Macular Vessel Density, Perfusion Density, Foveal Avascular Zone in Emmetropia and Myopia: Quantitative Assessment Using Optical Coherence Tomography Angiography

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Abstract

Background To assess vessel density, perfusion density among emmetropic and myopic person, and to demonstrate detailed changes in superficial retinal microvascular network. Methods This was a single-centered, cross-sectional study of 120 participants. Emmetropic, low, moderate and high myopic group each account for 1/4. Enface 3mmx3mm optical coherence tomography angiography images were obtained using Cirrus™ HD-OCT 5000. Quantifiable measure of vessel density, perfusion density and foveal avascular zone were performed by AngioVue software. Results Gender, age, SBP, DBP, MOPP and IOP showed no differences among emmetropic and myopic groups. In inferior quadrant, vessel density and perfusion density of emmetropic and low myopia group showed statistical significance from moderate and high myopia group (all $P<0.05$). In temporal quadrant, vessel density and perfusion density of emmetropic, low and moderate myopia group showed statistical significance from high myopia group (all $P<0.05$).In emmetropic group, vessel density and perfusion density showed no difference among superior, inferior, temporal and nasal quadrants. In low myopic group, vessel density and perfusion density of temporal quadrant showed statistical significance from superior, inferior and nasal quadrants (all $P<0.05$). In moderate and high myopic group, vessel density and perfusion density of superior quadrant showed statistical significance from temporal quadrant (all $P<0.05$) and inferior quadrant(all $P<0.05$) . And vessel density of nasal quadrant showed statistical significance from inferior quadrant in moderate myopic group($P=0.039$) . Conclusion Along with the increase of myopia degree, vessel density and perfusion density of inferior and temporal quadrants showed a statistically significant tendency of decrease. Vessel density and perfusion density of nasal quadrant showed a relatively decreasing tendency. Closer attention should be paid to moderate myopia.

Background

Nowadays myopia has become a global public health concern, since about one-quarter of the population are clinically diagnosed with myopia. Among the myopia population, high myopia accounts for over 20-26%[1]. The percentage is estimated to be 50% for myopia and 20% for high myopia until 2050[1-3]. As known to all, high myopia is related to several pathological changes of fundus, including posterior scleral staphyloma, choroidal atrophy, retinal degeneration, macular hole, retinal detachment, and choroidal neovascularization (CNV), which might lead to permanent vision impairment and blindness. Thus, prevention and treatment of myopia, especially for high myopia, turns out to be a serious problem for government and ophthalmologist.

As we reported before, along with the increase of myopia degree, subfoveal choroid thickness (SFCT) shows a tendency of thinning[4]. Decreased SFCT implies decreased choroidal blood flow. According to Dimitrova's and Chen Ruip's study[5], in myopic patients with CNV, along with the increase of myopia degree, central retinal and posterior ciliary blood velocity shows a decreasing tendency. Decreased choroidal and retinal blood flow are considered to be important physiological changes related to occurrence of CNV. However, none of these studies revealed detailed changes of retinal microvascular network as well as differences of vascular density and perfusion among different myopia degrees, which is exactly where we are interested in.

Traditional ways to evaluate choroidal and retinal microvascular network were fundus fluorescein angiography (FFA) and indocyanine green angiography (ICGA), which both need injection of contrast agent into vein and might cause several complications. Besides, both tests take 10-30 minutes to obtain dynamic, two-dimensional images of blood flow[6-9]. During test, dye leakage, pooling, and staining might interfere with clear observation of retinal pathology. By contrast, optical coherence tomography angiography (OCTA) is considered to be a non-contact, noninvasive, rapid, safe and efficient examination. OCTA provides precise segmentation of different layers from

the internal limiting membrane (ILM) to the choroid[10, 11] and an adjustable scan scale from 2mm*2mm to 12mm*12mm, which meets meet different demands in clinic and research. More importantly, quantitative analysis of retinal microvascular network is available by software of OCTA, which is practical and proved with good repeatability and reproducibility in researches [12, 13].

In this study ,we aim to analysis differences of vessel density, vessel perfusion among emmetropic and myopic person by OCTA, and to demonstrate detailed changes in superficial retinal microvascular network.

Methods

Study Subject

This was a single-centered, cross-sectional study. A total of 120 participants who worked in the Seventh Affiliated Hospital of Sun Yat-sen University with a clinically definite diagnosis of emmetropia and myopia from December 2017 to January 2018 were enrolled. Emmetropic, low, moderate and high myopic group each account for 1/4. Inclusion criteria for emmetropic group were as follows: over 18 years old, uncorrected visual acuity not less than 5.0, binocular postcycloplegic spherical equivalent between 0 diopter and +1diopter. Inclusion criteria for myopic groups were as follows: over 18 years old, best corrected visual acuity not less than 5.0, binocular postcycloplegic spherical equivalent less than 0 diopter. Low myopia was defined as greater than -3 diopters. Moderate myopia was defined between -3 diopters and -6 diopters. High myopia was defined as less than -6 diopters. Eyes with diseases which might cause choroidal structural changes, such as retinal tears, retinal detachment and retinal vein obstruction were excluded. Other exclusion criteria were including history of ocular surgeries, like refractive surgery, ocular diseases including glaucoma, cataract and dominant strabismus, systemic diseases including hypertension, diabetes and hyperlipidemia, pregnancy, smoking or drinking alcohol and caffeine before examination, incapability of obtaining clear choroidal images. This study followed the tenets of the Declaration of Helsinki. The protocol was approved by research ethics committee of the Seventh Affiliated Hospital of Sun Yat-sen University. All participants had signed informed consents to join the study.

All participants had provided a careful history and went through detailed physical and ophthalmic examinations.Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken after resting for at least fifteen minutes before ophthalmic examination with a mercury sphygmomanometer. Ophthalmic examinations included uncorrected and best corrected visual acuity, intraocular pressure(IOP) with non-contact tonometer, slit-lamp biomicroscopy,

funduscopy, optometry, axial length(AL) with IOL master(IOLMaster500，Carl Zeiss), OCTA. Mean ocular perfusion pressure (MOPP) was calculated as follows: MOPP=2/3[DBP+1/3(SPB-DBP)]-IOP[14]. All subjects were examined at 8:00 to 9:00 daily and by a same experienced technician.

Optical Coherence Tomography Angiography (OCTA)

All eyes underwent retinal imaging with the fourth generation of frequency-domain OCT (Cirrus™ HD-OCT 5000,Carl Zeiss). Pupils were under natural condition without using cycloplegia. All participants were in sitting position and used internal fixation for clear imaging. Both enhanced depth imaging (EDI) for SFCT and angiography for superficial microvascular analysis in a 3*3mm region centered on the macula were conducted sequentially, as shown in Figure 1-A. Imaging processing and data analysis were performed using Cirrus HD-OCT5000 Review Software V.10 DEMO. Superficial capillary plexus(SCP) was imaged from the nerve fiber layer to the inner border of the inner plexiform layer(IPL), as shown in Figure 1-B. Definition for SFCT was the average value of vertical distance betweem the retinal pigment epithelium and the choroid sclera junction in the horizontal and vertical direction across macular fovea. Definition for regions being analysised in angiography was a circle with 3mm diameter centered on fovea, including both the foveal and parafoveal regions. Definition for foveal region was a circle with 1mm diameter centered on fovea, referring to medium quadrant. Definition for parafoveal region was the rest ring part surrounding the foveal region. Parafoveal region was equally divided into four quadrants by two oblique lines across fovea that were perpendicular to each other,defined as superior, inferior, temporal and nasal quadrants. Definition for vascular density(VD) was total length of blood vessels of superficial capillary networks in regions, as shown in Figure 1-C. Definition for perfusion density(PD) was the area ratio of blood vessels of superficial capillary networks to whole region, as shown in Figure 1-D. Foveal avascular zone(FAZ) is recognized as the capillary-free area in the central macula. Area and perimeter of FAZ were automatically recognized and calculated by software.Definition for index of FAZ was the similarity ratio of FAZ compared to a circle, as shown in Figure 1-E.

Statistical Analysis

Statistical analyses were performed using the SPSS statistical package version 25.0 for Windows. All data were tested for normality. One-way ANOVA was used for comparing differences among groups as well as medium, superior, inferior, temporal and nasal quadrants in the same group. P-value was considered significant when $P < 0.05$.

Results

General Information

58 female participants and 62 male participants were enrolled in the study. Maximum spherical equivalent (SE) was +0.875 diopter. Minimum SE was -8.500 diopter. As shown in Table 1, gender, age, SBP, DBP, MOPP and IOP showed no differences among groups(P=0.180, 0.086, 0.786, 0.397, 0.700, 0.897). SFCT, AL and SE showed statistically different among emmetropic, low myopic, moderate myopic and high myopic groups(P<0.001).

Vascular Density

As shown in Table 2, One-way ANOVA revealed significant differences in inferior(P=0.001) and temporal(P=0.033) quadrants among four groups. As for inferior quadrant, pairwise comparison showed differences between emmetropic and moderate myopic group(P=0.001), emmetropic and high myopic group(P=0.002),low and moderate myopic group(P=0.012),low and high myopic group(P=0.021). As for temporal quadrant, pairwise comparison was statistically significant between emmetropic and high myopic group(P=0.005),low and high myopic group(P=0.002), moderate and high myopic group(P=0.007).

In emmetropic group, vascular density showed no difference among superior, inferior, temporal and nasal quadrants(P=0.102). In low myopic group, vascular density of temporal quadrant was statistically significant from superior(P=0.003), inferior(P=0.003), nasal(P=0.005) quadrants. In moderate myopic group, vascular density of temporal quadrant remained significant from superior quadrant(P=0.036),but showed no difference from inferior and nasal quadrants. Meanwhile, vascular density of inferior quadrant demonstrated significant difference from superior(P=0.006) and nasal quadrants(P=0.039). In high myopic group, vascular density remained statistically significant between temporal and superior quadrant(P=0.003), nasal and superior quadrant(P=0.037), while vascular density of inferior quadrant showed no difference from nasal quadrant.

Therefore, with the increase of myopia degree, vascular density of temporal and inferior quadrants showed a statistically decreasing tendency. Changes in medium, superior and nasal quadrants were not obvious.

Perfusion Density

As shown in table 3, One-way ANOVA revealed significant differences in inferior(P=0.004) and temporal(P=0.022) quadrants among four groups. As for inferior quadrant, pairwise comparison showed differences between emmetropic and moderate myopic group(P=0.041), emmetropic and high myopic group(P=0.002), low and moderate myopic group(P=0.005), low and high myopic group(P=0.002). As for temporal quadrant, pairwise comparison was statistically significant between emmetropic and high myopic group(P=0.002), low and high myopic group(P=0.011), moderate and high myopic group(P=0.026).

In emmetropic group, perfusion density showed no difference among superior, inferior, temporal and nasal quadrants(P=0.704). In low myopic group, perfusion density of temporal quadrant was statistically significant from superior(P=0.006), inferior(P=0.036), nasal(P=0.010) quadrants. In moderate myopic group, perfusion density of temporal quadrant remained significant from superior quadrant(P=0.002), but showed no difference from inferior and nasal quadrants. Meanwhile, perfusion density of inferior quadrant demonstrated significant difference from superior quadrant(P=0.003). In high myopic group, perfusion density remained statistically significant between temporal and superior quadrants(P=0.001), inferior and superior quadrants(P=0.007).

Similar to vascular density, along with the increase of myopia degree, perfusion density of temporal and inferior quadrants showed a statistically decreasing tendency. Changes in medium, superior and nasal quadrants were not obvious.

Foveal Avascular Zone (FAZ)

Table 4 demonstrated that area, length and index of FAZ showed no differences among emmetropic, low, moderate and high myopic group(P=0681, 0.546, 0.731). It suggested that changes of myopia degree has no direct contact wiht area, length and index of FAZ.

Discussion

Previous researches of OCTA centered on macrovascular changes or differences in ocular fundus disease or glaucoma. No studies have demonstrated changes of superficial retinal microvascular network in different myopia. Since myopia has become a neglectable concern in China, it is important to distinguish structural and functional changes in myopia people from emmetropic people.

According to our study, vascular density and perfusion density of inferior quadrant decreased significantly from low to moderate myopic group, while no differences were observed between emmetropic and low myopic group as well as moderate and high myopic group. Since microvascular changes occurred before high myopia, it was an indication that we should pay closer attention to moderate myopia, which was different from our previous cognition that only high myopia need be focused on. Besides, vascular density and perfusion density of temporal quadrant dropped significantly from moderate t o high myopic group, while no differences were observed among emmetropic, low and moderate groups. The tendency of vascular density and perfusion density of inferior and temporal quadrants was not exactly the same. Changes of vascular density and perfusion density of inferior quadrant occurred earlier in moderate myopia, while changes of temporal quadrant showed statistical significance in high myopia. We assumed that as myopia degrees increased, stretching of scleral, choroidal, and retinal tissue occurred both in four quadrants, leading to stretching of blood vessel, thus vascular density and perfusion density decreased, but changes in inferior quadrant was most rapid, followed by temporal, nasal and superior quadrants. As known to all, high myopia has a close relationship with several fundus complications, such as CNV, which may result from decreased choroidal and retinal blood flow. Thus, another assumption was made that CNV in myopia may be most common in inferior and temporal quadrants of macular zone, which need to be further proved.

As our study revealed, a conclusion that increasing degrees of myopia affected vascular density and perfusion density of temporal quadrant first, followed by inferior and nasal quadrants could be drawn. In emmetropic group, vascular density showed no difference among superior, inferior, temporal and nasal quadrants of macular zone. As low myopia occurred, vascular density of temporal quadrant decreased significantly. This might indicated that myopia affected temporal quadrant of superficial retinal microvascular network first. Different from low myopia group, vascular density of temporal quadrant showed no significance from inferior and nasal quadrants, while vascular density of superior and inferior quadrant as well as nasal and inferior quadrant became statistically significant. This result implied that as myopia progressed, vessel density of inferior and nasal quadrants were both affected, but vessel density of inferior quadrant decreased more obviously than of nasal quadrant. In high myopic group, vessel density of inferior and nasal quadrants showed no significance, which further proved that vessel density of nasal quadrant was decreasing as myopia degrees increased. Trends of perfusion density in different groups were similar to that of vascular density, except that perfusion density of nasal and inferior quadrants showed no difference in moderate group.

FAZ is the center area of macular zone containing no blood vessels, surrounded by a continuous network of capillaries called macular vascular ring[15]. In our study, we focused on superficial vascular plexus, and found no correlation between parameters of FAZ and myopia. Previous studies have drawn several conclusions about FAZ shape, area and capillary plexuses. Samara and colleagues reported that FAZ area was significantly larger in the deep plexus than superficial plexus[16]. Shahlaee and colleagues found that deep vascular density was statistically higher than superficial in the parafoveal region, while the trend was opposite in the foveal region[17]. Several studies have shown that FAZ area has a negative relationship with central foveal thickness[16, 18]. These researches provided us a wider scope and prospect for further study.

Our study also pointed out that MOPP among emmetropic, low, moderate and high myopic group showed no differences. This indicated that changes of vascular density and perfusion density were not related to ocular perfusion pressure, blood pressure or IOP, but related to structural changes caused by stretching of retina, which was confirmed to our previous assumption.

There were some limitations in our study. Sample size was not large enough to confirm some differences between quadrants.Higher degrees of myopia were not included in this study to demonstrate more relations. The conclusion drawn from a cross-sectional study was not strong enough to support our assumption. Therefore, further study should be was needed to analysis regular pattern of changes of vascular density and perfusion density in myopic patients.

Conclusions

Macular vessel density and perfusion density showed different decreasing trends in different quadrants with the increase of the degree of myopia, which might be an explanation of occurrence of CNV and an indication of location of CNV in pathological myopia. Significant decreases in macular vessel density and perfusion density had been observed in moderate myopia. Thus, instead of high myopia, closer attention should be paid to moderate myopia.

Declarations

Ethics approval and consent to participate This study was approved by the The Seventh Affiliated Hospital of Sun Yat-sen University Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. All participants had signed consent form.

Consent for publication Required.

Availability of data and material The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests The authors declare that they have no competing interests.

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Authors' contributions Jiang XM: substantial contributions to the conception and design of the work, and acquisition, and interpretation of data for the work and revision of the draft critically for important intellectual content; Zheng C: substantial contributions to the analysis and, interpretation of data for the work and drafting the work. Tan Q, Du FF: substantial contributions to acquisition and analysis and interpretation of data for the work. Xiang WX: substantial contributions to acquisition of data for the work. All authors were involved in the final approval of the version to be published, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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List Of Abbreviations

CNV	choroidal neovascularization
SFCT	subfoveal choroid thickness
FFA	fundus fluorescein angiography
ICGA	indocyanine green angiography
OCTA	optical coherence tomography angiography
ILM	internal limiting membrane
SBP	systolic blood pressure
DBP	diastolic blood pressure
IOP	intraocular pressure
AL	axial length
MOPP	mean ocular perfusion pressure
EDI	enhanced depth imaging
SCP	superficial capillary plexus
IPL	inner plexiform layer
VD	vascular density
PD	perfusion density
FAZ	foveal avascular zone
SE	spherical equivalent

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Tables

Table 1 General information of emmetropic, low, moderate and high myopic group

	Gender(M:F)	Age(y)	SBP(mmHg)	DBP(mmHg)	MOPP(mmHg)	SFCT(mm)	AL(mm)	IOP(mmHg)	SE(D)
Emmetropic G	17:13	24.00±1.79	104.00±5.33	75.00±6.26	40.78±3.65	296.80±25.16	22.72±0.56	15.67±2.42	0.30±0.31
Low myopic G	14:16	29.25±5.58	108.25±13.06	72.50±8.79	39.78±6.70	302.25±64.50	23.92±0.91	16.50±2.28	-1.71±0.85
Moderate myopic G	13:17	26.50±4.06	110.00±13.61	74.00±7.15	41.33±6.25	203.75±52.22	25.36±0.71	16.00±3.08	-4.43±0.99
High myopic G	15:15	25.40±4.28	107.60±3.36	67.60±6.73	37.76±3.62	188.50±71.16	26.49±0.56	16.20±0.44	-7.24±0.79
statistics	0.185a	2.380b	0.355b	1.016b	0.478b	9.328b	29.557b	0.199b	66.310a
P value	0.954	0.086	0.786	0.397	0.700	<0.001	<0.001	0.897	<0.001

a Chi-Square b One-way ANOVA

Table 2 Comparison of vascular density among groups and quadrants.

Mean value	Medium	Superior	Inferior	Temporal	Nasal	Statistics	P vaule
Emmetropic G	11.715±2.52	23.317±0.722	23.592±0.753	22.692±0.909	23.358±1.098	185.696	<0.001
Low myopic G	11.074±2.58	22.903±1.152	22.906±1.025	22.863±1.070	22.091±1.290	399.773	<0.001
Moderate myopic G	11.662±3.79	23.148±1.117	22.067±1.366	22.333±0.093	22.605±1.291	123.724	<0.001
High myopic G	11.856±2.52	23.122±0.826	21.867±1.667	21.278±1.141	22.400±1.113	60.418	<0.001
Statistic	0.303	0.520	6.047	3.063	1.238	-	-
P vaule	0.823	0.670	0.001	0.033	0.302	-	-

Table 3 Comparison of perfusion density among groups and quadrants.

Mean value	Medium	Superior	Inferior	Temporal	Nasal	F vaule	P vaule
Emmetropic G	0.200±0.043	0.411±0.012	0.413±0.014	0.406±0.020	0.412±0.019	196.743	<0.001
Low myopic G	0.190±0.045	0.412±0.023	0.408±0.020	0.396±0.028	0.407±0.024	374.954	<0.001
Moderate myopic G	0.197±0.064	0.417±0.016	0.396±0.026	0.394±0.019	0.404±0.026	145.964	<0.001
High myopic G	0.195±0.052	0.414±0.015	0.381±0.031	0.373±0.025	0.392±0.022	70.817	<0.001
Statistic	0.142	0.379	4.888	3.414	1.372	-	-
P vaule	0.934	0.768	0.004	0.022	0.258	-	-

Table 4 Comparison of area, length and index of FAZ among groups

Mean value	FAZA	FAZL	FAZI
Emmetropic G	0.27±0.10	2.19±0.41	0.71±0.06
Low myopic G	0.29±0.09	2.25±0.32	0.70±0.09
Moderate myopic G	0.27±0.13	2.18±0.50	0.68±0.12
High myopic G	0.24±0.09	2.04±0.40	0.71±0.05
Statistic	0.503	0.715	0.432
P vaule	0.681	0.546	0.731

Figures

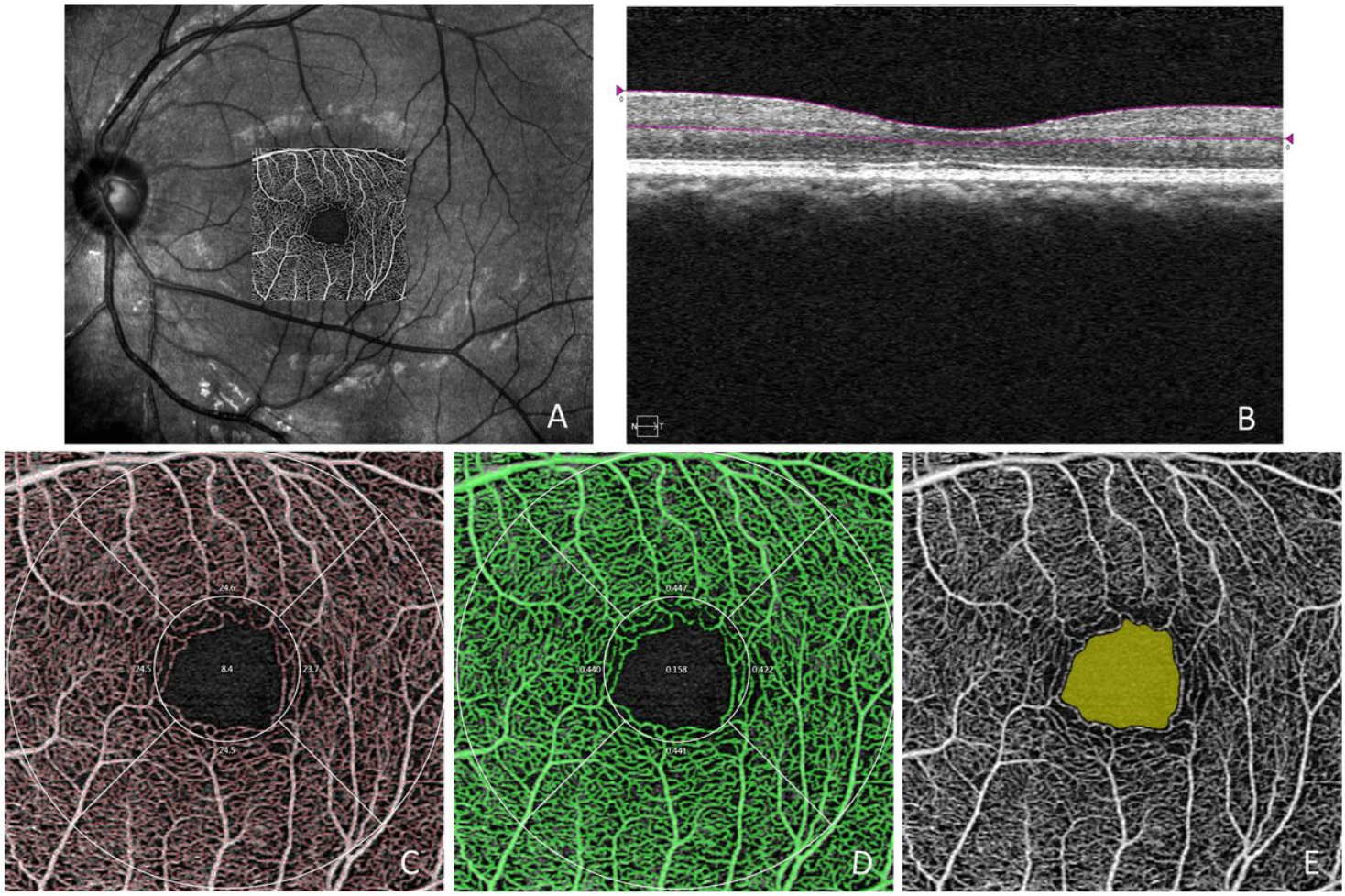

Figure 1

Demonstration of quantitative assessment of macular vascular density, perfusion density and foveal avascular zone: scan region of OCTA (A), demonstration of SCP (B), demonstration of VD (C), demonstration of PD (D), demonstration of index of FAZ (E).