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Choroidal vascularity index and thickness in sarcoidosis

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Abstract

Sarcoidosis is a multisystem granulomatous disease which is observed worldwide. Sarcoidosis is one of the common causes of ocular inflammation. The choroidal vascularity index, defined as the ratio of the luminal area to the total choroidal area, is used as one of the biomarkers for assessing the choroid vascular state. We aimed to compare choroidal vascularity index and thickness measurements between sarcoidosis patients and healthy controls.

Thirty-one patients with sarcoidosis and 31 age-gender matched healthy participants were recruited in this cross-sectional and comparative study. Choroidal vascularity index was defined as the ratio of luminal area to total choroidal area after binarization on optical coherence tomography images. Anterior segment examinations included central corneal thickness, corneal volume, anterior chamber depth, anterior chamber volume, and iridocorneal angle. Spectral-domain optical coherence tomography was used to measure peripapillary retinal nerve fiber layer thickness, choroidal thickness, and retinal vessel caliber.

The mean choroidal vascularity index value was 61.6% in sarcoidosis patients and 62.4% in healthy controls ($P = .69$). The choroidal vascularity index and thickness were significantly correlated in both sarcoidosis ($r = 0.41$, $P = .026$) and control groups ($r = 0.51$, $P = .006$). Both the sarcoidosis and control groups had similar measured values for central corneal thickness, corneal volume, anterior chamber depth, anterior chamber volume, and iridocorneal angle ($P > .05$). Mean retinal nerve fiber layer, retinal arteriole and venule caliber, and choroidal thickness measurements did not differ significantly between the groups ($P > .05$).

Sarcoidosis patients in quiescent period have similar choroidal vascularity index and thickness with healthy controls.

Abbreviations: CVI = choroidal vascularity index, OCT = optical coherence tomography, RNFL = retinal nerve fiber layer.

Keywords: choroidal thickness, choroidal vascularity index, retinal nerve fiber layer thickness, retinal vessel caliper, sarcoidosis

1. Introduction

Sarcoidosis is a multisystem granulomatous disease which is observed worldwide.[1,2] Sarcoidosis may affect any organ, including mainly lungs, eyes, and skin.[3,4] The underlying etiology of sarcoidosis is still unknown. The reported incidence of sarcoidosis ranges from 2 to 107 cases per 100,000 people in different races.[3,5,6] Formation of epithelioid granulomas is the characteristic feature of sarcoidosis.[1,2,7]

Sarcoidosis is one of the common causes of ocular inflammation.[8] Ocular and peri-ocular manifestations are seen in approximately 25% to 83% of patients with sarcoidosis.[3,4] All ocular structures, mostly uvea and lacrimal system, may be affected in sarcoidosis.[3,8] Uveitis, the sight threatening complication, can be diagnosed up to 20% to 30% of patients during the course of the disease.[3,8] Intraocular findings suggestive for the diagnosis of ocular sarcoidosis include conjunctival nodules, keratic precipitates, episcleritis, iris nodules, peripheral anterior synechiae, vitreous opacities, choroidal granulomas, retinal vasculitis, and optic disc nodules.[8–10]

The choroid consists of a network of capillaries and larger choroidal vessels. The choroid, which is the most vascular structure of the eye, is affected by many systemic diseases.[11] Choroidal thickness has been shown to alter in inflammatory diseases even without a direct correlation with systemic disease activity.[12] There are studies reporting reduction in choroidal thickness in patients with rheumatoid arthritis and systemic lupus erythematosus,[12,13] and changes in choroidal thickness even in subclinical sarcoidosis.[14] The choroidal vascularity index (CVI), defined as the ratio of the luminal area to the total choroidal area, is used as one of the biomarkers for assessing the choroid vascular state.[15,16] Some reports suggest that CVI has a lower variability than choroidal thickness and is influenced by fewer physiological factors.[15,16] CVI may be accepted as a relatively stable parameter for evaluating the changes in the choroidal vasculature.[15,16]

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Since it may be important to diagnose subtle ocular changes before manifest disease in sarcoidosis patients, the aim of our study was to examine the choroidal vascularity index and thickness of sarcoidosis patients.

2. Methods

Sixty-two participants (31 patients in the sarcoidosis group and 31 healthy adults in the control group) were recruited for this analytical cross-sectional study. The present study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the decree of the Ethics Council of our university with the decree dated 10.01.2017 and numbered 01.

2.1. Study population

The study group consisted of 31 patients with sarcoidosis in the quiescent disease stage applied at our Department of Chest Diseases. Their sarcoidosis diagnoses were confirmed with the help of tissue biopsy (i.e., biopsy positive), chest radiography, chest computed tomography, analyzing fluids and cells obtained by bronchoalveolar lavage, and measuring serum angiotensin-converting enzyme levels. Since sarcoidosis is relatively rare, it was not possible to find and include systemic-treatment naive patients. Exclusion criteria included any ocular surgery and a history of any ocular disease other than mild cataract or low-grade refractive errors. None of the patients exhibited signs of uveitis at the time of examinations. Participants with ametropia >2 diopters spherical equivalent or another systemic disease that could in some way affect the corneal, anterior chamber, retinal, and optic disc measurements were excluded. Subjects who had low-quality spectral-domain optical coherence tomography (OCT) or Scheimpflug photography images were also excluded.

2.2. Ocular examination techniques

Peripapillary choroidal thickness, retinal vessel caliber, and peripapillary retinal nerve fiber layer (RNFL) thickness measurements were taken using the spectral-domain OCT (Spectralis with software version 6.0, Heidelberg, Germany). The Spectralis OCT can perform 40,000 A scans per second, with an optical resolution of axial 7 μm and lateral 14 μm, using an 870-nm wavelength superluminescent diode laser.

CVI was defined as the ratio of luminal area (i.e., choroidal vessel lumen) to total choroidal area after binarization on OCT images. Nasal localization was selected due to ensure standardization for all the participants and to avoid effect of macula. Binarization of images of nasal peripapillary choroid was done by using Image J software (https://imagej.net; Version 1.50a; National Institutes of Health, Bethesda, MD, USA) (Fig. 1). Firstly, a block of grey-scale choroidal image was selected and converted to an 8-bit image. Using Image J software, a new image with only white and black colors was created according to the threshold levels obtained by Otsu method.[17] A separate threshold was determined for each image. A pixel above its local threshold is labeled as white (choroidal stroma) and a pixel below its local threshold is labeled as black (choroidal vessel lumen).

For peripapillary RNFL analysis, the thicknesses of all quadrants (superior, inferior, temporal, and nasal) were recorded separately, along with the average thickness. Retinal arteriole and venule caliber measurements were taken using manual caliber tools provided by the Spectralis software on the peripapillary RNFL analysis screen. For retinal vascular caliper examination, temporal retinal arterioles and venules that passed through an area one-half to one-disc diameter from the optic disc margin were measured (Fig. 2). The average thicknesses of the superior and inferior temporal retinal vessels were calculated for each eye. The peripapillary choroidal thickness values were measured from the outer surface of the hyper-reflective line that corresponds to the retinal pigment epithelium to the inner part of the sclera in 4 quadrants (i.e., superior, inferior, nasal, and temporal) (Fig. 3). The average thickness of the 4 quadrants was recorded as the choroidal thickness. One eye of each participant was included randomly in the analysis to ensure the avoidance of selection bias. The CVI and retina-choroidal thickness manual measurements were performed by 2 researchers (GP, SA) and average of their values were recorded in order to avoid measurement bias.

Central corneal thickness, corneal volume, iridocorneal angle, anterior chamber depth, and anterior chamber volume measurements were obtained by the Pentacam HR (Oculus, Wetzlar, Germany). A Pentacam HR provided objective measurements of the ocular anterior segment structures; it uses a rotating Scheimpflug camera to capture images and software to analyze

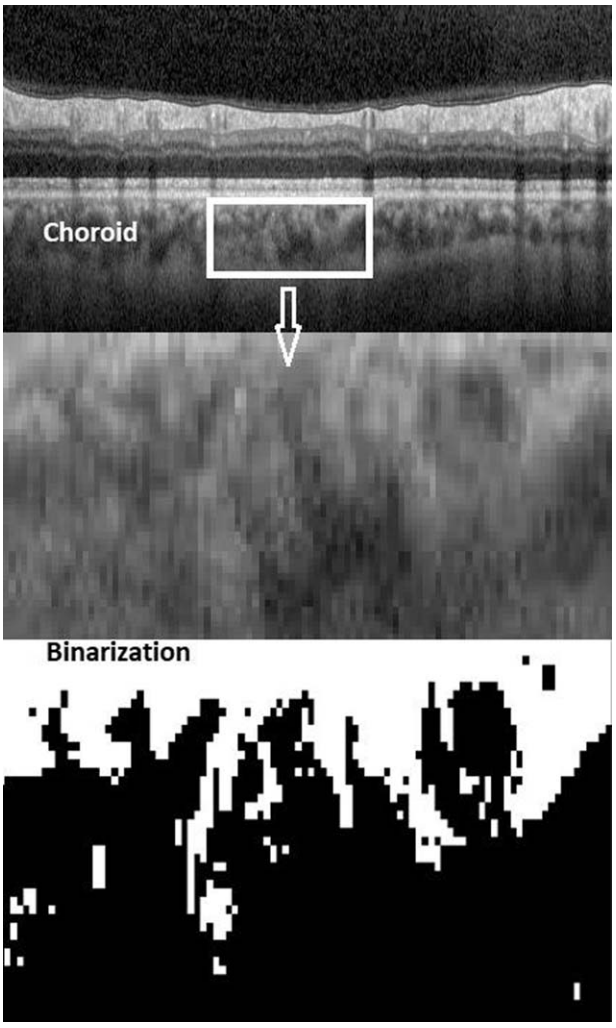

Figure 1. Binarization of an image of nasal peripapillary choroid is shown.

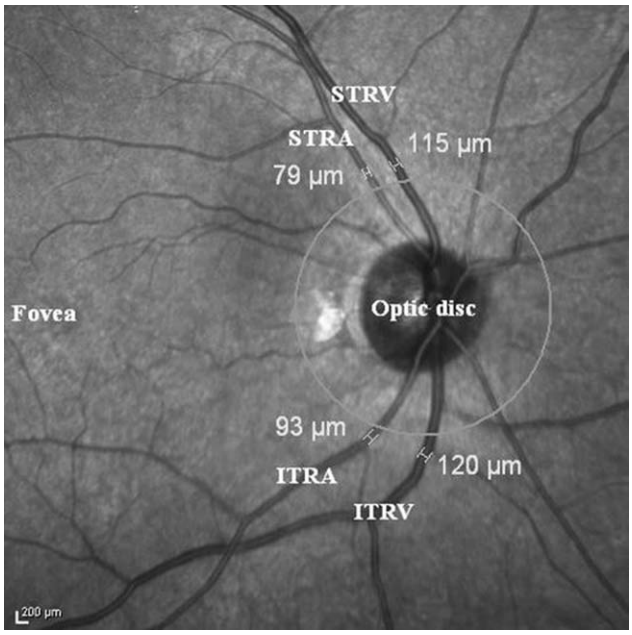

Figure 2. Retinal arteriolar (RAC) and venular caliber (RVC) measurement screen is shown (ITRA = infero-temporal retinal arteriole, ITRV = infero-temporal retinal venule, STRA = supero-temporal retinal arteriole, STRV = supero-temporal retinal venule).

the cornea and anterior chamber. For lacrimal system assessment (i.e., to investigate for aqueous tear deficiency), the Schirmer test (with 1 drop of topical anesthetic) was performed using a strip of filter paper measuring 35×5 mm that was bent at one end and placed in the lower conjunctival sac about a third of the palpebral width from the temporal canthus. Since lacrimal gland involvement may be seen in sarcoidosis, the Schirmer test can determine whether the eye produces sufficient tears to maintain moistness in those patients. The intraocular pressure (IOP) measurements were taken with an air-puff tonometry (TonoRef II, Nidek, Japan).

Table 1

Some of the clinical characteristics of the patients are shown.

	Sarcoidosis group	Control group	*P* value
VA (logMAR)	0.006 ± 0.025	0.000 ± 0.000	.16
Refraction (SE)	0.02 ± 0.90	0.23 ± 0.83	.35
IOP, mm Hg	14.4 ± 3.2	14.8 ± 2.5	.57
Schirmer test, mm	9.2 ± 5.2	9.1 ± 4.5	.92

IOP = intraocular pressure, SE = spherical equivalent diopters, VA = visual acuity.

2.3. Statistical analysis

In the statistical analysis, Statistical Package for the Social Sciences 17.0 software for Windows (SPSS Inc., Chicago, IL) was used to analyze outcomes. "*P*" values $< .05$ were taken as statistically significant and all data were written as "mean ± standard deviation." A *t* test with independent samples was used to compare the studied parameters between the study group and the control group where patients with missing data were excluded from statistical analysis. Pearson test was used to search for the correlations between the studied parameters. For sample size calculation we used a *t* test table by taking alpha 0.05, beta 0.20, and standard effect size 0.70. The existence of a normal distribution was tested with the Shapiro-Wilk test ($P > .05$ for the studied parameters). The homogeneity of variance was tested with the Levene test ($P > .05$ for the studied parameters). Visual acuity values were converted to logMAR for statistical analysis.

3. Results

The mean age of the sarcoidosis patients was 48.6 ± 11.6 years and the mean age of the control group was 47.1 ± 7.0 years ($P = .54$). There were 10 male participants (32%) and 21 female participants (68%) in both the sarcoidosis and control groups. Table 1 presents some of the clinical data. Both of the groups had similar visual acuity, refractive error, intraocular pressure, and Schirmer test results.

The mean choroidal vascularity index value was 61.6% in sarcoidosis patients and 62.4% in healthy controls ($P = .69$). The

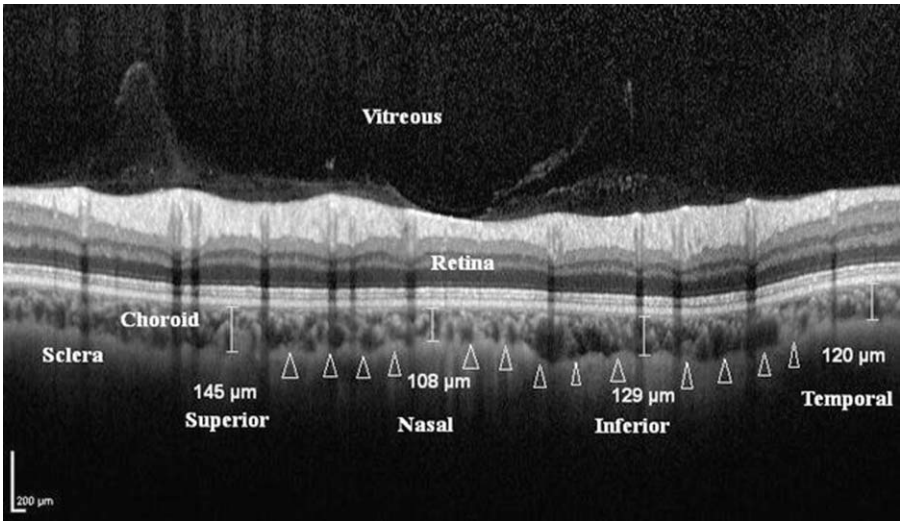

Figure 3. Peripapillary choroidal thickness measurement screen is shown (white arrow heads show the border of the sclera and choroid).

Table 2

Sectoral peripapillary RNFL thickness (inferior, superior, nasal, and temporal quadrants) measurements are demonstrated.

	Sarcoidosis group	Control group	*P* value
Inferior quadrant, μm	132.3 ± 17.7	135.4 ± 15.5	.47
Superior quadrant, μm	127.6 ± 18.5	130.9 ± 15.4	.44
Nasal quadrant, μm	81.6 ± 17.8	86.5 ± 18.4	.30
Temporal quadrant, μm	71.1 ± 8.1	73.5 ± 11.3	.33

RNFL = retinal nerve fiber layer.

mean peripapillary choroidal thickness value was 173.0 ± 42.6 μm in the sarcoidosis group and 186.3 ± 54.9 μm in the control group ($P = .30$). The choroidal vascularity index and choroidal thickness were significantly correlated in both sarcoidosis ($r = 0.41$, $P = .026$) and control groups ($r = 0.51$, $P = .006$). The mean peripapillary RNFL thickness was 103.1 ± 11.1 μm for the sarcoidosis group and 106.6 ± 9.5 μm for the control group ($P = .19$). Table 2 contains the mean sectoral peripapillary RNFL thickness measurements. All sectoral RNFL thickness values were similar between the groups ($P > .05$).

Table 3 shows the anterior segment measurements of the participants. Both the sarcoidosis and control groups had similar measurements in terms of central corneal thickness, corneal volume, anterior chamber depth, anterior chamber volume, and iridocorneal angle. The mean retinal arteriole caliber value was 84.4 ± 7.5 μm in the sarcoidosis group and 84.3 ± 5.8 μm in the control group ($P = .96$), while the mean retinal venule caliber value was 122.6 ± 11.3 μm in the sarcoidosis group and 122.4 ± 12.7 μm in the control group ($P = .95$).

Peripapillary choroidal thickness was correlated with retinal venule caliber only in sarcoidosis patients ($r = 0.38$, $P = .04$), while not correlated with retinal venule caliber in healthy controls ($r = 0.11$, $P = .58$). On the other hand, choroidal thickness was correlated with anterior chamber depth only in healthy controls ($r = –0.46$, $P = .01$), while not correlated with anterior chamber depth in sarcoidosis patients ($r = –0.13$, $P = .49$).

4. Discussion

The outcomes of the present research show that sarcoidosis patients who are in quiescent period exhibit similar CVI and choroidal thickness with healthy adults. Although sarcoidosis may affect almost every structure of eye; cornea, anterior chamber, preocular tear film production, intraocular pressure, RNFL, choroid and retinal vessels are not deteriorated in patients without clinical ocular manifestations. But one cannot be sure whether those patients would not have ocular complications in future.

In eye, choroid may be affected by many systemic inflammatory diseases. Recently CVI has been used as a biomarker of systemic diseases in several research.[11,18] CVI can be calculated both in the subfoveal and peripapillary regions.[19] In the present study, peripapillary CVI was similar in patients with sarcoidosis and healthy controls. The findings of this study may suggest that choroidal vasculature may not be affected in sarcoidosis in quiescent period. In the present study, the peripapillary choroidal vascularity index and thickness were significantly correlated in both sarcoidosis and control groups, which may be considered as a normal physiological finding.

Sarcoidosis may cause severe visual acuity disturbance when single or multiple involvement of the ocular structures occur.[9] In this study, the visual acuity values were similar in both the sarcoidosis patients and healthy adults. The increase of intraocular pressure is not rare in patients with sarcoidosis related uveitis.[20,21] Since the patients in the present study did not have uveitis history, intraocular pressure was in normal range in sarcoidosis patients. Lacrimal system problems, such as swelling of the lacrimal glands and dry eye syndrome, are among the most common complications of ocular sarcoidosis.[22,23] In this research, aqueous tear production was not found to be decreased in sarcoidosis patients by means of Schirmer test and we surmise that lacrimal gland involvement might not be present in those patients.

Other ocular complications of sarcoidosis include uveitis, anterior uveitis, and peripheral anterior synechiae.[21,24–26] In the present study, cornea, anterior chamber, and iridocorneal angle, which are among the favorite sites for sarcoidosis related ocular inflammation, were investigated. It was found that corneal morphology, anterior chamber morphology, and iridocorneal angle are not influenced in sarcoidosis without clinically apparent ocular involvement.

In the present study, posterior segment findings such as peripapillary choroidal thickness, retinal arteriole caliber, retinal venule caliber, and peripapillary RNFL thickness were similar in the sarcoidosis patients and healthy controls. Güngör et al[14] reported that patients with ocular sarcoidosis had thinner subfoveal choroids in the quiescent periods compared with healthy participants. Different from their study, we measured choroidal thickness in the peripapillary region rather than subfoveal region and our patients did not have a history of ocular involvement of sarcoidosis. In the present study, there was a positive correlation between peripapillary choroidal thickness and retinal venule caliber in sarcoidosis patients but not in healthy controls, which might be an incidental finding. It might be expected that the RNFL thickness could be affected in sarcoidosis, since the most common neuro-ophthalmic presentation of sarcoidosis is optic neuropathy.[27] Although not observed in the patients of the present study, retinal perivascular sheathing, a common finding in ocular sarcoidosis, might increase the measured retinal vascular caliber values.[28]

The present paper has its limitations. First of all, the sample size was relatively small; because sarcoidosis is a rare disease and the incidence of sarcoidosis is approximately 5 to 10 cases per 100,000 population in Turkey.[29] Second, only the patients in the quiescent disease stage, which did not have a history of ocular involvement, were included. Third, choroidal thickness measurements were only performed in the peripapillary region. Lastly, some other ocular imaging techniques, such as OCT angiogra-

Table 3

Anterior segment measurements of the participants taken via Pentacam HR are shown.

	Sarcoidosis group	Control group	*P* value
CCT, μm	542.5 ± 34.3	535.6 ± 33.7	.43
CV, mm^3	59.2 ± 3.2	58.6 ± 3.1	.48
ACD, mm	2.75 ± 0.40	2.72 ± 0.33	.78
ACV, mm^3	145.0 ± 39.5	146.3 ± 33.0	.89
ICA, °	31.4 ± 6.5	32.7 ± 5.2	.41

ACD = anterior chamber depth, ACV = anterior chamber volume, CCT = central corneal thickness, CV = corneal volume, ICA = iridocorneal angle.

phy, might be performed to better visualize the vascular status of superficial and deep layers of retina.

In conclusion, in quiescent disease period, sarcoidosis patients without a history of ocular involvement, have similar ocular anterior and posterior segment measurements when compared with healthy controls. A novel measurement parameter, choroidal vascularity index, was also found to be similar between those groups. Future research including ocular measurements with novel devices in eyes with sarcoidosis related active inflammation would provide better insight about the topic.

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Writing – review & editing: Erhan Ugurlu, Gokhan Pekel, Goksel Altinisik.

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