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Determinants of Macular Microvasculature in Highly Myopic Eyes without Pathologic Change

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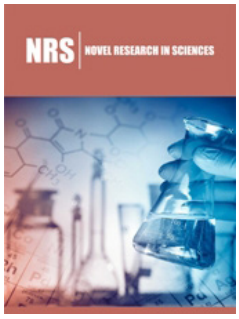

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Abstract

Purpose: To determine the effects of ocular and systemic factors on macular Capillary Density (CD) in highly myopic eyes without pathologic change.

Methods: A total of 604 eyes with high myopia were enrolled. A fovea-centered 6×6mm Optical Coherence Tomography Angiography (OCTA) scan was performed to obtain the macular Capillary Densities (CDs) in the Superficial Capillary Plexus (SCP) and Deep Capillary Plexus (DCP). Linear mixed models were used to examine the effect of various ocular and systemic factors on macular CDs.

Result: The whole image CDs were 34.86±1.38% and 46.33±1.18% in the SCP and DCP, respectively. In the final multivariate analysis, the reduced whole image CD of SCP was statistically significantly associated with older age (estimate, -0.02; 95% Confidence Interval [CI], -0.03 to -0.00; P=0.013), lower Diastolic Blood Pressure (DBP) (estimate, 0.02; 95% CI, 0.01 to 0.04; P=0.002) and lower Image Quality Score (IQS) (estimate, 0.05; 95% CI, 0.02 to 0.07; P<0.001), while the reduced whole image CD of DCP was statistically significantly associated with longer Axial Length (AL) (estimate, -0.15; 95% CI, -0.25 to -0.04; P=0.007) and lower IQS (estimate, 0.05; 95% CI, 0.02 to 0.07; P<0.001).

Conclusions: In highly myopic eyes, age, DBP, AL, and IQS were significantly associated with macular CD measurements with OCTA. These factors need to be considered when assessing changes in macular CD in ocular pathologies related to high myopia.

Keywords: Whole image; Measurements; Pathologic changes; Microvascular changes; Capillary densities

Introduction

High myopia is one of the major worldwide concerns [1]. It is projected that the global incidence of high myopia will increase from 163 million people in the year 2000 to 938 million people in 2050 [2]. High myopia brings further vision challenges because it increases the risk of pathologic ocular changes, including myopic macular degeneration and open-angle glaucoma, of which can lead to irreversible vision impairment and even blindness [3-7]. The mechanical stretching of Axial Length (AL) causing the changes of macular vascular may play an important role in these pathologic changes [8-11]. Thus, knowledge about normal macular vascular change and its determinant factors are essential for assessing various ocular pathologies related to high myopia. Optical Coherence Tomography (OCT) Angiography (OCTA) is a noninvasive imaging technique that enables clinicians to detect subtle changes in macular vascular in vivo [12,13]. Previous studies using OCTA have measured macular microvascular changes in eyes with high myopia, and reported that decreased macular vessel density was significantly correlated with AL elongation [9,14-16]. However, most of these studies were with limited sample size and

existed potential selection bias [9,14-16] Moreover, few studies have evaluated the factors affecting the macular microvascular changes in highly myopia eyes. However, understanding the factors that can affect the change of microvascular is important to interpret the changes seen in the disease conditions meaningfully. Swept-Source OCT (SS-OCT), featuring faster scanning speeds (100 000 A scans/s), a longer wavelength (1050nm), and reduced sensitivity roll-off, has offered advantages for imaging highly myopic eyes with long AL [17,18] In this study, we measured the macular Capillary Densities (CDs) in the Superficial Capillary Plexus (SCP) and Deep Capillary Plexus (DCP), and determined systemic and ocular factors influencing macular CDs measured by SS-OCTA technology in highly myopic eyes without pathologic change.

Methods

Participants

Data for the analysis were obtained from a longitudinal observational high myopia registry cohort study, initiated in Guangzhou, China in June 2019 (ClinicalTrials.gov; identifier: NCT04302220) [19]. The study was approved by the Ethics Committee of the Zhongshan Ophthalmic Center (ZOC), Sun Yat-sen University, China. All examinations adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all study participants. The inclusion criteria were as follows: (1) age≥18 years; (2) Best-Corrected Visual Acuity (BCVA)≥20/40; (3) diagnosis of high myopia (defined as AL of ≥26.0 mm); and (4) normal optic disc appearance with intact neuroretinal rim and retinal nerve fiber layer. Exclusion criteria were: (1) any kind of ophthalmic disease that can affect the ocular microvasculature, such as glaucoma, retinal diseases, and neuro-ophthalmic diseases; (2) myopic maculopathy equal to or more serious than "diffuse choroidal atrophy" and/or the presence of a distinct posterior staphyloma as assessed on fundus photos [20,21] (3) history of ocular surgery; (4) smoking history; (5) intake of coffee or alcohol within 24 hours before the procedure; and (6) systemic hypertension and/or diabetes mellitus.

Systemic and ocular examinations

All participants underwent a comprehensive ocular examination, including slit-lamp examination, assessment of BCVA, automatic refractometry (autorefractor, KR-800, Topcon Co, Tokyo, Japan), tonometry using Goldmann applanation tonometry, ocular biometry including measurement of central corneal thickness and AL (IOL Master 700, Carl Zeiss Meditec, Jena, Germany), fundus photography (Nonmyd WX3D, Kowa, Aichi, Japan), and OCT and OCTA scans. Additionally, Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were measured using an Omron M7 Blood Pressure Monitor (Matsusaka, Mie, Japan). Body Mass Index (BMI) was calculated as body weight (kilograms) divided by the square of body height (meters).

OCT and OCTA imaging

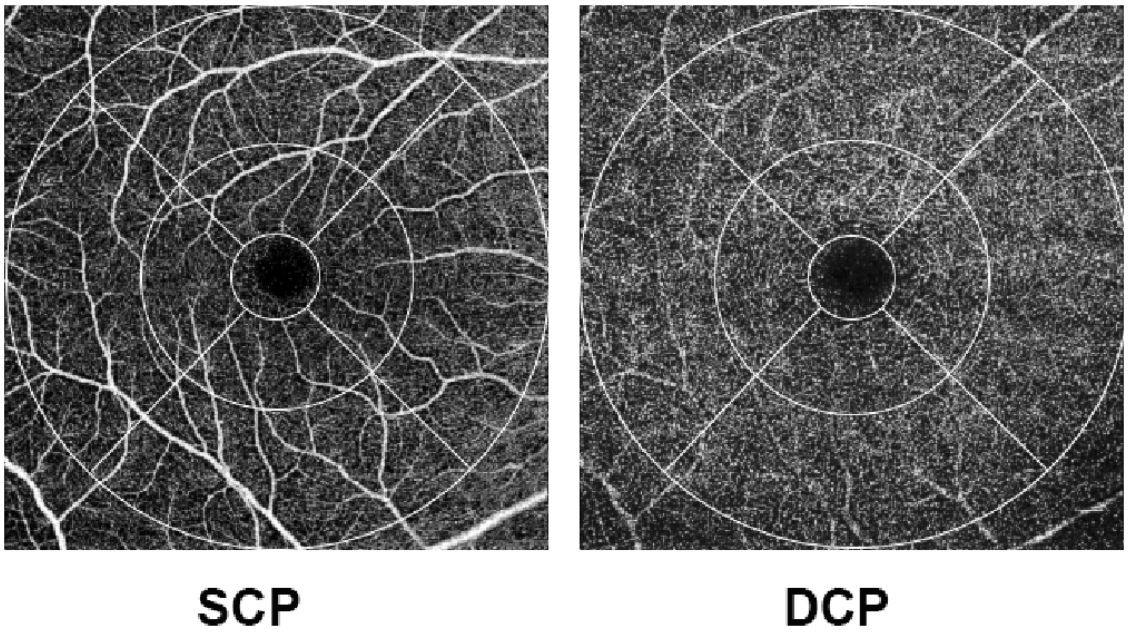

Figure 1

An experienced operator performed the OCT and OCTA imaging after pupil dilation using SS-OCT equipment (Triton, DRI-OCT 2, TOPCON, Tokyo, Japan). The instrument has a wavelength of 1050nm at a scanning speed of 100 000 A-scans per second and provides both thickness and vascular measurements. Macular 6×6mm angiography model, each consisting 320×320 A-scans were obtained from each eye. The en-face OCTA images were generated by the built-in software of the SS-OCTA (IMAGEnet6, Version 1.28.17642, Basic License 1). The software automates and segments the slabs of the SCP and DCP. The SCP was delineated from 2.6-μm below the internal limiting membrane to 15.6-μm below the junction between the inner plexiform and inner nuclear

layers. The DCP was delineated from 15.6-μm below the inner plexiform and inner nuclear layers to 70.2-μm below these layers [17,22]. Projection artifacts and motion were minimized by the instrument's built-in OCTA algorithm and the active eye tracker [17]. All OCTA images were reviewed by three trained graders (F Lin, Z Zhao, and D Xiaokaiti) and passed image quality control. Any image with a quality score (IQS) <50, artifacts, segmentation failure, blurry regions, poor centration, and/or signal loss was excluded [23,24]. Eligible OCTA images were then corrected for ocular magnification based on the AL, using the Littman and the modified Bennett formulae (scaling factor=3.382× 0.013062×[AL-1.82]) [25,26]. A customized Python (Version 3.5) script was used to automatically calculate the series of OCTA parameters, including Foveal Avascular Zone (FAZ) area, whole image CD, and CDs within the Early Treatment Diabetic Retinopathy Study (ETDRS) grid (Figure 1). The ETDRS grid divides the images into inner and outer rings centered on the fovea, ranging from 1 to 3mm and 3 to 6mm, respectively. Repeatability and reproducibility of the CDs have been reported in our previous study [11,27]. The ganglion cell-inner plexiform layer (GC-IPL) thickness images that covered a 6×6mm macular region, were obtained using the SS-OCT macular cube scans. Only eligible OCT images, defined as scans with a quality score ≥50, without segmentation failure, without eye movement, and without artifacts, were included in the analysis.

Statistical analysis

Each eligible eye was regarded as a unit of analysis in the study. A generalized estimated equation was used to adjust for inter-eye correlation in the same subject. The distribution of continuous variables was examined using the Shapiro-Wilk normality test. Data were presented as mean±standard deviation (interquartile range) for normally distributed continuous variables. Linear mixed models were used to investigate the effect of ocular and systemic factors on macular CDs of the SCP and DCP. All variables which had a P-value of ≤0.1 in the univariable analysis were included in the multivariate equation. Statistical analyses were performed using Stata 16.0 software (Stata Corp., T.X., USA) and SPSS version 27.0 software (IBM Corporation, Armonk, NY, USA). A P-value of <0.05 was considered statistically significant.

Result

Demographic and ocular characteristics of the participants

A total of 657 highly myopic eyes of 443 participants were initially enrolled. Fifty-three eyes were excluded due to poor-quality OCT (14 eyes) or OCTA (39 eyes) images. The remaining 604 eyes from 405 participants were included in the final analysis (Table 1). The mean age was 29.89±8.85 years, the average BCVA was 0.00±0.02 logMAR units, the mean AL was 27.15±0.90mm, and the average GC-IPL thickness was 66.58±3.93um. Table 2 shows the distributions of macular CDs in the SCP and DCP of the study participants. The whole image CDs were 34.86±1.38% and 46.33±1.18% in the SCP and DCP, respectively. The average CD of SCP and DCP were both higher in the inner ring than in the outer ring (37.70±2.35% versus 34.87±1.63% in the SCP, P<0.001; and 48.05±1.82% versus 47.42±1.28% in the DCP, P<0.001). Among the inner and outer rings, the nasal sector had the highest CD than other sectors, except the inner nasal of the DCP.

Table 1: Demographic and ocular characteristics of study participants.

Characteristics	Description
By subject, no	405
Age, years	29.89±8.85 (23.00, 36.00)
Female, no (%)	247 (60.99)
Self-reported history of Diabetes, no (%)	0 (0)
Self-reported history of Hypertension, no (%)	0 (0)
SBP, mmHg	116.70±13.62 (107.00, 125.00)
DBP, mmHg	68.52±10.54 (61.00, 74.00)
BMI, kg/m^2	21.40±3.15 (19.32, 23.01)
By eye, no	604
BCVA, logMAR	0.00±0.02 (0.00, 0.00)
IOP, mmHg	13.91±2.46 (12.00, 15.33)
Spherical equivalent, diopter	-8.99±2.24 (-10.25, -7.38)
Axial length, mm	27.15±0.90 (26.47, 27.64)
CCT, um	542.34±34.05 (520.00, 564.00)
GC-IPL average thickness, um	66.58±3.93 (63.80, 69.38)
IQS of OCTA	67.98±4.48 (65.00, 71.00)

Abbreviations: SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: BODY MASS INDEX; BCVA: Best-Corrected Visual Acuity; IOP: Intraocular Pressure; CCT: Central Corneal Thickness; GC-IPL: Ganglion Cell-Inner Plexiform Layer; OCTA: Optical Coherence Tomography Angiography; IQS: Image Quality Score.

Data presented with mean ± standard deviation (interquartile range) if there is not otherwise indicated.

Table 2: Distribution of macular optical coherence tomography angiography parameters in the superficial capillary plexus and deep capillary plexus of the study participants.

Characteristics	Mean	SD	IQR
Superficial capillary plexus			
Whole image, %	34.86	1.38	34.04, 35.80
FAZ area, mm^2	0.33	0.11	0.25, 0.39
Inner ring, %			
Average inner ring	37.70	2.35	36.32, 39.23
Inner superior	36.24	3.09	34.21, 38.25
Inner inferior	35.59	3.70	33.20, 38.31
Inner nasal	40.46	3.30	38.63, 42.62
Inner temporal	38.50	3.03	36.48, 40.48
Outer ring, %			
Average outer ring	34.87	1.63	33.75, 35.96
Outer superior	33.67	2.61	31.98, 35.35
Outer inferior	34.01	2.83	32.22, 35.92
Outer nasal	40.17	2.39	38.71, 41.62
Outer temporal	31.55	2.54	29.87, 33.35
Deep capillary plexus			
Whole image, %	46.33	1.18	45.46, 47.15
FAZ area, mm2	0.34	0.09	0.26, 0.40
Inner ring, %			
Average inner ring	48.05	1.82	46.98, 49.20
Inner superior	48.33	2.64	46.79, 50.23
Inner inferior	49.01	2.48	47.48, 50.76
Inner nasal	47.84	2.67	46.21, 49.64
Inner temporal	47.04	2.76	45.34, 48.84
Outer ring, %			
Average outer ring	47.42	1.28	46.53, 48.31
Outer superior	47.44	2.58	45.93, 49.19
Outer inferior	47.45	2.40	46.07, 49.24
Outer nasal	48.53	2.84	46.87, 50.50
Outer temporal	46.25	2.81	44.18, 48.19

Abbreviations: CD: Capillary Density; FAZ: Foveal Avascular Zone; SD: Standard Deviation; IQR: Interquartile Range.

Effect of systemic and ocular factors on macular CDs in the SCP

The univariate analysis showed that age, SBP, DBP, and IQS were significantly associated with whole image CD in the SCP (estimate, -0.02; 95% Confidence Interval [CI], -0.03 to -0.00; P=0.022; estimate, 0.01; 95% CI, 0.00 to 0.02; P=0.005; estimate, 0.02; 95% CI, 0.01 to 0.03; <0.001; and estimate, 0.04; 95% CI, 0.02 to 0.06; P=0.001) (Table 3). In the multivariate analysis, age, DBP, and IQS were the only factors statistically significantly associated with SCP whole image CD (estimate, -0.02; 95% CI, -0.03 to -0.00; P=0.013; estimate, 0.02; 95% CI, 0.00 to 0.04; P=0.002; estimate, 0.05; 95% CI, 0.02 to 0.07; P<0.001) (Table 3). After adjusting for DBP and IQS, further region and quadrant analysis showed that older age increased the FAZ area (P=0.041), reduced outer ring CDs (particularly the outer nasal sector) (P<0.05), but did not change the inner ring CD in the SCP (P=0.371) (Supplement Table 1). In contrast, lower DBP reduced both CDs in the inner ring and outer ring (P<0.05), but did not affect the FAZ area in the SCP (P=0.412), after adjusting for age and IQS (Supplement Table 2). Figure 2 show the relationship between age, DBP, and IQS with the whole image CD in the SCP, respectively.

Table 3: Linear mixed model analysis of the effect of determinants on whole image capillary density in the superficial capillary plexus.

Characteristics	Univariate Estimate (95% CI)	P value	Multivariate* Estimate (95% CI)	P value
Age, per 1 year	-0.02 (-0.03, 0.00)	**0.022**	-0.02 (-0.03, -0.00)	0.013
Female vs. male	-0.14 (-0.36, 0.10)	0.242		
SBP, per 1 mmHg	0.01 (0.00, 0.02)	0.005	0.00 (-0.01, 0.01)	0.737
DBP, per 1 mmHg	0.02 (0.01, 0.03)	**<0.001**	0.02 (0.01, 0.04)	**0.002**
BMI, per 1 kg/m^2	0.01 (-0.03, 0.05)	0.563		
BCVA, logMAR	1.40 (-3.93, 6.72)	0.607		
IOP, per 1 mmHg	0.02 (-0.03, 0.07)	0.374		
Axial length, per 1 mm	-0.03 (-0.15, 0.10)	0.665		
CCT, per 1 um	0.00 (-0.00, 0.01)	0.102		
Average GC-IPL thickness, per 1 um	0.02 (-0.01, 0.05)	0.217		
IQS of OCTA, per 1 score	0.04 (0.02, 0.06)	0.001	0.05 (0.02, 0.07)	<0.001

Abbreviations: CI: Confidence Interval; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; BCVA: Best-Corrected Visual Acuity; IOP: Intraocular Pressure; CCT: Central Corneal Thickness; GC-IPL: Ganglion Cell-Inner Plexiform Layer; OCTA: Optical Coherence Tomography Angiography; IQS: Image Quality Score.

*Multivariate analysis included factors of P values ≤0.1 in univariate analysis.

Supplemental Table S1: Linear mixed model analysis of age (per 1 year) on macular optical coherence tomography angiography parameters in the superficial capillary plexus.

Characteristics	Univariate Estimate (95% CI)	P value	Multivariate* Estimate (95% CI)	P value
FAZ area, mm^2	0.00 (0.00, 0.00)	**0.042**	0.00 (0.00, 0.00)	**0.041**
Inner ring, %				
Average inner ring	-0.01 (-0.03, 0.01)	0.441	-0.01 (-0.03, 0.01)	0.371
Inner superior	0.01 (-0.02, 0.04)	0.407	0.01 (-0.02, 0.04)	0.414
Inner inferior	-0.01 (-0.05, 0.02)	0.485	-0.01 (-0.05, 0.02)	0.442
Inner nasal	-0.02 (-0.05, 0.01)	0.275	-0.02 (-0.05, 0.01)	0.248
Inner temporal	-0.02 (-0.05, 0.01)	0.238	-0.02 (-0.05, 0.10)	0.177
Outer ring, %				
Average outer ring	-0.02 (-0.03, 0.00)	0.051	-0.02 (-0.03, -0.00)	**0.028**
Outer superior	-0.02 (-0.05, 0.00)	0.085	-0.02 (-0.05, 0.00)	0.057
Outer inferior	0.00 (-0.02, 0.03)	0.792	0.00 (-0.03, 0.03)	0.945
Outer nasal	-0.03 (-0.05, -0.00)	**0.019**	-0.03 (-0.05, -0.01)	**0.016**
Outer temporal	-0.02 (-0.04, 0.01)	0.165	-0.02 (-0.04, 0.01)	0.139

Abbreviations: CI: Confidence Interval; FAZ: Foveal Avascular Zone.

*Adjusted for diastolic blood pressure and OCTA image quality score.

Supplemental Table S2: Linear mixed model analysis of diastolic blood pressure (per 1mmHg) on macular optical coherence tomography angiography parameters in the superficial capillary plexus.

Characteristics	Univariate Estimate (95% CI)	P value	Multivariate* Estimate (95% CI)	P value
FAZ area, mm^2	0.00 (-0.00, 0.00)	0.615	0.00 (-0.00, 0.00)	0.412
Inner ring, %				
Average inner ring	0.03 (0.01, 0.05)	**0.001**	0.03 (0.02, 0.05)	**<0.001**
Inner superior	0.02 (-0.01, 0.04)	0.110	0.02 (0.00, 0.05)	**0.048**
Inner inferior	0.03 (0.00, 0.06)	**0.027**	0.04 (0.01, 0.07)	**0.007**
Inner nasal	0.02 (-0.00, 0.05)	0.066	0.03 (0.00, 0.05)	**0.024**
Inner temporal	0.04 (0.02, 0.06)	**<0.001**	0.05 (0.02, 0.07)	**<0.001**
Outer ring, %				

Average outer ring	0.03 (0.01, 0.04)	**<0.001**	0.03 (0.02, 0.04)	**<0.001**
Outer superior	0.03 (0.01, 0.05)	**0.001**	0.04 (0.02, 0.05)	**0.001**
Outer inferior	0.04 (0.01, 0.06)	**0.001**	0.03 (0.01, 0.06)	**0.002**
Outer nasal	0.01 (-0.01, 0.03)	0.259	0.01 (-0.01, 0.03)	0.216
Outer temporal	0.02 (0.00, 0.04)	**0.030**	0.03 (0.01, 0.04)	**0.012**

Abbreviations: CI: Confidence Interval; FAZ: Foveal Avascular Zone.

*Adjusted for diastolic blood pressure and OCTA image quality score.

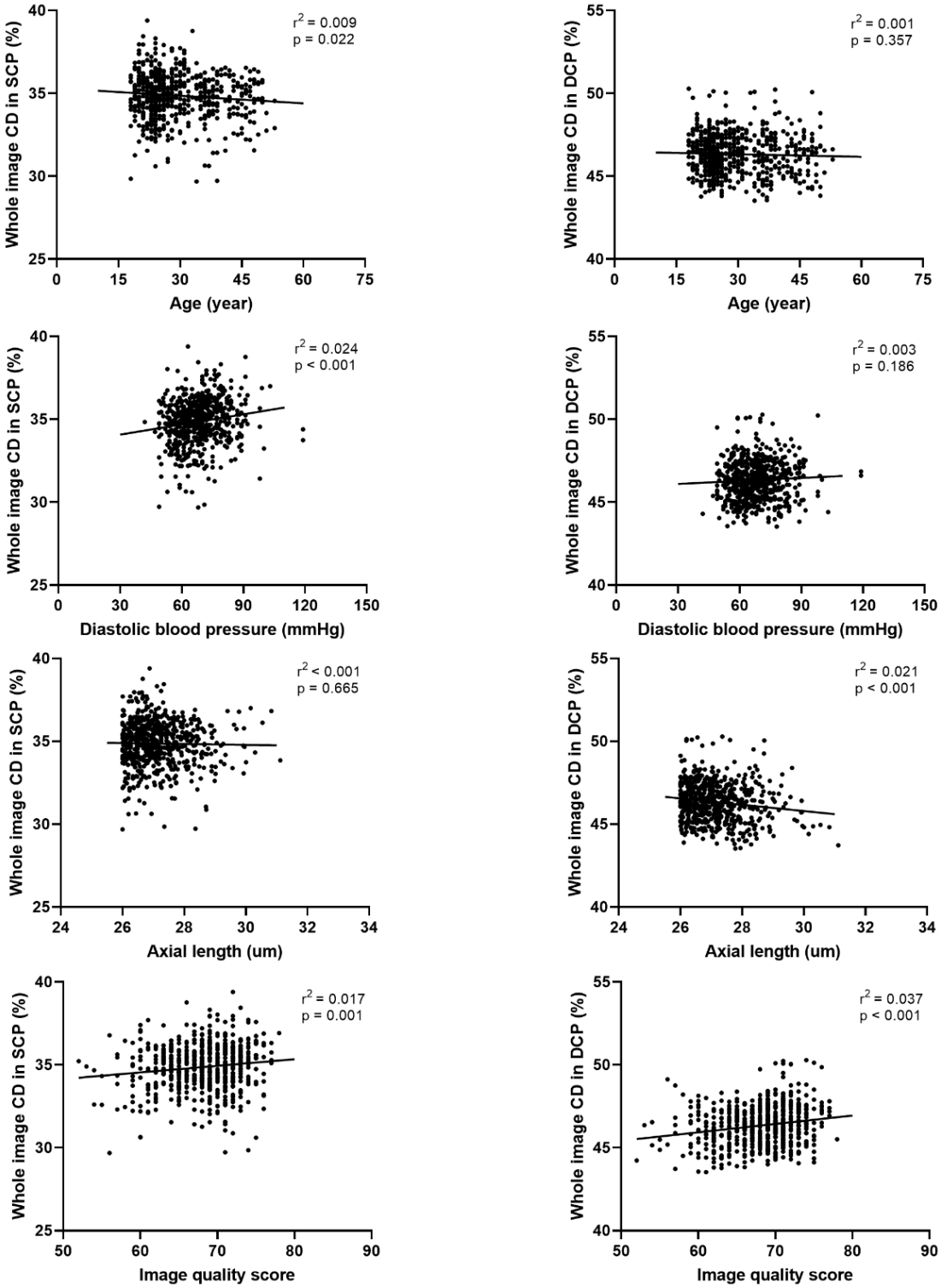

Figure 2

Effect of systemic and ocular factors on macular CDs in the DCP

Univariate linear mixed model analysis showed significant association of reduced whole image CD in the DCP with longer AL (estimate, -0.19; 95% CI, -0.29 to -0.09; P<0.001) and worse IQS (estimate, 0.05; 95% CI, 0.03 to 0.07; P<0.001) (Table 4). And the associations remained significant in the multivariate analysis (longer AL: estimate, -0.15; 95% CI, -0.25 to -0.04; P=0.007; and worse IQS: estimate, 0.05; 95% CI, 0.02 to 0.07; P<0.001) (Table 4). After adjusting for IQS, further region and quadrant analysis showed that AL was positive associated with FAZ area and was negatively associated with the outer ring of CDs (particularly outer inferior quadrant) (P<0.05), but not the inner ring (P>0.05) in the DCP (Supplement Table 3). Figure 2 illustrate the relationship between AL and IQS with whole image CD in the DCP, respectively.

Table 4: Linear mixed model analysis of the effect of determinants on whole image capillary density in the deep capillary plexus.

Characteristics	Univariate Estimate (95% CI)	P value	Multivariate* Estimate (95% CI)	P value
Age, per 1 year	-0.01 (-0.02, 0.01)	0.357		
Female vs. male	-0.12 (-0.32, 0.07)	0.216		
SBP, per 1 mmHg	-0.00 (-0.01, 0.01)	0.804		
DBP, per 1 mmHg	0.01 (-0.00, 0.02)	0.186		
BMI, per 1 kg/m^2	-0.02 (-0.05, 0.01)	0.108		
BCVA, logMAR	-0.48 (-5.04, 4.07)	0.836		
IOP, per 1 mmHg	0.02 (-0.02, 0.06)	0.261		
Axial length, per 1 mm	-0.19 (-0.29, -0.09)	**<0.001**	-0.15 (-0.25, -0.04)	0.007
CCT, per 1 um	0.00 (-0.00, 0.00)	0.543		
Average GC-IPL thickness, per 1 um	-0.00 (-0.03, 0.02)	0.759		
IQS of OCTA, per 1 score	0.05 (0.03, 0.07)	**<0.001**	0.05 (0.02, 0.07)	<0.001

Abbreviations: CI: Confidence Interval; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; BCVA: Best-Corrected Visual Acuity; IOP: Intraocular Pressure; CCT: Central Corneal Thickness; GC-IPL: Ganglion Cell-Inner Plexiform Layer; OCTA: Optical Coherence Tomography Angiography; IQS: Image Quality Score.

*Multivariate analysis included factors of P values ≤0.1 in univariate analysis.

Supplemental Table S3: Linear mixed model analysis of axial length (per 1mm) on macular optical coherence tomography angiography parameters in the deep capillary plexus.

Characteristics	Univariate Estimate (95% CI)	P value	Multivariate* Estimate (95% CI)	P value
FAZ area, mm^2	0.02 (0.01, 0.02)	<0.001	0.02 (0.01, 0.02)	**<0.001**
Inner ring, %				
Average inner ring	-0.13 (-0.29, 0.03)	0.120	-0.05 (-0.21, 0.11)	0.538
Inner superior	-0.22 (-0.45, 0.02)	0.068	-0.13 (-0.36, 0.11)	0.288
Inner inferior	-0.04 (-0.26, 0.18)	0.698	0.02 (-0.21, 0.24)	0.873
Inner nasal	-0.03 (-0.27, 0.21)	0.808	0.05 (-0.19, 0.29)	0.698
Inner temporal	-0.23 (-0.47, 0.02)	0.072	-0.14 (-0.39, 0.10)	0.255
Outer ring, %				
Average outer ring	-0.28 (-0.39, -0.17)	**<0.001**	-0.23 (-0.34, -0.12)	**<0.001**
Outer superior	-0.30 (-0.53, -0.07)	**0.010**	-0.22 (-0.45, 0.01)	0.059
Outer inferior	-0.39 (-0.60, -0.18)	**<0.001**	-0.31 (-0.53, -0.10)	**0.004**
Outer nasal	-0.19 (-0.44, 0.06)	0.136	-0.17 (-0.42, 0.09)	0.205
Outer temporal	-0.26 (-0.50, -0.01)	**0.045**	-0.22 (-0.47, 0.04)	**0.097**

Abbreviations: CI: Confidence Interval; FAZ, Foveal Avascular Zone.

*Adjusted for OCTA image quality score.

Discussion

In the current study, we reported the distributions of macular OCTA parameters, including FAZ area and CDs of the SCP and DCP, in a large sample of highly myopic eyes. Moreover, we found that reduced CD of SCP was significantly associated with older age, lower DBP and worse IQS, while a reduced CD of DCP was significantly associated with longer AL and worse IQS. These associations must be considered when interpreting clinical quantitative OCTA

data in eyes with high myopia. Many studies have reported the relationship between macular CDs and high myopia [10,11,14-16] and indicated that macular CDs help distinguish glaucomatous damage in eyes with high myopia [10,11] However, to the best of our knowledge, no previous studies with a large sample size have reported microvasculature distributions in perifoveal regions for highly myopic eyes. Using SS-OCTA, our current study showed the distributions of FAZ area, and CDs in whole image, regions, and sections, of the SCP and DCP. We found that CDs of the SCP and DCP were higher in the inner ring than in the outer ring. The trend is in line with previous population-based studies in normal healthy eyes, which observed that macular thickness was thickest in the inner region, followed by the outer region, and thinnest at the fovea [28,29].

Additionally, we identified the nasal section to be the highest CD in both the inner and outer regions in eyes with high myopia (except the inner nasal of DCP), which was consistent with prior studies in normal eyes that the nasal quadrant to be the thickest in all quadrants [28,30]. Among the determinants of OCTA parameters, we demonstrate that a significant reduction in CDs of SCP associated with aging in highly myopic adults. Our results align with previous studies in normal healthy subjects, which indicated that vessel density in the macula decreases and the FAZ area increases as age progresses [31,32]. The association of lower density with older age may be explained by the physiologic age-related loss in vascularity. However, it's important to note that not all regions showed a correlation with age. After adjusting for DBP and IQS, we found that increased age was only linked to a reduction in CD in the outer ring, but it did not affect the CD in the inner ring of the SCP. One explanation for this finding could be that the outer macular region is more susceptible to age-related changes in vascular perfusion compared to other regions of the retina [32]. In our study, we also showed that lower systemic DBP was associated with a significantly reduced CD of SCP in whole image and regions. Our result supports previous studies in glaucoma, which reports that low DBP was associated with glaucoma incidence and progression [33-35] and provides a significant clue for clarifying the mechanisms behind that. The superficial vascular plexus slab supplies the retinal nerve fiber layer [12]. Therefore, hypoperfusion of the SCP may lead to hypoxia and nutritional deficiency of the retinal ganglion cells, [12] thus increasing the risk for glaucoma incidence and progression. However, it is still unclear why low DBP appears to be more frequently associated with CD of SCP than that of DCP. A possible explanation could be inferred from the anatomic of the retinal.

The arterioles and larger venules in the SCP might be more sensitive to alterations of BP than the capillaries in the DCP [12,36]. Further studies are needed to clarify the underlying mechanisms. The AL was another significant factor affecting macular density. In general, a longer AL was associated with a reduced CD of DCP. This finding supports the hypothesis that axial elongation due to HM affects most in the DCP, which we provided in the prior primary open-angle glaucoma and high myopia study [11]. In addition, it has been confirmed in many other previous studies [37-39]. However, it is noteworthy that not all the regions were correlated with AL. After adjusting for IQS, the FAZ area increased and outer ring CD (particularly outer inferior CD) decreased with an increase in AL, but not inner ring CD of the DCP. The partly results were compatible with previous OCT studies that average outer macular thickness and overall average macular thickness decreased as AL increased, except the inner macular thickness [28,30,40] However, whether FAZ area increased with AL has been controversial [15,38,41]. He J et al. [38] reported that enlarged area of FAZ was observed in highly myopic eyes [38] which is similar to ours. On the other hand, Wang et al. and Li et al. showed no correlation of FAZ area with AL [15,41] The small sample size and narrow axial scale of the latter two studies caused the low statistical efficiency, may be possible reasons for the difference.

The quality of the scanned image is important in microvascular analysis using OCTA [24,42] In the current study, we found that CDs of both the SCP and DCP decreased with lower IQS, which is agree with the findings of previous studies [43-46]. Lim et al. examined the effect of sign strength on OCTA parameters and found that the vessel density and perfusion density decreased with the sign strength [43,44]. Bansal et al. [45] reported that lower sign strength was significantly associated with reduced peripapillary and macular vessel density in healthy individuals [45]. Chang et al. [46] also showed that sign strength was positively associated with peripapillary vessel density [46]. The low image quality gives worse clarity particularly of microvasculature density than high quality may help to explain the positive association between IQS and values of CDs. Hence IQS is important when reading the OCTA results and should be controlled in analysis for OCTA parameters. The strengths of this study include its prospective study design, a large sample of highly myopic study participants, and standardized assessment of systemic and ocular factors. This study also had several limitations. First, the cross-sectional study design prevented the establishment of the causal relationships between macular microvascular and the factors studied. Second, only eyes with good-quality OCTA images were included in the study, which may have introduced selection bias and affected the generalizability. Third, although we used the latest built-in OCTA algorithm (OCTARA) [17] the artifacts like projection removal artifact cannot be completely avoided [42]. Methods to compensate for the artifacts are still forthcoming.

Conclusion

Our study described the macular OCTA parameters, including FAZ area and CDs of SCP and DCP in eyes with high myopia. In addition, our findings indicate that reduced CDs in the SCP were associated with older age and lower DBP, while decreased CDs in the DCP correlate with greater AL. Moreover, lower IQS reduced both CDs of the SCP and DCP. Such findings suggested that these factors should be taken into consideration when interpreting the OCTA-based macular microvasculature measurements in highly myopic eyes.

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Author Contributions

Lin had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

a. Study concept and design: Lin and Liu.

b. Acquisition, analysis, or interpretation of data: All authors.

c. Drafting of the manuscript: Zhao and Xiaokaiti.

d. Critical revision of the manuscript for important intellectual content: Lin and Liu.

e. Statistical analysis: Zhao and Lin.

f. Obtained funding: Lin and Zhao

g. Supervision: Lin and Liu.

h. Patient consent for publication: Not required.

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