

The Influence of Seasonal Allergic Conjunctivitis and Its Treatment on Choroidal Vascular Index



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ABSTRACT

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Purpose: To evaluate the effects of seasonal allergic conjunctivitis (AC) and its treatment upon choroidal structure such as choroidal thickness (ChT) and choroidal vascular index (CVI) through the use of topical antihistamine agents. **Methods.** The 60 eyes of 30 patients were included in the AC group. Another 30 patients were included in the control group. The choroid was imaged by using enhanced depth imaging optical coherence tomography (EDI-OCT) instrument without pupillary dilation. ChT was defined as the area between the outer hyperreflective border of the RPE and the sclerochoroidal border at the fovea, 750 μ m temporal to the fovea and 750 μ m nasal to the fovea. Image J was used to measure CVI. With the images obtained from EDI-OCT, the total choroidal area (TCA), luminal area (LA), stromal area (SA), and CVI were calculated using the binarization method. **Results.** The mean ChT value in the AC group was 358.5 ± 93.8 μ m at baseline and 356.8 ± 86.6 μ m following 1 month of treatment. Meanwhile, the mean ChT in the control group was 316.6 ± 60.7 μ m. The mean CVI value was 66.65 ± 2.98 in the control group, 70.75 ± 3.26 in the AC group at baseline, and 69.50 ± 3.17 following 1 month of treatment. Statistically significant difference was tracked between control and AC group ($p = 0.028$) and control group and posttreatment values ($p = 0.031$). There were no statistically significant difference between initial AC treatment values and posttreatment values for all of the measurements. **Conclusion.** ChT and CVI can increase in patients with AC due to inflammation and increased vascular permeability. Although symptoms and signs related to AC may disappear after the treatment, effects in the choroid do not immediately normalize.

Keywords: Allergic conjunctivitis, binarization method, inflammation, choroidal thickness, choroidal vascular index

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Влияние сезонного аллергического конъюнктивита и его лечения на хориоидальный сосудистый индекс

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РЕЗЮМЕ

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Цель: оценить влияние сезонного аллергического конъюнктивита (АС) и его лечения с помощью местных антигистаминных препаратов на толщину хориоидеи (ХТ) и хориоидальный сосудистый индекс (ХВИ). **Методы.** В группу АС были включены 60 глаз 30 пациентов. 30 пациентов вошли в контрольную группу. Сосудистую оболочку визуализировали с помощью прибора оптической когерентной томографии с улучшенной глубинной визуализацией (EDI-OCT) без расширения зрачков. ХТ определяли как площадь между внешней гиперрефлексивной границей РПЭ и склерохориоидальной границей в ямке, 750 мкм в височную сторону от ямки и 750 мкм в носовую сторону. Изображение J использовалось для измерения CVI. На изображении, полученных с помощью EDI-OCT, с использованием метода бинаризации рассчитывали общую площадь хориоидеи (ТСА), площадь просвета (LA), площадь стромы (SA) и CVI. **Результаты.** Среднее значение ХТ в группе АС составило $358,5 \pm 93,8$ мкм исходно и $356,8 \pm 86,6$ мкм через 1 месяц лечения. При этом средний ХТ в контрольной группе составил $316,6 \pm 60,7$ мкм. Среднее значение CVI составляло $66,65 \pm 2,98$ в контрольной группе, $70,75 \pm 3,26$ в группе АС на исходном уровне и $69,50 \pm 3,17$ через 1 месяц лечения. Статистически значимая разница наблюдалась между контролем и группой АС ($p = 0,028$) после лечения ($p = 0,031$). **Заключение.** ХТ и ХВИ могут увеличиваться у больных АС вследствие воспаления и повышения проницаемости сосудов. Хотя симптомы и признаки, связанные с ОХ, могут исчезнуть после лечения, эффекты в сосудистой оболочке не нормализуются сразу.

Ключевые слова: аллергический конъюнктивит, метод бинаризации, воспаление, толщина сосудистой оболочки, хориоидальный сосудистый индекс

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Конфликт интересов отсутствует

INTRODUCTION

Allergic conjunctivitis (AC) refers to a group of inflammatory diseases affecting the ocular surface that are caused by an abnormal immune-hypersensitivity to environmental allergens. AC is histologically characterized by the infiltration of inflammatory cells, including neutrophils, eosinophils, lymphocytes, and macrophages, into the conjunctiva [1].

Situated between Bruch's membrane and the sclera, the choroid layer is a highly vascularized tissue that receives approximately 85 % of the blood that enters all ocular tissue and plays important roles in ocular function. Among others, it provides the retina pigment epithelium (RPE) and outer retina with nutrients and oxygen, as well as secretes vital growth factors [2]. The choroid's structure is primarily determined by the route and branching pattern of both the anterior and posterior ciliary arteries [3, 4]. The choroid's dense sympathetic and parasympathetic autonomic innervation due to short and long ciliary nerves suggests its association with the autonomic nerve system in regulating choroidal thickness (ChT) by modulating choroidal blood flow and altering the tone of nonvascular smooth muscle [2].

Improvements in optical coherence tomography (OCT) technology have allowed reliable, repeatable measurements of the choroid by using enhanced depth imaging OCT (EDI-OCT) [5, 6]. Objective supplemental information about the choroid's structure, including ChT and the choroidal vascular

index (CVI), has also been made available in recent years by virtue of binarization, a method that allows viewing the choroid in greater detail [7]. Such techniques have revealed that ChT and CVI are affected by refractive abnormalities, age, and ethnicity [8, 9]. In other recent studies, short-term alterations in ChT and CVI have also been identified as being associated with time of day, caffeine consumption, and smoking [10–13]. It has additionally been demonstrated that the choroid's stromal and vascular structure is affected by a wide variety of systemic diseases [14–20].

However, to the best of our knowledge, no study has investigated the effect of AC and its treatment on CVI. Thus, the aim of our study was to evaluate the effects of AC and its treatment on aspects of the choroid's structure, namely ChT and CVI, during the use of topical antihistamine agents.

METHODS

The primary outcome targeted in our study was whether ChT and CVI values showed differences between patients with AC and healthy controls. The secondary outcome was the effect of treatment with topical antihistamine agents on ChT and CVI.

To gauge those outcomes, the 60 eyes of 30 patients with AC were included in the study following a biomicroscopic evaluation of all patients who applied to our clinic with the complaints of stinging, burning, and watering. In addition, 30 sex- and age-matched healthy patients were recruited as

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a control group. The study was approved by Fatih Sultan Mehmet Training and Research Hospital's Ethics Committee and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

All patients received a full ophthalmologic examination including autorefractometry, the measurement of intraocular pressure (IOP) by air puff tonometry, the assessment of best corrected visual acuity (BCVA) according to the Snellen chart, slit lamp biomicroscopy, and a fundus examination. We included only patients with IOP ≤ 18 mmHg, BCVA 20/20, and ≤ -1 diopter of refractive errors in spherical equivalents and ≤ -1 diopter of refractive errors in cylindrical equivalents. Patients in either group with a history of ophthalmic disease were excluded, as were patients with any systemic disease that might affect ChT and CVI (e.g., hypertension and diabetes).

The choroid was imaged by using an SD-OCT instrument (RS-3000 Advance, Nidek, Japan) without pupillary dilation. All examinations were performed between 11:00 and 12:00 a.m. to avoid the effect of diurnal variation on ChT and CVI. ChT was defined as the area between the outer hyper-reflective border of the RPE and the sclerochoroidal border at the fovea, 750 μ m temporal to the fovea and 750 μ m nasal to the fovea (Fig. 1).

Image J (National Institutes of Health, Bethesda, MD, USA) was used to measure CVI. EDI-OCT images were converted to 8-bit images and binarized with Niblack's auto local thresholding tool to determine total choroidal area (TCA) by manually drawing the sclerochoroidal border and lower border of the RPE. Afterward, the images were converted to red–green–blue color types to allow the delimitation of the luminal area (LA) and stromal area (SA), with dark pixels corresponding to the LA (i.e., the vascular area) and white ones corresponding to the SA (Fig. 2).

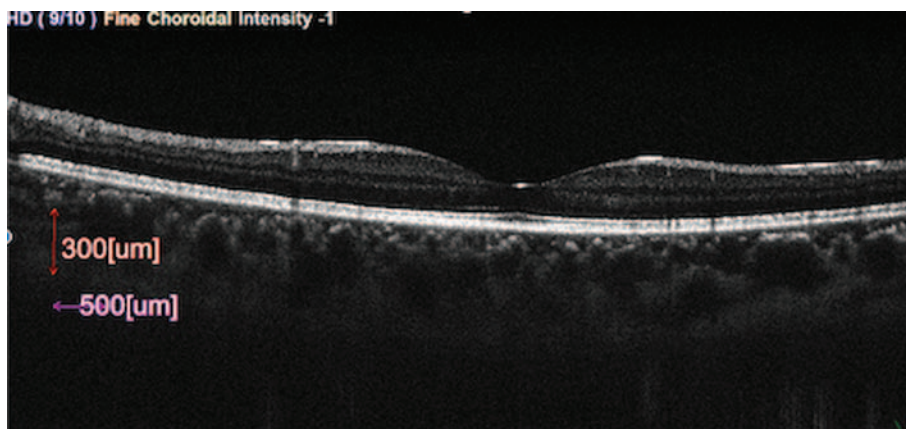


Fig. 1. A representative enhanced-depth imaging domain optical coherence tomography (EDI-OCT) imaging of a patient

Рис. 1. Оптическая когерентная томография (EDI-OCT) с увеличенной глубиной изображения

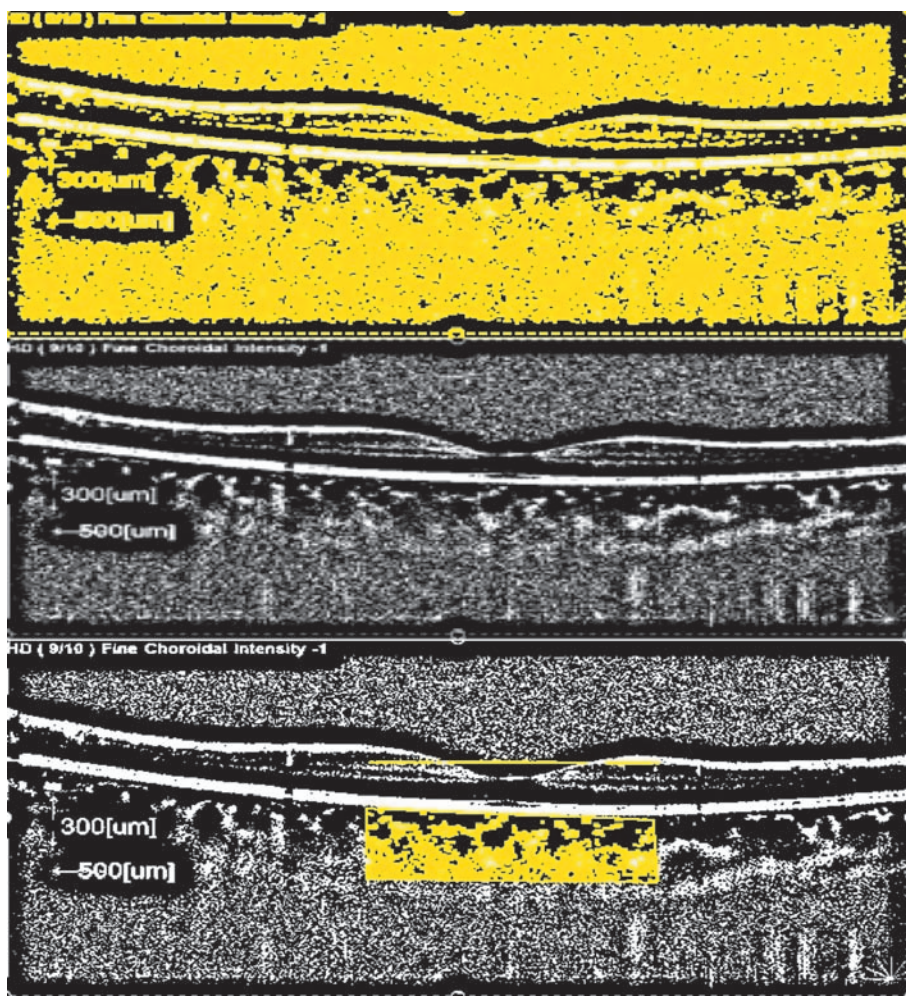


Fig. 2. Choroidal vascularity index (CVI) calculation with binarization of enhanced-depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT) image. The CVI is calculated dividing luminal area by total choroidal area

Рис. 2. Расчет индекса васкуляризации хориоидеи (CVI) с бинаризацией (SD-OCT) с увеличенной глубиной изображения (EDI). CVI рассчитывается путем деления площади просвета на общую площадь хориоидеи

CVI was calculated as the ratio of LA/TCA. All measurements were made in triplicate by an experienced ophthalmologist (UC), and the average of the three measurements was used in statistical analysis. Measurements with a difference of more than 10 % were considered to be inconsistent and thus excluded from the study.

All patients with seasonal AC underwent SD-OCT examination before and after 1 month of antihistamine treatment so that the initial values could be compared with the values determined 1 month post-treatment. The initial and post-treatment values were also compared with the values of the control group. Anti-allergic therapeutic agents such as antihistamine and mast cell stabilizers (0.1 % Olopatadine hydrochloride) were prescribed to participants in the experimental group and recommended to be used 2 times a day for 1 month.

All statistical analyses were performed in SPSS for Windows version 23.0 (IBM, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous variables. After determining that all continuous variables were normally distributed, post-treatment ChT and CVI values were compared with the baseline values using a paired *t* test, and both values were compared with those of the control group using the independent *t* test. All *p* values less than .05 were considered to indicate statistical significance.

RESULTS

The 60 eyes of 30 patients—15 males and 15 females—were included in the AC group. Their mean age was 26.4 ± 7.5 years. Another 30 patients—also 15 males and 15 females—were included in the control group; their mean age was 27.5 ± 6.2 years. Thus, no statistically significant differences in age or gender emerged between the groups, as shown in Table 1.

The mean ChT value in the AC group was 358.5 ± 93.8 μm at baseline and 356.8 ± 86.6 μm following 1 month of treatment. Meanwhile, the mean ChT in the control group was 316.6 ± 60.7 μm . Statistically significant differences were found between the control and AC groups at baseline ($p = .028$) and between the control group's values and the post-treatment values ($p = .031$), as shown in Table 2.

The mean CVI value was 66.65 ± 2.98 in the control group, 70.75 ± 3.26 in the AC group at baseline, and 69.50 ± 3.17 following 1 month of treatment. Other statistically significant differences emerged between the control and AC groups at baseline ($p < .001$) and between the control group's values

and the post-treatment values ($p < .001$), as also shown in Table 2.

Among other results, mean TCA and LA values were significantly lower in control group than in the AC group at baseline and after treatment (all $p < .001$). However, there were no statistically significant differences between initial AC treatment values and post-treatment values for any of the measurements.

DISCUSSION

In our study, we investigated whether a difference exists in ChT and CVI values among patients with clinical symptoms and signs of seasonal AC. We also examined the effect of antihistamine treatment on ChT and CVI among such patients. To the best of our knowledge, no previous study has investigated the effect of AC and its treatment on CVI values.

Seasonal AC is characterized by increased levels of histamine, tryptase, prostaglandins, and leukotrienes in tears due to the activation of specific IgE-mediated conjunctival mast cells. Activated mast cells also release several cytokines that stimulate epithelial cells and fibroblasts to produce pro-inflammatory cytokines and chemokines, which lead to persistent conjunctival inflammation and an inflammatory response to allergens, both of which increase blood flow [1].

A highly vascular tissue, the choroid has been shown to play a role in the pathogenesis of various ocular diseases [14–21]. Beyond that, changes in ChT [15, 16] and CVI [17–19] have been shown to be associated with ocular pathologies—for example, age-related macular degeneration and central serous chorioretinopathy (CSC)—and recovery following ocular surgery and oral treatments [22, 23]. In Maruko et al.'s study, eyes with CSC was significantly greater

Table 2. Choroidal vascularity index (CVI), subfoveal choroidal thickness (ChT), total choroidal area (TCA), luminal area (LA) and stromal area (SA) measurements of the groups

Таблица 2. Индекс васкуляризации хориоидеи (CVI), субфовеальная толщина хориоидеи (ChT), общая площадь хориоидеи (TCA), площадь просвета (LA) и площадь стромы (SA) в группах

	Control group	Allergic conjunctivitis	Allergic conjunctivitis (post treatment first month)	<i>p</i>
ChT (μm)	316.6 ± 60.7	358.5 ± 93.8	356.8 ± 86.6	* 0,758 † 0,028 ‡ 0,031
TCA (mm^2)	0.65 ± 0.14	0.76 ± 0.18	0.75 ± 0.16	* 0,443 † <0,001 ‡ <0,001
LA (mm^2)	0.43 ± 0.06	0.53 ± 0.08	0.52 ± 0.09	* 0,458 † <0,001 ‡ <0,001
SA (mm^2)	0.22 ± 0.04	0.23 ± 0.06	0.23 ± 0.05	* 0,694 † 0,443 ‡ 0,397
CVI (%)	66.65 ± 2.98	70.75 ± 3.26	69.50 ± 3.17	* 0,386 † <0,001 ‡ <0,001

Note: ChT — choroidal thickness, TCA — total choroidal area, LA — luminal area, SA — stromal area, CVI — choroidal vascular index. * — Paired *T* Test between initial and posttreatment values. † — Independent *T* Test between control group and initial values. ‡ — Independent *T* Test between control group and posttreatment values.

Table 1. Demographic data of the groups

Таблица 1. Демографические данные групп

Variables	Allergic conjunctivitis group (n = 30)	Control group (n = 30)	<i>p</i>
Sex; Male	15	15	1
Female	15	15	
Age (years)	$26,4 \pm 7,5$	$27,5 \pm 6,2$	0,889

than that in fellow eyes, while the eyes without subfoveal ChT in CSC but with choroidal vascular hyperpermeability had greater ChT [21]. Other research has shown that CVI values are significantly lower in eyes with chronic CSC and choroidal neovascularization than in non-neovascularized ones [17]. In the same vein, Ozcaliskan et al. showed that the eyes with intermediate age-related macular degeneration demonstrated had low CVI compared with healthy eyes [18]. In our study, inflammation due to allergies may have increased the ChT and CVI values that we calculated. Likewise, Rizzo et al. showed that CVI values decrease following epiretinal membrane removal when compared with fellow eyes. They attributed that finding to secondary inflammation resulting from mechanical traction that induces ChT by increasing the vascularization of the choroid [19]. In another study, in patients with posterior uveitis due to Behçet's disease, ChT increased in the acute phase of the disease but decreased thereafter [20].

Yenigun et al. evaluated whether there was any statistically significant difference in ChT between their control group and a group with allergic rhinitis. The mean subfoveal ChT was $367.49 \pm 92.73 \mu\text{m}$ among the 61 patients with allergic rhinitis and $327.62 \pm 72.39 \mu\text{m}$ among the 35 patients without the condition [24]. Our data corroborate those data, for we found higher values in the AC group. In another study, the mean subfoveal, nasal, and temporal ChT were $382.1 \pm 121.7 \mu\text{m}$, $328.6 \pm 111.8 \mu\text{m}$, and $368.1 \pm 98.2 \mu\text{m}$, respectively, in patients with allergic rhinitis and 378.5 ± 87 , $309 \pm 77 \mu\text{m}$, and $354.2 \pm 94.2 \mu\text{m}$, also respectively, in the group of healthy participants. Although the values were higher in the group with allergic rhinitis, as in the previous study, they were not statistically significant [25].

In a study conducted by Ayyıldız et al. involving the 60 eyes of 30 children and adolescents with AC and the 60 eyes of 30 healthy controls, the mean initial subfoveal ChT

was $364.1 \pm 63.8 \mu\text{m}$ in the AC group but $333.5 \pm 52.1 \mu\text{m}$ 1 month after treatment. Meanwhile, in the control group, the mean subfoveal ChT was $320.6 \pm 80.9 \mu\text{m}$. Similar to us, they also found a significant difference in baseline ChT between the AC and control groups. Although the values did not return to normal even 1 month after treatment in our study, in their study post-treatment values were similar to the ones observed in the control group, along with a statistically significant decrease in ChT after the treatment of patients with AC. In our study, no significant change occurred after treatment among such patients. In our study, we evaluated the change in CVI values, whereas the other authors compared only ChT [26]. By comparison, Yılmaz et al. compared the right eyes of 59 patients with asthma (i.e., 20 males and 39 females) and the right eyes of 50 healthy controls (i.e., 19 males and 31 females) in terms of CVI and ChT. Both values were significantly lower among the patients with asthma [27]. Last, Kocak et al. reported that CVI values were significantly lower among smokers than among healthy controls [11]. In the case of hypoxemia due to asthma or smoking, it can be expected that CVI values would decrease even further.

Altogether, ChT and CVI can increase in patients with AC due to inflammation and increased vascular permeability. Such hyperpermeability can cause choroidal thickening owing to the accumulation of fluid, and the expansion of the choroidal vessels could play a partial role as well. Although symptoms and signs related to AC may disappear, effects in the choroid do not immediately normalize. To the best of our knowledge, ours was the first study to demonstrate the probable relationship between increased CVI and AC. Even so, because our sample was small, studies with more patients are needed to confirm our findings and to fully clarify the mechanism of increased ChT and CVI among patients with AC.

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