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Short-term effect of angiotensin converting enzyme inhibitor on choroidal vascularity

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ABSTRACT

Purpose: To determine the effect of angiotensin-converting enzyme (ACE) inhibitors on choroidal vascularity using the binarization method in a group of treatment-naïve hypertensive patients.
Methods: There were 48 treatment-naive hypertensive patients who were diagnosed according to the "2013 European Society of Hypertension/European Society of Cardiology" guideline and started angiotensin-converting enzyme inhibitor perindopril (Coversyl) in the study. As a control group, 48 healthy volunteers were randomly selected among people who attended the outpatient clinic for routine ophthalmological examination. Enhanced-depth imaging optical coherence tomography (EDI-OCT) images were captured at baseline and at 1 month after treatment. Binarization of the EDI-OCT images was performed by Image-J software. The choroidal thickness (CT), total choroidal area, luminal area, stromal area, and choroidal vascularity index (CVI) were measured.
Results: There was a statistically significant increase in CT at all locations (subfoveal, nasal, and temporal) at 1 month after treatment compared with baseline (for all, $p<0.001$). Choroidal structural parameters and the mean CVI were statistically significantly increased at 1 month after treatment (for all, $p<0.001$). When compared, there was no statistically significant difference for the vascular parameters between the control group and the patient group at 1 month (for all, $p>0.05$).
Conlusion: A statistically significant improvement was demonstrated in the choroidal vascular parameters except for the stromal area after treating with an ACE inhibitor in a group of hypertensive patients.

1. Introduction

Angiotensin-converting enzyme (ACE) inhibitors are a group of drugs used primarily for the treatment of elevated blood pressure. They inhibit the activity of ACE, an important component of the renin-angiotensin system which converts angiotensin I to angiotensin II and breaks down bradykinin [1]. Angiotensin II causes constriction of arterioles and venules, inhibits the reuptake of norepinephrine, stimulates the release of catecholamines, and hypertrophy of vascular smooth muscle cells. Another hypothesis is that ACE inhibitors interfere with the degradation of bradykinin, a peptide that causes vasodilation. Therefore, ACE inhibitors decrease the formation of angiotensin II, a vasoconstrictor, and increase the level of bradykinin, a peptide vasodilator [1].

The main function of the choroid is to provide vascular supply to the outer retinal layers, provide oxygen and clear waste products. Choroidal blood flow does not have an autoregulatory capacity like the retinal vascular system. Imaging of the choroidal vascular system, in vivo, can be performed by various modalities including fluorescein angiography, indocyanine green angiography, and optical coherence tomography (OCT) [2,3]. Enhanced depth imaging (EDI) OCT is a recent technique that has enabled high-quality non-invasive imaging of the choroid [4–8].

Though hypertension-related choroidal changes have been vastly studied in the past, data regarding the effect of antihypertensive drugs on choroidal vascularity is very limited. In this study, we aimed to determine the effect of ACE inhibitors on choroidal vascularity using the binarization method in a group of treatment-naïve hypertensive patients.

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2. Methods

This cross-sectional prospective study was carried out at Kırşehir Training and Research Hospital between February 2021 and May 2021. There were 48 treatment-naive hypertensive patients who were diagnosed according to the "2013 European Society of Hypertension/European Society of Cardiology" guideline and started angiotensin-converting enzyme inhibitor perindopril (Coversyl) in the study. As a control group, 48 healthy volunteers were randomly selected among people who attended the outpatient clinic for routine ophthalmological examination. The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee. An informed consent form was obtained from all participants.

Exclusion criteria were as follows: eyes with Snellen chart best-corrected visual acuity less than 20/25, spherical equivalent refractive error more than ±2.0 diopters and intraocular pressure more than 21 mmHg, systemic (infectious diseases, malignancy, diabetes mellitus, migraine, pulmonary diseases, cardiac arrhythmia, any arterial disease, obstructive sleep apnea syndrome) or ocular conditions (glaucoma, uveitis, high myopia, age-related macular degeneration), history of intraocular surgery (cataract surgery, vitrectomy). None of the participants in the study have ever smoked. The participants did not consume caffeine and/or alcohol before the examinations.

After confirming the diagnosis, at the start of the treatment, all patients were consulted to the Ophthalmology Clinic for a detailed ophthalmological examination. The patient group and the controls underwent a comprehensive ophthalmologic examination, including best-corrected visual acuity, anterior segment and dilated fundus examinations, intraocular pressure (IOP) measurement (non-contact tonometer), and axial length (AL) measurement (Lenstar LS 900, Hagg-Streit AG, Koeniz, Switzerland).

Macular imaging was performed using EDI mode of spectral domain-OCT (software version 6.3.3.0, Heidelberg Engineering Inc., Heidelberg, Germany). All measurements were made at baseline and at 1 month after treatment. Before capturing the images, keratorefractive values of the subjects were entered into the software of the OCT device to estimate optical magnification. EDI-OCT images were captured under dim light conditions between 9:00 am and 12:00 pm in the same room by a single experienced staff technician. The images were assessed by the blinded staff physicians who were experienced in the technique. Only one eye per patient was included if both eyes met the criteria.

The OCT device contained a superluminescent diode with a wavelength of 870 nm and could obtain 40.000 A-scans per second. The axial and transverse resolutions were 7 and 14 μm, respectively. Two high-quality horizontal line scans were obtained through the fovea using a1×30-degree areas. One hundred scans were averaged for each section. The automatic real-time averaging mode that maximizes the signal-to-noise ratio was used to ensure high-quality images.

Choroidal thickness (CT) was measured from the posterior edge of the retinal pigment epithelium to the sclerochoroidal junction. The CT was measured at the following 3 locations; subfoveal, 1500 mm nasal to the fovea, and 1500 mm temporal to the fovea (Fig. 1).

Binarization was done with Image J (Version 1.50a; National Institutes of Health, Bethesda, MD, USA). The 3000-micrometer wide area with margins of 1500 micrometer temporally to the fovea was selected. The choroid was delineated as the area between the outer RPE and the inner sclera and the borders were positioned manually with the ROI Manager. Image adjusted by the Niblack auto local threshold (Fig. 2). The total circumscribed choroidal area (TCA), luminal area (LA), and stromal area (SA) were automatically calculated. Choroidal vascularity index (CVI) was formulated as the ratio between LA and TCA.

SPSS 11.5 (SPSS Inc., Chicago, IL) was used for all comparisons. All results are given as mean±standard deviation. Paired sample *t*-test was used for intragroup comparisons, independent sample *t*-test and chi-square tests were used for intergroup comparisons. The results were considered statistically significant when the p value was less than 0.05.

3. Results

The mean age of the participants was 51.4 ± 9.3 years (range, 40–77) in the patient group and 51.1 ± 9.4 years (range, 41–78) in the control group ($p = 0.642$). There were 24 (50.0%) females and 24 (50.0%) males in both groups ($p = 0.544$).

The mean AL was 23.1 ± 0.9 mm (range, 21.2–24.6) in the patient group and 23.2 ± 0.8 mm (range, 21.4–24.5) in the control group. The mean IOP was 14.3 mmHg (range, 11–15) in the patient group and 14.1 mmHg (range, 11–15) in the control group ($p = 0.641$ and $p = 0.528$, respectively).

The demographic data and clinical parameters of the study groups were summarized in Table 1.

The mean subfoveal CT in the patient group was 302.4 ± 64.5 μm at baseline and 342.6 ± 73.5 μm in the control group ($p = 0.004$). The mean subfoveal CT was increased to 336.4 ± 66.2 μm at 1 month after treatment. The mean nasal CT was 272.4 ± 61.8 μm in the patient group at baseline, and 302.5 ± 65.2 μm in the control group ($p = 0.021$). The mean nasal CT was increased to 294.3 ± 63.2 μm at 1 month. The mean temporal CT was 274.4 ± 52.8 μm in the patient group at baseline, and 329.4 ± 88.5 μm in the control group ($p = 0.001$). The mean temporal CT was increased to 318.4 ± 54.5 at 1 month. There was a statistically significant increase in all locations at 1 month after treatment compared with baseline (for all, p<0.001). When compared, the difference between the control group and the patient group at 1 month was not statistically significant (for all, $p>0.05$).

The CT measurements and statistical comparisons in the study groups were given in Table 2.

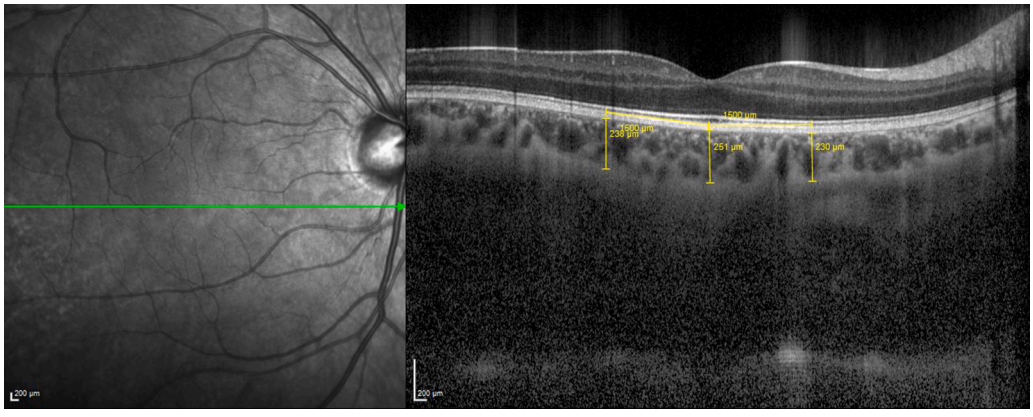

Fig. 1. The choroidal thickness was measured at the following 3 locations; subfoveal, 1500 mm nasal to the fovea, and 1500 mm temporal to the fovea.

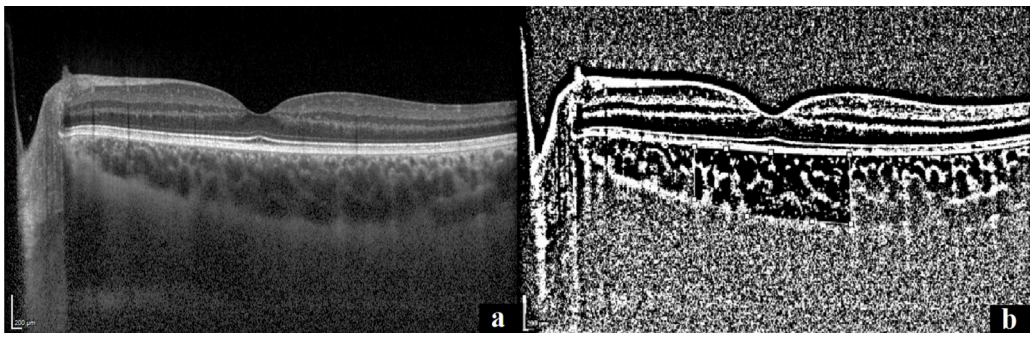

Fig. 2. a: EDI-OCT image of an eye in the control group.
b: Converted binary image using ImageJ with the area of interest in the choroid demarcated with a white line. The choroidal area was measured at approximately 3000 micrometers wide with the margins of 1500 micrometer nasal and 1500 micrometer temporal from the foveal center.

Table 1
Demographic data and clinical parameters of the study groups.

	Patients group	Control group	*p*-value
Age (years) Mean±SD (Range)	51.4 ± 9.3 (40–77)	51.1 ± 9.4 (41–78)	0.642
Female/Male	24/24	24/`4	1.000
AL (mm) Mean±SD (Range)	23.1 ± 0.9 (21.2–24.6)	23.2 ± 0.8 (21.4–24.5)	0.641
IOP (mmHg) Mean±SD (Range)	14.3(11–15)	14.1 (11–15)	0.528

SD: Standard deviation; AL: Axial length; IOP: Intraocular pressure

Table 2
Choroidal thickness changes before and after treatment in hypertensive group.

Parameter (Mean±SD)	Baseline	At 1 month after treatment	Controls	*p*-value
Subfoveal choroidal thickness	302.4 ± 64.5	336.4 ± 66.2	342.6 ± 73.5	<0.001[1] 0.004[2] 0.051[3]
Nasal choroidal thickness	272.4 ± 61.8	294.3 ± 63.2	302.5 ± 65.2	<0.001[1] 0.021[2] 0.165[3]
Temporal choroidal thickness	274.4 ± 52.8	318.4 ± 54.5	329.4 ± 88.5	<0.001[1] 0.001[2] 0.056[3]

[1] Baseline versus treatment.
[2] Baseline versus control.
[3] Treatment versus control.

The mean TCA was 0.774±0.091 mm^2 in the patient group and 0.901±0.07 mm^2 in the control group ($p = 0.003$). The mean TCA was 0.841±0.073 mm^2 at 1 month after treatment. The mean LA was 0.568±0.125 mm^2 in the patient group and 0.678±0.109 mm^2 in the control group ($p = 0.008$). The mean LA was 0.630±0.101 mm^2 at 1 month after treatment. The mean SA was 0.206±0.075 mm^2 in the patient group and 0.223±0.070 mm^2 in the control group ($p = 0.319$). The mean SA was 0.211±0.082 mm^2 at 1 month after treatment. The mean CVI was%72.97±0.110 in the patient group and%74.93±8.66 in the control group ($p = 0.028$). The mean CVI was%74.69±11.2 at 1 month after treatment. Choroidal structural parameters and the mean CVI except the SA were statistically significantly increased at 1 month after treatment (for all, p<0.001). When compared, there was no statistically significant difference for the vascular parameters between the control group and the patient group at 1 month (for all, $p>0.05$).

Binarized choroidal parameters in the study groups were listed in Table 3.

Table 3
Binarized choroidal parameters before and after treatment in hypertensive group.

Parameter (Mean±SD)	Baseline	At 1 month after treatment	Controls	*p*-value
Total choroidal area (mm^2)	0.774±0.091	0.841±0.073	0.901±0.07	<0.001[1] 0.003[2] 0.146[3]
Luminal area (mm^2)	0.568±0.125	0.630±0.101	0.678±0.109	<0.001[1] 0.008[2] 0.186[3]
Stromal area (mm^2)	0.206±0.075	0.211±0.082	0.223±0.070	0.753[1] 0.319[2] 0.529[3]
Choroidal vascularity index (%)	72.97±11.0	74.69±11.2	74.93±8.66	<0.001[1] 0.028[2] 0.486[3]

[1] Baseline versus treatment.
[2] Baseline versus control.
[3] Treatment versus control.

4. Discussion

In the current study, for the first time in the literature, the short-term effect of the ACE inhibitor on the choroidal vascular parameters was evaluated in a group of previously untreated and newly diagnosed hypertensive patients.

Branchini et al. [9] were the first to use an automated software to calculate the area of dark and light pixels corresponding to the luminal and stromal areas of the choroid. Sonoda et al. [10] described a different technique to compute luminal and stromal areas using binarized EDI-OCT scans. Agrawal et al. [4] proposed a new quantitative parameter called CVI as a new OCT parameter for measuring the vasculature status of the choroid in healthy eyes. They evaluated the vascularity of the choroid in healthy eyes and found that about two-third of the subfoveal choroid in a single scan was composed of vascular tissue. Later, numerous studies have been published so far regarding choroidal vascular parameters and the potential applications in the evaluation and management of several disorders of the retina and the choroid [11–13].

Angiotensin-converting enzyme inhibitors are currently recommended in guidelines for the reduction of cardiovascular risk in patients with systemic hypertension. By preventing bradykinin breakdown, they activate the nitric oxide pathway and reduce the formation of the vasoconstrictive peptide, endothelin-1, that has been shown to cause contraction on the human ophthalmic artery [14]. Among the ACE inhibitor group, the agent perindopril, in particular, has multiple effects that are superior to the other ACE inhibitors, including bradykinin selectivity and subsequent enhancement of nitric oxide and inhibition of endothelial cell apoptosis [15].

Renin angiotensin system are locally synthesized in the eyes, lungs

and liver of the human body [16]. The possible role of this system is to maintain the local vascular homeostasis. Senanayake et al. evaluated the distribution of angiotensin II and its receptors in the human retina and identified angiotensin II and its metabolites in the Müller cell layer. They also detected angiotensin receptors in the blood vessels and neural cells and suggested that both local signaling and the autonomous system can modulate the severity of vascular diseases of the retina [17]. The EUCLID Study enrolled the diabetic patients and observed that the ACE inhibitor lisinopril reduced the risk of progression of retinopathy and also significantly reduced the risk of progression to proliferative retinopathy [18].

According to the results of our study, at baseline, the choroidal parameters were significantly decreased when compared with healthy controls. There was a statistically significant increase in the TCA, LA, SA, and CVI values in the patient group at 1 month after the ACE inhibitor treatment in comparison to the baseline measurements. When we evaluated the luminal and stromal components of the choroidal vasculature, we observed that the enlargement included both compartments, but that the enlargement of LA was more prominent. When compared, there was not any statistically significant difference for the vascular parameters between the control group and the patient group at 1 month.

The innervation of the choroidal flow is mediated by the sympathetic and parasympathetic nervous systems, via central mechanisms regulated mainly by the retinal metabolic demands and systemic blood pressure, but additionally, regulation of local perfusion pressure seems to be affected by local autoregulatory myogenic mechanisms. The autonomic nervous system and its sympathetic arm also play an important role in the regulation of systemic blood pressure. Therefore, in the study, the choroidal parameters at baseline might be decreased due to an impairment in the neural control of the choroidal vascularity in the hypertensive patient group. Prolonged activation of the sympathetic nervous system can act on vascular smooth muscles of the choroidal vessels and promote constriction of the capillaries which may affect the total choroidal structure. After the start of the ACE inhibitor, a significant improvement occurred in all parameters in a short time period. This supported the hypothesis that the effect of the ACE inhibitor on choroidal vascularity was modulated by the vascular innervation.

The only study on the effect of ACE inhibitors and angiotensin receptor blockers on the choroidal tissue was reported by Balbaba et al. [19] According to their results, ACE inhibitors and angiotensin receptor blockers, used in the treatment of hypertension, caused an increase in the CT in the short-term. The authors did not find a significant difference in the CT between the two drug groups. In this study, the CT at baseline showed a significant increase in all three locations at 1 month after treatment. The difference between the control group and the patient group at 1 month was not statistically significant.

Up to now, the CT has been widely used as a robust tool in recent clinical researches, although it only reflects the total choroidal volume without distinctions between the stromal and luminal vascular components [20,21]. A continued interest still remains to find a better clinical tool as a biomarker to assist in the treatment and follow-up of cardiovascular diseases. As a pure vascular structure, the choroid may reflect a vascular change that may be the local expression of systemic vascular disease. The early changes may lead to the use of the choroidal parameters, for instance, the CVI, as a noninvasive screening test for local and systemic vascular diseases. Repeating the EDI-OCT imaging of the choroid may also be useful for supervision of the vascular changes in order to avoid further ocular damage.

The patient group comprised an older Caucasian population, and therefore any results derived from this study may not be applicable to those of different ethnicities and younger ages. The relationship between the CVI and age has been investigated in previous studies. While Oh et al. [22] reported no significant correlations of CVI with age, Ruiz-Medrano and co-workers [23] found CVI to be significantly higher in subjects under 18 years of age compared with the older subjects. Further analysis of CVI variation between older and younger adults is needed. Hypertension rarely presents as an isolated condition, and it is usually associated with cardiovascular comorbidities, like coronary heart disease, cerebrovascular events, heart failure, diabetes mellitus, etc. Prior to the study, a detailed medical history regarding the associated comorbidities was recorded and patients with systemic and local diseases affecting the choroidal vasculature were not included.

The study had some limitations. First, it had a cross-sectional design, therefore longitudinal studies should investigate the effect of ACE inhibitors on the choroidal structure further. Second, the sample size is relatively small. We were unable to increase the number of the patients due to the pandemic research conditions and strict exclusion criteria, as including only the treatment-naive patients. Third, the RPE line and scleral border were determined manually which may be a source of error in measuring the CT. The strength of our study is the evaluation of the short-term effect of an ACE inhibitor on choroidal vascularity in a group of patients with newly diagnosed hypertension.

In conclusion, in the current study, a statistically significant improvement was demonstrated in the choroidal vascular parameters except for the stromal area after treating with an ACE inhibitor in a group of hypertensive patients. In order to better understand the short- and long-term effects of ACE inhibitors on the choroidal vascular system, it would be useful to extend this study further with a larger population of patients across a range of different ethnicities.

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