several studies have reported significant thinning of the RNFL and pGCL-IPL in patients with DM, although some findings remain inconsistent.^{3,12,32} Recent meta-analyses have highlighted the need for duration-stratified studies to clarify these inconsistencies, as neural damage may accumulate gradually over time rather than presenting as a binary outcome.³³

In this study, a trend toward reduced pRNFL thickness was observed in patients with diabetes without clinical DR compared to non-diabetic controls, though the difference was not statistically significant. However, significant differences in pRNFL thickness were found among the DM subgroups, particularly in the S, I, IT, TI, and ST sectors. Previous findings have also indicated a reduction in temporal pRNFL thickness in diabetic patients, which may be due to the inherently thinner RNFL in the temporal region, making early changes more detectable.³⁴ Consistent with our sector-specific pRNFL thinning, Orduna-Hospital et al⁸ reported focal RNFL reductions in T1DM patients without DR, emphasizing that regional changes may precede global thinning. In contrast, Lim et al¹² observed significant global pRNFL thinning in T2DM patients during longitudinal follow-up, which may reflect differences in study design (longitudinal vs cross-sectional) or diabetes type. Our cross-sectional data complement these longitudinal findings by demonstrating that even in the absence of global thinning, sector-specific pRNFL changes are associated with disease duration, providing a potential early marker for risk stratification.¹⁰

No significant differences in peripapillary pGCL-IPL or macular pGCL-IPL thickness were identified between the diabetic and control groups. However, macular pGCL-IPL thickness was significantly reduced in DM group 3 compared to DM group 1. This finding aligns with Jia et al,⁹ who reported that GCL-IPL thinning in T2DM patients without DR is associated with disease duration, supporting the notion that neuronal damage accumulates over time. In contrast, Rodrigues et al¹⁰ did not detect GCL-IPL changes in early DM, which may be attributed to smaller sample size or shorter diabetes duration in their cohort. Our results extend this line of research by showing that macular GCL-IPL thinning is specifically associated with longer disease duration (>10 years), highlighting the importance of duration stratification in detecting early neurodegeneration.^{9,13}

In contrast, SCP pVD was significantly reduced in patients with diabetes without DR compared to control participants and showed a continued decline with longer disease duration. Lee et al examined the peripapillary RNFL/vascular density ratio to investigate the sequence of diabetic retinal neurodegeneration (DRN) and microvascular injury.³⁵ A higher RNFL/VD ratio in patients with type 2 diabetes mellitus (T2DM) without clinical DR was interpreted as evidence that microvascular damage may precede retinal thinning due to DRN. The findings of this study are largely consistent with this hypothesis. Although earlier studies have proposed that DRN precedes microvascular impairment in DM,³² the present results suggest that damage

to the peripapillary microvasculature may occur prior to neuronal degeneration. Prolonged hyperglycemia may contribute to greater microvascular compromise. Vujosevic et al²⁵ also reported reduced peripapillary SCP pVD in T2DM patients without DR, further validating our observation of early microvascular dysfunction. This discrepancy in the sequence of injury may be explained by differences in study populations (eg, T1DM vs T2DM) or parameter selection, underscoring the need for integrated neuro-vascular assessments.¹⁷

CVI is less influenced by factors such as age, axial length, spherical equivalent refraction, and other anatomical variables, thereby providing improved measurement stability. As a result, CVI serves as a more reliable parameter for assessing choroidal alterations.³⁵ Consistent with previous studies, diabetic patients showed significantly reduced CVI compared to healthy controls.^{2,3,6} Xu et al³⁶ reported a significant decrease in choroidal capillary CVI in patients with pre-diabetic retinopathy (pre-DR) and early DR,³ while Aksoy et al¹⁸ also found a negative correlation between CVI and diabetes duration in eyes without DR ($P=0.006$), suggesting progressive subclinical dysfunction of the choroid associated with disease duration in diabetic patients. CVI has previously been used to assess choroidal characteristics in diabetic populations in Singapore³⁷ and Aksoy,¹⁸ with both studies reporting a reduction in CVI among patients with diabetes compared to healthy controls. Similarly, decreased CVI values have been observed in patients with DM without clinical signs of DR, aligning with the findings of this study. Our results extend these observations by demonstrating that pCVV differs among DM subgroups, indicating that choroidal vascular volume declines progressively with diabetes duration. This is consistent with Yulek et al,²² who linked longer diabetes duration to choroidal vascular changes, but contrasts with Marques et al,³⁸ who found no CVI difference between non-DR diabetic eyes and controls—likely due to their smaller sample size and lack of subgroup stratification by disease duration. Notably, our finding of progressive pCVV reduction without significant pCT or pCVI changes adds novel insights to choroidal involvement in preclinical DR, as most prior studies have focused on CVI or CT alone rather than vascular volume.^{18,37}

However, few studies have addressed changes in the peripapillary choroid with diabetes duration. The present study found that in diabetic patients without DR, CVV showed a progressive decrease with prolonged disease duration, while CT and CVI remained unchanged. This indicates that the early impact of diabetes on the choroid is mainly reflected in the diffuse loss of its overall volume. Two explanations are proposed for this phenomenon: first, compared to choroidal thickness measured at a single point, choroidal volume, as a three-dimensional parameter, can more sensitively capture diffuse atrophy of the entire posterior pole choroid. Second, the reduction in choroidal volume without changes in CVI strongly suggests that diabetes-induced choroidal atrophy is a non-selective process, ie, vascular and stromal components decrease synchronously in similar proportions. It reveals that diabetes has already impaired the overall structural integrity of the choroid before the onset of microvascular lesions. Future studies should focus on using this indicator for early risk stratification and exploring its association with retinal neurodegeneration and subsequent development of microvascular lesions.

In the current analysis, reduced pCVI values were observed in diabetic patients compared with the control group. Additionally, differences in pCVV were identified among the DM subgroups. Although CVI is known to decline with age even in healthy eyes, no significant age differences were noted between the control and diabetic groups in this study. These findings support the notion that diabetic choroidopathy may be detectable prior to the clinical onset of retinopathy, potentially representing early, preclinical changes in the diabetic choroid. This suggests that the choroid may serve as an underlying contributor to the pathogenesis of DR. Recent studies have proposed that choroidal dysfunction may exacerbate retinal ischemia by impairing outer retinal perfusion, highlighting the clinical relevance of our findings for early DR intervention.³⁹

The role of choroidal mechanisms in the development of DR remains incompletely understood. One possible explanation for the observed alterations is that chronic hyperglycemia may lead to vascular endothelial cell damage, subsequently contributing to RPE dysfunction. Supporting this hypothesis, Cao et al⁴⁰ demonstrated a fourfold increase in choriocapillaris loss in diabetic eyes compared to non-diabetic eyes. Curvature and loss of intermediate-to-large blood vessels within Haller's and Sattler's layers have been observed in diabetic patients using optical coherence tomography (OCT) imaging.⁴¹ These findings may be attributed to vascular stenosis secondary to choroidal hypoxia, resulting in reduced blood flow. Gong et al⁷ also reported that reduced pCT was associated with a higher risk of developing DR. However, it remains unclear whether choroidal thinning precedes retinal ischemia and hypoxia, or whether retinal ischemia and hypoxia contribute to subsequent changes in both the retina and choroid.

Further experimental studies are required to clarify this causality. Additionally, inconsistencies across previous findings may be influenced by variations in choroidal assessment methodologies. For instance, OCT imaging is frequently centered on the macular region, and numerous confounding factors can influence CT measurements. Our focus on peripapillary choroidal parameters addresses this limitation, as the peripapillary region is less susceptible to foveal anatomical variations and provides a more uniform assessment area.⁴²

In this study, SCP pVD in patients with DM was significantly associated with DM duration, HTN, pRNFL thickness, and pCT. The association between pRNFL thickness and SCP pVD was consistent with findings from previous studies. Vujosevic et al reported a significant correlation between peripapillary vascular density and pRNFL thickness in patients with T2DM without DR.⁴² In contrast, Mase et al found that peripapillary vascular density may be insufficient for accurately assessing pRNFL thickness.³⁰ Although these parameters may reflect impairment in each other, further investigation is needed to clarify the nature of their relationship. Our multivariate analysis adds value by controlling for confounding factors (eg, HTN) and confirming that diabetes duration is an independent predictor of SCP pVD reduction.^{11,12}

HTN and pCT also emerged as important factors influencing SCP pVD in patients with diabetes. The close interrelationship between systemic and ocular circulation underlies these associations.

Among patients with DM, FBG and HbA1c were not identified as significant factors affecting SCP pVD. Consistent with these findings, Sohn et al³² reported that HbA1c levels did not influence pGC-IPL or RNFL thickness in a longitudinal study. Although poor glycemic control is considered a contributor to nerve and vascular damage, further longitudinal studies are warranted to clarify its long-term impact. This finding may reflect the cumulative effect of diabetes duration on microvascular damage, which may be more predictive of structural changes than short-term glycemic fluctuations.^{11,33}

This study has several strengths. A relatively large sample size was included, and only high-quality OCTA images were selected to ensure reliable measurements. Furthermore, SS-OCTA was used, allowing clear visualization and accurate quantification of retinal and choroidal perfusion. Currently, no prior studies have reported the effects of prolonged DM duration on pRNFL and peripapillary vasculature compared with patients who are non-diabetic. This study is the first to demonstrate that changes in peripapillary choroidal blood flow occur over the course of diabetes in the absence of clinical DR, and that microvascular alterations in the peripapillary retina may precede detectable neurodegenerative changes. Additionally, the integration of neural, vascular, and choroidal parameters provides a comprehensive assessment of the diabetic neurovascular unit, addressing a critical gap in existing literature that often focuses on isolated components.¹⁰

However, this study has certain limitations. First, its retrospective cross-sectional design precludes the ability to infer causality or temporal progression. Second, visual function parameters such as microperimetry or contrast sensitivity, were not assessed. Although eyes with refractive errors exceeding ± 4.00 diopters were excluded, further studies are required to account for axial length as a potential confounding factor in CT measurements. Third, the definition of diabetes duration may be subject to recall bias, as it relies on self-reported data from patients. Fourth, we did not fully control for all potential confounding factors, including renal function, blood lipid levels, and short-term blood glucose fluctuations, which may have influenced the observed associations between diabetes and ocular structural changes. Fifth, the generalizability of our findings may be limited by the single-center nature of the study, and multi-center studies with more diverse populations are needed to validate our results.

To translate our findings into clinical practice, it is essential to address key barriers to widespread application of the proposed duration-stratified, multi-parameter assessment strategy. First, cost and accessibility remain prominent challenges: SS-OCTA equipment is currently expensive, leading to limited availability in primary care settings and resource-constrained regions. Potential solutions include technological advancements to simplify device design and reduce manufacturing costs, as well as policy initiatives such as centralized procurement or reimbursement support to improve access at the grassroots level. Second, standardization and batch consistency require urgent resolution: variations in imaging algorithms, segmentation criteria, and measurement protocols across different device manufacturers hinder result comparability. This can be addressed through multi-center collaborative efforts to develop unified, regulatory body-endorsed standards for data acquisition and analysis, coupled with regular equipment calibration and quality control programs to ensure consistent performance across batches and clinical centers. Third, operator dependence and efficiency

constraints may limit scalability: manual analysis of SS-OCTA images is time-consuming and subject to inter-observer variability. Developing artificial intelligence-driven automated analysis systems will be critical to enabling large-scale screening, reducing human error, and facilitating widespread implementation in clinical workflows. Addressing these barriers will be pivotal to realizing the potential of our findings in improving early DR detection and personalized patient management.

Future Directions

Based on the findings of this study, we will conduct prospective cohort studies to clarify whether the decline of SCP pVD and pCVI can predict the subsequent incidence risk and timeline of DR, thereby establishing their value as predictive biomarkers. Meanwhile, it is necessary to combine multimodal imaging techniques (such as OCT angiography, fundus autofluorescence, and functional magnetic resonance imaging) to further explore the pathological mechanisms underlying the inconsistent GCL-IPL damage between the macular region and peripapillary area. Future clinical trials can investigate whether interventions (such as stricter glycemic and blood pressure control or the use of neurovascular protective agents) implemented upon detection of these subclinical microvascular and choroidal lesions (ie, prior to the onset of clinical DR) can delay or prevent the development of clinical DR. Additionally, future studies should incorporate assessments of visual function parameters (eg, microperimetry, contrast sensitivity) and control for confounding factors such as renal function, blood lipids, and axial length to further validate the clinical significance of our structural findings. Multi-center collaborative studies are also warranted to standardize measurement protocols and enhance the generalizability of the proposed multi-parameter assessment strategy.

Conclusion

SCP pVD was significantly reduced in patients with diabetes compared to non-diabetic controls and declined further with increasing duration of diabetes. No significant differences were observed in average pRNFL or pGCL-IPL thickness between diabetic and control groups. However, pCVI was reduced in the diabetic group, and pCVV varied among the DM subgroups. Additionally, SCP pVD was significantly associated with diabetes duration, pRNFL thickness, pCT, and HTN in diabetic individuals. These findings indicate that microvascular and choroidal injury may occur and progress even in the absence of clinically apparent DR. Specifically, the progressive reduction of SCP pVD and pCVV with disease duration, combined with spatial heterogeneity in GCL thinning, highlights the need for duration-stratified, multi-parameter assessments for early DR screening. These assessments, integrating structural and functional ocular biomarkers, could improve risk stratification of preclinical DR and guide personalized monitoring protocols. Further studies are necessary to develop effective strategies for preventing or mitigating such injuries, including prospective cohort studies to validate SCP pVD and pCVV as predictive biomarkers for DR onset, multimodal imaging studies to unravel the pathological mechanisms underlying regional GCL-IPL damage heterogeneity, and interventional trials to evaluate whether targeted therapies (eg, optimized metabolic control or neurovascular protectants) can halt or reverse subclinical lesions before clinical DR manifests.

Abbreviations

BCVA, best-corrected visual acuity; CVV, choroid vessel volume; CVI, choroid vessel index; DM, diabetes mellitus; DR, diabetic retinopathy; DC, diabetic choroidopathy; DME, diabetic macular edema; DRN, diabetic retinal neurodegeneration; EMRS, electronic medical record system; FBG, fasting blood glucose; HBP, high blood pressure; HbA1c, glycated hemoglobin; pRNFL, peripapillary retinal nerve fibre layer; pGCL-IPL, peripapillary ganglion cell layer plus inner plexiform layer; SCP pVD, peripapillary superficial capillary plexus vascular density; pCVI, peripapillary choroid vessel index; SS-OCTA, swept-source optical coherence tomography angiography; SCP pVD, peripapillary superficial capillary plexus vascular density; T2DM, type 2 diabetes mellitus.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of General Hospital of Central Theater Command (No. [2024]013-01). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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Author Contributions

Ming Yan: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing. Wen-Jing Zhang: Conceptualization, Formal Analysis, Writing – original draft. Cong Chen: Conceptualization, Writing – original draft, Writing – review & editing. Zhen Huang: Data curation, Formal Analysis, Writing – review & editing. Ya Ye: Data curation, Formal Analysis, Writing – review & editing. Dong-Qiang Xu: Data curation, Formal Analysis, Writing – review & editing. Yu-Meng Deng: Data curation, Formal Analysis, Writing – review & editing. Yan-Ping Song: Conceptualization, Funding acquisition, Writing – review & editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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