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Association between OCT-based microangiography perfusion indices and diabetic retinopathy severity

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Abstract

Aim—To evaluate the association between retinal capillary non-perfusion and diabetic retinopathy (DR) severity using optical coherence tomography-based microangiography (OMAG).

Methods—33 patients (51 eyes) with a history of diabetes underwent imaging with a 68 kHz Cirrus-5000 spectral domain OMAG prototype. Demographic and clinical characteristics were collected. The perfusion index (PI) was defined as per cent coverage of area by retinal vessels with flow, measured within a minimum of 6.8×6.8 mm² OMAG scan. The PI in each ETDRS zone was analysed using an automated algorithm. Univariate and multivariate analyses were used to determine the degree of association between PI and DR severity.

Results—51 eyes with different DR severities were imaged. More severe DR was significantly associated with lower PI after adjusting for logarithm of the minimum angle of resolution best-corrected visual acuity, hyperlipidaemia, diabetes type and ETDRS ring in a multivariate mixed linear model. Compared with the none–mild non-proliferative diabetic retinopathy (NPDR) group, the moderate–severe NPDR group had 2.7 lower PI (p=0.03) and proliferative DR group had 4.3 lower PI (p=0.003). All ETDRS zones except for the foveal centre showed inverse associations between PI and DR severity (p values<0.001 to 0.862).

Conclusions—A statistically significant inverse association exists between PI and DR severity. Our study suggests that PI may become a useful biomarker in evaluating and following the progression of DR.

INTRODUCTION

Diabetes mellitus causes considerable morbidity and mortality and affects >422 million people. Diabetic retinopathy (DR) is the leading cause of blindness in the working-age

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population and accounts for 2.8% of blindness worldwide. Patients with diabetes are approximately 25 times more likely to become vision impaired than the general population.¹² Multiple studies have demonstrated that hyperglycaemia, hyperlipidaemia and hypertension contribute to the pathogenesis of DR.³⁴ Proposed pathways include vascular disruptions characterised by abnormal vascular flow, disruptions in structure, permeability and non-perfusion of capillaries.⁵⁶ Thus, evaluating capillary perfusion and measuring areas of non-perfusion are critical in understanding DR.

The current gold standard for evaluating the retinal capillary perfusion is fluorescein angiography (FA). However, FA is invasive, requiring intravenous injection of fluorescein dye with possible side effects including urticaria, hypotension, nausea/emesis and rarely anaphylaxis.⁷ Additionally, FA can be a time-intensive procedure requiring multiple personnel to complete the imaging process. While FA is effective and accurate in delineating the foveal avascular zone, the evaluation of the adjacent multilaminar networks is limited; therefore, the earliest non-perfusion of capillaries in vaso-occlusive diseases may not be visualised.⁸ Furthermore, while FA shows the anatomical arrangement of the superficial retinal vessels, it does not correlate with the deeper retinal capillaries.⁹

With recent advances in optical coherence tomography angiography (OCTA), the ability to assess the microvasculature throughout different retinal layers in DR has transformed. Areas of non-perfusion in both superficial and deep vascular plexuses and loss of normal capillaries are easily detected with OCTA.^{10–12} OCT-based microangiography (OMAG), a type of OCTA, is an effective non-invasive imaging modality and has been used to evaluate the retinal and choroidal vasculature in various pathologies.^{13–15} By using both amplitude and phase in the OCT signals, OMAG allows imaging and measurements of both the morphological and functional parameters of blood perfusion in patients with DR.¹⁴¹⁵

While multiple studies have evaluated the characteristic features of DR using OCTA,¹⁰¹¹ the association between capillary non-perfusion and the severity of DR has not been clearly established. The purpose of this study is to evaluate the association between the retinal capillary non-perfusion and the severity of DR using OMAG.

METHODS

Patients with a diagnosis of diabetes who were seen in retina clinics at the University of Washington, Seattle, Washington, USA between 1 January 2014 and 1 November 2015 were voluntarily enrolled in the study. Exclusion criteria included age <18 years old, non-English speakers or any other documented retinal vascular pathology. After a written informed consent, bilateral OMAG images were obtained. Images with poor signal strength or severe motion artefact were excluded from the final analysis.

OMAG imaging

A total of 33 patients (51 eyes) underwent imaging with a 68 kHz Cirrus-5000 SD-OCT-based angiography prototype (Carl Zeiss Meditec, USA), which operates at a central wavelength of 840 nm. To achieve OMAG imaging of retinal vasculature, a repeated B-mode scanning protocol was implemented in the prototype. Four repeated B-scans were

acquired at one position and used to extract the blood flow signal as previously described¹³ with the total time for single-volume acquisition being 3.6 s excluding the adjustment time prior to data collection.

In this study, the Cirrus-5000 SD-OCT-based angiography prototype was equipped with motion tracking through an auxiliary real-time line scan ophthalmoscope and allowed montaging of images.¹⁶ The minimum array for the grid was 3×3, giving a field of view (FOV) of 6.8×6.8 mm² (approximately 30–40° FOV) while maximum array was 4×6, providing a coverage of 9.0×13.4 mm². Previously described OMAG algorithm¹⁴¹⁵¹⁷ was applied to all the volumetric data sets, and the large FOV en face OMAG was obtained by stitching the images automatically by use of a software coded with Matlab. Images were then converted into a binary format for data analysis using an automated algorithm. The en face images were created by using a maximum amplitude projection (MAP) method for total retinal flow. Before the MAP, a 3×3×3 pixel-kernel Gaussian filter was applied to enhance the quality of the images.

Perfusion index

Each en face projection of retinal circulation was aligned such that the fovea was the centre of the image and regions were segmented according to the nine ETDRS regions of the macula.¹⁸ The foveal region was defined as the central circle 1 mm in diameter. The inner ring was defined as having radii of 1–3 mm. The outer ring was defined as having radii of 3–6 mm. The inner and outer rings were further subdivided into superior, nasal, inferior and temporal regions.¹⁸ Each ETDRS region was used to independently sample perfusion. PI was defined as the per cent coverage of the area by retinal vessels with flow.

The following clinical characteristics were collected on each patient: age, gender, best-corrected visual acuity (BCVA) on logarithm of the minimum angle of resolution (logMAR) scale, type of diabetes (type 1 vs type 2), most recent haemoglobin A1c value (HbA1c), use of insulin, clinical severity of DR, history of hypertension and history of hyperlipidaemia on the last recorded date closest to the acquisition of the OMAG image.

STATISTICAL ANALYSES

Patients were divided a priori into three groups (none–mild non-proliferative diabetic retinopathy (NPDR), moderate–severe NPDR and proliferative diabetic retinopathy (PDR)) based on diabetic severity determined by the clinical examination of retina-trained specialists using the ETDRS criteria.¹⁸ Analysis of variance and Fisher's exact test were performed for univariate analysis on continuous and categorical variables, respectively. Clinical variables trending towards significance on univariate analysis ($p < 0.200$) were force entered into multivariate mixed linear regression models, which were used to determine the association of capillary PI with DR severity using R (<http://www.r-project.org>). All univariate analyses and the multivariate sub-field analyses included adjustment for within-subject correlation using mixed modelling. Multivariate analysis examining the perfusion by annulus ring included adjustment for within-subject and within-eye correlation using mixed modelling.

RESULTS

Representative images of each group of DR are shown in figure 1A–C. The analysis of capillary PI was performed in 51 eyes (17 with none–mild NPDR, 21 with moderate–severe NPDR and 13 with PDR). Demographic data for the 51 eyes are summarised in table 1. The mean±SD of age of the study population was 52.4±10.6 years, 47.6±11.7 years and 46.2±12.9 years for the none–mild NPDR group, moderate–severe NPDR group and PDR group, respectively. The mean±SD of BCVA on logMAR scale was 0.10±0.12 in the none–mild NPDR group, 0.15±0.16 in the moderate–severe NPDR group and 0.25±0.33 in the PDR group. The use of insulin varied from 52% to 77% with the lowest use being in the moderate–severe group and the highest being in the PDR group. The proportion of type 1 diabetics was similar in the moderate–severe NPDR and PDR groups (33% vs 31%) but lower in the none–mild NPDR group (24%). The association between capillary PI and each clinical variable including age, gender, logMAR BCVA, type of diabetes and presence of hypertension or hyperlipidaemia was analysed with univariate models, and those with p values of <0.200 were forced entered into multivariate analysis (table 2).

The PI was inversely proportional to the severity of DR. The mean capillary perfusion was 40.1 (SD=9.4) in none–mild NPDR, 37.6 (SD=11.0) in moderate–severe NPDR and 35.4 (SD=12.3) in PDR. A statistically significant, inverse relationship was found between the capillary PI and the severity of DR after adjusting for logMAR BCVA, hyperlipidaemia, diabetes type and ETDRS ring on a multivariate mixed model adjusting for within-subject and within-eye correlation (table 3). The mean PI values were nearly identical across subfields within each annulus (inner or outer). Increasing DR severity was significantly associated with lower capillary perfusion indices. In comparison to the none–mild NPDR group, the moderate–severe NPDR group had 2.7 lower PI (p=0.03) and the PDR group had 4.3 lower PI (p=0.003). No significant association was found between capillary perfusion indices and logMAR BCVA (p=0.95), hyperlipidaemia (p=0.35) or diabetes type (p=0.25).

The negative association between the PI and the severity of DR was found to be significant within each ETDRS zone (figure 2). All ETDRS zones showed a similar pattern of capillary perfusion indices inversely correlating with diabetic severity scale (p value range <0.001 to 0.862) (table 4). The inner ETDRS zones demonstrated a stronger inverse association (p value range <0.001 to 0.818) between DR severity than the outer ETDRS zones.

DISCUSSION

This study demonstrates that the capillary PI is inversely proportional to the severity of DR after adjusting for age, logMAR BCVA, hyperlipidaemia, diabetes type and ETDRS subfields. This inverse relationship between increasing DR severity and decreasing capillary perfusion indices was significant both within each DR severity group as a whole, as well as within each ETDRS zone. Additionally, increasing age was significantly associated with decreasing capillary perfusion indices.

Measuring capillary perfusion and areas of non-perfusion are crucial components of DR evaluation.⁵⁶ Currently, the gold standard of assessing perfusion is FA; however, the ETDRS

trial has shown that substantial interobserver variation exists when evaluating capillary loss, capillary dilation and narrowing of arteriolar branches in DR (weighted kappa, 0.41–0.60).¹⁹ Therefore, a consistently reliable, objective method of evaluating retinal capillary perfusion is needed.

Several studies have shown OCTA as a better imaging modality to examine the capillary perfusion. Spaide *et al*¹² demonstrated that OCTA is superior in delineating the retinal capillary networks compared with FA. The radial peripapillary capillary networks in different layers of the retina were fully mapped on OCTA but only in few superotemporal or inferotemporal regions on FA. OCTA was shown to better image all different layers of the retinal vasculature unlike FA. This finding was consistent with the study by Weinhaus *et al*,⁸ which showed that FA was only able to delineate a fraction of the adjacent multilaminar capillary network compared with histology in monkey retinas. Thus, OCTA allows more detailed detection of the retinal microvasculature than FA.

Few studies have used OCTA to quantify the degree of capillary non-perfusion in DR. Ishibazawa *et al*¹⁰ compared the vascular abnormalities detected on FA versus OCTA in 47 eyes of 25 patients with DR. OCTA was superior in detecting the microaneurysms, areas of neovascularisation and areas of capillary non-perfusion. In this study, the areas of perceived non-perfusion were outlined manually by two masked observers, which differed from our study's automated calculation of non-perfusion. A total of seven eyes underwent quantitative analysis of capillary non-perfusion near the macula, revealing larger areas of non-perfusion in the superficial plexus compared with deeper plexus. The number of eyes that underwent these evaluations were relatively small, and capillary non-perfusion was not used as a means of grading the severity of DR. Agemy *et al*²⁰ focused on mapping of retinal vascular perfusion density in diabetic patients using OCTA and compared the capillary perfusion densities of 21 control and 56 eyes with DR. Skeletonised OCTA maps were used to examine the different layers of the retinal vasculature both in a 3×3 mm and 6×6 mm scan. A statistically significant difference was found between the capillary perfusion densities of control and diabetic patients. However, the subgroup analysis comparing the capillary perfusion density between eyes of varying stages of DR did not show a statistical significant difference in any group, except when comparing PDR to mild NPDR using 3×3 mm scan data. Our study differed in scanning techniques and analysis in several ways. First, their study used a different imaging system, Avanti RTVue-XR commercial spectral domain OCT system. Second, all of our scans were at least 6.8×6.8 mm², thus we were able to analyse a larger area in its entirety as well as within each ETDRS zone. Lastly, a multivariate mixed model was used in our study to compare the capillary PI among stages of DR after adjusting for other clinical and demographic variables and for within-subject correlation.

Several reasons may explain an inverse relationship between capillary perfusion and DR severity. Hyperglycaemia results in microvascular damage through oxidant stress and the polyol pathway, specifically affecting the health of pericytes.⁵²¹ Multiple studies have demonstrated that the retinal vascular tone is regulated both by pericytes and smooth muscle cells.⁵²² Therefore, damage or loss of pericytes, one of the earliest manifestations in DR, results in disruptions of retinal haemodynamics and decreased capillary perfusion.²¹²³ Multiple animal models have demonstrated the toxic effects of hyperglycaemia on pericytes,

resulting in cell death and loss of pericyte function.²⁴²⁵ Thus, an increase in DR severity could result in increased microvascular damage, and consequently manifest as decreased capillary perfusion, which was observed in our study.

Not surprisingly, higher HbA1c values were weakly associated with higher degree of DR severity ($p=0.37$) in our study. This may represent the variable level of systemic diabetes control in our patient population. Interestingly, we found that the inner ETDRS zones had higher inverse associations with increasing diabetic severity than the outer ETDRS zones. We hypothesise that the significant variations in size of the larger retinal arcades and venules may have played a role in capillary perfusion variability and therefore may have limited the ability to detect more significant differences in capillary non-perfusion.

Several limitations exist in our study. We only sampled the macula region; thus, our PI may not reflect fully the degree of perfusion loss that exists in the periphery. Widefield OCTA may provide more accurate information on the PI by including peripheral vasculature. Furthermore, a larger sample size would have allowed for further classification of DR severity. Only one OCTA system was used; therefore, our results may not be generalisable to other algorithms. In addition, our patients had relatively good vision even in the PDR group, which could suggest some selection bias towards people with relatively good vision in the study (ie, patients with severe macular ischaemia may not have been recruited to our study due to poor fixation or vision). However, this bias would have decreased the probability of finding a significant association between the capillary index and DR severity. Lastly, our study did not include any evaluations of neovascularisation, a key aspect of PDR, and a future OCTA analysis on preretinal perfusion would be a useful method of correlating PDR versus NPDR.

In conclusion, this study demonstrates that the capillary PI has significant inverse associations with the severity of DR using OMAG. Capillary PI detected using OCTA may be used as an important clinical end point for follow-up and management of DR. Future studies to determine the temporal sequence of decrease in capillary perfusion and progression of DR may lead to important insights in the pathogenesis and potential preventive measures of DR progression.

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Competing interests RW received research support from Carl Zeiss Meditec and co-owns a patent that is related to the subject matter discussed in this manuscript with Oregon Health & Science University.

Ethics approval This study was approved by the Institutional Review Board of the University of Washington and was in adherence with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act.

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Figure 1.

En face ocular coherence tomography-based microangiography images of macular capillary networks for the following diabetic retinopathy groups: none-mild non-proliferative diabetic retinopathy (A), moderate-severe non-proliferative diabetic retinopathy (B) and proliferative diabetic retinopathy (C).

Figure 2.

Perfusion index association with diabetic retinopathy severity groups across ETDRS zones. Macular retinal mean perfusion indices with SE bars by diabetic retinopathy severity groups: no to mild non-proliferative diabetic retinopathy (NPDR), moderate to severe non-proliferative diabetic retinopathy, proliferative diabetic retinopathy (PDR), calculated for each individual ETDRS zone. CF, central foveal; II, inner inferior; IN, inner nasal; IS, inner superior; IT, inner temporal; OI, outer inferior; ON, outer nasal, OS, outer superior; OT, outer temporal.

Table 1

Patient demographic and clinical characteristics

	No-mild NPDR (n=17)	Moderate-severe NPDR (n=21)	PDR (n=13)	p Value
Age, mean (SD)	52.4 (10.6)	47.6 (11.7)	46.2 (12.9)	0.32
BCVA, mean (SD)	0.10 (0.12)	0.15 (0.16)	0.25 (0.33)	0.17
HbA1c, mean (SD)	7.40 (1.41)	8.27 (1.47)	8.90 (2.11)	0.11
Female gender, n (%)	7 (41%)	3 (14%)	6 (46%)	0.08
HTN, n (%)	7 (41%)	12 (57%)	8 (62%)	0.56
HLD, n (%)	11 (65%)	9 (43%)	8 (62%)	0.38
DM type 1, n (%)	4 (24%)	7 (33%)	4 (31%)	0.86
Insulin use, n (%)	10 (56%)	11 (52%)	10 (77%)	0.36

BCVA, best-corrected visual acuity; DM, diabetes mellitus; HbA1c, haemoglobin A1c; HLD, hyperlipidaemia; HTN, hypertension; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2

Mixed model univariate analysis of capillary perfusion index

Factor	Estimates	p Value
Grade of retinopathy		
None–mild NPDR	Reference	
Moderate–severe NPDR	−2.271	0.096
PDR	−4.200	0.005 *
Age	−0.063	0.206
Male	0.046	0.972
logMAR BCVA	−5.177	0.154
HgbA1c	−0.336	0.370
Type 2 DM	−1.844	0.149
Hypertension	−0.973	0.417
Hyperlipidaemia	−1.576	0.188
ETDRS zone		
Central foveal	Reference	
Inner inferior	34.725	<0.001 *
Inner nasal	34.484	<0.001 *
Inner superior	34.583	<0.001 *
Inner temporal	34.418	<0.001 *
Outer inferior	38.506	<0.001 *
Outer nasal	37.550	<0.001 *
Outer superior	38.479	<0.001 *
Outer temporal	38.224	<0.001 *

* p Values <0.05.

BCVA, best-corrected visual acuity; DM, diabetes mellitus; HbA1c, haemoglobin A1c; logMAR, logarithm of the minimum angle of resolution; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 3

Mixed model multivariate analysis of capillary perfusion index

Factor	Estimates	p Value
Grade of retinopathy		
None–mild NPDR	Reference	
Moderate–severe NPDR	−2.744	0.033 *
PDR	−4.314	0.003 *
logMAR BCVA	0.244	0.947
Type 2 DM	−1.541	0.246
HLD	−1.154	0.345
ETDRS ring		
Inner ring	Reference	
Outer ring	10.548	<0.001 *

* p Values <0.05.

BCVA, best-corrected visual acuity; DM, diabetes mellitus; HLD, hyperlipidaemia; logMAR, logarithm of the minimum angle of resolution; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 4

Mixed model multivariate analysis of capillary perfusion index by ETDRS zone adjusted for BCVA, type 2 DM, HLD and with Bonferroni adjusted p values

ETDRS field	None-mild NPDR		Moderate-severe NPDR			PDR		
	Crude mean perfusion	Estimates	p Value	Adjusted p value	Crude mean perfusion	Estimates	p Value	Adjusted p value
Central foveal	1.57	1.45	0.818	1.000	1.17	-0.323	0.258	1.000
Inner inferior	39.52	36.31	0.038 *	0.343	31.81	-7.802	<0.001 *	0.004 *
Inner nasal	38.99	35.78	0.070	0.629	32.32	-5.978	0.007 *	0.066
Inner superior	39.25	35.44	0.008 *	0.071	32.86	-6.346	<0.001 *	0.003 *
Inner temporal	39.91	34.80	0.010 *	0.093	32.36	-6.787	0.003 *	0.031 *
Outer inferior	41.74	39.94	0.284	1.000	37.68	-3.076	0.073	0.655
Outer nasal	39.38	38.99	0.492	1.000	38.42	-0.860	0.678	6.102
Outer superior	40.13	39.76	0.719	1.000	39.81	0.243	0.862	7.758
Outer temporal	41.62	39.20	0.129	1.000	37.88	-2.370	0.141	1.269

* p Values <0.05.

BCVA, best-corrected visual acuity; DM, diabetes mellitus; HLD, hyperlipidaemia; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.