Evaluation of retinal vascular density and related factors using OCTA in children and adolescents with myopia without maculopathy

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Abstract

Background: Myopia is the most common ophthalmic condition worldwide with a rapidly increasing prevalence. This study aimed to compare the retinal microvasculature in the superficial capillary plexus (SCP) in children and adolescents with mild and moderate/high myopia using optical coherence tomography angiography, determine the relationship between retinal parameters and axial length (AL), and understand the occurrence and progression of myopia in microcirculation.

Methods: This prospective observational study included 39 participants with mild myopia and 33 participants with moderate/high myopia. Vessel density (VD) and perfusion density (PD) in the SCP, the foveal avascular zone (FAZ), and AL were compared between the groups and the relationship between these retinal parameters and AL was assessed.

Results: No difference in SCP VD or PD was observed between the two groups. The FAZ did not differ significantly between groups whereas significant differences in age, height, refractive status, and AL were observed. Significantly shorter AL was observed in participants with mild myopia compared with the moderate/high myopia group. Age was positively correlated with height ($r = 0.852$) and refractive status was negatively correlated with AL ($r = -0.588$). AL was positively correlated with VD ($r = 0.317$) and PD ($r = 0.308$) in the SCP and AL was negatively correlated with the FAZ ($r = -0.434$).

Conclusions: This study revealed that superficial foveal microvessel density was unaffected in children and adolescents without pathological myopia. However, myopia progression was associated with a change in AL, and an AL increase altered macular blood flow.

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Background

Myopia is regarded as the most common type of refractive error. The prevalence of myopia has been on the rise in recent years, especially in Asia.[1–3] Myopia has become a key public health problem and a general concern. High myopia is a blinding eye disease that can lead to complicated cataracts, retinal detachment, choroidal neovascularization, myopic maculopathy, and several other serious complications. Practitioners should be alert to the signs of these conditions, which can gravely affect vision quality and quality of life.[4–5]

At present, the literature regarding individuals with myopia with macular area choroid thinning[6–8] includes more than the study of blood flow to the macular area. Optical coherence tomography angiography (OCTA) using optical microangiography is based on the light-scattering signal generated by the backscattering of moving red blood cells in blood vessels. The method further uses the amplitude and phase changes of the optical coherence tomography signal to show blood flow in tissues,[9–11] thus providing real-time monitoring and quantitative analysis of blood vessels in the retina and three-dimensional images of blood flow. With the advantages of speed and repeatability, this non-invasive examination method represents one of the most important advancements in ophthalmologic detection technology in the past few years.

This study used OCTA technology to investigate the superficial retinal parapapillary in children and adolescents with varying degrees of myopia and measured the change in blood flow to the macular area to understand the pathogenesis of child and adolescent myopia at the retinal microvascular level. Exploring the pathogenesis of myopia can guide disease intervention.

Methods

Participants

Seventy-two eyes from 72 healthy children and adolescents (36 boys and 36 girls) were selected between July 2019 and January 2020 at the Department of Ophthalmology of Ningde City Hospital, which is affiliated with Ningde Normal University. All patient details were de-identified in this prospective observational study. The study was approved on 28 March 2019 by the appropriate ethics committee of Ningde City Hospital-affiliated Ningde Normal University (reference number 20200328) and was based on the principles of the Declaration of Helsinki. Written informed consent was obtained from each participant and from the parents or guardians of participants who were under the age of 16 years. The reporting of this study conforms to STROBE guidelines.[12]

All participants were required to provide a detailed medical history and undergo height measurement and a thorough ophthalmic examination, which included the measurement of refractive status, best corrected visual acuity, and intraocular pressure (using CT-80 TOPCON Japan); slit-lamp examination; and axial length (AL) measurement using optical low-coherence

reflectometry (Lenstar; Haag-Streit Holding, Koeniz, Switzerland). Retinal microvasculature imaging was performed with OCTA (Cirrus HD-OCT-5000; Carl Zeiss Meditec, Dublin, CA, USA).

The inclusion criteria were as follows: age between 8 and 16 years, astigmatism within ± 0.50 D, best corrected visual acuity of 20/25 or better, and intraocular pressure less than 21 mmHg. Participants with any sign of pathological myopia (i.e., chorioretinal atrophy, choroidal neovascularization, lacquer cracks, staphylomas, or lattice degeneration), a history of intraocular surgery or ocular trauma, or any ocular or systemic disorder such as diabetes mellitus or glaucoma that might diminish ocular circulation were excluded.

We randomly selected one eye of each participant for data analysis and divided participants into two groups based on refractive degree: mild myopia (39 eyes, -3.00 D $\leq$ mean spherical equivalent ≤ -0.50 D), moderate/high myopia (33 eyes, mean spherical equivalent < -3.00 D).

OCTA Image Acquisition

All participants were examined with the Zeiss Cirrus HD-5000 Spectral-Domain OCT with AngioPlex OCT Angiography (Carl Zeiss Meditec, Dublin, CA, USA), which has a scan rate of 68,000 A-scans per second, a central wavelength of 840 nm, motion tracking to reduce motion artifact, and an optical microangiography algorithm for analysis.[11] We followed relevant Equator guidelines.[13] A 6×6-mm image centered on the fovea was acquired. OCTA images that were of poor scan quality (i.e., less than 6/10 signal strength) because of low resolution or poor saturation and those that exhibited motion artifacts because of poor cooperation were excluded. The superficial capillary plexus (SCP) was segmented with an inner boundary at the internal limiting membrane and

an outer boundary set at the inner plexiform layer,[13] which is automatically detected by the software (HD Zeiss, version 10.0.0.14618, Meditec, Dublin, CA, USA). The software quantified the average vessel density (VD) and perfusion density (PD) using a grid overlay according to the standard Early Treatment Diabetic Retinopathy Study subfields. VD was defined as the total length of perfused retinal microvasculature per unit area in the region of measurement whereas PD was defined as the total area of perfused retinal microvasculature per unit area in the region of measurement. VD and PD were calculated for the 1-mm circle and over the entire Early Treatment Diabetic Retinopathy Study 6-mm circle for 6×6-mm scans. The foveal avascular zone (FAZ) boundaries were calculated automatically by the software; values with inaccurate boundaries identified on manual review were excluded[15] (Figure 1).

Statistical Analysis

All data were analyzed with SPSS software (version 23.0, IBM Corp., Armonk, NY, USA). Measurement data met normal distribution and data were displayed as mean $\pm$ SD. Data that did not fit a normal distribution were expressed as medians. If data met the normal distribution, the independent sample t-test was used. If the normal distribution was not satisfied, the Mann–Whitney test was used. Pearson correlation analysis was used to measure correlations between VD, PD, FAZ, AL, age, and height. A P-value of < 0.05 was deemed to be statistically significant.

Results

Initially, 76 participants were enrolled in this study. After examination, four participants were excluded because of poor image quality. Seventy-two participants were included in the subsequent analysis.
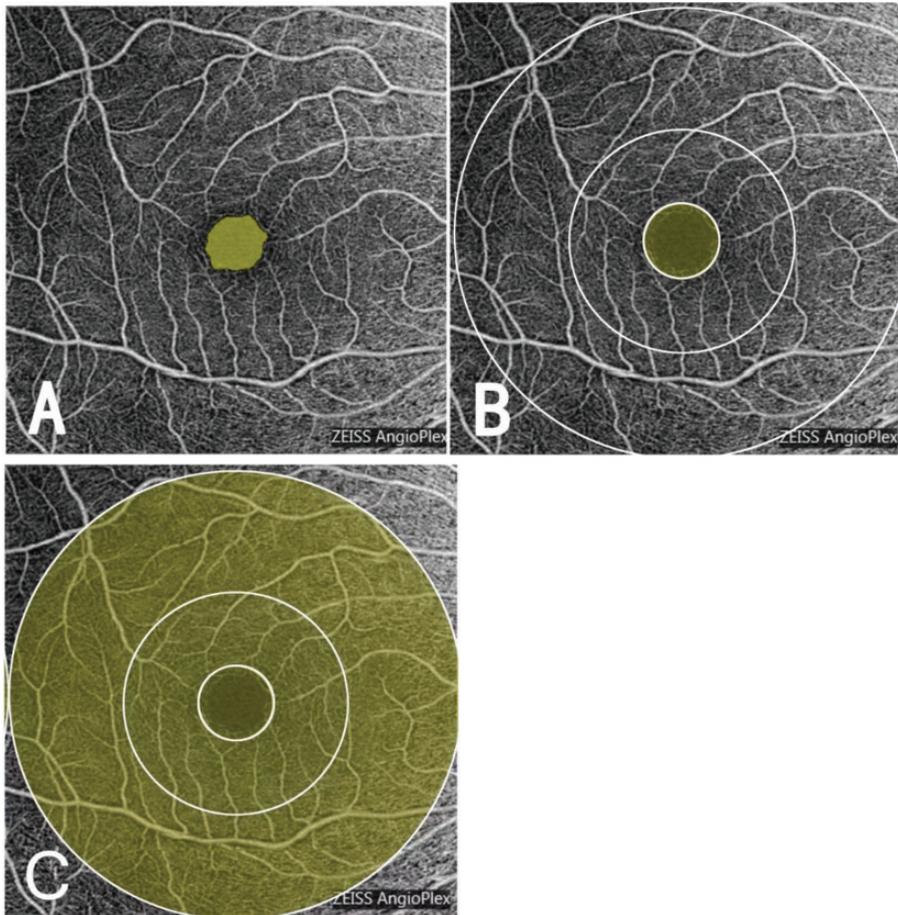
Figure 1. Optical coherence tomography angiography 6 × 6 mm scans segmented at the superficial capillary plexus. (a) Manual outlining (green) of the borders of the foveal avascular zone at the superficial capillary plexus (bottom). (b) Area 1 was the inner 3-mm circle of the standard ETDRS subfields over the entire ETDRS 6-mm circle for 6 × 6-mm scans and (c) Area 4 was over the entire ETDRS 6-mm circle for 6×6-mm scans.
ETDRS: Early Treatment Diabetic Retinopathy Study.

Table 1 shows that no significant differences in sex were observed between the mild myopia and moderate/high myopia groups; however, statistically significant differences in SE, AL, age, and height were observed between the groups.

No difference in SCP VD or PD was observed between the two groups (P > 0.05). Moreover, the FAZ area and signal strength did not differ significantly between the groups (P > 0.05; Table 2).

Positive correlations were observed between AL and VD1/PD1 whereas a negative correlation was seen between AL and FAZ (Figure 2). No significant correlations were observed between AL and age or height, and a negative correlation was seen between the spherical equivalent and AL. Moreover, AL had no significant correlation with VD4 and PD4, and a negative correlation was observed between FAZ and VD1/PD1 (Table 3).

Table 1. Basic data for the two groups of participants.

Variables	Mild myopia	Moderate and high myopia	P-value
No. of eyes	39	33	
Age (years)	12	11	**0.018[#]**
Boys (%)	51.28	48.48	0.833*
Spherical equivalent (D)	−1.75	−3.75	**0.001[#]**
Axial length (mm)	24.32	25.44	**0.001[#]**
Height (cm)	160	147	**0.001[#]**

*using the χ^2 test; [#]using the Mann–Whitney test. Significant P-values are in bold.

Table 2. Vascular density in each macular area and signal strength in the two groups.

Variables	Mild myopia	Moderate and high myopia	P-value
VD1	10.83 ± 1.86	10.05 ± 3.36	0.241[&]
VD4	18.8	18.5	0.300[#]
PD1	0.244 ± 0.044	0.226 ± 0.079	0.241[&]
PD4	0.463	0.463	0.429[#]
FAZ	0.25 ± 0.06	0.25 ± 0.11	0.992[&]
Signal strength	9	9	0.091[#]

[&]Using the independent sample t-test; [#]using the Mann–Whitney test; VD: vessel density; PD: perfusion density; FAZ: foveal avascular zone.

Discussion

In this study, we analyzed retinal vascular density in the eyes of children and adolescents with myopia. We observed no significant differences in vascular density in the SCP in the two groups. This finding was inconsistent with the results of previous research.[16] A key finding of this study was the lack of a statistically significant difference in vascular density in the fovea between the two groups. This may indicate that the degree of myopia did not affect vascular density in the fovea of eyes without pathological changes in myopia, revealing that superficial foveal microvascular density is unaffected by healthy myopia. In addition, we observed that the vascular density

in the SCP fovea increased significantly (P = 0.007) and the FAZ decreased considerably with an increase in AL.

Myopia is a common eye disease. Previous studies have shown that the degree of myopia increases and that axial expansion leads to changes such as the thinning of the retina and choroid in the retinal fundus, thus reducing the thickness of the retinal nerve fiber layer.[15–19] However, the mechanism of myopia progression remains unclear. Retinal tissue is mainly supplied with oxygen and nutrients by the choroid and is susceptible to the changes in the fundus that are associated with myopia.[20] The foveal macula is the most sensitive area of vision; therefore, the study of retinal blood flow parameters in the macular area can provide a basis for clinical diagnosis and treatment. OCTA is one of the available methods for providing noninvasive, depth-resolved imaging of the retinal microvascular layers. OCTA provides detailed and clear images of the retinal microvascular because of its high-resolution optical imaging[21–25] and has been widely used in the research and diagnosis of various retinal macular diseases including diabetic retinopathy, retinal vascular occlusion, and choroidal neovascularization. OCTA is safer and simpler to perform than fluorescein angiography or indocyanine green angiography because it does not require dye injection. High myopia is a major risk factor for choroidal neovascularization. Therefore, we aimed to identify the early changes in macular microvasculature in myopia. We used OCTA to examine the macular microvasculature in various refractive states.[26] Our study aimed to understand retinal vascular density and its correlation with AL in children and adolescents with varying degrees of myopia.

In this study, no significant differences were observed in the vascular density in the SCP between the two groups. This finding was inconsistent with previous research.
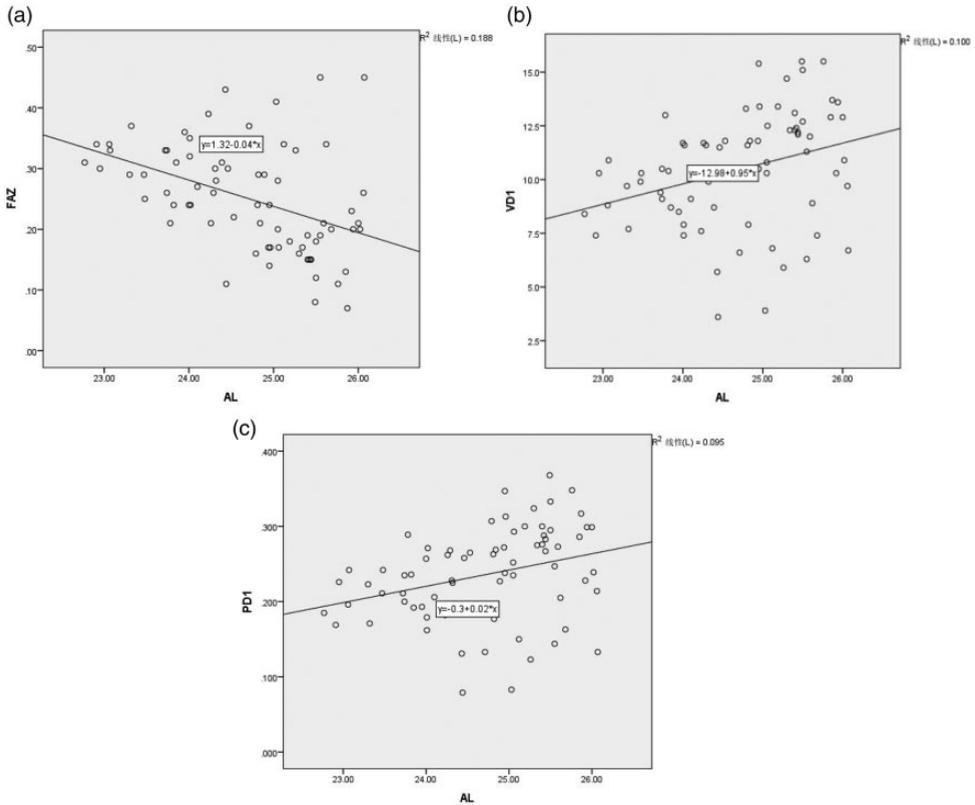
Figure 2. The association between axial length and the foveal avascular zone (a), vessel density 1 (b), and perfusion density 1 (c).

Table 3. Correlations.

	Age	Height	SE	AL	VD1	PD1	VD4	PD4	FAZ
AL									
Pearson correlation	.186	.142	−.588**	1	.317**	.308**	.40	−.091	−.434**
P-value	0.119	0.235	**<0.001**		**0.007**	**0.008**	0.738	0.448	**<0.001**
FAZ									
Pearson correlation	−.205	−.178	.113	−.434**	−.769**	−.772**	−.127	−.160	1
P (values)	0.084	0.134	0.345	**<0.001**	**<0.001**	**<0.001**	0.289	0.18	

**At 0.01 level (two-tailed), the correlation was significant. Significant P-values are in bold.
AL: axial length; SE: spherical equivalent; VD: vessel density; PD: perfusion density: FAZ: foveal avascular zone.

Yang et al.[16] observed that the average VD of the superficial retina in eyes with high myopia was significantly lower than that in our study and correlated with AL elongation. However, in our study, AL fluctuated between 22.77 mm and 26.07 mm and AL elongation was not significant. Age may be a reason for this difference. Participant age was between 8 and 14 years and the vessel density of the

superficial retina of these participants was different from that of adults with myopia. We believe that the age difference among participants led to inconsistent results, indicating that the vessel density of the superficial retina in children and adolescents is affected by growth hormones and other factors. Further research is needed to understand these age-related differences.

The FAZ area did not differ significantly between the groups but was negatively correlated with AL. Previous studies have indicated that choroids may play a role in the development of myopia; however, the mechanism of action involved in the development of myopia remains unclear.[27] During development, the choroid of the human eye becomes thinner and some choroids may appear. Moreover, changes in blood circulation including decreased intraocular perfusion pressure[28] and a slowdown in choroidal vessel perfusion occur.[29] Shih et al.[30] demonstrated that choroidal blood flow was reduced in chicks with form-deprivation myopia. The authors considered that the decrease in choroidal blood flow was due to choroid pulling, which was in turn caused by eyeball enlargement in eyes with myopia.[30] Extension and thinning also suggested that the decreased choroidal blood flow may be the cause of myopia.[31] An adaptive response to retinal thinning, normal choroid hyperemia flow is important for nutrition and oxygen supply to the outer retina. The choroid is the only source of the five layers of oxygen and nutrients outside the retina, including the macular FAZ. The changes in choroid vascular structure, vascular density, and blood flow directly affect retinal metabolism and function. In addition, the corresponding retinal structure and function are affected.[32] Therefore, monitoring the morphology and vascular distribution of the retina is important. The choroid supplies nutrition to the FAZ, which can indirectly affect choroidal blood flow. The FAZ is large and the choroidal blood flow is abundant. Consistent with the results of some previous studies,[7,28–30] the FAZ was negatively correlated with AL and choroidal blood flow was decreased in eyes with myopia.

The AL was positively correlated with VD1 and PD1, but no correlation was observed with VD4 and PD4. Results were inconsistent with those of previous studies and suggest that AL is associated with the density of superficial vessels in the fovea.[26] Which was in eyes with high myopia and longer AL the SCP density was reduced. VD1 and PD1 are closely related to the FAZ, which was negatively correlated with VD1 and PD1 but not with VD4 and PD4. The changes in the macular vascular density of eyes with myopia and the pathophysiological mechanism behind these changes remain unclear. Future studies with larger sample sizes and basic and clinical research with multi-directional objectives are needed to clarify the facets of this mechanism.[33] Consistent with findings from previous studies, AL was negatively correlated with SE.[7] The higher the degree of myopia, the longer the AL. AL and myopia progression are causative.

This study had some limitations. First, given the small sample size and narrow age range, the results of this study cannot be generalized. Second, pathological myopia was not included in this study and participants with high myopia were few. Thus, the results cannot reflect the changes in the retinal flow density in all eyes with high myopia. Third, the present study involved the observation of retinal flow density at a single time point. Future studies to observe the dynamic changes of retinal flow density in eyes with myopia could provide a reasonable explanation for the pathogenesis of myopia. Fourth, given the limited scanning range of the OCTA device, retinal microvasculature in the deep capillary plexus cannot be measured and the changes in blood vessels outside the

macular area and surrounding retinal area cannot be reflected. In addition, artifacts appeared during the image acquisition process and blood flow lower than the slowest detectable flow could not be detected.[33,34] Finally, OCTA has a threshold limit that can obscure important data and lead to a misunderstanding of the data.[35]

Conclusions

Our study revealed no significant differences in superficial macular and foveal vascular density between the two groups. This result showed that SE does not affect the vascular density of the fovea in eyes without pathological myopia, revealing that superficial foveal microvascular density is unaffected by healthy myopia. In addition, AL was significantly correlated with the FAZ, VD1, and PD1, although causality is uncertain. As a practical technique for the quantitative evaluation of the retinal microvascular network, OCTA imaging contributes to understanding the underlying mechanisms of the pathological changes in early myopia and provides a potential approach for managing the development of myopia. The results of this study may help clinicians better understand the pathogenesis of myopia and its complications.

Author contributions

LL: data curation, writing – original draft preparation, writing – reviewing and editing, and conceptualization, CT: visualization and investigation, XH: supervision, methodology, and software, and ZD: supervision and methodology.

Declaration of conflicting interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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