Associations between Retinal Microvascular Flow, Geometry, and Progression of Diabetic Retinopathy in Type 2 Diabetes: A 2-Year Longitudinal Study

Running title: Retinal microvasculature and DR progression

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Abstract

Purpose: To determine the association between retinal blood vessel flow and geometric parameters, and the risk of diabetic retinopathy (DR) progression through a 2-year prospective cohort study.

Methods: Patients with type 2 diabetes mellitus (T2DM) were recruited from a diabetic registry between November 2017 and March 2019. All participants underwent standardized examinations at the baseline and 2-year follow-up visit, and the presence and severity of DR was assessed based on standard seven-field color fundus photographs. They also underwent swept-source optical coherence tomography angiography (OCTA) imaging to obtain measurements of foveal avascular zone (FAZ) area, blood vessel density (VD), fractal dimension (FD), blood vessel tortuosity (BVT) in the superficial capillary plexus (SCP) and deep capillary plexus (DCP).

Results: A total of 233 eyes of 125 patients were included, and 40 eyes (17.17%) experienced DR progression within 2 years. DR progression was significantly associated with lower baseline VD (odds ratio [OR], 2.323 per SD decrease; 95% confidence interval [CI], 1.456-3.708; *P*<0.001), lower FD (OR, 2.484 per SD decrease; 95% CI, 1.268-4.867; *P*=0.008), and higher BVT (OR, 2.076 per SD increase; 95% CI, 1.382-3.121; *P*<0.001) of the DCP after adjusting for confounding factors. The addition of OCTA metrics improved the predictive ability of the original model for DR progression (area under the curve [AUC], from 0.725 to 0.805; *P*=0.022).

Conclusions: OCTA-derived VD, FD and BVT in the DCP were independent predictors of DR progression and showed additive value when added to established risk models predicting DR progression.

Keywords: OCTA, disease progression, diabetic retinopathy, longitudinal, cohort

Introduction

Diabetic retinopathy (DR) is the leading cause of avoidable blindness in adults aged 20-74 years[1]. The early detection and management of DR can substantially reduce the risk of visual impairment and blindness. Currently, the identification of populations likely to experience DR progression is still challenging. This is because established risk factors, such as duration of diabetes, glucose control, lipid profiles, and blood pressure are insufficient for predicting DR progression[2, 3]. The identification of novel predictors for DR progression will aid in implementing preventative intervention strategies and more frequent follow-up visits for high-risk populations. Recently, novel factors encompassing nutrients, genetics, and epigenetics have been explored and confirmed to be associated with the mechanisms of DR and capable of predicting the progression of DR[4, 5]. Exploration of potential factors would allow health professionals to better control DR at the population level and reduce morbidity and the quality of life losses that result from vision impairment.

Optical coherence tomography angiography (OCTA) enables the in vivo visualization and quantification of the retinal microvasculature, thus allowing the detection of vascular alterations in the superficial capillary plexus (SCP) and deep capillary plexus (DCP) [6, 7]. Chronic hyperglycemia is known to cause ischemia and vessel remodeling in the retinal microvasculature, implying that such vascular regions are likely to be involved in DR. Several cross-sectional studies have been conducted on OCTA flow metrics, including the vessel density (VD) and foveal avascular zone (FAZ). These metrics showed significant alterations in diabetic eyes without clinical indications of DR, indicating their underlying prognostic value for DR progression[8]. However, recent longitudinal studies have yielded inconsistent results[7, 9, 10].

The analysis of microvascular geometry provides valuable information about the quality of vascular networks and quantifies deviations from normal retinal vascular networks that indicate vascular impairment. Fractal dimension (FD) and blood

vascular tortuosity (BVT) are sensitive OCTA metrics for the diagnosis of proliferative DR (PDR) [11, 12]. Nonetheless, the prognostic value of FD has been questioned, and the efficiency of BVT in predicting DR progression has yet to be evaluated[6, 7]. To fill this gap, the aim of this study was to determine the value of retinal flow and geometry for predicting DR progression based on the prospective cohort.

Methods

Participants

This prospective cohort study (ISRCTN registry no.15853192) was performed at the Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen University, Guangzhou, China. It adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of ZOC (2017KYPJ094). Written informed consent was obtained from all participants.

Patients with type 2 diabetes mellitus (T2DM) aged 35-80 years were recruited from the Guangzhou Community Diabetic Registry from November 2017 to March 2019 and followed up annually[13, 14]. The baseline inclusion criteria were as follows: (1) mild or moderate non-PDR confirmed by seven-field fundus images and OCT imaging; (2) no history of ocular treatment (ocular treatment naïve); (3) best-corrected visual acuity (BCVA) of 0.1 or better; and (4) spherical degree of > -6 diopters, astigmatism of < 1.5 diopters, and axial length (AL) of < 26.0 mm.

Participants were excluded under the following circumstances: (1) a history of serious systemic diseases, such as ischemic heart disease, stroke, malignant tumor, or nephropathy; (2) the inability to consent or cooperate with examinations; (3) a history of major intervention, such as coronary bypass or renal dialysis; (4) eye diseases other than DR, such as glaucoma, age-related macular disease, vitreous macular diseases, or amblyopia; (5) a history of intraocular surgery, laser therapy, or intravitreal injection; (6) the presence of ocular media opacity, corneal ulcer, or contraindications of mydriasis, such as shallow anterior chamber; (7) a history or

presence of diabetic macular edema (DME); and (8) severe non-PDR or PDR.

Assessment of DR Progression

At baseline and follow-up visits, standard seven-field color fundus photographs conforming to the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria were taken with a digital retinal camera (Canon CR-2, Tokyo, Japan) after pharmacological pupil dilation. One retinal specialist blinded to the general patient information and OCTA images assessed the presence and severity of DR based on the retinal images according to the modified ETDRS severity scale, which uses a 15-step DR severity scale. DR was considered present when the retinopathy level was ≥14. Furthermore, the DR severity was stratified into mild NPDR (level 14-35), moderate NPDR (level 43-47), severe NPDR (level 53), and PDR (level ≥60). DR progression was defined as a ≥ two-step increase within the ETDRS severity scale at the 2-year follow-up visit compared with baseline[15, 16].

Measurement of OCT Angiography Metrics

We adopted a commercial swept-source OCTA (SS-OCTA) (DRI-OCT-2 Triton; Topcon Inc., Tokyo, Japan) device equipped with a tunable laser with a central wavelength of 1,050 nm, an acquisition speed of 100,000 A-scans/s, and an axial and lateral resolution of 7 and 20 μm in tissue to perform 3 × 3 mm^2 macula-centered Angio scans with 320 A-scans × 320 B-scans density. Motion artifacts and projection artifacts were removed by a built-in eye tracker system and an artifact removal algorithm. The built-in software (IMAGEnet 6, v1.24) automatically segmented the scans into SCP and DCP with concurrent removal of the projection artifacts of the DCP. The SCP layer was defined as 2.6 μm below the internal limiting membrane (ILM) to 15.6 μm below the junction between the inner plexiform layer (IPL) and the INL (IPL/INL), whereas the DCP layer was defined as 15.6 μm below the IPL/INL to 70.2 μm below the IPL/INL. Two experienced investigators reviewed the segmentations and manually adjusted them if necessary.

Ineligible images were excluded according to the following criteria: (1) image quality score (IQS)<50; (2) blurry images that prevented distinguishing the fine capillary networks from the background signal; (3) residual motion artifacts; (4) local weak signal or shadowing artifacts; (5) incorrect segmentation of the retinal layers; (6) signal loss; (7) poor central fixation; and (8) uncompensated projection artifacts on DCP. Eligible OCTA images from each participant were adjusted for the magnification factor based on AL according to Littmann's formula and Bennett's method. All images were manually centered at the fovea, standardized, and subsequently analyzed using the Fiji software (National Institutes of Health, Bethesda, MD, USA) for quantitative metrics, including the parafoveal VD, FD, and BVT in the SCP and DCP layers (**Figure 1**) [11, 17-20]. The FAZ area was measured based on the en face images of the full-thickness retinal slab.

Assessment of Other Risk Factors

Baseline general information, including age, sex, duration of diabetes, and medical history data, was collected through standardized interview-administered questionnaires using fixed questions and answer options to ensure comparability and consistency of survey results. Body height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were measured by nurses. Fasting venous blood and urine samples were obtained for the following laboratory parameters: glycated hemoglobin (HbA1c), total cholesterol, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), triglyceride, serum creatinine, C-reactive protein (CRP), and microalbuminuria (MAU). All participants underwent comprehensive ophthalmic examinations, including slit-lamp biomicroscopy (BQ-900, Haag-Streit, Switzerland), visual acuity test by ETDRS LogMAR E charts (Precision Vision, Villa Park, IL), refraction by an autorefractor (Topcon KR8800, Topcon Corporation, Tokyo, Japan), and the measurement of intraocular pressure (IOP) by a non-contact tonometer (Topcon CT-80A, Topcon, Tokyo, Japan). The AL was obtained using optical low-coherence reflectometry (Lenstar LS900; Haag-Streit AG, Koeniz, Switzerland).

Statistical Analysis

Statistical analysis was performed using Stata (version 17.0, Stata Corp., College Station, TX, USA). The Kolmogorov-Smirnov test confirmed the normality of the continuous variables, which were reported as the mean and standard deviation (SD). We performed the Student's t-test and chi-square test for the continuous variables and categorical variables, respectively, to compare baseline characteristics between participants with and without DR progression. Univariable and multivariable logistic analyses were performed to investigate the association between the baseline OCTA metrics and DR progression using generalized estimated equations (GEE) to account for the inter-eye correlation in individual participants. The established risk factors for DR progression, as detailed by Sun et al.[6] were integrated and adjusted in the multivariable model. These included age, duration of diabetes, HbA1c level, mean arterial blood pressure, and DR severity at baseline. The receiver operating characteristic (ROC) curves examined the incremental value of adding significantly associated OCTA metrics to the original DR prediction model to assess the added value of these parameters. A p-value less than 0.05 was considered be statistically significant.

Results

Baseline Characteristics of Included Participants

Initially, this study included 286 eligible eyes from 153 patients with T2DM at baseline. We excluded 53 eyes (28 patients) owing to loss to follow-up, unsatisfactory image quality, or missing data. The excluded patients had higher HbA1c, lower total cholesterol and HDL-c levels (**Supplementary table 1**). Eventually, a total of 233 eyes from 125 patients were included in the analysis, and 40 eyes (17.17%) presented DR progression within 2 years. **Table 1** summarizes the baseline demographic and clinical characteristics of included patients. Of them, 54.94% patients were women, with the average age of 64.4±6.3 years and the average disease duration of 13.2±7.5 years. **Table 2** displays the quantitative measurements

of baseline OCTA metrics stratified by DR status. The BMI, SBP, DBP, and MAP had decreasing trend during follow-up (**Supplementary table 2**). However, the HbA1c increased from 7.61 (1.43) at baseline to 8.17 (1.58) at 2-year follow-up (P<0.001). The reduced perfusion and impaired geometry were correlated with higher CMT, but only FD in DCP arrived at significance (**Supplementary table 3**).

Association of OCTA Metrics and the Risk of DR Progression

Table 3 shows the associations between baseline OCTA metrics and DR progression. After adjusting for other established factors, lower VD (OR, 2.323 per SD decrease; 95% CI, 1.456-3.708; P<0.001), lower FD (OR, 2.484 per SD decrease; 95% CI, 1.268-4.867; P=0.008), and higher BVT (OR, 2.076 per SD increase; 95% CI, 1.382-3.121; P<0.001) of the DCP layer were associated with DR progression. The FAZ and SCP metrics were not independently associated with future DR progression (all P>0.05). **Figure 2** shows a representative patient with OCTA alterations at baseline and ≥ two-step progression during follow-up.

Additional Value of OCTA Metrics in the Prediction Model

We entered all significant OCTA metrics correlated with DR progression and the established risk factors detailed by Sun et al.[6] into the multivariate logistic regression analysis. **Figure 3** illustrates the effects of adding VD, BVT, and FD to the original model. The addition of OCTA metrics significantly optimized the performance of the DR progression prediction models (area under the curve [AUC], 0.805; 95% CI, 0.726-0.883 versus AUC, 0.725; 95% CI, 0.639-0.811, respectively) (*P*=0.022).

Discussion

The role of retinal microvascular flow and geometry in DR has attracted growing interest in recent years; nonetheless, its value in predicting DR progression remains controversial. This 2-year prospective SS-OCTA cohort study demonstrated that reduced VD and FD of the DCP and increased BVT of DCP were strongly associated

with the increased risk of DR progression, independent of confounding factors. These parameters showed additional value to the currently used DR progression prediction models, thereby suggesting their future implementation in a more efficient risk stratification of DR progression. To our knowledge, this is the first study to assess the associations between BVT and the risk of DR progression.

Previous studies on relationship between OCTA-derived parameters and DR progression achieved mixed results (**Table 4**). Sun et al. observed the significant relationship of baseline larger FAZ area, lower VD, lower FD of DCP, and DR progression, while none of the SCP metrics was associated with DR progression. Similarly, Custo Greig et al. demonstrated that larger FAZ area, reduced peripapillary VD in the superior temporal sector and inferior temporal sector were significantly associated with increased odds of DR progression. However, You et al. reported DR progression was significantly associated with the extrafoveal avascular area of SCP, but not associated with those of DCP. In addition, studies by Tsai et al. and Marques et al. showed no significant inter-group differences in baseline OCTA parameters between DR progressive and stable eyes[10, 21]. This study advanced previous studies by incorporating the OCTA-derived parameters for prediction of DR progression in Chinese DM patients. The primary analysis of this study validated the predictive value of VD in DR progression, which is in accordance with previous studies suggesting the association of macular ischemic changes with DR severity and progression[22, 23], and decreasing VD as DR severity increases[24-26]. Moreover, it was congruent with previous fluorescein angiography studies, which demonstrated ischemic macular changes in the development of DR[27].

OCTA-derived BVT is a parameter that quantifies microvascular complexity but its association with DR progression has not been well established. Lim et al.[28] and Cheung et al.[29] quantitatively analyzed fundoscopy images and reported that greater venular and arterial tortuosity of large vessels were associated with DR progression at 1-year and 6-year follow-up, respectively; however, this effect was

not observed by Klein et al.[16] after 5-year follow-up. Fundoscopy images are the possible reason for these discrepancies, as the resolution is insufficient to obtain accurate measurements of detailed microvascular networks. The application of OCTA in our study provided superior resolution and could detect motion changes more accurately to determine the retinal microarchitecture within superficial and deep capillary networks. The present study is the first to report the association between OCTA-derived BVT and DR progression using longitudinal data. However, due to the novelty of OCTA-derived BVT parameters, reference values for potential clinical applications in the future still require extensive research with large sample sizes to be established.

FD has been proposed as a biomarker for DR severity, despite the inconsistent conclusions about its predictive ability in longitudinal studies[20, 30, 31]. Sun et al.[6] demonstrated that FD of the DCP was correlated with DR progression, whereas no significant association was noted on the full-depth retinal projection in the Time-2b study[7]. These discrepancies likely arise from different segmentation methods of retinal layers and the relatively small sample size. Our study observed each SD decrease in FD was associated with a 1.484 times greater risk of DR progression after adjusting for confounding factors. As a lower FD value represents decreased global complexity of the vascular tree, our findings suggest DR patients with greater deviations from normal retinal microvascular networks are at a higher risk of DR progression. Chronic hyperglycemia inflicts microvascular network remodeling in vivo, which could lead to changes in shear forces and helical flow, ultimately resulting in fragile blood vessels. Therefore, FD alterations are present before the clinical indications of DR progression, implying a potential biomarker for monitoring DR deterioration. In addition, FD has a debatable reliability for un-replicated segmentation methods based on fundoscopy images[32]. SS-OCTA adopted in this study enabled FD detection with higher imaging resolution and unified image quality inspection compared with previous studies. Future studies should follow classical methods to ensure consistent and comparable findings.

Conventional risk factors cannot adequately predict DR progression, thus necessitating other biomarkers to better control DR and its societal impact[2, 3, 33]. We verified the value of adding VD, FD, and BVT parameters to another risk model for predicting DR progression, elevating the original AUC from 0.725 to 0.805 (*P*=0.022). Such predictive power implicated retinal vessel geometry and flow in the pathology of DR and implied that the model may be of interest to clinical trials and guidelines. Interestingly, all OCTA parameters associated with DR progression were present in the DCP layer, and none of the SCP layer parameters had similar prognostic values. Microvascular changes associated with DR progression may occur earlier in the DCP layer than those in the SCP layer, consistent with histological studies revealing that DCP is more sensitive to hyperglycaemia[34, 35] and cross-sectional OCTA studies that reported on higher diagnostic power of DCP-derived OCTA metrics for differentiating patients with DM from healthy controls[26, 36-38]. These findings highlight the potential role of OCTA parameters in grading DR risk and will aid in clinical decision-making for DR patients likely to experience a worsening prognosis. Ideally, we intend to examine and validate the proposed model in a real-world setting in future to assess its clinical value for DR progression risk assessments.

The strengths of this study were its prospective cohort design and relatively large sample size. The adjustment for all known confounding factors through a multivariate model and the corrected image magnification owing to AL variation are also features of this study that have been neglected by previous authors[39]. Previous literature has demonstrated that the magnification error caused by axial length variation affects the measurement of FAZ derived from OCTA, particularly in higher aberrations of axial length. Since axial length strongly correlates with the refractive error, high myopic patients with spherical degree of ≤ -6 D and axial length of >26 mm were excluded at baseline. The study had several limitations. First, the 2-year follow-up was relatively short, which restricted the number of times DR progression could be captured. Second, all patients were Chinese with T2DM, which

may limit the generalizability of our results to other ethnicities. Third, SS-OCTA metrics were centered only on the macula and had a small field of view, which limited conclusions about the predictive power of the peripheral retina. Fourth, because this study used a commercial SS-OCTA, errors from the default settings may result in measurement bias. To minimize this possibility, we performed manual corrections when necessary. Fifth, 53 eyes of 286 eligible eyes (18.53%) were excluded from the analysis, increasing the possibility of selection bias. Sixth, only DM patients were included which prevents the directly comparisons between normal subjects and DM patients. You et al.[40] had reported that the mean values of parafoveal VD on SCP and DCP were 49.21% (34.27% to 66.01%) and 59.35% (29.83% to 69.23%) in the population-based samples, respectively. The mean values of VD in SCP and DCP were higher than those in normal population but within the range. Future studies are needed to compare the trajectory of OCTA metrics among normal subjects, patients with high risk for DR progression, and patients with low risk for DR progression. Finally, DME occurred in 10 eyes (4.46%), which is lower than the 8.76% reported by Sun et al.[6], which may be due to the discrepancy in patient recruitment strategy. In the Sun et al. study, patients were recruited from patients attending ophthalmology specialties, while the present study was recruited from the community, where the patients had lower disease severity. The lens density might influence the OCTA metrics, and the LOCS-3 grading are on-going.

In conclusion, reduced VD and FD and increased BVT of DCP were significantly associated with a higher risk of DR progression in 2 years. The addition of these parameters into conventional prediction models significantly increased the AUC, which implied that retinal blood flow and geometries are important pathological changes preceding DR. Future studies should determine the validity of integrating these OCTA metrics into prediction models in a real-world setting and their impact on improving clinical decision-making for DR management.

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Figure legends

Figure 1. Flow and geometric metrics based on OCT angiography (OCTA) images in the superficial capillary plexus (SCP) and deep capillary plexus (DCP). FAZ=foveal avascular zone area; VD=vessel density; FD=fractal dimension; BVT=blood vessel tortuosity

Figure 2. Representative case showing > 2 step worsening of retinopathy alongside significant OCTA changes. Significant rarefaction of VD and discontinuous FAZ area were observed in both SCP and DCP. OCTA=optical coherence tomography angiography; DR=diabetic retinopathy; FAZ=foveal avascular zone area; SCP=superficial capillary plexus; DCP=deep capillary plexus.

Figure 3. Receiver operating characteristic (ROC) curves based on traditional risk factors and the addition of significant OCTA metrics in predicting DR progression. OCTA=optical coherence tomography angiography; DR=diabetic retinopathy; AUC=area under the curve.