Evaluation of The Chorioretinal Thickness in Patients with Internal Carotid Artery Stenosis Using Spectral-Domain Optical Coherence Tomography

İnternal Karotis Arter Tıkanıklığı Olan Hastalarda Spektral Domain Optik Koherens Tomografi Kullanılarak Korioretinal Kalınlığın Değerlendirilmesi

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ABSTRACT

Purpose: To assess the chorioretinal thickness using spectral-domain optical coherence tomography (SD-OCT) in patients with internal carotid artery (ICA) stenosis.

Materials and Methods: Twenty-one consecutive subjects (14 male and 7 female) with an age range of 51-85 years who had ICA stenosis (with ≥40% ICA stenosis on one side and less than 40% stenosis on the other side) were included in our study. 21 eyes with ≥40% ipsilateral ICA stenosis as the patient group and 21 eyes with less than 40% ipsilateral ICA stenosis as the control group of 21 subjects were included in the study. Choroidal thicknesses (CT) were measured at eleven locations: the fovea, 500-1500-3000µm temporal to the fovea, 500-1500-3000µm nasal to the fovea, 1000-2000µm superior to the fovea, and 1000-2000µm inferior to the fovea by enhanced depth imaging optical coherence tomography (EDI-OCT). The correlation between CT values and ipsilateral ICA stenosis ratios was explored.

Results: Except at 3000µm temporal and 1000µm inferior, all CT measurements at other nine localizations were significantly decreased in the patient group as compared to the control group ($p<0.05$). There was no a proportional relationship between the CT values and ipsilateral ICA stenosis ratios.

Conclusion: Choroidal thickness is decreased on the same side with >40% carotid artery stenosis as compared to the fellow eyes with <40% stenosis. It is important to diagnose and treat ICA stenosis before permanent complications occur. Therefore, we suggest investigating patients with CT reduction for early detection of ICA stenosis.

Key Words: Carotid artery stenosis, Choroidal thickness, EDI-OCT, 3D Carotid artery angiography.

ÖZ

Amaç: İnternal karotis arter (İKA) tıkanıklığı olan hastalarda, spektral domain optik koherens tomografi (SD-OKT) kullanılarak, korioretinal kalınlık değişikliklerinin değerlendirilmesi.

Gereç ve Yöntemler: Bizim çalışmamıza, bir taraf İKA arterlerinde ≥% 40 ve diğer tarafta <% 40 darlığı olan, 51-85 yaş arası 21 olgu dahil edildi. 21 olgunun İKA'de ≥% 40 darlığı olan taraftaki 21 gözü hasta grup, diğer taraftaki 21 gözü ise kontrol grubu olarak çalışmaya alındı. Koroidal kalınlık EDI- OKT kullanılarak on bir bölgeden ölçüldü (fovea, 500-1500-3000 µm fovea temporali, 500-1500-3000 µm fovea nazali, 1000-2000 µm fovea süperioru ve 1000-2000 µm fovea inferioru). Koroidal kalınlık değerleri ile aynı taraf İKA tıkanıklık oranları arasındaki korrelasyon araştırıldı.

Bulgular: Koroidal kalınlık ölçümleri hasta grupta, kontrol grubuna göre temporal 3000 µm, ve inferior 1000 µm hariç, diğer 9 bölgede istatiksel anlamlı azalmış bulundu ($p<0.05$). Koroidal kalınlık ölçümleri ile aynı taraf İKA darlık oranları arasında ilişki saptanmadı.

Sonuç: Koroidal kalınlık, %40 ve üzeri İKA tıkanıklığı olan gözlerde, %40'tan az tıkanıklığı olan diğer göze göre azalmıştır. İKA tıkanıklığını, kalıcı komplikasyonlar gelişmeden önce teşhis ve tedavi etmek önemlidir. Bu yüzden, koroidal kalınlığı azalmış hastalarda, erken dönemde İKA tıkanıklığını saptamak için araştırma yapılmasını öneriyoruz.

Anahtar Sözcükler: Karotis arter tıkanıklığı, Koroidal kalınlık, EDI-OKT, 3D Karotis arter anjiografi

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INTRODUCTION

Branches of Ophthalmic artery (OA) which is the first intracranial branch of Internal Carotid Artery (ICA) supply all parts of the eye.[1] The choroid is supplied by short, long posterior ciliary arteries and anterior ciliary artery and it is one of the best-supplied tissue in the human body. The main component of the choroid is blood vessels.[2] It has a critical role in oxygen and nutrient supply to outer retinal layer.[3]

ICA stenosis is one of the most common neurological diseases. Occlusion on ICA can decrease ocular blood flow and cause hypoperfusion.[4] The severity of the disease depends on the existence of both cerebral ischemic and ocular ischemic symptoms. Ocular symptoms are the ocular ischemic syndrome, neovascular glaucoma (NVG) and vascular occlusion.[5] Some patients have amaurosis fugax, diplopia, decreased visual acuity or permanent blindness. These may be the reason of the importance of early diagnosis of ICA stenosis.[6]

Because of its rich vessel content, choroid is the best tissue to evaluate the ocular perfusion. A previous study by using indocyanine green (ICG) angiography showed that obstruction of choriocapillary vessels due to the ICA obstruction caused a severe choroidal hypoperfusion.[7]

Longer wavelength swept source OCT and enhanced depth imaging OCT (EDI OCT), which are two of the recently developed optical coherence tomography (OCT) image modalities, provide better visualization of choroid compared to the older techniques like ICG angiography and ultrasonography.[8] By means of the choroid thickness measurement, we can evaluate the physiopathology underlying most of the diseases such as central serous chorioretinopathy, degenerative myopia, Vogt-Koyanagi-Harada disease and polypoidal choroidal vasculopathy.[9-12]

We hypothesize that; on the same side with the stenotic carotid artery, the choroidal thickness may be affected because of ocular hypoperfusion due to the carotid artery stenosis. We compare the choroid thickness of eyes in the patient group that has ≥40 % ipsilateral and control group that has less than 40% ipsilateral ICA stenosis by using OCT and EDI-OCT methods.

MATERIALS AND METHODS

This study was approved by the local ethics committee of the site at which it was conducted and performed in agreement with the ethical standards outlined in the Declaration of Helsinki. Informed consent was obtained from all participating subjects before their inclusion in the study. Twenty-one consecutive subjects (14 male and 7 female) with an age range of 51-85 years who had ICA stenosis (with≥40% ICA stenosis on one side and less than 40% stenosis on the other side) which underwent both carotid artery color doppler sonography and carotid CTA were included in our study. The patients were recruited from cardiovascular surgery outpatient clinic and their eyes were grouped as patient group and control group. The patient group consisted of 21 eyes with≥40% ipsilateral ICA stenosis and the control group consisted of 21 eyes with less than 40% ipsilateral ICA stenosis of same subjects.

Exclusion criteria were: Best-corrected visual acuity (BCVA) <20/40; refractive error >± 4 spherical equivalent; axial length <22mm and >26mm; poor image quality <6/10 because of severe cataracts or unstable fixation; pre-existing macular pathologies such as age-related macular degeneration, epiretinal membrane or macular hole; other retinopathies such as retinal vascular occlusion or retinal dystrophy; pre-existing ocular diseases such as glaucoma or uveitis; previous intraocular surgery or laser treatment except for cataract surgery performed at least 12 months before enrollment; previous interventions to carotid arteries.

All patients underwent a complete ophthalmologic examination including best-corrected visual acuity (BCVA) measurements, anterior- posterior segment biomicroscopy, intraocular pressure(IOP) with Goldman's applanation tonometry, central corneal thickness (CCT) measurements with optic pachymeter (Lenstar LS 900, Haag-Streit AG, Köniz, Switzerland), axial length (AL) and ocular biometry measurements with optical biometry (Lenstar LS 900, Haag-Streit AG, Köniz, Switzerland), dilated fundus examination, fundus photography (Visucam NM-FA, Carl Zeiss Meditec Inc., Germany) and spectral domain- OCT (SD-OCT) measurements (Cirrus HD-OCT model 5000, Carl Zeiss Meditec Inc., Dublin, CA USA).

SD-OCT Measurements: SD-OCT was used to measure the macular thickness using macular cube 512x128 protocol and retinal nerve fiber layer (RNFL) thickness using optic disc cube 200x200 protocol. EDI-OCT was used to measure the choroidal thickness. EDI-OCT measurements were performed by two technicians blind to patients' diagnoses using the Cirrus HD-OCT Model 5000. Choroidal thickness imaging was performed by the same independent technician using EDI-OCT as described in previous literature.[13] The participants were asked not to consume caffeine for at least 12 h before the examination. Three consecutive measurements of OCT at each localization were performed over three days and average values were calculated. All measurements were performed between 9 a.m and 11 a.m on the same day. All scans were required to have a signal strength of at least 6/10 to be included in the data analysis. Two technicians blind to the patients' diagnoses measured the perpendicular choroidal thickness from the outer edge of the hyperreflective retinal pigment epithelium to the inner sclera at eleven locations: at the fovea; at 500, 1500, and 3000 microns temporal to the fovea; at 500, 1500, 3000 microns nasal to the fovea; at

1000 and 2000 microns superior to the fovea; and at 1000 and 2000 microns inferior to the fovea (Figure 1a,1b). Three consecutive measurements were taken at each location and the average value was calculated.

Carotid artery gray scale and color Doppler sonography examination was performed on all patients using Esaote MyLab 50 X-vision Color Doppler Ultrasonography (CDU) device equipped with 7,5 MHz linear array transducer. All examinations were performed by the same examiner. Both gray-scale and color Doppler ultrasonography examination were performed while the patient was lying in the supine position. Both common and internal carotid arteries were scanned in axial and longitudinal planes. The intima-media thickness, plaque morphology and neighboring anatomical structural abnormalities were screened with gray-scale ultrasonography. The blood flow kinetics were examined using CDU. Peak systolic velocity (PSV), end-diastolic velocity (EDV), pulsatility index (PI) and resistive index (RI) were measured in all arteries. The presence of plaque on gray-scale imaging and PSV of ICA were primary parameters for grading the stenosis. In case of indeterminate primary parameters, ICA/CCA PSV ratio and the ICA end diastolic velocity were used as secondary parameters.

Following CDU examination, patients who had heavily calcified carotid plaque or high riding carotid bulbus failed to be imaged for possible stenosis with doppler US, underwent computed tomography for carotid artery computed tomography angiography examination using a 64-row multislice helical scanner (Philips Brilliance 64 Computed Tomography Scanner). Patients were placed in a supine position with the head tilted back. 100 mL Nonionic contrast medium containing 300 mg of iodine/mL was injected using a power injector into an antecubital vein at a rate of 4 mL/s. A bolus tracking system was used and images were started to be obtained when bolus reached to the aortic arch. The patients were scanned from aortic arch to the vertex. The slice thickness 3 mm, the pitch was 1.0, the field of view was large, 120 kV and 365 mA. A contiguous 2,5 mm axial raw data were reformatted into was 0,67 mm axial sections. DICOM images were transferred to a separate workstation. Reformatted 0,67-mm axial images, maximum intensity projection reformats and 3D volume rendering images (Figure 1c) were obtained by using a vessel analysis postprocessing software (Philips' Advanced Vessel Analysis software). The criteria for grading ICA and CCA stenosis was based on North American Symptomatic Carotid Endarterectomy Trial Collaborators (NASCET) criteria. According to NASCET criteria, % ICA stenosis was calculated as the following formula: % ICA stenosis = (1

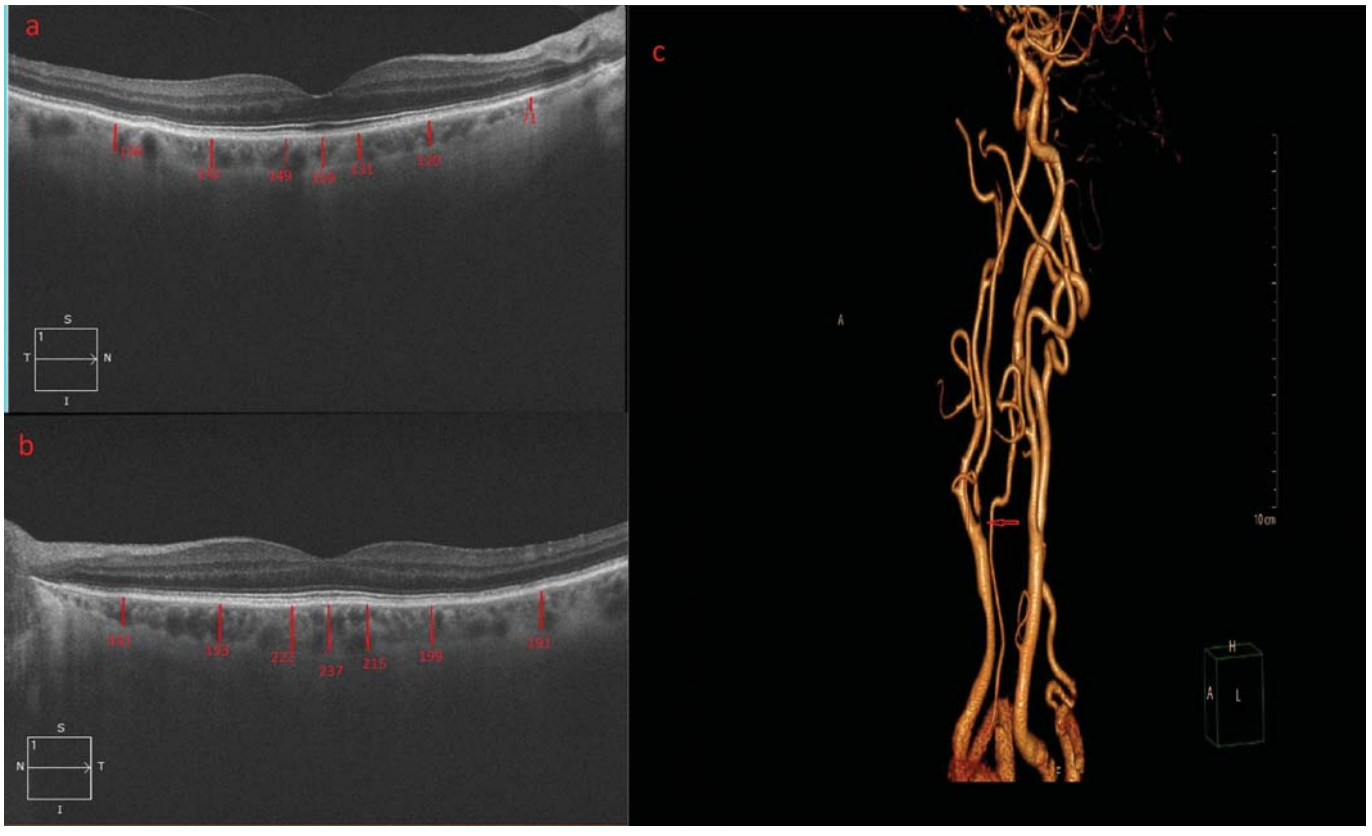

Figure 1a: *Choroidal thickness measurement at central subfoveal, 500-1500-3000 µm temporal to the fovea and 500-1500-3000 µm nasal to the fovea in the right eye of a patient with ipsilateral >95% ICA stenosis.* **1b***; EDI-OCT image of the left eye of the same patient with ipsilateral 20% ICA stenosis.* **1c***; 3D Carotid artery computed tomography angiography image of the same patient. Red arrow demonstrates >95 % right ICA stenosis.*

- [narrowest ICA diameter/diameter normal distal cervical ICA]) x 100.[14]

STATISTICAL ANALYSIS

All numerical data were checked for normallity assumption by Shapiro-Wilk test. The differences between pairs that were not normally distributed, were compared by Wilcoxon Signed Ranks Test. All correlation values were calculated with 2-tailed significance. All data are expressed as mean±standart deviation (SD) for continuous data and numbers (percentage) for categorical data. A p value less than 0.05 was considered statistically significant.

RESULTS

Twenty-one eyes with≥40 % ipsilateral ICA stenosis (patient group) and contralateral 21 eyes with < 40 % ICA stenosis (control group) of 21 subjects [mean age (±SD) 67.4±9.3; 14 males and 7 females] were included in the analyses. All subjects were Caucasian. The two groups were homogenous regarding CCT, IOP and AL values (p>0.05). The percentage of ipsilateral ICA stenosis of the patient and the control group was 76.8±22.5 and 24.7±13.7, respectively. There was a statistically significant difference between two groups with regard to stenosis (p=0.038). Eight of the individuals had associated diabetes mellitus (DM), 10 had hypertension (HT), and 5 had coronary artery disease. Those patients were under medications with oral anti-diabetics, anti-hypertensive, and anti-thrombotic agents, respectively. Ten individuals were smoker. Table 1 shows the clinical characteristic of study subjects.

Table 2 shows the differences between patient group and control group regarding choroidal thickness (CT) at each location. The CT of patient group and control group were as follows respectively: 193±66 and 249.2±74.4 (p=0.025) at fovea, 184.5±60.3 and 243.3±68.3 (p=0.026) at 0.5 mm temporal, 172.2±54.8 and 218.1±52.7 (p=0.044) at 0.5 mm nasal, 173.7±59.8 and 235.5±64.1 (p=0.025) at 1.5 mm temporal, 149.3±48.5 and 186.8±38.1 (p=0.028) at 1.5 mm nasal, 155.1±47.1 and 177.8±46.8 (p=0.084) at 3 mm temporal, 96.7±47.2 and 122.4±29.9 (p=0.022) at 3 mm nasal, 177.2±54.6 and 225.6±53.1 (p=0.028) at 1 mm superior, 183.4±66.5 and 216.2±56 (p=0.136) at 1 mm inferior, 180±55 and 225.4±49.7 (p=0.035) at 2 mm superior and 159.4±60 and 205±54.3 (p=0.039) at 2 mm inferior. Except CT measurements at 3 mm temporal and 1 mm inferior, all CT measurements were statistically significantly decreased in patient group as compared to control group (p<0.05).

No significant correlations were found between the percentage of ipsilateral ICA stenosis and CT values at each location (p>0.05) (Table 3). The mean thickness of the RNFL, GC-IPL and macula in the patient and control group was shown in table 4. There was no statistically significant difference in these parameters between two groups (p> 0.05).

DISCUSSION

In our study we found that; CT was statistically significantly decreased on the ipsilateral ICA stenotic side (≥40%) as compared to ipsilateral ICA stenotic side (< 40 %). Besides, there was no significant difference between two eyes in terms of RNFL, CC-IPL and macular thickness. There are several studies on literature, report choroidal thickness by using EDI-OCT.[1,2,15-18] There are lots of studies about pathologies affect the choroidal thickness and posterior segment of eye.[9-12,19-21] CT was shown to be decreased in patients with glaucoma, pathological myopia, senile macular degeneration, retinitis pigmentosa; while it was found to be increased in central serous chorioretinopathy, polypoidal choroidal vasculopathy and Vogt–Koyanagi-Harada disease. Furthermore, sildenafi[l] and pseudoephedrine like drugs cause an increase in choroidal circulation and thickness.[22] In some neuro- degenerative disease like Alzheimer and

Table 1. *Clinical Characteristics of Study Subjects*

Clinical Characteristics of Study Subjects			
	Patient Group (Ipsilateral ICA stenosis≥40%)	**Control Group** (Ipsilateral ICA stenosis <40%)	**P Value**
Patients/Eyes	21/21	21/21	N/A
Lateralite (R/L)	10/11	11/10	N/A
Internal carotid artery stenosis %	76.8±22.5	24.7±13.2	0.038*
Intra ocular pressure (mm Hg)	15.2±2.7	15.2±2.8	0.791*
Central corneal thickness (µm)	554.2±33.3	563.4±32.9	0.757*
Axial length (mm)	22.73±0.46	22.72±0.42	0.803*

ICA: internal carotid artery, R: right, L: left, M: male, F: female
* Mann-Whitney U test

Table 2. *Comparison of the choroidal thickness between patient (≥40% ICA stenosis) and control group (<40%ICA stenosis)*

Comparison of the choroidal thickness between patient (≥40% ICA stenosis) and control group (<40%ICA stenosis)			
CT measurement location	Mean CT (µm)		P value *
	Patient group n=21 (≥40% ICA stenosis)	**Control group n=21** (<40% ICA stenosis)	
Subfoveal	193±66	249.2±74.4	**0.025**
Temporal 0.5 mm	184.5±60.3	243.3±68.3	**0.026**
Nasal 0.5 mm	172.2±54.8	218.1±52.7	**0.044**
Temporal 1.5 mm	173.7±59.8	235.5±64.1	**0.025**
Nasal 1.5 mm	149.3±48.5	186.8±38.1	**0.028**
Temporal 3 mm	155.1±47.1	177.8±46.8	0.084
Nasal 3 mm	96.7±47.2	122.4±29.9	**0.022**
Superior 1 mm	177.2±54.6	225.6±53.1	**0.028**
Inferior 1 mm	183.4±66.5	216.2±56	0.136
Superior 2 mm	180±55	225.4±49.7	**0.035**
Inferior 2 mm	159.4±60	205±54.3	**0.039**

*Wilcoxon Signed Ranks Test
ICA: internal carotid artery CT: Choroidal thickness n: number of eyes, p<0.05: statistically significant

Table 3. *Correlation Analyses Between the Percentage of ICA Stenosis and Choroidal Thickness*

		Choroidal Thickness										
		Sub-foveal	T 0.5 mm	N 0.5 mm	T 1.5 mm	N 1.5 mm	T 3 mm	N 3 mm	S 1 mm	I 1 mm	S 2 mm	I 2 mm
Stenosis of ICA	p* value	0.97	0.902	0.943	0.518	0.558	0.759	0.184	0.738	0.516	0.252	0.194
	r* value	-0.06	-0.021	-0.012	-0.108	-0.098	-0.051	-0.22	-0.056	-0.109	-0.190	-0.216

ICA: internal carotid artery
T: temporal, N: nasal, S: superior, I: inferior
*Pearson correlation test

Table 4. **Comparison of the RNFL, Macula and GC-IPL thickness between patient and control group**

	Patient group n=21 (≥40% ICA stenosis)	**Control group n=21** (<40%ICA stenosis)	P value*
Average RNFL thickness (µm)	81.2±12.6	87.4±8.3	0.196
Average GC-IPL thickness (µm)	76.1±9.7	77.4±9.8	0.352
Average macular thickness (µm)	279.1±35.4	276.2±16.6	0.733
Central macular thickness (µm)	264.1±38.6	258.4±19.3	0.877

RNFL: retinal nerve fiber layer, GC-IPL: ganglion cell – inner plexiform layer, ICA: internal carotid artery
n: number of eyes, p<0.05: statistically significant
*Wilcoxon Signed Ranks Test

in older ages choroid thickness is decreased.[18,23,24] Recent studies showed that smoking and coffee decreased CT.[25,26] Also some systemic diseases like DM, HT may affect CT.[27] In our study, we used contralateral eye as the control group which had <40 % stenosis at the ipsilateral ICA. This provided us to minimize the subjective variabilities and thus only parameter effecting choroid thickness was presumed as ICA stenosis in our study.

Choroidal circulation is one of the highest blood flow parts of the body. The choroid is supplied by the ophthalmic artery that is the first intracranial branch of ICA. We hypothesized that since the choroid is a richly vascularised tissue and because of its nutrient vascular structures are branched from OA via ICA, choroidal blood flow and CT may be affected by ICA stenosis. There are some reports which show decreased ocular blood flow as a result of ICA stenosis.[4,28,29] But reports about CT changes after ICA stenosis is very limited. In a study of Ivashina et al.[15] by using an ultrasound method, choroid thickness was evaluated and they reported that in ICA stenotic group CT was less than the healthy control group. In previous studies reported by Sayın et al.[1] and Kim et al.[42], similar to our study, by using OCT, both subfoveal and peripheral CT values were statistically lower in the stenotic group. We also found that central subfoveal and peripheral CT values were decreased. ICA stenosis may result in low ocular blood flow and vasoconstriction of orbital and choroidal vessels, and thus may decrease the CT values. Chronic ischemia caused by vasoconstriction in patients with ICA stenosis might also decrease CT. The difference of our and Kim's studies from Sayın's report are that, we use the contralateral side of the same patients as the control group. Thus, we minimized the effect of some predisposing factors like drug usage, HT, DM. We evaluated the effect of ICA stenosis on CT alterations, solely.

We found no difference in RFNL, GC-IPL, subfoveal macular thickness, mean macular thickness values between two sides. Also, no significant correlations were found between the percentage of ipsilateral ICA stenosis and CT values at each location. Our results were similar to the results of Sayın et al.[1]

Akçay et al.[16] reported in a study recently published that subfoveal CT values increased in those eyes that had more severe ICA stenosis (> 70% ICA stenosis) compared to those with less severe ICA stenosis (< 70% ICA stenosis), which was on the contrary to what was found in our study and in the two aforementioned studiesstudies.[1,15] Furthermore, they also found a positive correlation between the percentage of ICA stenosis and subfoveal CT values. Akçay et al. argued in that study that the vasculature of choriocapillaris might become dilated and thus subfoveal CT values might have increased in order to prevent choroidal ischemia caused by decreased blood flow into the choroid due to ICA stenosis with a view to meet the high metabolic needs of the choroid. The discrepancies between those studies indicate that there is a need for more comprehensive studies.

ICA stenosis is one of the common neurological diseases. Ocular ischemic symptoms are one of the parameters shows the severity of stenosis. Stenosis on ICA cause flow decrease in the ocular artery (OA) and it cause the ocular ischemic disease. Symptoms of the ocular disease are narrowing in retinal artery and vein, ischemic optic neuropathy, eye swelling or periorbital pain (ischemia of anterior ocular segment), amaurosis fugax, neovascular glaucoma and permanent blindness. Also, ICA stenosis may result in stroke due to the brain ischemia[31]. Treatment option of carotid artery stenosis include medical, surgical (carotid endareterctomy) or interventional procedures (carotid artery stenting). The decision to proceed with surgery is made on the basis of NASCET criteria. According to these criteria, symptomatic patients with >70% stenosis, asymptomatic patients with >80% stenosis, and patients with ulcerated plaque causing >50% stenosis undergo carotid endarterectomy[14]. However, a study by Wolintz et al. reported that even though cerebral and ocular blood flow increase after carotid surgery, neither cerebral nor ischemic findings were not found to be improved[32]. Moreover, in spite of increased ocular blood flow, those with severe ocular ischemic syndrome have potential to develop vision loss and fundus lesions may become irreversible. Thus, it is important to diagnose and treat the pathology before permanent complications occur. We think that, CT measurements maybe helpful in early diagnosis of ICA stenosis and may play a role in preventing further complications. On the basis of results of our study, we suggest performing carotid doppler US for patients who has significant CT differences in both eyes. Further studies with larger study populations to find out particular cut-off points for determination of patient selection would be beneficial to use this knowledge in clinical practice in the future.

Our study has a number of limitations. First, our sample size was relatively small for statistical analyses. Future studies with larger study populations are necessary to confirm our results. Also, SD-OCT measurements were performed manually. In our study, we tried to minimize this negative effect by doing measurement by two separate doctors, three measurements from the same location and use the mean values. We hope, to overcome this limitation, more advanced softwares to measure CT automatically can be developed in the future. Our results must be supported by comprehensive studies.

In conclusion, measurement of CT using SD-OCT is a non-invasive and easily applicable method. CT values may be decreased in patients with ICA stenosis. RNFL, GC-IPL and macular thickness are not affected from the ICA stenosis. We suggest evaluation of CT reduction for early detection of ICA stenosis. Thus, further morbidities and permanent complications of ICA stenosis may be prevented.

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