ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

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Choroidal Thickness in the Primary Open-Angle Glaucoma and Evaluation of the Association with Visual Field Damage: Case Control Study

Primer Açık Açılı Glokomda Koroid Kalınlığının Ölçülmesi ve Görme Alanı Hasarı ile İlişkisinin Değerlendirilmesi: Vaka Kontrol Çalışması

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ABSTRACT Objective: To measure the macular and peripapillary choroidal thickness in the primary open-angle glaucoma (POAG), and to investigate the association between the visual field loss and choroidal thickness. **Material and Methods:** The study enrolled 90 eyes of 50 patients diagnosed with POAG, and 30 eyes of 19 patients as the control group (Group 0). Patients with POAG were divided into 3 groups as mild (Group 1), moderate (Group 2), and severe (Group 3) according to Hodapp, Anderson, Parrish criteria and 30 eyes were included in each group. The macular and peripapillary choroidal thicknesses were compared between the groups through enhanced depth imaging spectral-domain optic coherence tomography. Visual fields were measured by automated perimetry. **Results:** The peripapillary choroidal thickness in Group 3 with severe glaucomatous injury was significantly thinner when compared with the control group at all peripapillary locations except nasal location. Furthermore, the peripapillary choroidal thickness in Group 3 was significantly thinner than Group 1 at the mean, temporal, superior, superonasal, and inferonasal locations. Macular choroidal thickness did not differ between the groups. The age was inversely correlated with macular and peripapillary choroidal thickness. **Conclusion:** The peripapillary choroidal thickness was thinner in eyes with severe glaucomatous damage compared to normal and mildly glaucomatous damaged eyes. Treatments that support choroidal circulation may be beneficial in cases with severe POAG.

Keywords: Choroidal thickness; primary open-angle glaucoma; visual field; enhanced depth imaging optical coherence tomography; mean deviation

ÖZET Amaç: Bu çalışmanın amacı, primer açık açılı glokomda (PAAG) makular ve peripapiller koroid kalınlığının ölçülerek görme alanı kaybı ile koroid kalınlığı arasındaki ilişkinin araştırılmasıdır. **Gereç ve Yöntemler:** Çalışmaya her grupta toplam 30 göz olacak şekilde PAAG tanılı 50 hastanın 90 gözü ve kontrol grubu (Grup 0) olarak 19 hastanın 30 gözü dâhil edildi. PAAG'li hastalar Hodapp, Anderson, Parrish kriterlerine göre hafif (Grup 1), orta (Grup 2) ve ağır (Grup 3) görme alanı kaybı olmak üzere 3 gruba ayrıldı ve her gruba 30 göz dâhil edildi. Gruplar arasında ve kontrol grubunda makular ve peripapiller koroid kalınlığı geliştirilmiş derinlik görüntüleme spektral domain optik koherens tomografi ile ölçülerek karşılaştırıldı. Görme alanları otomatik perimetri ile ölçüldü. **Bulgular:** Ağır glokomatöz hasar olan Grup 3'te peripapiller koroid kalınlığı kontrol grubuna göre nazal lokalizasyon haricindeki tüm peripapiller lokalizasyonlarda anlamlı derecede ince bulundu. Yine Grup 3'te peripapiller koroid kalınlığı Grup 1'e göre ortalama, temporal, superior, superonazal ve inferonazal lokalizasyonlarda anlamlı derecede ince bulundu. Makular bölgeden yapılan koroid kalınlık ölçümlerinde gruplar arasında anlamlı farklılık bulunmadı. Yaşın makular ve peripapiller koroid kalınlığı ile negatif korele olduğu görüldü. **Sonuç:** Peripapiller koroid kalınlığı ağır glokomatöz hasar olan gözlerde normal ve hafif glokomatöz hasarlı gözlere göre incelmektedir. Şiddetli PAAG'li olgularda koroid dolaşımını destekleyen tedaviler faydalı olabilir.

Anahtar Kelimeler: Koroid kalınlığı; primer açık açılı glokom; görme alanı; geliştirilmiş derinlik görüntüleme optik koherens tomografi; ortalama deviasyon

Primary open-angle glaucoma (POAG) is a neurodegenerative optic neuropathy characterized by progressive retinal ganglion cell damage, progressive cavitation, atrophy on the optic nerve head (ONH), and visual field (VF) defects accompanied by intraocular pressure (IOP) increase.[1]

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Increase of IOP is a major risk factor for POAG.[2] The only current treatment method is to reduce the IOP. Progression of glaucomatous optic neuropathy (GON) after reduction of IOP in some patients and the presence of normotensive glaucoma (NTG) cases indicates that other factors play a role in the pathogenesis of glaucoma.[3,4] Although the pathogenesis of GON is not fully understood, there are 2 predominantly accepted theories. Of these, the vascular/hemodynamic theory suggests development of ischemic injury in ONH after deteriorated blood supply following decreased blood flow at lamina cribrosa level in GON. According to this theory, the development of GON is related to the blood flow in the prelaminary region of the ONH, and supply of this region from the branches in the peripapillary choroid suggests that the choroid may play a role in the pathogenesis of glaucoma.

The choroid is a pigmented and vascularized tissue that extending from the ora serrata to the optic disc (OD). It constitutes 85% of the ocular blood flow and is the nutrient source of the outer retina and ONH, especially the prelaminar region, and the thickness may depend in association with diseases such as elevation of IOP.[5,6] Despite studies conducted on the association between GON and deteriorated choroidal circulation or the blood flow of the ONH, the role of choroid in the pathogenesis of GON has not been clarified yet.[7-9] The enhanced depth imaging (EDI) optic coherence tomography (OCT) technique may provide an evaluation of the choroid layer and clarify the association between the glaucoma and choroid.

In this study, we aimed to evaluate the relationship between POAG and the choroidal thickness in order to determine the role of pathophysiological processes originated from the choroid in glaucoma.

MATERIAL AND METHODS

This study was conducted in the Glaucoma Unit of Ophthalmology Clinic in Yüzüncü Yıl University Faculty of Medicine between January 2014 and June 2014. Approval was obtained from the Yüzüncü Yıl University Faculty of Medicine Ethics Committee prior to the study (date: December 5, 2013, no: 13). The principles of the Helsinki Declaration were followed during the study. Informed consent was obtained from all patients.

A detailed ophthalmological examination including measurements of best corrected visual acuity, IOP by Goldmann's applanation tonometry, gonioscopy, examination of the dilated fundus, and threshold perimetry of 30-2 full VF was carried out. Test results with false positive and false negative values below 20% and fixation loss below 20% were accepted as safe. VF examination was repeated in the next day for test results that do not comply with reliability criteria.

Patients with spherical or cylindrical refractive error above 3 diopters, those with opacity of optic environment (severe cataract, corneal opacity, vitreous opacity, etc.) that may affect the VF and OCT images, patients with diabetes, severe hypertensive retinopathy, age related macula degeneration that may cause loss of sensitivity in the VF, those with optic nerve pathology except glaucoma, and patients with a history of ocular surgery (i.e. cataract, refractive surgery) were not included in the POAG and control groups of this study.

Subfoveal (SF) high resolution macular slices at EDI mode were obtained in measurements by Spectralis OCT (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany) after pupil dilatation of the patients. The peripapillary choroid measurements were then obtained through circular scan with a diameter of 3.4 mm around the OD at EDI mode. The thickness was defined as the area of visible choroidal vasculature between the outer retinal pigment epithelial border and the inner the choroidoscleral junction and measured manually in microns. The first measurement below the foveal center was recorded with the abbreviation of SF. Then, 3 individual measurement points with 500-micron distances each were determined on the temporal and nasal directions over retinal pigment epithelium (RPE) hyperreflective band, and such points were named with abbreviations as T1, T2, and T3 on the temporal region, and as N1, N2, and N3 at nasal region from the center to the periphery, respectively (Figure 1). Totally 8 points with equal distances at 45 degrees angle were marked on the RPE band on the

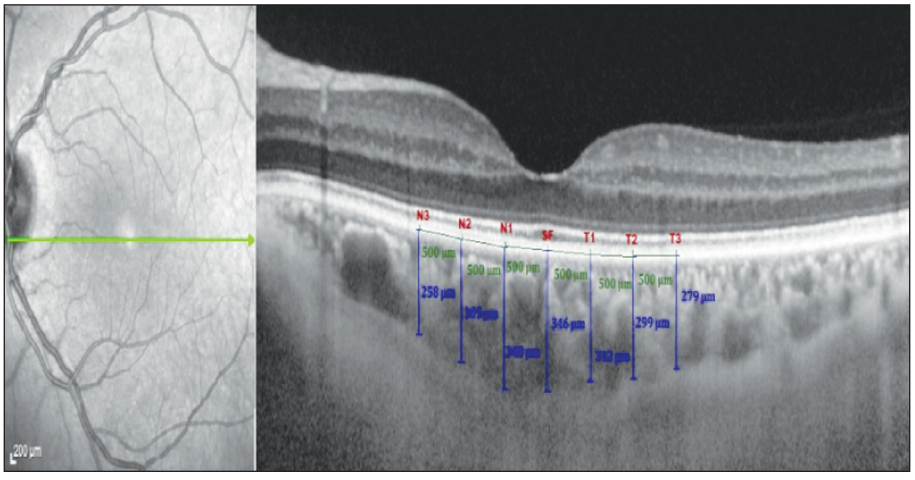

FIGURE 1: Measurement of choroidal thickness in the macular zone.
Image of the position of scanline passing through the central part of the fovea (A) and macular enhanced depth imaging optic coherence tomography scans (B).

peripapillary area; the distance between the RPE band and the margin at the choroidoscleral junction was measured manually; and superior, superotemporal, temporal, inferotemporal, nasal, superonasal, inferonasal, inferior, zone measurements were recorded as S, ST, T, IT, N, SN, IN, I respectively (Figure 2). Photos were taken by the same experienced technician (DA) under the same environmental conditions.

POAG patients with mild, moderate, and severe visual loss were divided into three groups including Group 1 (mild), Group 2 (moderate), and Group 3 (severe) by considering VF parameters according to Hodapp, Anderson, Parrish (HAP) criteria.

STATISTICAL ANALYSIS

Descriptive statistics for continuous variables were expressed in mean, standard deviation, minimum and maximum values; categorical variables were expressed in number and percent. Comparison of group averages for continuous variables was performed through one-way analysis of variance. Duncan test

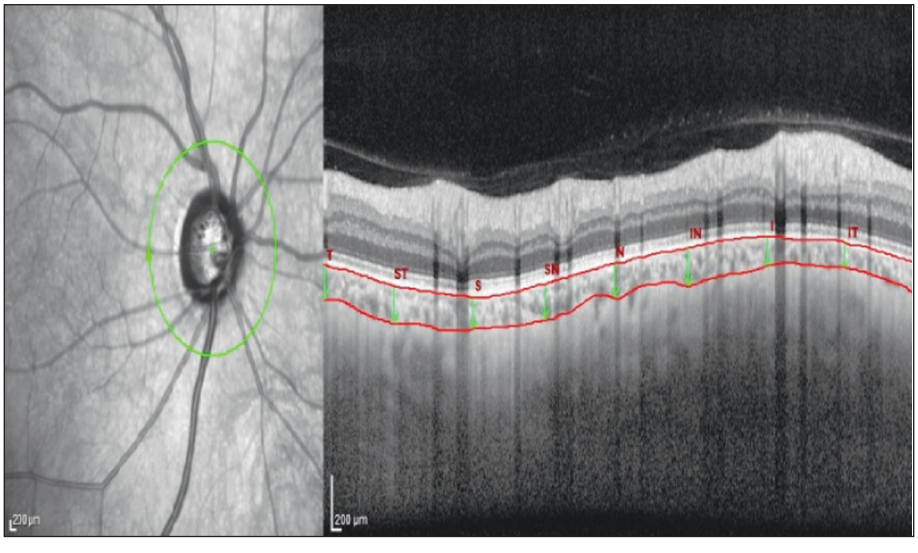

FIGURE 2: Measurement of choroidal thickness in the peripapillary zone.
Image of the position of scan line around disc (A) and 360° peripapillary enhanced depth imaging optic coherence tomography scans (B).

was used to determine different groups following the analysis of variance. Pearson's correlation coefficients were calculated individually for each group in order to determine the association between these variables. The association between the groups and categorical variables was analyzed by chi-square test. The statistical significance level was determined as 5% for calculations; the SPSS (ver.13) (SPSS, Inc., Chicago, IL, USA) statistical package program was used for calculations.

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF CASES

Ninety eyes of 50 subsequent patients followed-up due to POAG who have referred to the polyclinic including 30 eyes in 3 patient groups and 30 eyes of 19 healthy patients as the control group were enrolled into this study by considering VF parameters according to HAP criteria. The patients with POAG enrolled into the study included 33 males and 17 females whereas the control group (Group 0) included 10 males and 9 females. Demographic characteristics of the cases were presented in Table 1. SF measurements were the highest average measurements among 7 measurements performed on the macular zone in the control group and POAG groups. The choroid thickness average in SF measurements from larger to smaller were ranked as Group 1, Group 0, Group 2, and Group 3; there was not any statistically significant difference between the groups (p=0.110). There was not any statistically significant difference between the POAG groups and control group on other 6 measurements points on the macular zone (Table 2). The choroid measurements and global retinal nerve fiber layer (RNFL) thickness on the peripapillary zone were presented in Table 3 and Table 4. The comparison of peripapillary choroidal thickness measurements revealed a statistically significant difference between the Group 3 and control group on choroidal thickness at all peripapillary locations except nasal location. A statistically significant difference was detected between Group 3 and Group 1 for mean, temporal, superior, superonasal and inferonasal peripapillary choroidal thickness (Table 5). Global RNFL thickness was statistically significantly different between

TABLE 1: Demographics and ocular characteristics of subjects.

Parameter	Group 0	Group I	Group II	Group III	p value
No. of eyes	30	30	30	30	
Age (years)	54.17±6.38	51.43±11.73	54.03±8.26	55.57±7.16	p=0.315
Gender (female/male)	15/15	19/11	13/17	6/24	
IOP (mmHG)	15±1.55	14.27±2.84	14.67±2.98	14.53±3.54	p=0.79
MD (db)		-2.39±1.43	-7.55±3.15	-23.57±6.06	
SE (diopters)	0.10±0.52	-0.39±0.63	-0.22±1.15	-1.02±1.61	p>0.05

IOP: Intraocular pressure; MD: Mean deviation; SE: Spherical equivalent.

TABLE 2: Macular choroidal thickness in eyes with POAG and normal eyes.

	Choroidal thickness (µm)				
Location	Group 0	Group I	Group II	Group III	p value
SF	323.30±95.02	340.93±104.07	299.33±71.29	288.90±85.37	0.110
T1	277.30±77.13	299.50±86.02	274.83±60.78	258.97±75.20	0.226
T2	264.53±69.28	279.57±78.24	265.10±50.83	246.03±67.58	0.294
T3	246.07±70.75	261.50±69.46	244.23±51.41	230±66.88	0.322
N1	287.80±101.01	315±111.92	272.33±67.82	256.60±75.64	0.086
N2	271.33±90.93	296.30±110.49	262.93±69.97	241.63±72.16	0.117
N3	251.60±92.26	275±100.47	231.93±69.49	220.60±69.57	0.70

POAG: Primary open-angle glaucoma.

TABLE 3: Peripapillary choroidal thickness in eyes with POAG and normal eyes.

	Choroidal thickness (µm)				
Location	**Group 0**	**Group I**	**Group II**	**Group III**	**p value**
Temporal	221.17±81.39	204.87±82.76	186.67±68.12	160.93±64.23	0.016
Superotemporal	224.43±70.60	211.17±81.37	191.8±71.05	171.37±72.92	0.037
Superior	224.07±65.93	204.33±76.74	195.23±83.99	162.37±55.76	0.011
Superonasal	223.27±64.68	213.5±94.11	208.13±85.85	161.33±64.07	0.014
Nasal	211.07±57.34	197.27±93.72	196.83±70.69	167.1±79.63	0.159
Inferonasal	204.33±55.83	185.67±72.77	170.2±60.45	146.73±64.37	0.006
Inferior	180.57±74.49	161.83±75.35	154.67±58.82	127.07±59.74	0.025
Inferotemporal	207.57±94.12	188.53±84.36	176.93±73.43	150.57±62.15	0.049
Average	212.05±62.6	195.89±75.8	185.05±65.54	155.93±57.48	0.011

POAG: Primary open-angle glaucoma.

TABLE 4: RNFL thickness in eyes with POAG and normal eyes.

	RNFL thickness (µm)				
Location	**Group 0**	**Group I**	**Group II**	**Group III**	**p value**
Temporal	72.6±11.28	67.3±12.4	58.8±14.1	41.3±18.89	0.001
Superotemporal	137.2±27.14	138.23±24.55	114.73±41.37	63.1±23.27	0.001
Superior	141.1±30.34	128±37.46	107.53±37.42	66.13±42.13	0.001
Superonasal	126.47±24.87	109.9±22.92	92.9±27.16	56.83±24.33	0.001
Nasal	83.97±20.22	75.7±14.93	64.13±20.08	41.77±18.92	0.001
Inferonasal	125.73±27.64	117.9±22.08	98.1±29.87	57.13±25.66	0.001
Inferior	148.03±34.98	140.07±33.51	122.03±48.9	63.93±41.49	0.001
Inferotemporal	156.07±27.3	134.13±25.91	112.13±45.34	55.6±23.99	0.001
Average	107.4±12.09	98.13±12.79	83.1±21.66	49.63±17.58	0.001

RNFL: Retinal nerve fiber layer; POAG: Primary open-angle glaucoma.

TABLE 5: Statistical comparison of peripapillary choroidal thickness in POAG and normal groups.

Location	$P_{G0\text{-}GI}$	$P_{G0\text{-}GII}$	$P_{G0\text{-}GIII}$	$P_{GI\text{-}GII}$	$P_{GI\text{-}GIII}$	$P_{GII\text{-}GIII}$
Temporal	>0.05	>0.05	0.016	>0.05	0.016	>0.05
Superotemporal	>0.05	>0.05	0.037	>0.05	>0.05	>0.05
Superior	>0.05	>0.05	0.011	>0.05	0.011	>0.05
Superonasal	>0.05	>0.05	0.014	>0.05	0.014	0.014
Nasal	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Inferonasal	>0.05	>0.05	0.006	>0.05	0.006	>0.05
Inferior	>0.05	>0.05	0.025	>0.05	>0.05	>0.05
Inferotemporal	>0.05	>0.05	0.049	>0.05	>0.05	>0.05
Average	>0.05	>0.05	0.011	>0.05	0.011	>0.05

POAG: Primary open-angle glaucoma.

4 groups (p=0.001). Comparison of RFNL thickness between the groups at other locations was presented in Table 6.

There was not found any statistically significant correlation between mean deviation in the VF and choroidal thickness in the measurements taken from the macular and peripapillary areas in 3 groups except T3 measurement on the macular area in Group 3 (p=0.04). In the control group a reverse correlation was detected between the age and the choroid thickness measured on the macular area and the peripapillary area.

TABLE 6: Statistical comparison of RNFL thickness between groups.

Location	P_{G0-G1}	P_{G0-G2}	P_{G0-G3}	P_{G1-G2}	P_{G1-G3}	P_{G2-G3}
Temporal	>0.05	0.001	0.001	0.001	0.001	0.001
Superotemporal	>0.05	0.001	0.001	0.001	0.001	0.001
Superior	>0.05	0.001	0.001	0.001	0.001	0.001
Superonasal	0.001	0.001	0.001	0.001	0.001	0.001
Nasal	>0.05	0.001	0.001	0.001	0.001	0.001
Inferonasal	>0.05	0.001	0.001	0.001	0.001	0.001
Inferior	>0.05	0.001	0.001	>0.05	0.001	0.001
Inferotemporal	0.001	0.001	0.001	0.001	0.001	0.001
Average	0.001	0.001	0.001	0.001	0.001	0.001

RNFL: Retinal nerve fiber layer.

DISCUSSION

The mean peripapillary choroidal thickness was found significantly thinner on eyes with severe glaucomatous injury when compared to the control group and the group with mild glaucomatous injury. There was not any statistically significant difference between the control group and eyes with POAG including mild, moderate, and severe POAG for choroidal thickness measurements on the macular area.

Several studies were conducted to measure the choroidal thickness on glaucomatous eyes through histopathological or in vivo imaging techniques in order to understand the association between the choroid layer and glaucoma. A previous histological study reported thinning on the choroid on glaucomatous eyes when compared with normal eyes; however, another histological and 2 ultrasonic studies detected choroid thickening.[5,10-12] Results of these studies are conflicting. Furthermore, factors such as age, refractive error, and the axial length which have been proven to affect the choroidal thickness by some studies were not stated in any of such histological studies. However, histological measurement of the choroid may not reflect an in vivo measurement completely because of some processes that the tissue was exposed during preparation stage of cytological slices. Reliability of ultrasound scan is lower than spectral-domain (SD)-OCT because of the measurement technique and having a lower resolution than SD-OCT. Mwanza et al. reported that there was not any difference between the groups for choroidal thickness measurements on macular area taken from NTG, POAG, and healthy cases through EDI OCT method.[13] Furthermore, there was not any significant difference between the eyes with severe glaucoma and normal eyes as well as mild glaucomatous eyes in choroidal thickness measurements on the macular area.[14] Cennamo et al. conducted a study on 16 glaucomatous and 21 healthy patients, and detected that the choroidal thickness increased on macular area on glaucomatous eyes.[15] The healthy and glaucomatous patients included in the study above are quite smaller when compared to our study. Similar to other studies, we did not detect any significant difference in any of seven choroidal thickness measurements taken on the macular area.

Different findings were obtained in the literature for choroidal thickness of peripapillary area. Hirooka et al. compared patients with NTG and healthy individuals, and detected that the peripapillary choroidal thickness is significantly thinner on inferonasal, inferior, and inferotemporal quadrants on eyes with NTG when compared to normal eyes.[16] Usui et al. compared patients with high myopic NTG with an axial length of 27.6±0.5 and patients with high myopic control group with axial length of 27.2±0.5 through OCT. They have detected that the choroidal thickness was significantly thinner on NTG patients with high myopia in SF and peripapillary choroidal thickness measurements.[17] Researchers expressed that the cause of such choroidal thinning may be the impaired choroidal circulation and subsequent circulation disorder on prelaminary area. Li et al. compared 31 POAG patients who have unilateral loss of

vision by assigning both eyes into different groups with 31 healthy individuals. There was not any difference between 3 groups for peripapillary choroidal thickness.[18] However in study mentioned above have not evaluated POAG patients in different groups according to VF loss grades.

As is known, glaucoma is a focal disease that mostly affects the inferotemporal or superotemporal nerve fiber layers. Due to it is a focal disease, there may be a connection between the choroidal layer and glaucoma on the peripapillary area.

Lin et al. conducted a study on patients with POAG and NTG, and detected a significant thinning on the inferior and temporal peripapillary choroidal thickness in the POAG group when compared with the control group.[19] Park et al. evaluated 52 POAG patients, 56 NTG patients, and 48 healthy individuals for peripapillary and macular choroidal thickness in their study; POAG patients were divided into three groups including mild (21 eyes), moderate (19 eyes), and severe (12 eyes); no significant difference was detected when compared with the control group; a statistically significant thinning was detected in mean, temporal, nasal, superior and inferior peripapillary choroidal thickness in the NTG group when compared with the control group.[20] In this study patients especially included in severe glaucoma group in the POAG group were less than our study.

In our study, the peripapillary choroidal thickness of the patients with severe glaucomatous damage (Group 3) was found to be significantly thinner than the patients with mild glaucomatous damage (Group 1) and the control group, except for the nasal location.

This may be considered that thinning of the peripapillary choroid layer may appear in advanced stages of glaucoma. In this study, there was not any significant change detected on the choroidal thickness in early stage glaucoma.

Recognition of the association of the choroidal thickness with choroidal circulation would contribute to understandig the association with glaucoma. The choroid has a small auto-regulation that allows changes in the perfusion pressure by affecting its blood flow. Some studies exist on evaluation of the association between the choroidal circulation and choroidal thickness. Sogawa et al. included healthy individuals into their study and have not detected any correlation between SF choroidal thickness and choroidal blood flow.[21] However, Vance et al. detected an increase on the choroidal thickness of 8 healthy individuals enrolled into the study after administration of 100 mg of sildenafil citrate. Researchers reported that sildenafil citrate increases the choroidal thickness due to vasodilator effect on the choroidal circulation.[22] Accordingly, the choroidal circulation may affect the choroidal thickness and the choroidal thinning may be caused by the decreased blood flow in lamina cribrosa. The peripapillary choroidal thinning detected in severe glaucoma in our study might have appeared due to impairment of the choroidal thickness on that area. This also may explain the ischemia occurred on prelaminary zone of the ONH and subsequent glaucomatous optic nerve injury as stated by the vascular theory. Regional differences were detected in choroidal thickness between different peripapillary quadrants. Especially the inferior peripapillary choroid was detected significantly thinner on all other peripapillary locations in four groups. Ho et al. detected in a study conducted on healthy individuals that the peripapillary choroid was significantly thinner on the inferior when compared to all other locations ($p<0.001$).[23] They have expressed that such regional differences may depend on development of the eye, and blood flow of thinner choroidal areas may be lower. Schwartz et al. detected that the fluorescence pattern of the inferior peripapillary choroid was smaller compared to the temporal and nasal regions; they have expressed that such finding may indicate the blood flow when assessed with the vascular diameter. They have stated that such finding may cause a vulnerability to ischemic injury for the inferior area of the OD.[24] Such finding stated in the study above may explain the cause of effect on the inferior region first by the optic nerve.

The choroid layer is an important parameter which takes places in the pathogenesis of many ocular diseases and is affected by many factors including age, gender, axial length, and diurnal rhythm.[25-27] Basic limitations of the present study include taking

the measurements in different periods of the day, lack of measuring the axial length and systolic blood pressure of the patients even those with a history of systemic hypertension were excluded. In a previous study conducted by Ikuno et al. using OCT, a similar association was detected between the refractive error and axial length.[28] There was not any significant difference between the 3 groups with POAG and the control group for refraction error.

CONCLUSION

Detection of thinning on peripapillary choroidal thickness in patients with severe glaucoma than those with mild glaucoma and control group except the nasal region indicates that the choroidal layer is affected in advanced glaucoma patients. The glaucomatous damage in ONH can be prevented by developing treatments that support choroidal circulation in addition to standard antiglaucomatous treatments in patients with POAG whose progression continues despite decreased IOP. Further studies with larger patient series and elimination of systemic and ocular modifications to detect whether the choroidal blood flow is affected in POAG patients would shed the light on this topic.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

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