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ORIGINAL ARTICLE

The evaluation of giant-cell arteritis (temporal arteritis) cases with optical coherence tomography angiography (OCT-A)

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Abstract

To make measurements using optical coherence tomography angiography (OCT-A) in inactive giant cell arteritis (GCA) cases who have previously had GCA and have been treated and to compare the obtained data with healthy volunteers. In this observational case-control study, 18 eyes of 18 GCA cases previously diagnosed, treated with anterior arteritic ischemic optic neuropathy (AAION). 22 eyes of 22 ophthalmically healthy volunteers were included in the study. After external ophthalmic examinations of all participants were performed, their measurements were made with serial OCT-A. Superficial capillary plexus (SCP), deep capillary plexus (DCP), foveal avascular zone (FAZ), area covering 300 degrees around the fovea (FD-300), choriocapillaris (CC), retinal nerve fiber layer (RNFL), cup/disc (C/D) ratio and optic disc vessel densities (OD-VD) were evaluated. $p<0.05$ was considered significant. There was no difference between the two groups in terms of age, gender and shooting quality. Whole-SCP, SCP-foveal, SCP-parafoveal and SCP-perifoveal VD values were lower in the patient group. Whole-DCP, DCP-parafoveal and DCP-perifoveal VD values were also low in the patient group. FAZ areas were similar between groups, but the FD-300 VD was different. Whole-OD VD and inside-OD VD were significantly lower in the patient group. Peripapillary-OD VD and RNFL values were similar. The C/D ratio was higher in the patient group. The effect on the microvascular process was significant in OCT-A. This suggested that even if the ischemic process still continues and there is no active inflammation, microvascular structures may continue to be affected.

Keywords: Deep capillary plexus, giant cell arteritis, microvascular structures, optical coherence tomography angiography, superficial capillary plexus

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Introduction

Giant-Cell Arteritis (GCA), also known as Temporal Arteritis or Horton's Disease, is a type of chronic granulomatous vasculitis that typically affects the aortic arch and its primary and distal branch vessels. This disease is usually detected over the age of 50 and peaking at 70 years of age [1,2]. GCA-related vision loss is usually severe and irreversible. Several cases of vision loss caused by Anterior Arteritis Ischemic Optic Neuropathy (AAION), which occur most frequently secondarily to the involvement of the short posterior ciliary arteries, have been reported [3-6]. About twice as many women as men experience this disease. The frequency of ophthalmic manifestations in GCA ranges between 14% and 70% [5, 6]. Ischemia is detected in the laminar and prelaminar segments of the optic nerve. Pallor and edema of the optic disc may develop in classic AAION due to serious irregularity in blood circulation. Common clinical characteristics of GCA include headache, scalp and temporal artery tenderness, and symptoms of Polymyalgia Rheumatica (PMR). Chewing muscle ischemia is responsible for the symptoms of "jaw claudication". Visual symptoms, including monocular or binocular blindness and aortic aneurysm rupture or dissection, are the most severe complications of GCA. The diagnosis is based on a characteristic pattern of symptoms, physical examination outcomes, elevated acute phase reactants (Erythrocyte Sedimentation Rate [ESR] and C-Reactive Protein [CRP]), biopsy findings, and vascular imaging. Optical Coherence Tomographic Angiography (OCT-A) provides high-resolution, non-invasive, 3D imaging of retinal and choroidal vessels. The ability of OCT-A in showing deeply resolved details of the vasculature in the Z-axis provides a distinct advantage over conventional fluorescent angiography [3]. OCT-A is also an important diagnostic tool for a variety of retinopathies, including central serous chorioretinopathy, macular telangiectasia, and polypoidal choroidopathy, among others [4-6]. The distinctive characteristic of GCA that can be detected by Fluorescent Angiography (FA), is a delayed choroidal and retinal perfusion in the peripapillary region [3,4,7,8]. OCT-A with depth identification offers a novel, non-invasive, high-resolution imaging technique for the optic nerve head microvasculature [7,8]. Previous studies found that smoking increases the risk of GCA in women, but not in men. In addition, some researchers reported a possible relationship between GCA and Varicella Zoster Virus (VZV) [9,10]. To date, only a few studies described the use of OCT-A to characterize microvascular optic nerve head changes in acute ischemic optic neuropathy [11,12]. Given that ischemic is the most common recognized cause of vision loss in GCA, the investigation of ocular blood flow has actracted a great interest on the researchers about this topic. Studies such as fluorescein angiography have long been used to detect ocular ischemia, but OCT-A is also among the alternatives described. On OCT-A, patients with GCA-induced anterior ischemic optic neuropathy may show peripapillary microvascular dilation and focal non-perfusion status, which are nonspecific but common outcomes for GCA [13]. Wide-scope scan source OCT-A can confirm choroidal infarction in GCA [14]. Thus, OCT-A, as a recent diagnostic method in GCA, can make a useful contribution to the clinical diagnosis and understanding of this disease.

The aim of this study was to report the OCT-A outcomes in patients with GCA causing AAION and evaluated at the vascular level and to compare the results with those of healthy subjects.

Materials and Methods

OCT-A measurements of 18 eyes in 18 patients with giant-cell arteritis and 27 eyes of 27 systemic and ophthalmically healthy patients were collected between December 2022 and February 2023. The study was carried on the Afyonkarahisar Health Sciences Universtiy, Faculty of Medicine, Department of Ophthalmology unit. All patients underwent clinical examination and ophthalmological evaluation at the first and last visits and the cases with visual acuity measurement, cornea, and fundus examination were included in the study. Cases who had giant-cell arteritis and recovered were included in the study as the patient

group, whereas systemic and ophthalmically healthy patients were included in the study as the control group. All subjects affected by other diseases (active giant-cell arteritis, non-ischemic arteritis optic neuropathy, non-giant-cell arteritis vascular pathology, glaucoma, cataract, retinopathy, keratopathy, congenital ocular anomaly, systemic vascular disease including diabetes or systemic hypertension, pupil dilation, or hypersensitivity or intolerance to topical anesthetics or mydriatics), pregnant or breastfeeding women and patients who had undergone ocular surgery within 6 months, were excluded from the study. All participants underwent a complete ophthalmic examinations including best-corrected visual acuity, measurement of Intraocular Pressure (IOP) with Goldmann Applanation Tonometry, slit lamp examination, and fundus examination. B-scan ultrasonography was performed to evaluate the ocular and orbital structure. Central Corneal Thickness (CCT) and Axial Length (AL) were recorded by using Lenstar LS900 (Haag-Streit AG, Switzerland).

All interventional procedures in this study were performed in accordance with both ethical and Helsinki Declaration standards. Ethics Committee approval of this study was obtained from Clinical Research Ethics Committee of Afyonkarahisar Health Sciences University (Decision date: 02.09.2022, decision no: 2022/437).

Optical Coherence Tomography Angiography (OCT-A) Measurement

OCT provides detailed noninvasive visualization of the retina's structure. OCT-A can simultaneously visualize inner and outer retinal blood flow, allowing the visualization of 3D microcirculation vascular maps of the retina and choroid without using exogenous stains [15]. It is already known that the density of the vessels in the macula and the size of the Foveal Avascular Zone (FAZ) are very important in visual acuity. Recently, OCT-A has been used to diagnose and monitor retinal microvascular pathology by measuring the density of vessels in the macula in patients with diabetic retinopathy, central serous chorioretinopathy, and glaucoma, as well as in evaluating macular edema, age-related macular degeneration, and other disorders [16,17]. In this study, OCTA images were acquired from an optic nerve-centered 6×6 mm2 field by using Optovue AngioVue™ (RTVue XR Avanti, Optovue Inc., Fremont, CA., USA) and AngioAnalytics 2.0 quantization that used the Split-Spectrum Amplitude Decorrelation Angiography Algorithm. The wavelength was 840 nm, the scanning frequency was 70.000 Hz, and the lateral and axial direction discrimination was 15 μm and 5 μm, respectively. The scanning depth was 2-3 mm, the A-scan number was 304×304, and the B-scan was repeated twice in the same spot. Motion Correction Technique and DualTrac were applied throughout the entire process and HD Angio Disc 6 mm mode was used to scan a 6×6 mm area surrounding the optic nerve. The images of four layers were recorded for each patient (Superficial Capillary Plexus Density (SCPD), Deep Capillary Plexus Density (DCPD), Outer Retina (OR), and Choriocapillaris (CC). OCTA images of the macula were acquired with AngioPlex (Carl Zeiss Meditec, Dublin, CA, USA) by using a Cirrus High-Resolution OCT prototype. The macula was imaged by using a 3×3 mm scanning model. The tracking technology was used to reduce the effect of motion artifacts. Only high-quality images with a signal strength >8 were included for analysis. Parameters to evaluate the superficial and deep retinal vessels (from the inner boundary membrane layer to the inner plexus layer), including the Foveal Avascular Zone (FAZ), and vascular density, were calculated by using the manufacturer's angiometric software. Vascular Density (VD) was defined as the linear length of vessels divided into the selected area. Perfusion density represents the area of vessel distribution divided by the selected area. Although both eyes were suitable for the study, only the right eyes were selected in the final data analysis. Each position was measured twice and the peripapillary RNFL and VD were recorded. Optical disc 200×200 mode was made to obtain the RNFL results. Choroidal thickness measurements were made in the upper, lower, nasal, and temporal regions with selected locations including 500 μm, 1000 μm, 1500 μm, and 2000 μm from the fovea. All measurements were performed by an ophthalmologist.

Statistical Analysis

Data were examined by the IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) software. Average, standard deviation, median and Interquartile Range (IQR) were evaluated as basic descriptive statistical methods. Differences between the groups in term of age, gender distribution and shot quality were evaluated by X^2. The *Kolmogorov-Smirnov* test was used to test whether the data showed normal distribution. The Independent Sample t-test and *Mann-Whitney U*-test were used to test the difference between variables. The relationships of the variables were found by using the *Pearson* Correlation test. The results were evaluated at a 95% Confidence Interval and 5% significance level.

Results

18 eyes of 18 GCA patients (13 women, 5 men) and 27 eyes of 27 completely healthy participants (16 women, 11 men) were examined. There was no difference between the groups in terms of age, gender distribution and shot quality (p>0.05, respectively). The average age of the patient group was 55±16 years, while that of the control group was 56±20 years.

Patients with temporal arteritis met the remission criteria of the "2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis" [18]. The medications currently used by GCA patients in remission is reported in Table 1.

Comparing the superficial and deep vessel densities measured with OCT-A between the groups, all superficial, foveal, parafoveal, and perifoveal vessel densities resulted to be statistically different between the groups (p<0.05) (Table 2).

Deep vessel density measurements were also evaluated and all deep, parafoveal, and perifoveal deep vessel density values were found to be different (p<0.05). Although deep foveal vessel density was found to be relatively decreased in the patient group, the differences were not statistically significant (33.25±6.19, 36.75±7.97, and p>0.05, respectively). In general, superficial and deep vessel density values were found to be significantly decreased in GCA cases when compared to the healthy group. The mean FAZ in GCA cases was 0.33±0.07 mm^2 and was

Table 1. Drugs used by patients in remission.

Drug used	n	%
Metotreksat	12	%66.66
Tosilizumab	3	%16.66
Azatioprin	2	%11.11
Leflunomid	1	%5.55

Table 2. OCTA-VD: Optic Coherens Tomography Angiography-Vessel Density, SCP Whole: Whole Superficial Capillary Plexus, SCP FV: Foveal Superficial Capillary Plexus, SCP PARAFV: Parafoveal Superficial Capillary Plexus, SCP PERIFV: Perifoveal Superficial Capillary Plexus, DCP WHOLE: Whole Deep Capillary Plexus, DCP FV: Foveal Deep Capillary Plexus, DCP PARAFV: Parafoveal Deep Capillary Plexus, DCP PERIFV: Perifoveal Deep Capillary Plexus.

	Variables	Patient (18)	Control (22)	*p*-value
OCTA-VD	*SCP WHOLE*	48.95±4.6	52.9±4.1	0.016
	SCP FV	13.05±7.1	19.9±7	0.043
	SCP PARAFV	52.8±7	55±4.0	0.045
	SCP PERIFV	50.63±2.78	52.81±3.1	0.012*
	DCP WHOLE	54.45±7.5	57±6.7	0.005
	DCP FV	33.25±6.19	36.75±7.97	0.123*
	DCP PARAFV	57±5.1	60±5.2	0.001
	DCP PERIFV	55.6±6.4	59.1±6.7	0.002

larger than in the control group (0.30±0.09), but the differences were not statistically significant (p>0.05) (Table 3). However, a significant difference was found between the patient group and the healthy group in terms of vascular density in areas that covered 300 degrees of the fovea (p<0.05) (Table 3).

Comparison between the patient and control groups in terms of Flow Area (FA) values showed that vessel densities in the areas selected for the outer retina and choriocapillaris were not statistically different between the two groups (p>0.05 for all) (Table 4).

OCT analysis and OCT-A results are given in Table 5. The patient and control groups were similar in terms of mean RNFL (114.83±14.53, 114.44±11.41, and p>0.05, respectively), but the C/D ratio was different between the groups (0.11±0.07, 0.05±0.02, p<0.05, respectively). The values of the patient group were higher than the healthy controls in terms of C/D values. Significant differences were found between the groups in terms of vessel densities in the measurements made with OCT-A. Whole vessel density was 48.53±1.84 in the patient group and 49.94±2.18 in the control group (p<0.05). In terms of whole vessel density, the values of the patient group were lower than the healthy group. Also, inside vascular density was found to be lower in the patient group compared to the control group (49.23±6.32, 52.74±4.31, and p<0.05, for

Table 3. FAZ PARAMETERS: Foveal Avascular Zone Parameters, FAZ Area: Foveal Avascular Zone Area, PERIM: Perimeter, FD-300 (%): Vessel Density within a 300 μm wide region of the Foveal Avascular Zone (FAZ).

	Variables	Patient (18)	Control (22)	*p*-value
FAZ PARAMETERS	*FAZ AREA*	0.33±0.07	0.30±0.09	0.321*
	PERIM	2.23±0.27	2.16±0.42	0.504*
	FD-300 (%)	55.58±3.43	57.44±4.62	0.033

Table 4. FA: Flow Area, OR FA: Other Retina Flow Area, CC FA: Choriocapillaris Flow Area.

	Variables	Patient (18)	Control (22)	*p*-value
FLOW AREA (FA) PARAMETERS	OR FA	7.92±3.9	8.46±2.4	0.711
	CC FA	20.36±1.19	19.84±1.15	0.149*

Table 5. RNFL GLOBAL: Global Retina Nerve Layer Thickness, WHOLE VD: Whole Vessel Density, INSIDE VD: Inside Vessel Density, PERIPAPİLLARY VD: Peripapillary Vessel Density, CUP-DISC RATIO: Optic Disc Cup-Disc Ratio.

	Variables	Patient (18)	Control (22)	*p*-value
OPTIC DISC	*RNFL GLOBAL*	114.83±14.53	114.44±11.41	0.921*
	WHOLE VD	48.53±1.84	49.94±2.18	0.029*
	INSIDE VD	49.23±6.32	52.74±4.31	0.032*
	PERIPAPILLARY VD	52.26±2.14	52.20±2.69	0.992*
	CUP-DISC RATIO	0.11±0.07	0.05±0.02	0.002*

all). Peripapillary vessel density was similar between the groups (52.26±2.14, 52.20±2.69, and p>0.05, respectively). When the patient group correlations were investigated, it was determined that there was a positive, strong, and moderate linear relationship between all variables.

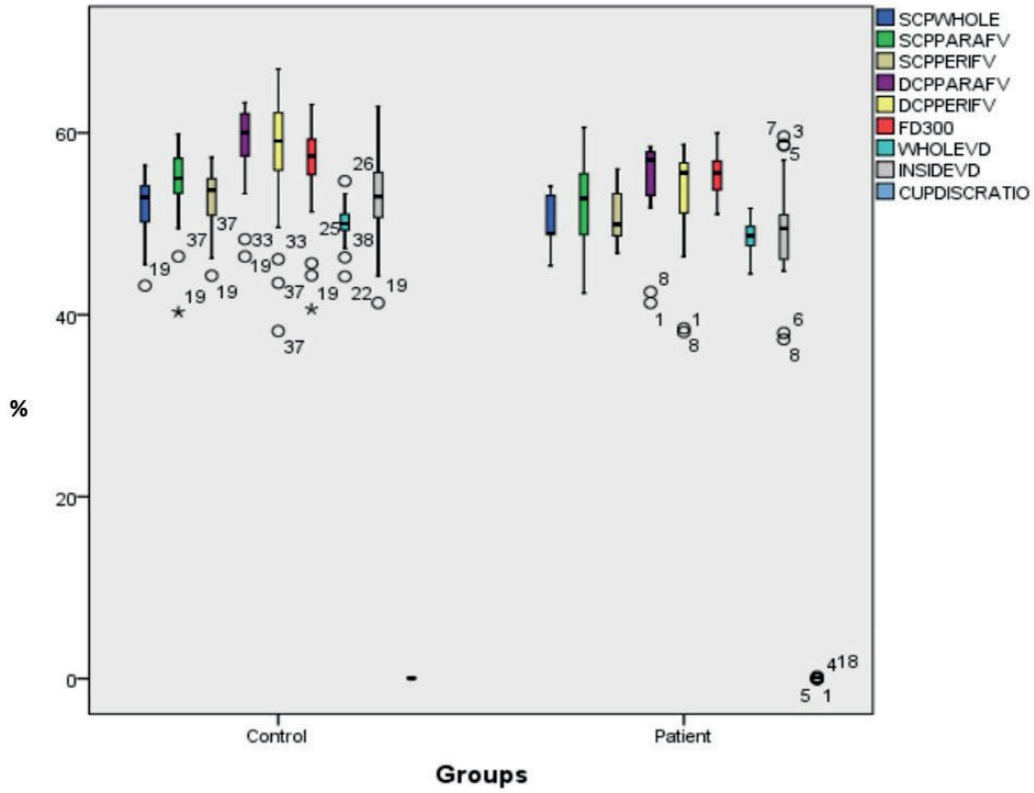

Figure 1. Distribution of SCP, DCP, VD and FD-300 in patient and control groups (SCP: Superficial capillary plexus, DCP: Deep capillary plexus, FD: Flow Density, VD: Optic disc intravascular density).

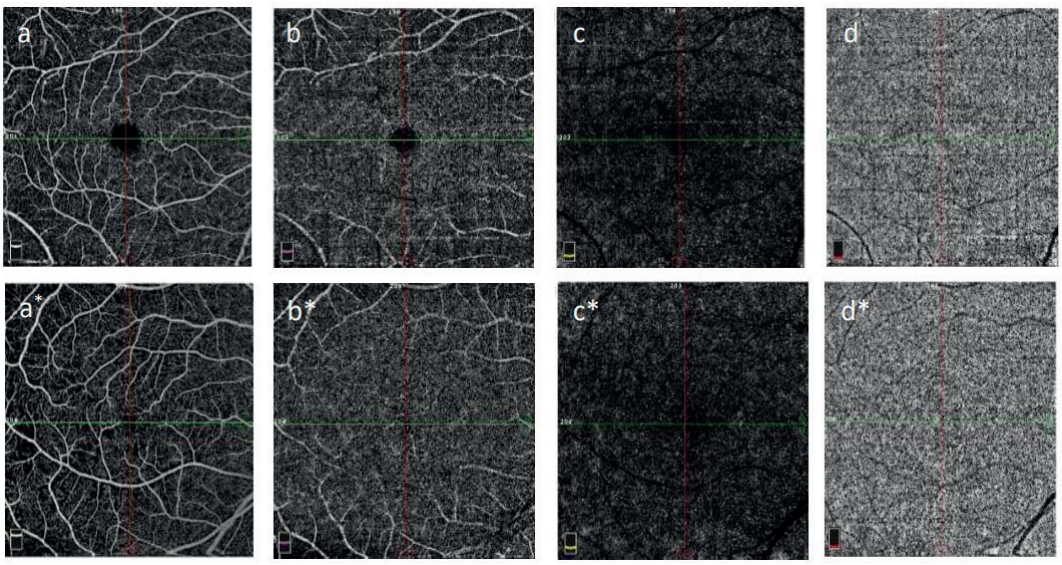

Figure 2. Right eye representation of the Angio Quickview (6.0×6.0 mm scan size with scan quality index = 8/10) segmented at the level of the süperficial capillar plexus (a, a*), deep capillary plexus (b, b*), outer retina (c,c*) and choriocapillaris (d,d*) from GCA patient (letters without asterixis) and healthy subject (letters with asterixis) respectively. Note the lower vessel densities in both superficial and deep capillary plexi in GCA patients (a,b) compared to healthy controls (a*, b*). GCA patients appear to have a similar foveal avascular region compared to healthy subjects. (a, b versus a*, b*).

Figure 1 shows the superficial and deep vessel densities that were measured with OCT-A between the groups. All superficial, foveal, parafoveal, and perifoveal vessel densities, deep, parafoveal, and perifoveal deep vessel densities are indicated. Figure 2 shows the OCTA findings of the patient group and healthy control group.

Discussion

Microvascular structures with OCT-A were investigated in patients previously affected by AAION because of GCA and the results were compared with healthy subjects. Significant reductions in superficial and deep vessel densities were detected in the study. Changes in the superficial microvascular structure, which were not seen in FA, were easily detected because of the superior resolution of OCT-A. The most common ophthalmologic manifestations of GCA are anterior ischemic optic neuropathy and central retinal artery occlusion [19]. It causes profound and irreversible vision loss in the involved eye. Pulse steroid therapy is recommended to preserve the vision of the other eye. SD-OCT shows a diffuse hyper reflection of the inner and middle retina, which represent severe ischemic injury [20]. In a recent study, Kadayifcilar et al., [21] reported that OCT-A showed thickness and reflection of inner retinal layers in the acute stage in patients with central retinal artery occlusion [20]. In the later stages, they showed that the decrease in microvascular vessel density with OCT-A became evident. In this study, decreases were found in SCP and DCP, which supports the study of Kadayifcilar et al [21]. In the present study, although the perfusion of the deep retinal capillary plexus was relatively preserved in focal acute paracentral acute middle maculopathy lesions, a significant decrease was detected in perfusion-related perfusion rate.

GCA is attributed to deep capillary ischemia because the lesion is located in the inner nuclear layer surrounded by the intermediate and deep retinal capillary plexus. Its development after persistent inner nuclear layer thinning explains an ischemic infarction. Reports were presented associating GCA with various retinal vascular diseases, including diabetic retinopathy, [22] retinal artery occlusion, central retinal vein occlusion, sickle cell and purtscher retinopathy. Retinopathy is based on ischemic pathogenesis. OCT-A is a novel method for invasive imaging of retinal vessels and can show individual retinal vessels in different layers. The neural retina is supplied by two independent circulatory systems (*i.e.,* the inner retina is supplied by the retinal artery system, and the outer retina is supplied by the choroidal circulatory system). Because retinal arterial occlusion develops in GCA, decreased vessel densities and thickening of the inner retinal layer may occur in SCP, DCP, and FD-300. Lavin et al., showed that CRAO patients have a higher risk of future cardiovascular and cerebrovascular events [23]. In the study, it was found that vessel density in SCP was reduced compared to normal control eyes. This result suggests that chronic microvascular change persists in GCA patients despite GCA recovery. Previous studies showed changes in FAZ [24] in certain vascular-related diseases such as diabetic retinopathy [25,26] and retinal vein occlusion (RVO) [27]. There are also studies reporting that FAZ is also associated with visual acuity in RVO [28] and diabetic retinopathy without diabetic macular edema [25]. Changes in FAZ can be demonstrated when the probable disease process continues. In this study, no significant changes were found in FAZ in GCA patients. The reason may be that patients whose disease process was terminated were included in the study and the inflammation process may have ended in these patients. In GCA patients, a reduction in vessel density was observed in both SCP and DCP compared to control group. Samara et al. found that both SCP and DCP vessel densities were lower in the RVO-affected eye compared to the unaffected eye in BRVO patients [28]. They also found that the vessel density of DCP was reduced in the unaffected side of the patient's BRVO eye compared to the corresponding side of the other eye [28]. FD-300 represents the vascular density of the whole retina around the 300 μm wide FAZ. FD-300 was found to be significantly reduced in GCA patients when compared to healthy controls and showed a positive correlation with the GCA stage [29]. In this study, FD-300 was found to be reduced in eyes with temporal arteritis compared to that of other eyes. In the present study, retinal vessel densities showed a positive correlation with

BCVA. Visual acuity was lower in cases with GCA and relatively permanent macular edema. More severe macular edema means a higher degree of retinal ischemia, thus considered to lead to worse BCVA. This result is consistent with the significant correlation reported by Ahn et al., regarding initial macular edema with final BCVA in CRAO patients [30].

The Radial Peripapillary Capillaries (RPC) contain straight, long vessels that originate from the peripapillary retinal arterioles located within the RNFL. In a previous study, it was shown that RPC was qualitatively attenuated in OCT-A in RAO patients [31]. In this study, significant reductions in RPCs and vascular densities of parapapillary vasculature were observed in GCA patients. Yu PK et al., reported a relationship between RNFL thickness and RPC volume in normal human donor eyes [32]. These authors argued that a positive correlation between RNFL thickness and RPC volume suggests a supportive role of RPCs for the RNFL. However, in the present study, a thinner RNFL thickness was not detected despite the decrease in RPC vessel density in the patient population. However, a significant increase was detected in the C/D ratio in the patient group. The most important limitation of the study was that the patient group included subjects who had undergone and improved GCA, in other words, none of the subjects had active GCA. Another limitation was the possibility that information outside the captured area could be missed, as OCT-A images can only capture a relatively small area around the macula or optic disc.

These parameters calculated by OCT-A analyses allowed us to acquire more insight into the eyes of GCA patients, so these parameters are promising to establish more significant clinical relevance for GCA patients. OCT-A is a new and valuable tool for evaluating ischemic changes in GCA patients.

Conclusion

In conclusion, the present study is the first in the literature reporting a decrease in capillary perfusion in both superficial and deep layers in GCA patients with OCT-A and involving a large number of participants. Previous studies in the literature are mostly case reports, in which OCT-A findings of active GCA cases were investigated. However, in the present study, the OCT-A findings of inactive and significant numbers of GCA cases were investigated. In OCT-A, the effect on the microvascular process was significant, which suggests that the ischemic process continues and microvascular structures may continue to be affected even if there is no active inflammation. Also, the study can be considered the first in which a large number of cases that would allow statistical analysis participated and the control group was included and compared with the patient group.

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Conflict of interest

The authors declared no conflict of interest.

Data availability statement

Data available on request from the authors.

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