

Application of OCTA in the Prediction of Myopia Progression in Children and Adolescents

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Research Article

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Abstract

Objectives To understand the correlation between the progression of myopia and macular blood flow density in children and adolescents, as well as the relationship between the myopia progression and the axial length changes and height changes, and the prevention and control strategies for myopia were explored

Methods This was a Prospective Cross-sectional, observational study, and was conducted from April 2020 to December 2020. A total of 54 myopia participants (54 eyes) were collected from the Optometry Clinic of Ning de City Hospital Affiliated to Ning de Normal University. The participants including 20 males and 34 females were all children and adolescents, age 11.56 ± 1.61 (range ,8-14 years old). All participants selected the examination data of the right eye, and those whose spherical equivalent degree(SE) changes ≥0.5 D were selected as the observation group, those with SE changes <0.5 D were classified as the control group, at the same time, they were further grouped by age, those whose age less than 12 years old were divided into the young group, and those whose age ≥12 years old were divided into the old group, and compared the difference in macular blood flow density , height, axial length, et. between the observation group and the control group in the same age group, as well as the correlation between changes of SE.

SPSS25.0 statistical software was used for statistical analysis, and independent sample t test, rank sum test, Pearson correlation, et were used for data analysis.

Results There was a statistically significant difference in the macular foveal avascular zone (FAZ) between the observation group and the control group in the young group($P<0.05$) at baseline, and there were no statistically significant differences between the observation group and the control group in the young group at baseline in the vessel density (VD) and perfusion density (PD) in superficial capillary plexus(SCP) in the macular area, as well as the height and eye axial $\cdot P>0.05\cdot$.

There was a statistically significant difference in axial length between the observation group and the control group at baseline in the old group, there was no significant difference between the observation group and the control group in the VD and PD in SCP in the macular area, height, FAZ at baseline in the old group. The change in SE was positively correlated with the change in the axial length, but there were no significant correlations with the changes in height, VD, PD, and FAZ.

Conclusion The area of FAZ in children with fast progression of myopia is smaller than those of slow progression. Adolescents with rapid progression of myopia have longer axial length than those with slower progression. FAZ area and axial length can be used as predictors of myopia progression.

Introduction

At present, the prevalence of myopia in the global is increasing gradually. Some scholars predict that there will be 4.758 billion people with myopia in the world (approximately 49.8% of the world's

population) in 2050. Among them, 938 million people will have high myopia (approximately 9.8% of the world's population) [1]. The severity of myopia in children and adolescents has become a big problem concerning the future of the country and nation. In recent years, the incidence of myopia in children and adolescents in our country has become more frequent and younger, and myopia prevention and control has risen to the national strategy. The prevalence of myopia in China ranks among the highest in the world. Myopia has become one of the public health problems that the public pay attention to. Currently, myopia is the main cause of vision loss in the world. High myopia related complications such as complicated cataract, choroidal atrophy and choroidal neovascularization, macular hole with or without retinal detachment, myopic related macular hemorrhage and changes in the optic papilla, etc. these complications often lead to irreversible damage to the photoreceptor cells of the retina, leading to a decrease in central vision and a serious impact on people's quality of life^[2].

Myopia is a complex disease with a multi-factorial etiology whose underlying pathophysiological mechanisms are not yet fully understood. The occurrence and development of myopia and the mechanism of myopia have always been research hotspots. More and more researches have focused on the pathogenesis of myopia, which can guide clinical and prevent myopia^[3-4], however, the occurrence and progress of myopia lack of "Rapid prediction index", which is not conducive to the prevention and control of myopia. In this study, we observed the macular blood flow in children and adolescents with myopia, and found the correlation between macular blood flow and the progression of myopia, we hope to find a "Rapid prediction index" for the occurrence and progress of myopia, and assist the prevention and control of myopia.

Optical Coherence Tomography angiography (OCTA) is a non-invasive method that can be repeated frequently, and provides near histology level resolution for assessment of capillary density. It can monitor the retinal blood vessels in real-time and can perform quantitative analysis, and can provide three-dimensional blood flow images. It has the advantages of rapidness and repeatability, and is one of the important advances in ophthalmic examination technology in recent years. In this study, OCTA technique was used to detect macular blood flow in myopic children and adolescents, and follow up its changes. The pathogenesis of myopia in children and adolescents is studied in depth from the level of retinal capillaries, hoping to find a "rapid predictor" of the occurrence and progress of myopia, and provide theoretical guidance for the prevention and control of myopia.

Objectives And Methods

1.1 Objectives

A total of 54 children and adolescents with myopia (54 eyes) were collected from the Optometry Clinic of Ning de City Hospital Affiliated to Ning de Normal University from April 2020 to December 2020. The participants were all use right eyes data, and the participants were 8–14 years old (11.56 ± 1.61 years old), including 20 males and 34 females. This study and protocols conform to the tenets of the Declaration of Helsinki. The ethics committee of Ning de City Hospital affiliated to Ning de Normal

University approved the research protocols (ethics batch number 20200328), Informed consent (parents) and assent (children) were obtained after verbal and written explanation of the nature and possible consequences of the study.

Inclusion criteria: children and adolescents, BCVA = 20/20, who can better cooperate with the required examination, anterior segment and fundus are normal, intraocular pressure of eye was 11 to 21mmHg (1mmHg = 0.133kPa), emmetropia or myopia, astigmatism \leq 1.0D. Exclusion criteria: 1. History of eye trauma; 2. History of eye surgery; 3. Eye undercover examination shows pathological changes, such as macular atrophy, macular hole, et; 4. Retinal disease; 5. Refractive interstitial opacity due to corneal diseases, cataracts and other eye diseases; 6. History of systemic diseases that may affect eye circulation, such as hypertension and diabetes.

1.2 Methods

All participants underwent the following examination at baseline and six months later.

1.2.1 Routine eye examination Uncorrected visual acuity, Best corrected visual acuity, Height, Intraocular pressure, Slit lamp microscope, Fundus examination, Cyclopentolate mydriasis test and optometry, Refraction (the final degree use spherical equivalent degree, i.e. spherical degree plus 1/2 cylindrical degree), Axial length examined in lenstar-900(HAAG-STREIT).

1.2.2 OCTA examination All participants were imaged with the Zeiss Cirrus HD-5000 Spectral-Domain OCT with Angio-Plex OCT Angiography (Carl Zeiss Meditec, Dublin, CA) that has a scan rate of 68 000 A-scans per second, central wavelength of 840 nm, motion tracking to reduce motion artifact, and an optical microangiography algorithm for analysis. 6x6-mm images centered on the fovea were acquired. OCT angiography images that were of poor scan quality (less than 8/10 signal strength) because of low resolution or poor saturation and those that exhibited motion artifacts because of poor cooperation were excluded. The inner boundary of the superficial capillary plexus (SCP) slab was defined as the internal limiting membrane and the outer boundary was defined as the inner plexiform layer, which was calculated as 70% of the distance from the internal limiting membrane to the estimated boundary of the outer plexiform layer, which in turn was determined as being 110 mm higher than the retinal pigment epithelium boundary as automatically detected by the software (Carl Zeiss Meditec, version 10.0.0.14618). The software quantified the average vessel density (VD) and perfusion density (PD) using a grid overlay according to the standard ETDRS subfields. Vessel density 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 a region of measurement. Vessel density and PD were calculated for the 1-mm circle, 3-mm ring and 6-mm ring, over the entire ETDRS 6-mm circle for 6x6-mm scans (Fig. 1). The foveal avascular zone (FAZ) boundaries were calculated automatically by the software; values with inaccurate boundaries identified on manual review were excluded(Fig. 1).All the examination should be performed by the same ophthalmologist skillfully and independently, and checked by another doctor.

1.2.3 Grouping method All participants selected the examination data of the right eye, and those whose spherical equivalent degree(SE) changes ≥ 0.5 D were selected as the observation group, those with SE changes < 0.5 D were classified as the control group, at the same time, they were further grouped by age, those whose age less than 12 years old were divided into the young group, and those whose age ≥ 12 years old were divided into the old group.

1.2.4 Data processing Compared the differences of VD, PD; FAZ; height; axial length between the observation group and the control group in the same age group, as well as the correlation between changes in height, axial length, FAZ, VD and PD in each area, and SE.

1.3 Statistical method

This was a Prospective Cross-sectional, observational study, and SPPS 25.0 statistical software was used for statistical analysis, and the measurement data was expressed as mean \pm standard deviation. For comparison between the two groups, t test of independent samples was used for those whose data meet normal distribution, rank sum test was used for those who do not meet normal distribution, chi square test was used for counting data, and Pearson correlation analysis was used for correlation between changes of SE and changes of VD, PD, FAZ, height, axial length, and $p < 0.05$ as the difference was statistically significant.

Results

A total of 54 children and adolescents were included in this study, the mean age was 11.56 ± 1.61 years (range,8–14), including 20 males (37.04%) and 34 females (62.96%). Follow-up six months, there were 21 cases with refractive degree change ≥ 0.50 D (selected as observation group) and 33 cases with degree change < 0.5 D (selected as control group);those whose age < 12 years selected as young group and those age ≥ 12 years selected as old group. In the observation group, there were 14 cases in the young group (6 males and 8 females) and there were 7 cases in the old group (3 males and 4 females); in the control group, there were 14 cases with age < 12 years in the young group (6 males and 8 females), and 19 cases in the old group (5 males and 14 females). (Table 1).

There was no significant difference between the observation group and the control group in age ($p=0.298$), height($p=0.096$), axial length($p=0.364$), and spherical equivalent degree (SE)($p=0.061$)at baseline in the younger group. There was a statistically significant difference in axial length ($p=0.049$) between the observation group and the control group at baseline in the old group, there was no significant difference between the observation group and the control group in the age($p=0.518$), height($p=0.216$)and SE($p=0.14$)at baseline in the old group ($P>0.05$). (Table 1)

VD1, VD2, VD3, VD4, PD1, PD2, PD3, PD4 measured at baseline in the young group were not statistically different between the observation group and the control group ($P> 0.05$), There was a statistically significant difference between the observation group and the control group in the FAZ area at baseline in the young group ($p = 0.03$). There was no significant difference between the observation group and the

control group in VD1, VD2, VD3, VD4, PD1, PD2, PD3, PD4, FAZ area at baseline in the old group ($P > 0.05$). (Table 2) The change in SE was positively correlated with changes in the axial length ($r = 0.301, p = 0.027$), and there was no significant correlation with changes in height, VD, PD, and FAZ. (Table 3), in the young control group the change of SE is 0.143 ± 0.13 D (range, 0-0.25D), the change of SE in the young observation group is 0.61 ± 0.16 D (range, 0.5-1.0D), in the old control group the change of SE is 0.12 ± 0.13 D (0-0.25D), in the old observation group SE change is 0.68 ± 0.24 D (0.50-1.0D).

Discussion

Myopia has become an international public health concern and creates a tremendous global economic burden. With the progression of myopia, the risk of ophthalmic diseases such as myopic macular disease, retinal detachment, glaucoma and cataract also increases^[5-9]. Although interventions to control myopia (such as spending more time outdoors, orthokeratology and topical application of atropine) can prevent the occurrence of myopia or slow its progression^[10], the mechanism of the progression of myopia at various stages is still unclear. Retinal tissue is mainly supplied with oxygen and nutrition by choroid, and is vulnerable to myopia related fundus changes^[11-13]. Fovea is the most sensitive part of vision, so the study of retinal blood flow parameters in macular area can provide clinical basis for diagnosis and treatment. In this study, we used OCTA to quantitatively analyze the relationship between the progression of myopia and macular blood flow, as well as the relationship with axial length in children and adolescents with myopia. As a new vascular imaging technology, OCTA can provide more detailed microvascular morphological information and stronger quantitative analysis capabilities in retinal and choroidal diseases. At present, it is commonly used in the diagnosis and treatment of retinal and choroidal diseases. In this study, we found that the area of FAZ that progresses quickly in children is smaller than that of slow progress, and in adolescents, the axial length with rapid myopia progress is longer than that with slow myopia progress. The change of SE was positively correlated with the change of axial length, but have no obvious correlation with the change of height, VD, PD and FAZ.

Previous studies have shown that the choroid may play an important role in the occurrence and development of myopia, but the mechanism of the choroid in the occurrence and development of myopia is still unclear^[14]. During the occurrence and development of myopia, the choroid of the human eye becomes thinner. There are also some indications of changes in choroidal blood circulation, such as decreased intraocular perfusion pressure^[15] and slowed choroidal vascular perfusion^[16], etc. Research by Shih et al. showed that due to form deprivation, the choroidal blood flow of myopia in chicks was reduced. The decrease in flow is due to the expansion and thinning of the choroid in myopic eyes. It is also pointed out that the decrease in choroidal blood flow may be an adaptive response to the thinning of the retina caused by myopia^[17], the normal high blood flow of choroid is very important for nourishment and oxygen supply to the outer retina, the choroid is the only source of oxygen and nutrients in the five layers of the outer retina, including the FAZ. The changes of vascular density, vascular structure and blood flow of choroid will directly affect the metabolism and function of retina, and cause pathological changes in the structure and function of retina^[3]. Therefore, in the occurrence and progression of myopia,

it is very important to monitor the morphology of the retina and the distribution of retinal blood vessels. The nutritional supply of FAZ comes from the choroid. And the value of FAZ can indirectly reflect the blood flow of the choroid. The blood flow of the choroid is abundant, and the area of FAZ is relatively large. In this study, the area of FAZ with rapid progression of myopia in children is smaller, and the area of FAZ with slow progression is larger, indicating that the progression of myopia is slow when the choroidal blood flow is abundant. For myopia prevention and control, we can try to increase choroidal blood flow to slow down the progression of myopia, such as the use of drugs that increase blood circulation or eye massage to increase blood circulation of the eyes, but there is no significant difference in the area of the FAZ of the adolescents in this study, that is, the old group. The author believes that this age group is at the peak of growth and development, the metabolism is relatively vigorous, and the choroidal blood flow is relatively rich, which has an impact on the area of FAZ. At the same time, the progress of myopia in adolescence has a certain relationship with growth and development. Researches such as Cheng Tianyu also believes that various hormones in the "Burst" may be the common internal motivation of physical development, sexual development, and refractive development^[18], so there is no difference in the size of FAZ in the adolescent group.

This study shows that in the adolescent group those with rapid progression of myopia the axial length is longer than those with slow progression of myopia, and the change of SE is positively correlated with the change of the axial length. The elongation of the axis of the eye is the most cause of myopia, and is closely related to the progression of myopia^[19–21]. Studies have shown that the thinning of the retina caused by the elongation of the axial length which will reduce its oxygen demand, thereby reducing blood circulation^[22], which affects choroidal blood flow, and at the same time, the decrease in blood circulation will cause the reduction of scleral blood supply and oxygen supply. The study of Hao WUA et al. proposed that scleral hypoxia is a new target for the progression of myopia^[23], so the longer axis of eye the relative faster progresses of myopia, but most of the participants in this study have mild to moderate myopia, especially in the young age group, who are basically mild to moderate myopia, and all the axial length were less than 26mm, so the impact on scleral hypoxia is not as great as that in the old age group with longer eye axis, which may be the reason why there is no difference in the eye axis between the observation group and the control group in the young group. Studies such as Fan and Saw have shown that axial elongation is highly correlated with the progression of myopia^[24–25], which was consistent with the positive correlation between the change of SE and the change of axial length in this study.

This study found that the speed of myopia progression is not related to the VD and PD of the superficial microvessels in the macular area, which is consistent with the study by Xiao Feng-qí and others researchers ,they also found that the blood flow density of the deep retinal microvessels in the macular region was lower in high myopia than in mild myopia^[26], the only source of oxygen and nutrients in the outer five layers of the retina is the choroid. The blood flow density of the deep retinal microvessels in the macular region reflects the choroidal blood flow, which is consistent with the reduction of choroidal blood flow in the progression of myopia mentioned earlier. The Angio-Plex OCT Angiography (Carl Zeiss Meditec, Dublin, CA) has no value for deep blood flow density, so there is no comparison of deep blood

flow density in this study. Mo et al. [27] used OCTA analysis and found that the density of superficial microvessels in the foveal area adjacent to the macular in the pathologic myopia (PM) was reduced. In this study, most of the participants were mild to moderate myopia, so the conclusion was inconsistent with Mo et al. In this study, there was no significant correlation between change of SE and the change of superficial vascular density VD, PD in the macular area, and the change of FAZ, change of height. The study by Xiao Feng-qj et al showed that there was no significant difference in the blood flow of the superficial retinal capillaries in the macular area among different myopia groups [26]. In this study, subjects followed up the progress of myopia, but the follow-up time was short, and the maximum progress of myopia was only 1.0D. Therefore, there weren't significant changes in VD and PD of the superficial retina in the macular area. Similarly, FAZ changes are not obvious. Multiple studies have shown that there is a significant correlation between the increase in height and the length of the eye axis [28–29]. However, unlike the consistent conclusions of multiple studies on the relationship between height and eye axis length, the relationship between height and refractive degree is still controversial. Some studies have found that the higher the height, the more refractive degree tends to myopia^[30–31], the higher the myopia rate^[32–33], but there are still many studies that have not found a significant correlation between height and refractive degree, which may be due to corneal compensation thinning counteracts the effect of axial elongation, leaving the refractive degree unchanged [28–29,34].

Through this study, we have learned that the area of FAZ with fast myopia progression in children is smaller than that with slow myopia progression, and the axial length with fast myopia progression in adolescents is longer than that with slow myopia progression. This provides an early warning indicator for our myopia prevention and control. In the stage of children, we can predict the trend of myopia progression by checking the OCTA of the macular area to understand the area of the FAZ. In the stage of adolescent, we can predict the trend of myopia progression by checking the eye axis. If there is a reminder that myopia is progressing fast, In myopia prevention and control, more effective prevention and control methods should be adopted, or a variety of methods should be used for myopia prevention and control. However, this study has some limitations. Firstly, the sample size is too small. Secondly, the selected subjects are all children and adolescents aged 8–14 in the region, which cannot represent the entire population. Thirdly, it is assumed that FAZ area and axial length can possible to provide a sensitive and "quick predictive index" of myopia progression. Because of the lack of benchmark data comparison, further research should be done to predict the standard value of the corresponding age group in order to better predict the progression of myopia through this method in clinical work. And better propose the prevention and control measures of myopia.

Declarations

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Declaration of 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

CRediT author statement

Ling li Lin: Data curation, Writing- Original draft preparation, Writing- Reviewing and Editing, Conceptualization, **Cui ting Wang:** Visualization, Investigation. **Xian han Zhang:** Supervision, Methodology, Software

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Tables

Table 1
Patient Demographic and Clinical Characteristics

	Young group			Old group		
	Observation group	Control group	P Value	Observation group	Control group	P Value
Number of eyes	14	14	/	7	19	/
Gender(female/male)	8/6	8/6	1*	4/3	5/14	0.078*
Age(years), $x \pm SD$	10.64 ± 0.84	10.07 ± 1.33	0.298#	13.29 ± 0.95	12.68 ± 0.82	0.518#
Height(cm), $x \pm SD$	149.52 ± 9.17	145.95 ± 8.10	0.096#	158.14 ± 6.96	156.16 ± 5.63	0.216#
Axial(mm), $x \pm SD$	24.84 ± 1.08	24.48 ± 0.86	0.364&	24.51 ± 0.86	24.25 ± 0.57	0.049&
SE(D), $x \pm SD$	-2.41 ± 2.13	-2.14 ± 0.94	0.661#	-2.68 ± 1.55	-1.88 ± 0.85	0.149#

x = mean, and SD = standard deviation SE = the equivalent spherical degree Age, Height, Axial length, SE were the data from the first check

*Chi-square test for gender

#K-Walis test for age\height and SE

& Independent-samples T test for optic axis

Table 2

Comparison of OCT Angiography Parameters for 1-mm circle,3-mm ring,6-mm ring and 6-mm circle Region among Participants between Observation group and control group in the younger group and the older group

	Young group			Old group		
	Observation group	Control group	P Value	Observation group	Control group	P Value
Number of eyes	14	14	/	7	19	/
VD1(/mm)	10.53 ± 2.28	10.39 ± 2.99	0.071&	11.63 ± 3.54	9.55 ± 2.61	0.335&
VD2(/mm)	18.19 ± 1.03	18.64 ± 0.512	0.278#	18.87 ± 0.46	18.34 ± 1.19	0.339#
VD3(/mm)	18.56 ± 1.05	18.74 ± 0.62	0.823#	19.19 ± 0.41	18.67 ± 0.97	0.433#
VD4(/mm)	18.25 ± 0.96	18.49 ± 0.55	0.945#	18.91 ± 0.47	18.34 ± 0.99	0.383#
PD1	0.236 ± 0.052	0.236 ± 0.073	0.056&	0.265 ± 0.085	0.215 ± 0.061	0.33&
PD2	0.437 ± 0.28	0.451 ± 0.014	0.069#	0.454 ± 0.014	0.438 ± 0.031	0.088#
PD3	0.461 ± 0.29	0.472 ± 0.012	0.55#	0.478 ± 0.006	0.467 ± 0.024	0.817#
PD4	0.449 ± 0.026	0.461 ± 0.012	0.476#	0.467 ± 0.010	0.468 ± 0.073	0.37#
FAZ (mm ²)	0.228 ± 0.074	0.262 ± 0.112	0.03&	0.224 ± 0.126	0.270 ± 0.083	0.126&

VD = vessel density; PD = perfusion density;1 = Early Treatment Diabetic Retinopathy Study(ETDRS) grid region 1-mm Circle region;2 = ETDRS grid region 3-mm ring region;3 = ETDRS grid region 6-mm ring region;4 = ETDRS grid region 6-mm circle regions; FAZ = foveal avascular zone; OCTA = OCT angiography

Mean ± SD, All the data were from the first check

#K-Walis test for VD2; VD3; VD4; PD2; PD3; PD4

& Independent-samples T test for VD1; PD; FAZ

Table 3

Correlation between the SE change and Height change; Axial change; VD change; PD change; FAZ change

SE change	r value	P value
Height change	-0.205	0.136
Axial change	0.301	0.027
VD1 change	0.003	0.981
VD2 change	0.039	0.777
VD3 change	-0.017	0.904
VD4 change	0.001	0.993
PD1 change	-0.004	0.977
PD2 change	0.013	0.928
PD3 change	0.12	0.389
PD4 change	0.126	0.36
FAZ change	-0.19	0.169

r = Pearson's correlation coefficient VD = vessel density; PD = perfusion density;1 = Early Treatment Diabetic Retinopathy Study(ETDRS) grid region 1-mm Circle region;2 = ETDRS grid region 3-mm ring region;3 = ETDRS grid region 6-mm ring region;4 = ETDRS grid region 6-mm circle regions; FAZ = foveal avascular zone

Figures

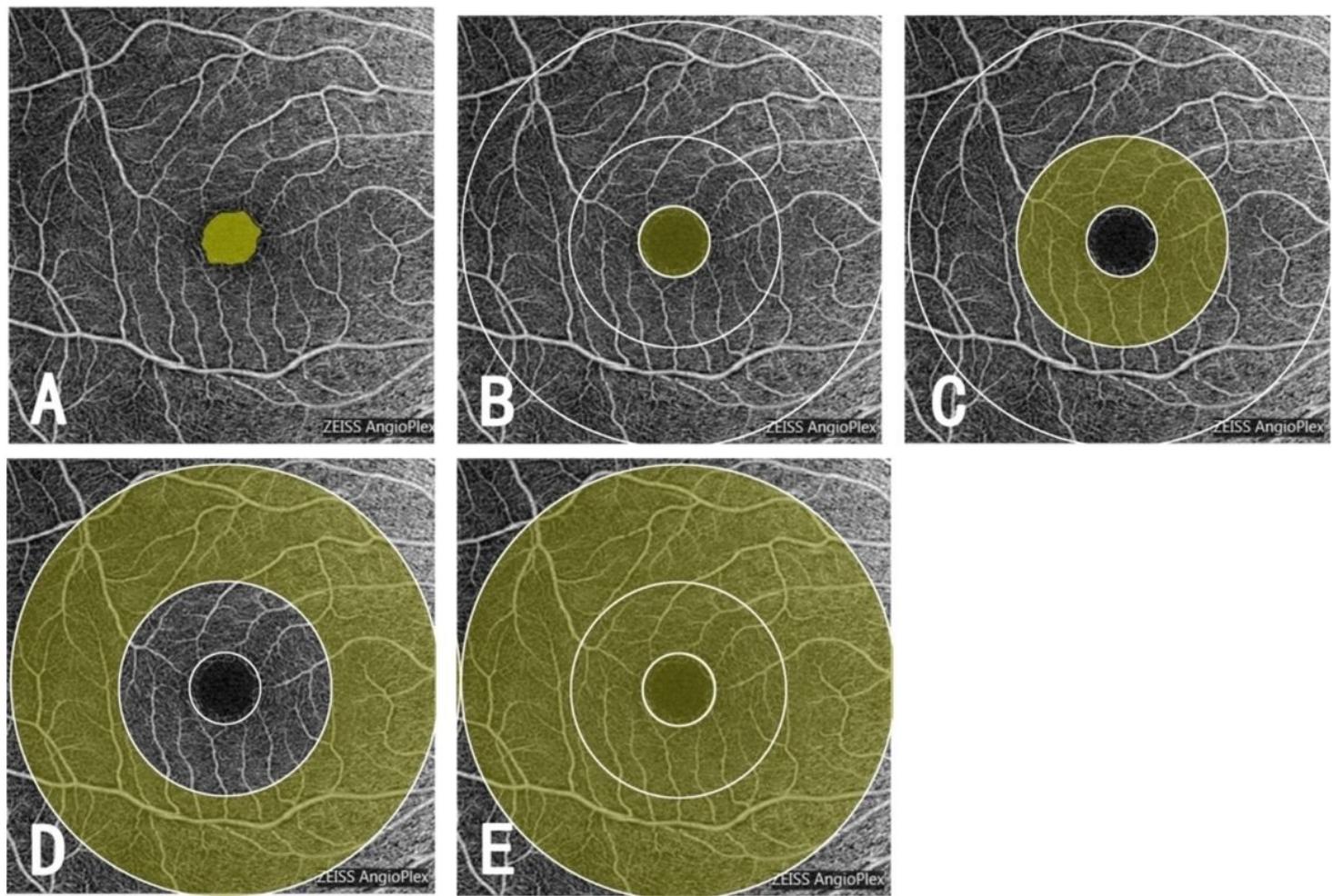


Figure 1

A Superficial area of FAZ after manual review Early Treatment Diabetic Retinopathy Study(ETDRS) grid regions (B) 1-mm circle, (C) 3-mm ring, (D) 6-mm ring, (E) 6-mm circle regions. Vessel density (VD) and perfusion density (PD) were averaged over the highlighted yellow area respective region.