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Vulnerable parafoveal microcirculation quadrant in patients with type 2 diabetes mellitus

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Diabetic retinopathy (DR) is a leading cause of vision loss among adults. This study evaluates Optical Coherence Tomography Angiography (OCTA) vessel density (VD) as a marker for DR in diabetes mellitus (DM) patients. An observational study was conducted with 47 type 2 DM patients and 21 healthy controls. OCTA measured superficial and deep retinal VD in the parafoveal region. Statistical analyses, including logistic regression and ROC curve analysis, were used to assess the association between VD and DR presence. Results showed that DM patients had lower parafoveal superficial (46.73 vs. 52.37%, $p = 0.002$) and deep VD (50.35 vs. 54.26%, $p = 0.019$) compared to controls. Within the DM group, DR patients had lower VD in the superior parafoveal superficial layer ($p = 0.042$) and temporal parafoveal deep layer ($p = 0.035$). ROC analysis identified a cutoff of 51.86% for the temporal deep parafoveal VD, with an AUC of 0.697 ($p = 0.035$) and 81.8% sensitivity for DR discrimination. Reduced VD in the temporal deep parafoveal region is linked to a higher DR likelihood. OCTA-derived VD metrics offer promise for early DR detection and underscore the importance of monitoring vascular changes in DM patients.

Keywords Diabetic retinopathy, Optical coherence tomography angiography, Vessel density

Diabetic microvascular diseases, including nephropathy, neuropathy, and retinopathy, play a pivotal role in morbidity and mortality[1,2]. Among these, diabetic retinopathy (DR) emerges as a leading cause of vision loss in adults[3–5]. As the prevalence of DR continues to increase, its impact on and threat to visual health have become significant. Detailed risk stratification in the preclinical or early stages of DR may benefit most patients with diabetic mellitus (DM).

Endothelial damage and pericyte loss are the two main pathophysiologies of the initial changes in DR, leading to increased capillary occlusion and vascular permeability[6,7]. The subsequent progression of DR is marked by characteristic microvascular changes, including microaneurysms, intraretinal hemorrhages, intraretinal microvascular abnormalities, and neovascularization, which manifest in distinct stages ranging from non-proliferative to proliferative disease. Traditionally, non-proliferative diabetic retinopathy (NPDR) has been graded based on the severity and extent of pathological findings compared with standard images from the Early Treatment Diabetic Retinopathy Study (ETDRS)[8]. This grading system ranges from no apparent DR (grade 0) to mild (grade 1), moderate (grade 2), and severe (grade 3) NPDR, corresponding to increasing disease

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severity. In addition, in clinical practice, the recommended examination schedule for ocular conditions relies primarily on the grading of DR and the presence of cystoid macular edema. In the general population with diabetes, the majority (approximately 70%) exhibit no signs of DR and are categorized as grade 0 DR[9–12]. The incidence of DR progression is approximately 10% per year[13]. The duration of mild DR development is typically around 8 years, longer than that of subsequent progressive stages[14]. However, once patients advance to the early stages of DR, the risk of developing proliferative DR (PDR) and clinically significant macular edema increases significantly[15]. In addition, current consensus guidelines typically recommend only yearly follow-up and control of underlying diseases in these individuals, without further evaluation or risk classification for those without apparent retinopathy[16,17].

In recent years, Optical Coherence Tomography Angiography (OCTA) has advanced the evaluation of the retinal microvasculature, providing high-resolution, non-invasive visualization. The emergence of OCTA has significantly contributed to the detection of microcirculatory changes in patients with systemic diseases, including DM, hypertension, cardiovascular disease, neurodegenerative diseases, and even the use of certain medications[18]. While the exact mechanisms remain to be fully established, these findings enhance our understanding of the connections between systemic conditions and ocular perfusion. In the context of DM, OCTA enables the detection of early stages of DR before clinical manifestation[19]. Moreover, even in the absence of DR, a decreased macular capillary plexus has been reported in prediabetic patients compared with healthy subjects[20]. By offering depth-resolved imaging of the retinal vasculature, OCTA holds promise for elucidating the early development of DR, contributing to our understanding of early disease progression, and even DM detection.

By detecting subtle alterations in microvascular perfusion, OCTA has the potential to serve as a valuable tool for identifying individuals at higher risk of developing advanced stages of DR[19]. Given the microvascular nature of DR, which predominantly affects terminal blood vessel circulation, we hypothesized that OCTA assessment of vessel density (VD) across different depths and sectors in patients with DM may serve as an indicator for early DR progression.

The purpose of this study was to assess the differences in VD between individuals with DM and healthy controls, as well as between patients with DM categorized as having no apparent DR and those with clinically detected DR. This evaluation aimed to determine the utility of vessel density as a risk stratification tool for the development of DR.

Methods

Participants

This was an observational, single-center study conducted at Taichung Veterans General Hospital. We enrolled participants from October 2022 to February 2024, including individuals aged 18 years or older who were diagnosed with type 2 DM. The exclusion criteria included pregnant individuals, patients undergoing renal dialysis, patients with cancer, susceptible populations, and those with a history of significant alcohol or substance abuse. The medical history of all participants was reviewed to record systemic diseases, including hypertension, hyperlipidemia, chronic kidney disease, coronary artery disease, and cerebrovascular disease. Blood glucose levels were assessed by measuring HbA1c levels in all participants. Ophthalmological evaluations were also performed, and participants presenting with significant ocular pathologies were excluded. Healthy control subjects without DM were enrolled for comparison. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital, and all procedures adhered to the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants before their inclusion.

Ophthalmologic evaluation

A comprehensive ophthalmologic examination was conducted for all participants, which included the assessment of best-corrected visual acuity (BCVA) and its transformation into logMAR units[21,22], refraction, intraocular pressure (IOP), central corneal thickness (CCT), endothelial cell density (ECD), axial length measurement, and color fundus photography. The presence and severity of DR were determined by an ophthalmologist based on the ETDRS standard images. Spectral-domain OCT scans (Heidelberg Engineering, Heidelberg, Germany) were performed to assess the macula and optic disc. OCTA was performed using RTVue XR Avanti (Optovue Inc., Fremont, CA, USA) after pupillary dilation. OCTA was used to evaluate both superficial and deep retinal VD in the parafoveal region as well as in various sectors, encompassing the superior, temporal, inferior, and nasal portions.

The autonomic image quality index ranges from 1 to 10, and scores of 5 or above were enrolled for further analysis. Eyes with significant refractive errors (> 6 diopters of spherical equivalent refraction) were excluded. Participants with significant ocular diseases revealed during the examination that could potentially influence retinal and choroidal circulation, such as glaucoma, uveitis, age-related macular degeneration, hypertensive retinopathy, retinal vascular diseases, ocular tumors, and autoimmune diseases, were also excluded.

Statistical analyses

Statistical analyses were performed using IBM SPSS software (version 22.0; International Business Machines Corp., New York, NY, USA). Data from the right eye were prioritized whenever available to standardize the analysis. If the right eye was excluded for the aforementioned reasons, data from the left eye were used. The Mann-Whitney U test and chi-square test were used for comparisons between continuous and categorical variables in the DR and non-DR groups. Logistic regression was employed to analyze the relationship between VD and the presence of DR. If the p value of a sectoral VD was less than 0.05 in the univariable analysis, it was included in the multivariable analysis. In the multivariable analysis, models were adjusted for confounders including age, sex, and the presence of comorbidities. Receiver operating characteristic (ROC) curves and the

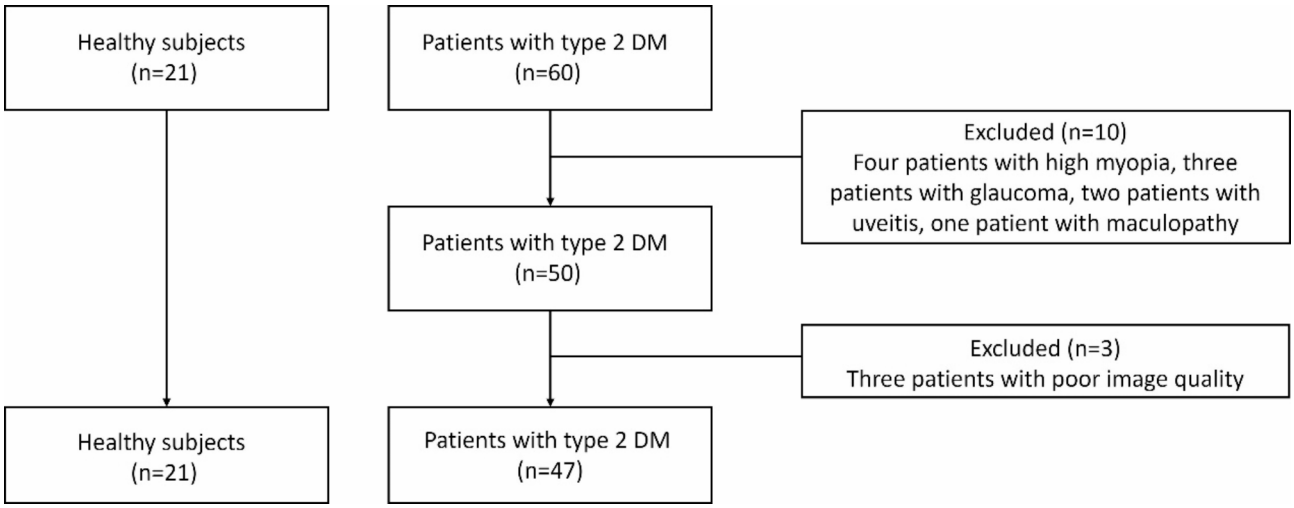

Fig. 1. Participants enrollment flowchart. A total of 21 healthy subjects and 60 patients with type 2 diabetes mellitus (DM) were enrolled. In the DM group, four patients with high myopia, three patients with glaucoma, two patients with uveitis, and one patient with maculopathy were excluded. Furthermore, three patients with poor image quality in both eyes were excluded. **DM* Diabetes mellitus.

	DM ($n=47$)	Control ($n=21$)	p value
Age, years	56.2 (44.7, 64.3)	37.6 (32.0, 54.3)	0.001*
Sex, n(%)			0.094
Women	21 (44.7%)	14 (66.7%)	
Men	26 (55.3%)	7 (33.3%)	
Hypertension n(%)	18 (38.3%)	2 (9.5%)	0.016*
Hyperlipidemia n(%)	39 (83.0%)	2(9.5%)	<0.001*
CKD n(%)	31 (66.0%)	10 (47.6%)	0.150
CAD n(%)	2 (4.3%)	0 (0.0%)	1.000
CVD n(%)	2 (4.3%)	1 (4.8%)	1.000
Presence of DR	11 (23.4%)	0 (0.0%)	–

Table 1. Demographic and clinical characteristics of DM groups and healthy control. Data are presented as median (interquartile range) in age row, and as case number (percentage) in other rows. *DM* diabetes mellitus, *CKD* chronic kidney disease, *CAD* coronary artery disease, *CVD* cerebrovascular disease, *DR* diabetic retinopathy. **p* value less than 0.05.

corresponding area under the curve (AUC) were generated, and an optimal cutoff point was determined. All statistical tests were two-tailed, and *p*-values less than 0.05 were considered statistically significant.

Results

In this study, we recruited 60 participants with type 2 DM and 21 healthy subjects who met none of the exclusion criteria outlined in the Methods and Materials section. After undergoing ocular examinations, 13 participants with DM were excluded for the following reasons: high myopia ($n=4$), glaucoma ($n=3$), uveitis ($n=2$), maculopathy ($n=1$), and poor-quality OCTA scans for both eyes ($n=3$). Figure 1 shows the flowchart of participant enrollment. Therefore, a total of 47 eyes from 47 patients with DM and 21 eyes from 21 healthy subjects were included in this study. Table 1 summarizes the demographic and clinical characteristics of both groups. There were no significant differences in gender distribution between the groups. The number of male patients in the DM group and healthy controls were 26 (55.3%) and 7 (33.3%), respectively ($p=0.094$). The comorbidities are also listed in Table 1. The proportion of hypertension and hyperlipidemia was higher in the DM group. There were no significant differences in the prevalence of chronic kidney disease or major adverse cardiovascular or cerebrovascular events. Additionally, participants with systemic diseases, such as hypertension and hyperlipidemia, were under medication treatment prescribed by internal medicine physicians.

The ocular examination results, OCTA parameters, and serological information of the two groups are presented in Table 2. The BCVA in the DM group and the healthy control group was 0.00 (IQR 0.00 – -0.08) and −0.08 (IQR −0.04 – -0.18) in logMAR, respectively ($p=0.004$). There were no significant differences in spherical equivalence, IOP, CCT, ECD, or axial length between the two groups. Regarding OCTA parameters, the foveal avascular zone (FAZ) in DM patients was larger (0.30 mm^2) than in those without DM (0.25 mm^2)

		DM ($n=47$)	Control ($n=21$)	p value
Ocular exam				
SE (diopter)		−0.50 (−4.00, 0.75)	−3.00 (−4.38, −0.75)	0.081
IOP (mmHg)		15.00 (13.00, 19.00)	17.00 (14.00, 17.50)	0.425
CCT (μm)		539.0 (506.0, 561.0)	542.0 (523.0, 567.0)	0.477
ECD (cell/mm2)		2743 (2448, 3010)	2781 (2595, 3052)	0.671
AxL (mm)		24.6 (23.5, 25.5)	24.5 (23.9, 25.0)	0.705
OCTA parameters				
FAZ (mm2)		0.30 (0.22, 0.38)	0.25 (0.18,0.30)	0.046*
Parafoveal superficial VD (%)		46.73 (43.66,50.66)	52.37 (48.90,53.92)	0.002*
Parafoveal deep VD (%)		50.35 (47.35,54.02)	54.26 (49.57,56.79)	0.019*
Sectoral VD of parafoveal superficial region (%)	Temporal	47.16 (42.82, 50.93)	50.85 (47.71,53.36)	0.012*
	Superior	47.86 (44.97, 51.22)	53.87 (50.07,55.31)	0.001*
	Nasal	45.43 (43.20, 50.01)	50.70 (46.18,53.83)	0.004*
	Inferior	46.96 (41.92, 51.89)	52.57 (48.84,54.41)	0.002*
Sectoral VD of parafoveal deep region (%)	Temporal	51.06 (48.73,55.35)	55.43 (51.62,57.51)	0.012*
	Superior	49.66 (45.97,52.68)	52.48 (47.36,56.14)	0.050
	Nasal	51.37 (48.29,55.35)	55.03 (51.93,58.48)	0.034*
	Inferior	49.15 (44.83,52.79)	53.31 (47.46,55.90)	0.018*
Serologic data				
HbA1c (%)		6.30 (5.83,6.60)	5.40 (5.30,5.78)	< 0.001*

Table 2. Data for ocular examination, OCTA parameters and serologic data. *SE* spherical equivalent, *IOP* intraocular pressure, *CCT* central corneal thickness, *ECD* endothelial cell density (cell/mm2), *AxL* axial length, *VD:* vessel density, *FAZ* foveal avascular zone (FAZ). *p value less than 0.05.

($p=0.046$). The mean parafoveal superficial VD was 46.73% in the DM group and 52.37% in the healthy control group, while the mean parafoveal deep VD was 50.35% in the DM group and 54.26% in the healthy control group. Significant reductions in VD were observed in the DM group compared to the healthy controls, both in the parafoveal superficial VD ($p=0.002$) and the parafoveal deep VD ($p=0.019$). Furthermore, significant differences were noted in all sectors, including the temporal, superior, nasal, and inferior quadrants, in both the superficial and deep plexuses. For the serologic examination, the mean HbA1c was 5.40% (IQR 5.30–5.78) in the healthy control group, compared to 6.40% (IQR 5.83–6.60) in the DM group ($p<0.001$).

In the subgroups of patients with DM, we conducted further analyses to explore the relationship between VD and the presence of DR. Participants in the DM group were categorized into those without DR and those with DR, according to the ETDRS standard images. Of the 47 eyes of the 47 patients with DM, 36 were classified as having no DR, while 11 were categorized as having DR. In the DR subgroup, nine eyes were identified as NPDR (six mild, two moderate, and one severe), and two eyes were identified as PDR. Table 3 presents the odds ratio (OR) of VD in the presence of DR, determined through regression analysis. In multivariable analysis, Model 1 shows the OR for the superior sector of parafoveal superficial region, while Model 2 shows the OR for the temporal sector of parafoveal deep region. Lower VD in the superior sector of the parafoveal superficial layer ($p=0.042$) and the temporal sector of the parafoveal deep layer ($p=0.035$) were significantly associated with a higher likelihood of DR. In the multivariable regression model, statistically significant associations between lower VD and a higher likelihood of DR were revealed in both regions (OR = 0.85, $p=0.032$ in the superior sector of the superficial layer; OR = 0.70, $p=0.020$ in the temporal sector of the deep layer).

Furthermore, ROC analysis was conducted based on the VD data and presence of DR. The corresponding AUC and optimal cutoff points were calculated, and the results are presented in Table 4. In the temporal sector of the parafoveal deep layer, the AUC was 0.697 ($p=0.035$), with a sensitivity of 81.8% at a VD cut-off point of 51.86% for discriminating between no apparent DR and clinically detected DR.

Discussion

In our study, we observed that parafoveal microcirculation was decreased in patients with DM compared with healthy controls, as well as in those with DR compared with those without DR within the DM group. Specifically, decreased parafoveal VD was associated with a higher likelihood of the presence of both DM and DR, with a particularly significant correlation observed in the deep temporal parafoveal region in the DM group with DR. Moreover, when the cutoff point for the temporal region of the deep parafoveal VD was set at 51.86%, it yielded acceptable sensitivity for discriminating DR.

Our study aimed to establish a cut-off point for discriminating DR in patients with DM using OCTA. Given that more than half of the growing population with DM presents with no apparent DR, and that progression to early stage DR increases the risk of developing PDR, macular edema, and other vision-threatening complications, our findings hold significant potential benefits for DM patients[15,19]. Previous reports have indicated that the frequency of DR progression is around 10%[23,24]. Specifically, the progression rates from none to mild stage, mild to moderate stage, and moderate to severe or proliferative stage were 6.1, 7.0, and 19.3%, respectively[5].

		Univariable analysis			Multivariable analysis (Model 1)			Multivariable analysis (Model 2)		
Region		**OR**	**95%CI**	***p* value**	**OR**	**95%CI**	***p* value**	**OR**	**95%CI**	***p* value**
Parafoveal superficial VD		0.92	(0.80,1.05)	0.229						
Sectoral VD of parafoveal superficial region	Temporal	0.91	(0.80,1.04)	0.163						
	Superior	0.87	(0.76,0.99)	0.042*	0.85	(0.73, 0.99)	0.032*			
	Nasal	1.01	(0.89,1.15)	0.826						
	Inferior	0.95	(0.85,1.06)	0.355						
Parafoveal deep VD		0.84	(0.70,1.02)	0.074						
Sectoral VD of parafoveal deep region	Temporal	0.81	(0.67,0.99)	0.035*				0.70	(0.52, 0.95)	0.020*
	Superior	0.89	(0.75,1.06)	0.194						
	Nasal	0.92	(0.78,1.08)	0.299						
	Inferior	0.88	(0.77,1.01)	0.067						
Age		1.00	(0.95, 1.05)	0.992	1.01	(0.95, 1.07)	0.806	0.99	(0.93, 1.06)	0.817
Sex (Male)		0.60	(0.15, 2.32)	0.454	0.54	(0.12, 2.42)	0.419	0.16	(0.02, 1.16)	0.069
Comorbidity		0.29	(0.02, 4.99)	0.391	0.12	(0.01, 2.78)	0.186	0.19	(0.01, 3.82)	0.276

Table 3. Regression analysis of vessel density for the presence of DR. Model 1: multivariable analysis of superior sector of superficial parafoveal VD, age, sex and comorbidity. Model 2: multivariable analysis of temporal sector of deep parafoveal VD, age, sex and comorbidity. *VD* vessel density, *OR* odds ratio, *CI* confidence interval. **p* value less than 0.05.

Region		**AUC**	**95% CI**	***p* value**	**Optimal cutoff point (%)**	**Sensitivity (%)**	**Specificity (%)**
Parafoveal superficial VD		0.581	(0.428–0.723)	0.454	≤41.96	36.4	83.3
Sectoral VD of parafoveal superficial region	T	0.601	(0.448–0.741)	0.318	≤39.09	27.3	97.2
	S	0.639	(0.486–0.774)	0.152	≤50.09	90.9	38.9
	N	0.505	(0.355–0.654)	0.964	≤48.68	54.6	22.2
	I	0.566	(0.413–0.710)	0.532	≤42.89	45.5	72.2
Parafoveal deep VD		0.687	(0.535–0.814)	0.048*	≤45.81	36.4	94.4
Sectoral VD of parafoveal deep region	T	0.697	(0.546–0.822)	0.035*	≤51.86	81.8	52.8
	S	0.631	(0.478–0.767)	0.199	≤45.54	36.4	88.9
	N	0.600	(0.447–0.740)	0.283	≤51.19	63.6	58.3
	I	0.682	(0.530–0.810)	0.050	≤50.75	90.9	41.7

Table 4. ROC curve and corresponding optimal cutoff point of vessel density for discriminating the presence of DR in DM patients. *ROC* Receiver operating characteristic, *AUC* Area under the ROC curve, *VD* vessel density, *OR* odds ratio, *CI* confidence interval, *T* temporal, *S* superior, *N* nasal, *I* inferior. **p* value less than 0.05.

Traditionally, before progression to DR, the recommendation is to observe and monitor patients annually[25,26]. However, the duration and proportion of non-DR in DM patients are longer and account for the majority[5,14]. By employing OCTA and establishing appropriate cut-off points for parafoveal VD, we can stratify the risk of progression to later stages of DR in cases of clinically undetectable retinopathy. For instance, in cases of no apparent DR, as defined by the ETDRS methods, with deep parafoveal VD in the temporal sector lower than 51.86%, the likelihood of progression to clinically detected DR is increased. Therefore, individuals in this subgroup should adhere more cautiously to diabetes management protocols and undergo more frequent ophthalmic monitoring.

Our study showed similar trends and findings to several previous studies investigating retinal VD using OCTA. Previous research on healthy subjects reported an average superficial parafoveal VD of approximately 50%, with higher densities observed in deeper plexuses[27,28]. This is consistent with our findings of 52.37% superficial VD and 54.26% deep VD. Compared to healthy subjects, the DM group exhibited decreased VD, regardless of the presence of clinically detectable DR[29]. Additionally, studies on patients with diabetes have highlighted a significant association between lower VD and an enlarged FAZ area, which is indicative of worsening DR[19,30].Taken together, these findings of VD changes in DM patients are consistent with our results of this study.

The reduced VD observed in patients with DR can be attributed to several factors. First, the persistent hyperglycemic state promotes pericyte loss, signifying the breakdown of the blood-retina barrier (BRB)[31]. This breakdown leads to endothelial damage and increases microvascular permeability. A compromised BRB fosters the proliferation of microvascular endothelial cells and constricts and obstructs capillaries[32]. Moreover, the expansion of endothelial cell interstitial spaces induced by increased permeability triggers inflammatory

responses. These responses lead to the accumulation of exudates, which compress the peripheral capillaries and disrupt tissue metabolism, exacerbating capillary blockage and degenerative processes[33]. In addition, retinal photoreceptors require high levels of oxygen and metabolic activity. In the presence of hyperglycemia, the sorbitol-aldose reductase pathway is activated, leading to the production of excessive reactive oxygen species and oxidative stress. Oxidative stress manifests in various presentations such as cell membrane damage, microvascular impairment, and cell apoptosis, particularly affecting the deeper layers of the retinal microvasculature[34–36].

Our research indicates that the temporal sector of the deep parafoveal plexus could emerge as a potentially valuable indicator for predicting the presence of DR. In line with this, similar observations have been highlighted in relevant studies, which have shown the lowest VD in the temporal region in cases of diabetic maculopathy, as well as the most significant reduction in VD during early stages of DR[29,30,37]. A potential explanation for this phenomenon is that terminal capillaries are located in the temporal macula and form the temporal horizontal raphe, which represents the vascular watershed zone between the superior and inferior retinal hemispheres[38–40]. In newborns, the rate of temporal retinal vascularization has been reported to be the most sensitive between healthy individuals and those with retinopathy of prematurity[41]. However, while both superficial and deep VD have been found to be lower in patients with diabetes than in healthy controls across various publications, the majority of studies have indicated a more pronounced difference in the deep retinal plexus[29,42]. Additionally, disparities in the deep capillary plexus have been deemed to have a greater discriminatory value in distinguishing between diabetic and non-diabetic groups[43].

These findings shed light on the potential reasons why the temporal sector of the parafoveal deep VD could serve as a unique discriminator for the presence of DR. Consequently, we propose that the VD in the temporal sector of the deep parafoveal plexus may be particularly susceptible and vulnerable to vasculopathy, making it a primary area for assessing and detecting subtle changes in retinopathy.

The present study had certain limitations. First, the sample sizes of the DM and control groups were relatively small, because of participants' lower willingness to undergo time-consuming examinations. Second, the ophthalmic information was cross-sectional. Future research incorporating prospective longitudinal assessments of retinal plexus density changes may provide a more comprehensive understanding of disease patterns.

Conclusion

In summary, our study highlights a notable reduction in VD, which enables effective discrimination between individuals with and without DM, as well as between those without apparent DR and those with clinically detected DR. By establishing appropriate cutoff points for VD in specific regions, we have demonstrated the potential to predict the presence of clinically significant DR. These findings provide valuable insights into the risk evaluation to DR, offering substantial benefits for individuals with DM in the future.

Data availability

The datasets utilized or examined in this study can be obtained from the corresponding author upon reasonable request.

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Author contributions

C.Y.L., I.J.W., and C.C.C. designed the experiment. Y.J.S. and C.C.C. conducted the experiment. C.Y.L., Y.J.S., Y.A.L., H.E.H., and collected the relevant materials. H.M.C., J.P.C., and Y.J.L. analyzed the data. C.Y.L., P.T.T., and H.J.L. contributed to the interpretation of the results. C.Y.L. and C.C.C wrote the article. C.J.C. and C.C.C. revised the article. All authors have read and approved the manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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