Posterior Retinal Ischemia Correlates With Vision in Patients With Diabetes

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Purpose. The purpose of this study was to investigate whether the topographic location of retinal non-perfusion influences visual function, specifically low luminance visual acuity (LLVA) and best-corrected visual acuity (BCVA), in individuals with diabetes.

Methods. In this cross-sectional observational study, individuals with diabetes across the spectrum of diabetic retinopathy (DR) severity were enrolled. LLVA and BCVA were measured according to the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol, with a 2.0-log unit neutral density filter for LLVA. Retinal ischemia was evaluated using ultra-widefield fluorescein angiography (UWF-FA) to manually quantify non-perfusion within (posterior ischemia) and outside (peripheral ischemia) the ETDRS seven fields. Macular ischemia was assessed by optical coherence tomography angiography (OCTA) using geometric perfusion deficits (GPDs) in both the superficial and deep capillary plexus (DCP). Associations between visual acuity and various explanatory variables, focusing on retinal ischemic parameters were assessed with linear mixed models.

Results. A total of 181 eyes from 126 patients without diabetic macular edema were analyzed. Increasing DR severity reduced both BCVA and LLVA. After adjusting other explanatory variables, age and posterior ischemia (estimate = −0.46, P = 0.046) were significant for LLVA. In contrast, age, sex, posterior ischemia (estimate = −0.50, P = 0.009), and GPD-DCP (estimate = −0.25, P = 0.049) were statistically significant for BCVA.

Conclusions. Retinal ischemia's topographic location differentially affects visual function in diabetes. Posterior ischemia predominantly impacts LLVA, whereas both macular and posterior ischemia contribute to BCVA decline. These results highlight the importance of assessing retinal ischemia beyond the macula to better understand visual function deficits in patients with diabetes.

Keywords: low luminance visual acuity (LLVA), best-corrected visual acuity (BCVA), diabetic retinopathy (DR), retinal ischemia, optical coherence tomography angiography (OCTA), ultra-widefield fluorescein angiography (UWF-FA)

Diabetic retinopathy (DR) is one of the leading causes of blindness in adults and a common microvascular complication among patients with diabetes mellitus (DM).[1] It is estimated that approximately 540 million people worldwide are affected by DM, with more than 30% reported to develop some form of DR.[2,3] In DR, progressive microvascular damage in the retina leads to retinal ischemia, resulting in decreased visual function.[4] Diabetic macular ischemia correlates with the severity and complications of DR and is thought to influence visual acuity.[5,6] Additionally, nonperfusion detected by ultra-widefield fluorescein angiography (UWF-FA) may predict the progression of DR.[7,8] Therefore, retinal ischemia is a key biomarker that reflects the severity of DR.[9] In assessing retinal ischemia in DR, optical coherence tomography angiography (OCTA) and UWF-FA capture distinct retinal regions. OCTA provides detailed imaging of the macular microvasculature, with depth resolution at the superficial and deep capillary plexus (SCP and DCP). In contrast, UWF-FA extends beyond the macula, captures ischemia in the posterior pole and peripheral retina, but does not allow depth localization of the capillary loss to the SCP or DCP.[10]

The relationship between ischemia and visual function remains an important but underexplored aspect of DR, perhaps due to the difficulty in matching the topographical areas sampled and the variable sensitivity of the tools used to study ischemia and vision. Visual function in DR is assessed by best-corrected visual acuity (BCVA), measured by the standardized Early Treatment Diabetic Retinopathy Study (ETDRS) chart, and is thought to reflect central foveal cone function.[11,12] However, BCVA may not be sensitive to subtle functional loss, which has motivated the search for more sensitive metrics to reflect early visual dysfunction in DR.[13,14] In contrast to BCVA, low luminance best-corrected visual acuity (LLVA) quantifies visual function under mesopic conditions, such as moonlight and standard indoor lighting, and is thought to represent the macular function not only of cones but also rods surrounding the fovea.[15,16] LLVA can

be assessed by adding a 2.0-log unit neutral density filter in conjunction with the ETDRS chart.[15] The exact pathophysiological mechanisms that drive impairments in LLVA remain unclear,[17] and studies of LLVA in DR are limited. Karatsai et al. investigated the relationship between LLVA and BCVA in proliferative diabetic retinopathy (PDR) and found that LLVA correlated with BCVA, and that LLVA recovery after treatment with aflibercept or panretinal photocoagulation was less pronounced compared to BCVA.[18] Our group recently investigated the relationship between OCTA parameters and vision, reporting that foveal avascular zone (FAZ) enlargement and geometric perfusion deficits (GPDs), particularly in the DCP, are linked to lower BCVA and LLVA.[19,20] In that study, we focused on macular ischemia and did not investigate the contribution of posterior and peripheral ischemia on UWF-FA to vision impairment.

Based on this background, we hypothesized that ischemia quantified by macular OCTA is the main driver of ischemia-related vision decline in DR. To test this hypothesis, we investigated whether macular ischemia (assessed by OCTA) was more strongly associated with BCVA and LLVA dysfunction in diabetes compared to posterior and peripheral ischemia (quantified by UWF-FA).

Methods

Study Design

This study is a cross-sectional observational study conducted at Northwestern Memorial Hospital in Chicago, Illinois, USA. The study protocol was approved by the Northwestern University Ethics Committee, adhering to the ethical principles outlined in the Declaration of Helsinki for human subject research. Prior to enrollment, all participants provided written informed consent for the study, including OCTA and fluorescein angiography (FA). The study was also conducted in full compliance with the Health Insurance Portability and Accountability Act (HIPAA).

Enrollment took place between October 2021 and September 2023. To be eligible for inclusion, patients were required to have type 1 or type 2 diabetes with or without DR across the entire severity spectrum. Exclusion criteria included the presence of diabetic macular edema involving the fovea (central subfield thickness $\geq$ 300 µm on the Heidelberg Spectralis OCT),[21] a history of intravitreal anti-VEGF or steroid treatment in the last 6 months, ocular conditions affecting retinopathy or visual acuity as determined by the investigator, an OCT signal strength index below 6, major ocular surgery within the past 3 months or planned within the next 6 months, current participation in another investigational trial, or an HbA1c level above 10.0%.

In this study, we excluded eyes with a history of retinal photocoagulation or eyes with an axial length of less than 22 mm or greater than 26 mm to ensure accurate quantification of retinal ischemia.

Severity Grading of Retinal Changes in Eyes With Diabetes

The severity of diabetic retinal changes was graded using pseudo-color fundus images acquired with an ultra-widefield scanning laser ophthalmoscope (Optos California system, Optomap Panoramic 200, Optos PLC) in accordance with the International Classification of Diabetic Retinopathy severity scale.[22] The classification system consists of five stages: no apparent retinopathy (DM no DR), mild nonproliferative diabetic retinopathy (NPDR) characterized by microaneurysms only, moderate NPDR with more than just microaneurysms but less than severe NPDR, severe NPDR defined by the presence of any of the "4-2-1" criteria ($\geq$ 20 intraretinal hemorrhages in each of 4 quadrants, definite venous beading in $\geq$ 2 quadrants, or prominent intraretinal microvascular abnormalities in $\geq$ 1 quadrant), and PDR, which includes eyes with neovascularization or vitreous/preretinal hemorrhage. The grading was performed as previously described.[6]

OCTA Imaging and Analysis

We acquired multiple 3 × 3 mm (304 × 304 pixels) OCTA scans centered on the fovea using the RTVue-XR Avanti system (Optovue Inc, version 2017.1.0.151) with split-spectrum amplitude-decorrelation angiography for angiographic data.[23] Default settings segmented the retinal microvasculature into DCP (10 µm above the inner plexiform layer to 10 µm below the outer plexiform layer), SCP (internal limiting membrane to 10 µm above the inner plexiform layer), and full retina slabs (combining DCP and SCP).

OCTA scans were exported and registered using Fiji software (NIH, USA) to enhance image quality and improve signal-to-noise ratio. Figure 1 illustrates the image processing pipeline for OCTA registration and averaging. Registration used the SCP angiogram of highest quality as the reference, with the "register virtual stack slices" plugin with a rigid feature extraction model and an elastic registration model to align the SCP slab images. The same transformation was applied to DCP and full retina slabs using the "transform virtual stack slices" plugin. Finally, the registered images were averaged to enhance image quality and increase the signal-to-noise ratio.[24]

Subsequently, as previously described,[6] we used a semi-automated macro on Fiji to measure the macular ischemia parameter, GPDs,[25] on the averaged images in the SCP and DCP slabs. GPD-SCP and GPD-DCP were considered as macular ischemia in the current study.

Ultra-Widefield Fluorescein Angiography

The UWF-FA images were acquired using the Optos California system (Optomap Panoramic 200, Optos PLC) following a standardized protocol. Using the proprietary OptosAdvance software (Optos PLC, version 4.4.33.107911), UWF-FA images were reviewed to quantify retinal nonperfusion as previously described.[6] To account for the projection of the three-dimensional retina onto a two-dimensional image, the software adjusted for magnification artifacts and transformed the outlined regions into a stereographic projection, enabling accurate measurement of the nonperfused areas.

For nonperfusion analysis, we selected the earliest high-quality UWF-FA image in which fluorescein dye had reached the peripheral retinal vessels, typically 30 to 60 seconds after injection. The grader manually outlined the region of the total visible retina, excluding artifacts. Regions of nonperfusion were assessed according to previously established criteria.[26] A template of the combined ETDRS seven fields was then digitally overlaid based on the locations of the fovea and optic nerve head. The grader identified and manually delineated any regions of nonperfusion in the posterior retina within the ETDRS seven fields, as well as in the peripheral retina outside the ETDRS seven fields.

The percentage of nonperfusion areas within the ETDRS seven fields was considered as posterior ischemia, and those

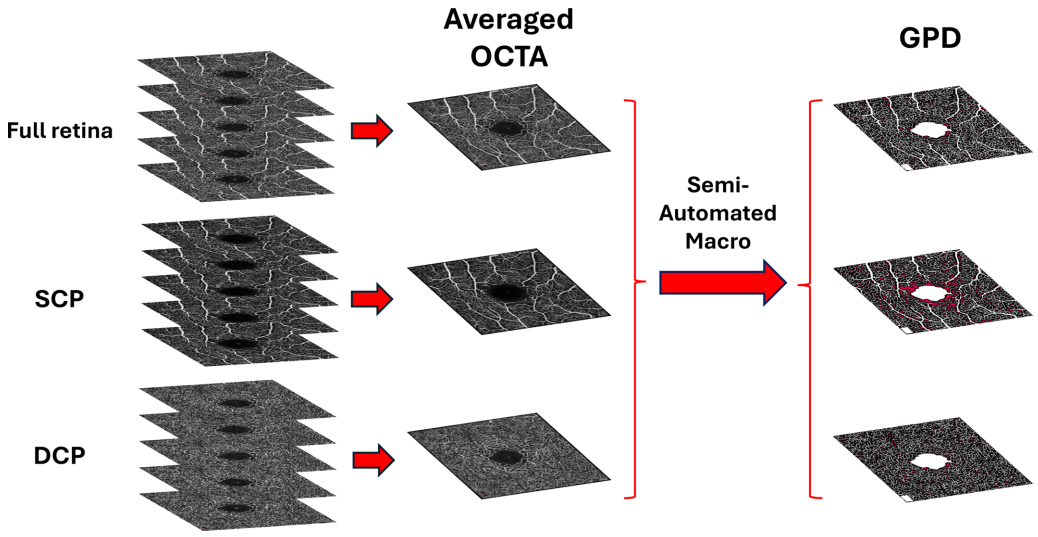

Figure 1. Image processing pipeline for geometric perfusion deficit analysis in OCTA. This figure provides an overview of the image processing pipeline used for the quantitative analysis of geometric perfusion deficits (GPD) in OCTA images from the superficial capillary plexus (SCP), deep capillary plexus (DCP), and full retina slab. The workflow begins with the averaging of exported images for each slab to enhance vessel visualization and reduce noise. A dedicated processing algorithm extracts GPD metrics by segmenting and analyzing perfusion characteristics across different retinal layers. This semi-automated approach ensures a standardized assessment of microvascular alterations, facilitating reliable quantification of ischemic changes in the macula. Among the quantified GPD values, those derived from the SCP and DCP are used for the analysis in this study.

outside the ETDRS seven fields were considered as peripheral ischemia. Figure 2 shows the topographic distribution of retinal ischemia, corresponding to the four key parameters: GPD-SCP, GPD-DCP, posterior ischemia, and peripheral ischemia.

Quantification of nonperfusion on UWF-FA and OCTA analysis were evaluated by different graders who were not involved in the other grading in this study. The graders were masked to each other's images and results, and did not access any additional clinical or imaging data during the grading process.

Visual Acuity

Visual acuity was assessed using the ETDRS protocol.[27] The BCVA and LLVA were measured using back-illuminated (75–125 foot candles) ETDRS charts at 4 meters, with consistent room lighting maintained at 50 to 100 foot candles. Corrective refraction was obtained with chart R. BCVA letter counts were then recorded using chart 1 for the right eye (OD) and chart 2 for the left eye (OS). Immediately after, the same procedure was repeated with a 2.0-log unit neutral density filter in front of chart 1 for OD and chart 2 for OS, reducing screen luminance by 100-fold.[15,27] Both BCVA and LLVA were recorded in letter counts.

Data Collection

Demographic and general health information included factors such as age, sex, and the presence of hypertension, ischemic heart disease, renal impairment, and cerebrovascular disease. Diabetes-specific data covered diabetes type, duration of diabetes, and the most recent hemoglobin A1c (HbA1c) level. In terms of ocular health, information was recorded for each eye on lens status (whether cataract surgery had been performed), BCVA scores, axial length measurements using the IOL Master (Carl Zeiss Meditec, Jena, Germany), and LLVA scores. Additionally, the number of OCTA scans and the OCTA quality score for each eye were noted. All collected data were securely entered and stored in REDCap; a web-based platform designed for Research Electronic Data Capture.

Statistics

Statistical analyses were conducted using R (version 4.4.2) and RStudio (version 2024.04.2). To compare BCVA and LLVA across different DR severity levels, linear mixed models were used, with LLVA or BCVA letter scores as the dependent variable, patient as a random effect, and DR severity (a categorical variable) as a fixed effect. Because both eyes from the same patient may not be independent, linear mixed models were used to account for intra-subject correlation. Following this, Dunnett's test was conducted to compare the BCVA and LLVA of each DR severity group with the no apparent DR group.

To assess the associations between vision and retinal ischemia, linear mixed models were used, with LLVA or BCVA letter scores as the dependent variable, and the patient included as a random effect. Several variables, including GPD-SCP, GPD-DCP, posterior ischemia, peripheral ischemia, age, sex, DM duration, DM type, HbA1c, axial length, lens status, a history of hypertension, ischemic heart disease, renal impairment, and cerebrovascular disease, were initially tested individually using univariate analyses to evaluate their statistical associations with the dependent variables. Explanatory variables that showed significant associations were subsequently included in final linear mixed models to identify fixed effects contributing to changes in LLVA and BCVA. Multicollinearity between explanatory variables was evaluated using the Variance Inflation Factor. A Q-Q plot and residual plot were used to assess the normality and homoscedasticity of the residuals, respec-

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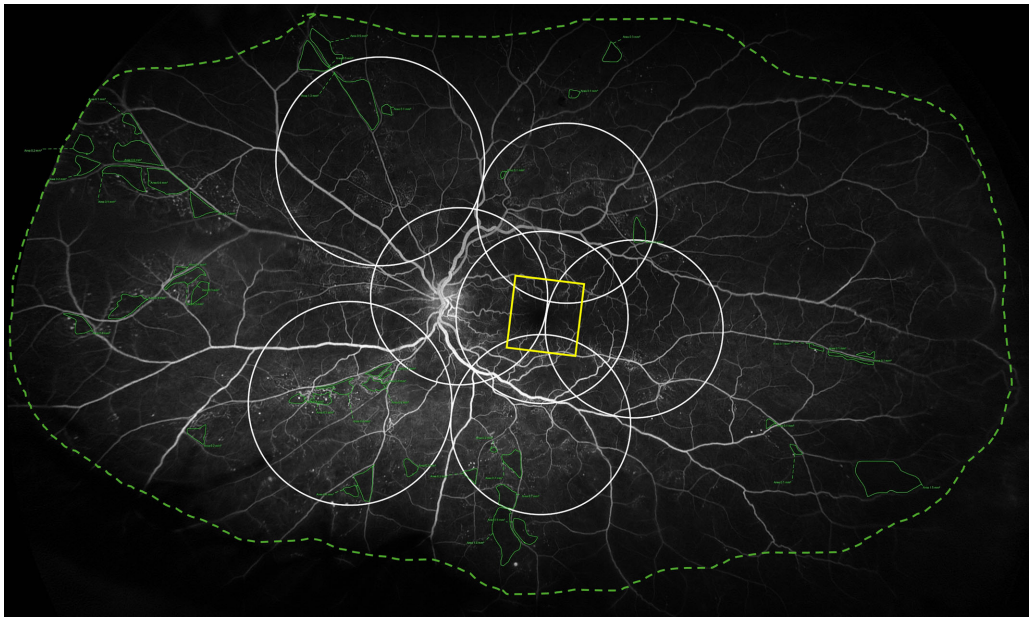

Figure 2. Topographic analysis of retinal ischemia using ultra-widefield fluorescein angiography and OCTA-based geometric perfusion deficits. Ultra-widefield fluorescein angiography (UWF-FA) illustrating the regions used to calculate four parameters that reflect the topographic distribution of retinal ischemia: GPD-SCP, GPD-DCP, posterior ischemia, and peripheral ischemia. A 3 × 3 mm area centered on the fovea was imaged using optical coherence tomography angiography (OCTA), from which geometric perfusion deficits in the superficial and deep capillary plexuses of the macula were calculated from the SCP and DCP slabs, respectively. The area within the *yellow square* corresponds to the specific region evaluated by OCTA for layer-specific ischemia. The nonperfusion index within the ETDRS seven fields was manually quantified as the proportion of retinal nonperfusion within the seven white circles that define the ETDRS seven fields, and it was considered posterior ischemia. The nonperfusion index outside the ETDRS seven fields was manually quantified as the proportion of retinal nonperfusion within the area bounded by the *green dashed line* and located outside the ETDRS seven fields, and it was considered peripheral ischemia. To account for the projection of the three-dimensional retina onto a two-dimensional image, the software corrected for magnification artifacts and transformed the marked regions into a stereographic projection, enabling accurate measurement of nonperfused areas.

tively. These plots indicated that the assumptions of normality and homoscedasticity were reasonably met.

To assess the unadjusted associations between LLVA and posterior retinal ischemia, Kendall's rank correlation analyses were performed using one eye per subject. When data from both eyes were available, the right eye was used; when only one eye was available, that eye was included in the analysis.

A P value of < 0.05 was considered statistically significant for all statistical analyses.

Results

A total of 181 eyes from 126 patients were included in the analysis. The mean age of the patients was 58.7 ± 13.3 years, and their demographics are summarized in Table 1. Among the 181 eyes, 65 had DM with no DR, 30 had mild NPDR, 46 had moderate NPDR, 27 had severe NPDR, and 13 had PDR. The mean letter scores for BCVA and LLVA were 85.11 ± 5.68 and 76.44 ± 6.94, respectively. Detailed outline of overall angiographic ischemic and ocular parameters for the 181 eyes are summarized in Table 2. The mean number of OCTA scans per study eye was 5.01 ± 1.33, and the mean OCTA quality score (Q-score) was 7.90 ± 1.13.

Table 3 shows the changes in both BCVA and LLVA according to DR severity, using DM without DR as the reference group. BCVA values gradually decreased as DR severity progressed, and this decrease reached statistical significance in the severe NPDR ($P = 0.001$) and PDR ($P = 0.003$) groups. Similarly, LLVA also declined according to increasing DR severity, showing significant reductions beginning in the moderate NPDR group ($P = 0.046$), and further worsening in the severe NPDR ($P = 0.024$) and PDR ($P = 0.017$) groups.

Table 1. Demographic Characteristics of Study Subjects

Variables	$N = 126$
Age, y	58.7 ± 13.3
Sex	
Male	68 (54.0%)
Female	58 (46.0%)
DM duration, y	16.7 ± 12.9
HbA1c, %	7.2 ± 1.0
Hypertension	75 (59.5%)
Ischemic heart disease	16 (12.7%)
Renal impairment	18 (14.3%)
Cerebrovascular disease	5 (4.0%)

To assess the associations between vision and retinal ischemia, we initially performed univariate analysis using LLVA as the dependent variable. Age, GPD-SCP, GPD-DCP, posterior ischemia, peripheral ischemia, DM duration, recent HbA1c level, hypertension, and ischemic heart disease were identified as statistically significant explanatory variables (Table 4). When these variables were included in a linear mixed model, only age and posterior ischemia remained statistically significant after adjusting for the other variables (Table 5). For each percentage point increase in posterior

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Table 2. Ocular Characteristics of Study Eyes

Variables	$N = 181$
BCVA	85.11 ± 5.68
LLVA	76.44 ± 6.94
GPD-SCP, %	8.74 ± 5.29
GPD-DCP, %	3.74 ± 3.40
Posterior ischemia, %	1.07 ± 2.61
Peripheral ischemia, %	1.68 ± 5.21
ICDR severity scale	
DM no DR	65 (35.9%)
Mild NPDR	30 (16.6%)
Moderate NPDR	46 (25.4%)
Severe NPDR	27 (14.9%)
PDR	13 (7.2%)
Axial length, mm	23.9 ± 1.02
Lens	
Phakia	144 (79.6%)
Pseudophakia	37 (20.4%)

BCVA, best-corrected visual acuity; DM, diabetes mellitus; DR, diabetes retinopathy; GPD-DCP, geometric perfusion deficits in deep capillary plexus; GPD-SCP, geometric perfusion deficits in superficial capillary plexus; ICDR, International Classification of Diabetic Retinopathy; LLVA, low luminance best-corrected visual acuity; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 4. Summary of Univariate Analysis for Fixed Effects Related to LLVA

Explanatory Variables	Estimate (95% CI)	*P* Value
Age, y	−0.26 (−0.33 to −0.18)	<0.001***
GPD-SCP, %	−0.28 (−0.46 to −0.09)	0.004**
GPD-DCP, %	−0.50 (−0.77 to −0.22)	<0.001***
Posterior ischemia, %	−0.50 (−0.77 to −0.22)	<0.001***
Peripheral ischemia, %	−0.29 (−0.48 to −0.10)	0.004**
DM duration, y	−0.16 (−0.24 to −0.07)	<0.001***
HbA1c, %	−1.36 (−2.50 to −0.22)	0.022**
Hypertension	−3.91 (−6.21 to −1.61)	0.001**
Ischemic heart disease	−4.27 (−7.76 to −0.77)	0.018*
Axial length, mm	0.67 (−0.43 to 1.78)	0.236
Lens status	−0.79 (−3.65 to 2.08)	0.591
DM type	−2.12 (−5.09 to 0.86)	0.166
Sex	1.53 (−0.84 to 3.91)	0.209
Renal impairment	−0.50 (−3.91 to 2.90)	0.774
Cerebrovascular disease	−1.52 (−7.43 to 4.39)	0.615

CI, confidence interval; DM, diabetes mellitus; GPD-DCP, geometric perfusion deficits in deep capillary plexus; GPD-SCP, geometric perfusion deficits in superficial capillary plexus; LLVA, low luminance best-corrected visual acuity.

Linear mixed models fitted with patient as a random effect and one variable as a fixed effect.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

ischemia, LLVA decreased by 0.46 letters (95% confidence interval [CI] = −0.92 to −0.01, $P = 0.046$). Additionally, LLVA decreased by 0.20 letters per year of age (95% CI = −0.28 to −0.13, $P < 0.001$). All variance inflation factors were below 2, indicating no significant multicollinearity among the explanatory variables. To complement the multivariate analysis, we performed Kendall's rank correlation using one eye per subject. LLVA showed a significant negative correlation with posterior ischemia (Kendall's $\tau = -0.291$, $P < 0.001$) and with peripheral ischemia (Kendall's $\tau = -0.184$, $P = 0.005$).

For BCVA, univariate analysis identified age, sex, GPD-SCP, GPD-DCP, posterior ischemia, peripheral ischemia, DM duration, DM type, HbA1c, hypertension, and ischemic heart disease as statistically significant explanatory variables (Table 6). In the multivariate linear mixed model, age, sex, GPD-DCP, and posterior ischemia remained statistically significant after adjusting for the other explanatory variables (Table 7).

Discussion

The purpose of this study was to determine whether the topographic locations of retinal ischemia (macular, posterior, or peripheral) are differentially associated with BCVA and LLVA. Whereas macular ischemia comprised the SCP and DCP on OCTA, posterior ischemia (UWF-FA ETDRS seven fields) encompassed the macula to the equatorial region. Given that BCVA and LLVA are considered to reflect foveal and macular function, we initially hypothesized that macular ischemia would be more important for both BCVA and LLVA. However, contrary to our expectations, posterior ischemia emerged as statistically associated with both BCVA and LLVA, whereas the GPD-DCP was the only OCTA parameter significantly associated with BCVA. These findings uncover the complex relationship between retinal ischemia and visual function under different luminance conditions in DR.[28]

In diabetes, rod dysfunction has been reported to occur early, in parallel with the timing of perfusion deficits in DCP, and well before the onset of clinically apparent retinopathy.[29,30] Functional evidence of rod dysfunction, such as decreased a-wave sensitivity[31,32] and delayed dark adaptation under dark-adapted conditions,[33,34] have been reported in individuals with no apparent retinopathy or minimal NPDR and become more pronounced as DR advances.[35,36] When we compared BCVA and LLVA across DR severity levels in our study, we saw that LLVA in moderate NPDR was

Table 3. Estimated Marginal Means of Visual Acuity Across Diabetic Retinopathy Severity Levels

DR Severity	BCVA	*P* Value	LLVA	*P* Value
DM no DR	86.9 (85.4 to 88.4)		78.5 (76.6 to 80.3)	
Mild NPDR	84.4 (82.3 to 86.5)	0.304	76.6 (74.0 to 79.2)	0.783
Moderate NPDR	84.9 (83.2 to 86.5)	0.358	74.7 (72.7 to 76.7)	0.046*
Severe NPDR	81.8 (79.7 to 83.9)	0.001*	73.6 (70.9 to 76.2)	0.024*
PDR	80.8 (77.8 to 83.7)	0.003*	72.0 (68.3 to 75.6)	0.017*

BCVA, best-corrected visual acuity; DM no DR, diabetes mellitus without apparent diabetic retinopathy; DR, diabetic retinopathy; LLVA, low-luminance visual acuity; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Data are expressed as estimated marginal means (95% confidence interval). The *P* values were calculated using Dunnett's test with DM no DR as the reference group for both BCVA and LLVA comparisons.

*$P < 0.05$.

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Table 5. Multivariate Linear Mixed Model Summary for Fixed Effects Associated with LLVA

Explanatory Variables	Estimate (95% CI)	*P* Value
(Intercept)	92.63 (85.18 to 100.07)	<0.001***
Age, y	−0.20 (−0.28 to −0.13)	<0.001***
Posterior ischemia, %	−0.46 (−0.92 to −0.01)	0.046*
GPD-SCP, %	0.05 (−0.16 to 0.25)	0.670
GPD-DCP, %	−0.25 (−0.55 to 0.06)	0.116
Peripheral ischemia, %	−0.05 (−0.25 to 0.16)	0.651
DM duration, y	−0.04 (−0.12 to 0.04)	0.374
HbA1c, %	−0.31 (−1.26 to 0.63)	0.519
Hypertension	−1.16 (−3.16 to 0.83)	0.257
Ischemic heart disease	−0.31 (−3.27 to 2.66)	0.840

CI, confidence interval; DM, diabetes mellitus; GPD-DCP, geometric perfusion deficits in deep capillary plexus; GPD-SCP, geometric perfusion deficits in superficial capillary plexus; LLVA, low luminance best-corrected visual acuity.

A linear mixed model fitted with patient as a random effect and all variables significant in the univariate analysis as fixed effects.

*$P < 0.05$; ***$P < 0.001$.

Table 6. Summary of Univariate Analysis for Fixed Effects Related to BCVA

Explanatory Variable	Estimate (95% CI)	*P* Value
Age, y	−0.18 (−0.25 to −0.12)	<0.001***
Sex	1.94 (0.03 to 3.85)	0.049*
GPD-SCP, %	−0.25 (−0.41 to −0.10)	0.001**
GPD-DCP, %	−0.49 (−0.71 to −0.27)	<0.001***
Posterior ischemia, %	−0.68 (−1.01 to −0.36)	<0.001***
Peripheral ischemia, %	−0.18 (−0.34 to −0.03)	0.024*
DM duration, y	−0.08 (−0.16 to −0.01)	0.034*
DM type	−2.53 (−4.92 to −0.15)	0.040*
HbA1c, %	−1.28 (−2.20 to −0.35)	0.008**
Hypertension	−2.79 (−4.67 to −0.90)	0.005**
Ischemic heart disease	−4.18 (−6.98 to −1.38)	0.004**
Axial length, mm	0.76 (−0.13 to 1.65)	0.098
Lens status	−1.50 (−3.80 to 0.81)	0.205
Renal impairment	−1.37 (−4.13 to 1.38)	0.331
Cerebrovascular disease	−2.84 (−7.60 to 1.93)	0.246

BCVA, best-corrected visual acuity; CI, confidence interval; DM, diabetes mellitus; GPD-DCP, geometric perfusion deficits in deep capillary plexus; GPD-SCP, geometric perfusion deficits in superficial capillary plexus.

Linear mixed models fitted with patient as a random effect and one variable as a fixed effect.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Table 7. Multivariate Linear Mixed Model Summary for Fixed Effects Associated With BCVA

Explanatory Variable	Estimate (95% CI)	*P* Value
(Intercept)	96.96 (90.55 to 103.36)	<0.001***
Age, y	−0.15 (−0.23 to −0.07)	<0.001***
Sex	2.06 (0.51 to 3.60)	0.011*
GPD-DCP, %	−0.25 (−0.50 to 0.00)	0.049*
Posterior ischemia, %	−0.50 (−0.88 to −0.13)	0.009**
Peripheral ischemia, %	0.02 (−0.15 to 0.19)	0.809
GPD-SCP, %	−0.01 (−0.18 to 0.16)	0.927
DM duration, y	0.04 (−0.05 to 0.14)	0.368
DM type	0.79 (−2.15 to 3.73)	0.601
HbA1c, %	−0.48 (−1.30 to 0.34)	0.258
Hypertension	−0.76 (−2.47 to 0.95)	0.384
Ischemic heart disease	−1.51 (−4.04 to 1.02)	0.246

BCVA, best-corrected visual acuity; CI, confidence interval; DM, diabetes mellitus; GPD-DCP, geometric perfusion deficits in deep capillary plexus; GPD-SCP, geometric perfusion deficits in superficial capillary plexus.

A linear mixed model fitted with patient as a random effect and all variables significant in the univariate analysis as fixed effects.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

significantly different, whereas BCVA was in severe NPDR (see Table 3). This supports the idea that rod dysfunction (as evaluated by LLVA) may represent an early sign of diabetic retinal dysfunction. The relationship of LLVA to posterior ischemia aligns with the idea that rod pathways—abundant in the midperipheral retina—may be particularly sensitive to retinal ischemia.[37]

Although we originally hypothesized that OCTA-based macular ischemia would be more important for both BCVA and LLVA, we were puzzled to see that, after adjusting for potential confounders, this relationship disappeared for LLVA. This contrasted with BCVA, where both OCTA-based and FA-based posterior nonperfusion were significantly correlated. We can interpret these results to suggest that the photoreceptors in the entire posterior pole (rather than just the macula) contribute to LLVA. Along this line, data in patients with reticular pseudodrusen (RPD), a subtype of drusen that predominantly affects the perifoveal or midperipheral retina,[38] a reduction in LLVA has been observed even when standard visual acuity was normal.[39] Unlike age-related macular degeneration, where LLVA has been explored as a risk factor for geographic atrophy disease progression,[14] and a potential predictor of treatment outcomes in neovascular AMD,[40] clinical studies that adopted LLVA in DR are limited.[18]

When we explored the relationship between ischemia and BCVA, we found that both macular (GPD-DCP) and posterior ischemia were statistically significant. The association between BCVA and GPD-DCP may reflect the contribution of the DCP to the functional integrity of the outer retina, especially the foveal cones, as reported previously.[25,41] One plausible explanation for the significant association between BCVA and posterior ischemia is that posterior ischemia may act as a surrogate marker for broader retinal neurodegeneration that ultimately impairs BCVA (and LLVA).

The influence of age on both BCVA and LLVA was expected, as previous studies have reported similar findings.[42,43] Further research is needed to elucidate the effects of age on visual function under low luminance conditions in DR. Specifically, future studies should investigate how age interacts with retinal ischemia and other factors associated with DR progression that affect visual function. Surprisingly, after adjusting for other variables, male sex was associated with better BCVA, whereas sex did not significantly influence LLVA. It is unclear whether this result has any biological significance. Further research is warranted to investigate whether the sex differences we observed in BCVA have any underlying biological basis in DR or whether they are due to sampling variability.

We would like to acknowledge several limitations in our study. First, we did not account for the potential influence of diabetes-related ischemia in the choroid or choriocapillaris, which could affect photoreceptor function.[44,45] Whereas choriocapillaris dysfunction has been reported in DR,[46] we used spectral-domain OCTA, which is more prone to artifacts in the setting of retinal exudates, or microaneurysms, making it difficult to analyze the choroid or choriocapillaris. Additionally, we excluded eyes that had undergone laser pan-retinal photocoagulation, as laser scars can

obscure retinal nonperfusion areas on UWF-FA, making it difficult to accurately assess ischemia. Therefore, the effect of PRP on LLVA remains unknown. Furthermore, this study was conducted on a cohort of relatively stable patients with DR without diabetic macular edema, and it is unclear whether our findings can be extrapolated to the entire spectrum of DR, such as those with advanced or unstable DR, or those with diabetic macular edema. Finally, although lens status was not significantly associated with either BCVA or LLVA in the univariate analyses, the potential influence of lens opacity on these measurements cannot be entirely ruled out. Nevertheless, there are several strengths of this study, including the use of both UWF-FA and OCTA to analyze ischemia, which allowed us to investigate the functional impact of the topography of ischemia. Furthermore, the use of averaged OCTA allowed us to obtain accurate quantification of macular ischemia by reducing the contribution of speckle noise.

In conclusion, our study demonstrated that posterior ischemia measured by UWF-FA was associated with both LLVA and BCVA in DR, whereas macular ischemia detectable by OCTA was associated with BCVA and not with LLVA. These findings offer insights into the mechanisms underlying visual impairment experienced by patients with DR in real-world conditions. Unlike BCVA, which reflects ideal lighting conditions, LLVA assesses visual function in low luminance environments commonly encountered in daily life and is a more sensitive indicator of everyday visual challenges than standard BCVA. Whereas BCVA remains the primary functional metric for assessing DR and guiding treatment, incorporating LLVA into routine evaluations could offer a more comprehensive understanding of real-world visual performance under low-light conditions.[15] Future research should investigate the mechanisms influencing LLVA, including the role of choroidal ischemia in DR, by combining swept-source OCTA-based layer analysis with broader functional tests, such as electroretinography and peripheral microperimetry, to validate our findings in larger cohorts. Prospective studies are needed to determine whether systematic testing of LLVA can improve clinical decision making and outcomes, such as timely interventions or tailored monitoring, ultimately enhancing patient care in DR.

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