Changes in Retinal and Choroidal Thickness and Microcirculation Detected by Optical Coherence Tomographic Angiography in Hypertension Associated with Diabetes

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Research Article

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Abstract

Background

Hypertension and diabetes can significantly affect the blood flow of the retina and choroid. But there has been no idea about the retinal and choroidal microcirculation of hypertensives associated with diabetes. The objective of the study is to detect the differences in the retinal and choroidal microcirculation of hypertensives, diabetics and hypertensives associated with diabetes by optical coherence tomography angiography (OCTA) and explore their clinical significance.

Methods

This was a cross-sectional and case-control study that 538 older subjects (538 eyes) were enrolled in. There were 187 cases assigned to the hypertensive group, 49 cases to the diabetic group, 129 cases to the hypertensive diabetic group, and 173 cases to the control group. OCTA were used to scan 6*6-mm macula. The related indicators included the thickness and flow density (FD) of each layer of the retina and choroid.

Results

The retinal superficial FD (SFD) in the hypertensive, diabetic, hypertensive diabetic and control group was 46.4%, 45.3%, 46.4% and 46.4%, respectively. It was significantly lower in the diabetic group than in the other three groups (all $P < 0.05$) and the hypertensive diabetic group had higher SFD similar to control group. The choriocapillaris FD (CFD) was 52.8%, 52.5%, 52.8% and 53.1% in four groups, which in the hypertensive diabetic group and the other two groups decreased to the same extent compared with the control group (all $P < 0.05$). Meanwhile, the deep FD (DFD) was marginally higher in the control group. However, there was no statistical difference among all the groups. The SFD correlated negatively with body mass index (BMI) (β=-0.102, $P = 0.0225$). But there was no significant difference in the thickness of each layer among the four groups.

Conclusion

OCTA can accurately and efficiently predict the occurrence and early development of hypertension and diabetes in the elderly. When the microcirculation of target organs is damaged, the choriocapillaris and FD may be the primary objects for early observation. In addition, the hypertensives associated with diabetes do not develop more severe lesions than patients with single disease in the population we studied.

Introduction

Hypertension and diabetes are both common systemic diseases in modern society, which have attracted much global public attention. It is estimated that there will be 642 million diabetics by 2040[1] and 1.56 billion hypertensives worldwide by 2025[2]. They often occur together in senile patients[3]. Poorly

controlled blood pressure and blood glucose can lead to irreversible damage to the anatomy and function of microcirculation throughout the body. In the end, the microvascular rarefaction and inadequate blood vessel perfusion will contribute to multiple organ dysfunction in the form of cerebrovascular and cardiovascular diseases, nephropathy, retinopathy and so on[4]. So the patients may observe a few similar pathologic changes caused by the above diseases in different tissues. In ophthalmology, hypertension and diabetes-related lesions can also be found in the fundus whose retinal and choroidal vascular system is the only noninvasively detectable microvascular system in the human body[5–7]. So it is significative and feasible to consider the changes in fundus blood vessels as early indicators for other complications.

For the past few years, optical coherence tomography angiography (OCTA) has been widely used in ophthalmic examination, especially for retina and choroid[8, 9]. It is a noninvasive imaging technology that can obtain high-resolution and three-dimensional angiograms of choroidal and retinal vessels in real time[10]. Located in the optic disc or macular area, some parameters related to microcirculation can be described or calculated quantitatively and accurately, including thickness, foveal avascular zone (FAZ), vessel density (VD), vessel diameter index (VDI) of each layer[11, 12]. Up to now there have been several studies on retinal OCTA manifestations in patients with hypertension or diabetes, which indeed demonstrate significant differences in the above measurements compared with the healthy population[13–17]. However, there are still three shortcomings. First, most of the relevant studies are based on hospital patients, but there is still a lack of data on large-scale community population. Secondly, it has been reported that hypertension and diabetes have great impacts on OCTA of choroidal microcirculation, but there are few relevant studies. So the evidence is not enough to support this view. Thirdly, most researchers mainly focus on the influence of single disease on OCTA parameters of fundus, while in reality, many patients suffer from hypertension and diabetes. The characteristics of OCTA in this group have not been evaluated.

In the present study, we intend to explore the differences among hypertensives, diabetics, hypertensivesin with diabetes and healthy people in the retinal and choroidal features obtained by OCTA scanning. The subjects were from the elderly population over 60 years old though community epidemiological investigation.

Materials And Methods

This was a cross-sectional and case-control study affiliated to the eye study among middle-aged and elderly people in Beichen district in Tianjin. It obtained the ethical approval from the Ethics Committee of Tianjin Medical University Eye Hospital (2019ky-22). The study was registered on the Chinese Clinical Trial Registry Website (ChiCTR2000032280). And all the subjects have signed the informed consents successfully.

Study participants.

There were 538 subjects (538 eyes) were selected from all the subjects enrolled from June 1, 2020 to November 1, 2020. And we chose only one eye of each patient with a better image quality. Diabetes was defined as meeting one of the following conditions: (1) self-report of having diabetes or taking hypoglycemic drugs, (2) the fasting blood glucose ≥ 7.00 mmol/L on the day. And the self-reported hypertension or use of blood pressure medications was enough to confirm the diagnosis of hypertension. The inclusion criteria mainly included the patients over 60 years of age who had been definitely diagnosed with hypertension or diabetes and the healthy people. And the results of fundus examination showed non-proliferative diabetic retinopathy (NPDR), hypertensive retinopathy or normal appearance without macular edema (ME). The study also excluded the people with (1) other fundus diseases, (2) high myopia of spherical equivalent degree > -6.0 diopters or ocular axial length > 26mm, (3) a history of ocular trauma, surgery and laser, (4) some conditions affecting OCTA imaging (maximum scan quality < 45 and obvious motion artifacts), (5) ocular hypertension in the study eye characterized by intraocular pressure (IOP) > 21mmHg. According to hypertension and diabetes, the participants were divided into four groups: normal control group (neither hypertension nor diabetes), hypertensive group (only hypertension, no diabetes), diabetic group (only diabetes, no hypertension), and hypertensive diabetic group (both hypertension and diabetes).

Above all, baseline information in each group, including gender, age, height, body weight and waist circumference were recorded. BMI was calculated as weight (kg)/height $(m)^2$. Five ml venous blood was drawn from subjects with fasting for more than 8 hours for blood routine and biochemical examination. In the report, cholesterol, creatinine, fasting blood glucose, and triglyceride have been focused on. Moreover, the subjects in four groups underwent comprehensive ophthalmology examinations including present visual acuity, best corrected visual acuity, IOP, refractive error, ocular axial length, as well as the condition of anterior and posterior segment. In addition, each participant was given a detailed questionnaire to collect some information about the course of hypertension and diabetes, unhealthy living habits and other medical or treatment histories.

OCT and OCTA examination

Each subject underwent a high-resolution optical coherence tomography (OCT) along with angiography (DRI OCT Triton, Topcon) in one eye. This swept source OCT (SS-OCT) used a wavelength swept laser source to emit long light waves with a wavelength of 1050nm, which was capable of detecting structural information up to 2.6mm away from inner limiting membrane (ILM). Apart from this, in order to receive the clear and smooth images, the scanning rate of A-scan was 100,000 times per second. Each B-scan position was repeatedly scanned 4 times. Of all people, the thickness of total retina, retinal nerve fiber layer (RNFL), GCL+ (ganglion cell layer and inner plexus layer), GCL++ (RNFL, ganglion cell layer and inner plexus layer) as well as choroid in macular area was obtained through a radial scanning mode on a 6*6 mm field of view that centered on macula (Fig. 1). OCT Data Import V5 was used to output the scan results about the thickness of different regions in different layers and record the average values.

On this basis, the system used OCTA Ratio Analysis (OCTARA) algorithm to complete OCTA imaging. It was paired with SS-OCT, which could provide improved detection sensitivity of low blood flow and reduce motion artifacts without compromising axial resolution. The OCTA scanning protocol was the same as OCT, except for linear scanning. By the default automatic segmentation algorithms, the en face OCT image was divided into four layers, namely superficial vascular plexus (SVP), deep vascular plexus (DVP), outer vascular plexus (OVP) and choriocapillaris. The range of the SVP was defined as 2.6μm beneath the ILM to 15. 6μm beneath the inner plexiform/nuclear layer (IPL/INL) (Fig. 2). The range of the DVP was defined as 15.6μm beneath the IPL/INL to 70.2μm beneath the IPL. The choriocapillaris was 0μm ~ 10.4μm below the Bruch's membrane (BM). In addition, we defined the part between DVP and choriocapillaris as the outer vascular layer (OVL). Checking the image quality manually to ensure that the center of the scanning area was located in the fovea. The flow density (FD) was defined as the percentage of vascular area in the total area scanned. According the Early Treatment Diabetic Retinopathy Study (ETDRS) partition, the macular area was split into five regions, including fovea, superior, inferior, nasal and temporal region. The FD value in each region and layer was obtained by IMAGENT 6.0, an automatic detection tool. And then the parafoveal FD was calculated and recorded manually.

Statistical analysis

SPSS 25.0 was used for data statistics and analysis. The measurement data with normal distribution confirmed by Shapiro-Wilk test were described as mean ± standard deviation, and underwent univariate comparison among the four groups by ANOVA. Otherwise, median (interquartile range) was used to describe the date, and Kruskal-Wallis test was for univariate comparison. For unordered categorical variables, proportion (%) given the description as well as Chi squared test was performed to assess differences between the groups. Simple linear regression models were applied further to analyze the variables with statistical differences. P-values less than 0.05 were considered statistically significant.

Result

Patient baseline characteristics

The study recruited 538 subjects and 538 eyes in total. Thereinto, there were 187 cases (35%) assigned to the hypertensive group, 49 cases (9%) to the diabetic group, 129 cases (24%) to the hypertensive diabetic group, and 173 cases (32%) to the control group. The image quality of all was greater than 45. The descriptions and comparisons of the patient baseline characteristics are shown in Table 1. The differences were not statistically significant among the four groups in age, IOP, triglyceride and the status of smoking or drinking. While the gender composition, mean arterial pressure (MAP), blood glucose, cholesterol, serum creatinine and BMI were significantly different. To eliminate the influence of the severity of hypertension and diabetes on the statistical results, the differences in the course of diabetes and the distribution of diabetic retinopathy (DR) between the diabetic group and the hypertensive diabetic group were compared. By the same way, the interference of hypertension was observed between the

hypertensive group and the hypertensive diabetic group as well. The above results were not statistically different, which is also mentioned in Table 1.

The parameters related to OCT and OCTA examinations

Univariate comparison was conducted on the flow density of the SVP, DVP, OVP and choriocapillaris. The macular area was divided into the foveal region and parafoveal region. They were analyzed separately. As shown in Table 2, the retinal superficial FD (SFD) in the parafoveal region for controls, hypertensives, diabetics, and hypertensives associated with diabetes were 46.5 ± 2.4%, 46.4 ± 2.4%, 45.3 ± 2.3% and 46.3 ± 2.9%. They were statistically different [P = 0.021]. Likewise, the choriocapillaris FD (CFD) in the parafoveal region were 53.1 (1.5)%, 52.8 (1.5)%, 52.5 (1.9)% and 52.8 (1.6)%. There was also difference among the four groups [P = 0.010]. About the foveal region, the retinal deep FDs (DFD) were 14.7 (6.6)%, 16.1 (7.3)%, 16.4 (4.5)% and 16.4 (6.0)% respectively, and the differences were still statistical [P = 0.030]. Multiple comparisons were performed on the above parameters for the exact difference among the groups. The diabetics had a lower retinal SFD in the parafoveal region compared with controls, hypertensives and hypertensives associated with diabetes [P = 0.027, P = 0.018, P = 0.031, respectively]. In addition, the CFDs were reduced in the hypertensive, diabetic and hypertensive diabetic group [P = 0.027, P = 0.018, P = 0.031, respectively]. While the retinal deep foveal FDs in the hypertensive, diabetic and hypertensive diabetic group were higher than that in the control group [P = 0.003, P = 0.04, P = 0.010, respectively].

Then gender, BMI, cholesterol and serum creatinine were added to carry out a multivariate comparison with the four groups, and the results are shown in Table 3. The differences in retinal superficial and choriocapillaris FD in the parafoveal region were still statistically significant. And interestingly, the result suggested that BMI also has an additional certain influence on retinal superficial parafoveal FD [β=-0.102, P = 0.025]. However, the retinal deep foveal FD in the four groups were no longer statistically different.

The comparison about the thickness of total retina, RNFL, GCL+, GCL + + as well as choroid in foveal, parafoveal and total macular regions are shown in Table 4. There was no significant difference in the thickness of each layer among the four groups. Therefore, we did not carry out the next step, multivariate comparison.

Discussion

In the cross-sectional study, the thickness and blood flow density of the retinal and choroidal lays as measured by OCT and OCTA were explored in hypertensives, diabetics, hypertensives associated with diabetes and healthy people. There are some pathological changes of microcirculation observed both in retina and choroid. As it is known, the retina is supplied blood with two circulatory systems, the central retinal vascular system and the ciliary vascular system, both from the ophthalmic artery. The central retinal artery (CRA) which passes through the optic disc branches in the retinal inner layers step by step. The lager vessels are mainly distributed in the RNFL, and the capillaries emanating from them run downward to the outer plexus layer (OPL). On the other side, the short posterior ciliary arteries pierce the

sclera at the posterior pole and arborize to form the arterioles of the outer choroid. Then the terminal small vessels interweave to form the choriocapillaris, adjacent to the BM[18, 19]. Hence, the CRA is responsible for blood supply to the inner retina, while the posterior ciliary arteries nourish the choroid along with the outer layer of retina by osmosis and diffusion[20]. Hypertension and diabetes are both commonly associated with macrovascular and microvascular complications[21]. The differential vascular remodeling of small arterioles and capillaries can cause microcirculation disorders, which also affect the capillary systems of retina and choroid in the fundus[22, 23]. The related tissues they provide nutrients for are damaged as well. This study observed some decrease in the retinal and choroidal flow density measured by OCTA in the patients with hypertension or diabetes, which could support the conclusion that the diseases cause microvascular damage. At the same time, it can be shown that OCTA is a novel, rapid and noninvasive method to quantify the ocular vascular system. In the early stage of hypertension and diabetes, the subtle changes of microcirculation can be timely and effectively observed, thereby providing a good reminder for the occurrence and development of the diseases.

The boundary between the SVP and DVP defined in OCTA examination is from the RNFL to OPL in the retina where the CRA and its branches distribute. Thus, the parameters related to the SVP and DVP reported by OCTA such as FD represent the state of the central retinal vascular system. In the same way, those of the OVP and choriocapillaris indicate whether the ciliary vascular system is healthy or not. Decreased FD means the damage of microcirculation in the corresponding layer[24]. It was observed in some patients with hypertension or diabetes in this study. The results suggest that the systemic diseases such as hypertension and diabetes can affect the vascular system of retina and choroid simultaneously, and it was consistent with some previous studies[25–28]. However, most existing studies only focused on the changes in the function and anatomy of the retina or choroid, which means there was no correlation investigated between the two in terms of time and degree. Only for hypertensives, their CFD was decreased while the other FDs still maintained normal level. But through reviewing the relevant papers, several studied mentioned that hypertension significantly reduced retinal DFD in patients[15, 25, 28, 29]. We think that the difference was firstly due to the milder condition of the hypertensives in this study, which did not cause obvious ocular lesions. Secondly, analyzing the data further on, we found that the retinal DFD was slightly lower in hypertensives than in healthy subjects, but there was no statistical significance. This finding seems to confirm the previous article and added that the damage of retina occurred later and milder than choroid. The conclusion has also been drawn in glaucoma and DR that the posterior ciliary arteries may suffered more severe damage than the retinal vessels due to structural pathological changes[30, 31]. And it may be explained by the far more restricted capacity for regulating the microcirculation with the absence of glial cells and the reduced pericyte ensheathment[32]. In addition, the choroidal circulation is controlled by sympathetic nerve and cannot regulate itself[33], but the retina, however, does the opposite. Then, for diabetics, the FDs of the SVP and choriocapillaris both declined, which has been mentioned in several existing studies respectively. Some other studies have emphasized that diabetes causes an extensive damage to the retinal and choroidal vascular systems, with exactly reduced FD of each layer[34–36]. However, we observed that most of the patients enrolled in the above

studies had DR, including proliferative diabetic retinopathy (PDR), and they did not limit the severity of the disease. There was another study about the diabetics without DR, which showed no difference in the retinal FDs compared with the control group, and only a decreased in choroidal blood flow [37]. Therefore, it is reasonable to assume that the lessening of DFD is not the primary manifestation of diabetes, and the change in choroid still precede the retina.

Next the transverse comparison of the FD in each layer was carried out among the four groups. It was found that only the diabetics had a decrease in retinal SFD, while both the hypertensives and hypertensives associated with diabetes were at the same level as the controls. The phenomenon has not been described in other studies that the hypertension seems to provide a certain degree of compensation for the retinal superficial microcirculation damage caused by diabetes. We attempt to explain the results from the angle of the anatomical and pathological basis of retinal blood vessels. As mentioned above, the changes of retinal microcirculation in hypertensives primarily occur at the DVP. Remodeling of the small arteries lead to lumen stenosis, wall stiffness, and even vascular occlusion, which indicated the increased resistance during blood stream perfusion[38–40]. The hardened arterioles, meanwhile, can press against the accompanying veins and block the flow of blood[41]. All of these factors will cause obstruction of blood flow from the SVP to DVP. The dilatation of the retinal superficial microvascular lumen increases the measured value of FD and compensates for the loss caused by diabetes consequently. Then focusing on the choriocapillaris, we found that the FDs in the hypertensives, diabetics and hypertensives associated with diabetes were lower than the controls. The result revealed that in the present case, the combination of the two diseases may impair the choroid microcirculation but does not exacerbate the damage caused by a single disease. Finally, we also found that the differences in the FDs were manifested in the parafoveal region rather than the foveal region. The similar result has also emerged from some other studies[37, 42, 43]. The researchers generally believed that the fovea was the avascular area and diseases had little effect on blood flow in this area. Similarly, this could also explain the phenomenon of no difference in the retinal outer FDs among the groups.

In the multivariate comparison, we were surprised to observe that BMI was inversely proportional to the retinal SFD. In reality, there have been not sufficient descriptions consistent with the result. Most studies analyzed the influence of BMI in obese people and the conclusions varied a lot. Even some were completely contrary to our finding[44–46]. Thus we intend to further verify the effect of BMI on retinal and choroidal microcirculation in real world. What's more, there was no difference in the thickness of each retinal layer among the groups in the study. On this point, different articles have various conclusions, with some suggesting that the thickness of the retinal layers decrease due to hypertension or diabetes[39, 47–49], while others says they are not related[24]. The difference in results can be explained by changes in vascular system prior to that in retinal structure, which has been recognized in several studies. Therefore, we believe that the FD is more sensitive than retinal thickness shown in OCTA examination for auxiliary prediction of damage to target organs caused by hyperglycemia and hypertension.

The strengths of this study include that the hypertensives, diabetics, and hypertensives associated with diabetes were enrolled simultaneously. It contributes to not only comparing the difference between hypertension and diabetes in the influence on fundus microstructure, but also exploring whether the combination of them will aggravate the symptoms. This has not been reported in previous relevant studies. At the same time, OCTA was used to observe the changes in the retina and choroid in each subject, which helped to identify the differences in the duration and extent of the damage in all layers. This study was based on a large sample of real people, so the conclusions are more accurate and realistic with certain reference value. However, the study also has several limitations. First, it is a retrospective and cross-sectional study. Then, there is less data obtained from OCTA examination, so that the characteristics of retinal and choroidal lesions cannot be comprehensively summarized. In the future, it will be meaningful to compare more parameters among the four groups described above.

In conclusion, the study demonstrates that OCTA is a novel and noninvasive tool for quantifying the retinal and choroidal blood vessels. It can accurately and efficiently predict the occurrence and early development of hypertension and diabetes. Both the diseases result in lower FDs of the choriocapillaris, which occurs earlier than retina. And the retinal SFD decreased obviously in diabetes. The hypertensives associated with diabetes do not develop more severe lesions than patients with single disease, and even had higher retinal superficial FD than diabetes. In addition, the negative correlation between BMI and retinal SFD suggests that BMI is a risk factor for microvascular impairment. And there is no significant difference in the thickness of each layer among the four groups. Hence decreased CFD may be the early indicator of microcirculation injury caused by diabetes or hypertension.

Abbreviations

OCTA	optical coherence tomography angiography
FD	flow density
SFD	superficial FD
DFD	deep FD
CFD	choriocapillaris FD
DFD	deep FD
BMI	body mass index
FAZ	foveal avascular zone
VD	vessel density
VDI	vessel diameter index
DR	diabetic retinopathy
NPDR	non-proliferative diabetic retinopathy
PDR	proliferative diabetic retinopathy
ME	macular edema
IOP	intraocular pressure
OCT	optical coherence tomography
SS-OCT	swept source OCT
ILM	inner limiting membrane
RNFL	retinal nerve fiber layer
OCTARA	OCTA Ratio Analysis
SVP	superficial vascular plexus
DVP	deep vascular plexus
OVP	outer vascular plexus
IPL	inner plexiform layer
INL	inner nuclear layer
BM	Bruch’s membrane
OVL	outer vascular layer
ETDRS	Early Treatment Diabetic Retinopathy Study
MAP	mean arterial pressure

CRA	central retinal artery
OPL	outer plexus layer

Declarations

Ethics approval and consent to participate

The study has obtained the ethical approval from the Ethics Committee of Tianjin Medical University Eye Hospital (2019ky-22) and was registered on the Chinese Clinical Trial Registry Website (ChiCTR2000032280). All the subjects have signed the informed consents.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed in the study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JL and XL participated in the study design and manuscript revision. JL contributed to the data analysis and manuscript writing. KX and FG contributed to collecting data and offering statistical assistance. All authors read and approved the final manuscript.

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Tables

Tables 1 to 4 are available in the Supplementary Files section.

Figures

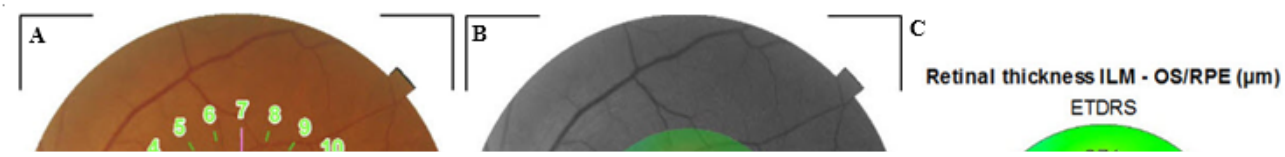

Figure 1

See image above for figure legend

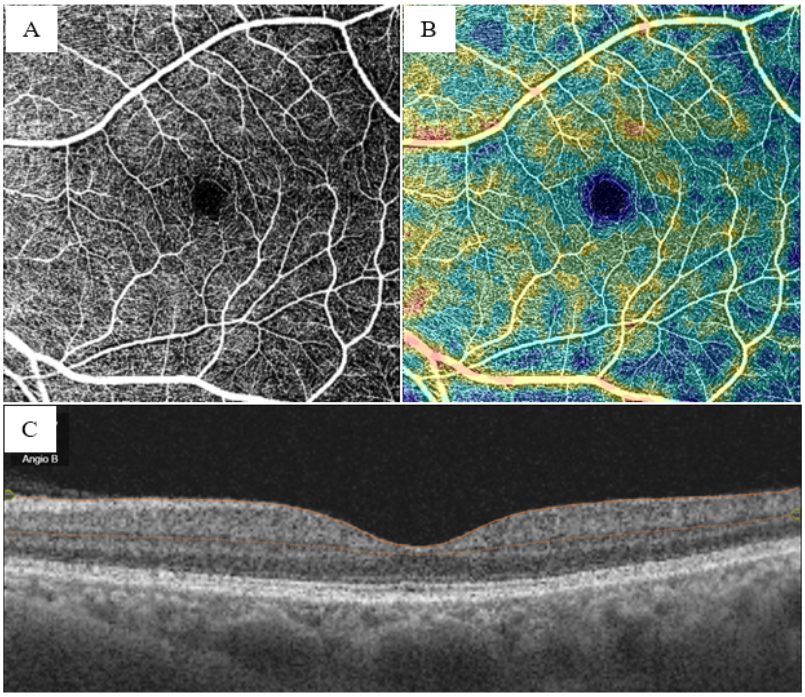

Fig 2. Superficial flow density assessed by optical coherence tomography angiography (OCTA). The blood vessels in the superficial vascular plexus were imaged by OCTA (A). IMAGENET 6.0 was used to display the vascular density map (B). The orange area in B-scan was the superficial vascular plexus automatically divided by the built-in software, ranging from 2.6μm beneath the inner limiting membrane (ILM) to 15. 6μm beneath the inner plexiform/nuclear layer (IPL/INL) (C).

Figure 2

See image above for figure legend

Supplementary Files

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