The effect of pseudoexfoliation syndrome on choroidal thickness in open-angle glaucoma

O efeito do glaucoma pseudoesfoliativo sobre a espessura da coroide em comparação com o glaucoma de ângulo abertos

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ABSTRACT | Purpose: To investigate the effect of pseudoexfoliation syndrome on choroidal thickness as compared with healthy individuals and subjects with primary open-angle glaucoma. **Methods:** This prospective, randomized study included 30 primary open angle glaucoma patients and 30 pseudoexfoliation glaucoma patients with similar demographic characteristics and 30 eyes of 30 healthy individuals comprised the control group. Regular optic nerve and macular images were obtained using a Cirrus HD spectral domain optical coherence tomography instrument, along with macular choroidal thickness measurements with enhanced depth imaging mode. **Results:** Age, sex, and axial length values were similar among the three groups (p>0.05). The primary open angle glaucoma and pseudoexfoliation glaucoma groups had comparable levels of glaucomatous damage. The mean subfoveal choroidal thickness values in the primary open angle glaucoma, pseudoexfoliation glaucoma, and control groups were 271.80 ± 19.96 μm, 241.43 ± 32.47 μm, and 268.03 ± 24.50 μm, respectively. The pseudoexfoliation glaucoma group had the lowest choroidal thickness values of the three groups (*p* values: pseudoexfoliation-control: 0.001; pseudoexfoliation-primary open angle glaucoma: <0.001, primary open angle glaucoma-control: 0.516, independent samples *t*-test). **Conclusion:** The macular choroid was thinner in patients with pseudoexfoliation glaucoma, as compared with both healthy individuals and open-angle glaucoma patients with similar degrees of glaucomatous damage.

Keywords: Exfoliation syndrome; Glaucoma, open-angle; Choroid; Tomography, optical coherence; Intraocular pressure

RESUMO | Objetivo: Investigar o efeito do glaucoma pseudoexfoliativo sobre a espessura da coroide em comparação com indivíduos saudáveis e com glaucoma primário de ângulo aberto. **Métodos:** Este estudo prospectivo e randomizado incluiu 30 pacientes com glaucoma primário de ângulo aberto e 30 com glaucoma pseudoexfoliativo, com características demográficas semelhantes e 30 olhos de 30 indivíduos saudáveis compuseram o grupo controle. Imagens da área macular e do nervo óptico foram obtidas usando um tomógrafo por coerência óptica no domínio espectral do modelo Cirrus HD, juntamente com medições da espessura da coroide na área macular através do modo de imagem de profundidade realçada. **Resultados:** Os valores de idade, sexo e comprimento axial foram semelhantes nos três grupos (p>0,05). Os grupos de glaucoma primário de ângulo aberto e de glaucoma pseudoexfoliativo tinham níveis comparáveis de lesões glaucomatosas. Os valores médios da espessura subfoveal da coroide nos grupos do glaucoma primário de ângulo aberto, glaucoma pseudoexfoliativo e de controle foram 271,80 ± 19,96 μm, 241,43 ± 32,47 μm e 268,03 ± 24,50 μm, respectivamente. O grupo glaucoma pseudoexfoliativo apresentou os menores valores de espessura de coroide dos três grupos (valores de p: pseudoexfoliativo-controle: 0,001; pseudoexfoliativo-glaucoma primário de ângulo aberto: <0,001, controle de glaucoma primário de ângulo aberto: 0,516; teste de *t* de amostras independentes). **Conclusão:** A coroide na área macular era mais fina em pacientes com glaucoma pseudoexfoliativo, quando comparada com indivíduos saudáveis e pacientes com glaucoma de ângulo aberto com graus similares de lesão glaucomatosa.

Descritores: Síndrome de exfoliação; Glaucoma de ângulo aberto; Coroide; Tomografia de coerência óptica; Pressão intraocular

INTRODUCTION

Pseudoexfoliation (PEX) syndrome is an age-related idiopathic condition characterized by progressive

production and accumulation of extracellular matrix fibrillary material in the intraocular and extraocular tissues[1,2]. In spite of this widespread ocular and systemic involvement, the most significant clinical finding of PEX syndrome is PEX glaucoma[3]. PEX glaucoma differs from primary open-angle glaucoma (POAG) in several ways, including a more severe clinical course, greater visual field loss, wider fluctuations in diurnal intraocular pressure (IOP), and poorer responses to medical treatment[4-6].

Ocular involvement in PEX syndrome primarily manifests with anterior segment findings[7]. PEX material accumulation has also been found in the posterior ciliary artery, vortex vein, and central retinal artery walls[7]. Moreover, various clinical studies have reported that PEX material affects ocular blood flow and vascular resistance[8,9]. In fact, PEX syndrome is also considered as a systemic vascular disease, referred to as PEX vasculopathy[2].

Until recently, studies on choroidal vascular changes in glaucoma were limited to postmortem histological studies, radiofrequency, and Doppler flow[10]. Technological advancements in optical coherence tomography (OCT) have made it possible to evaluate choroidal thickness *in vivo* with enhanced depth imaging (EDI)-OCT[11-14]. Research has therefore focused on investigating choroidal thickness in healthy individuals and associated influencing to evaluate variations in choroidal thickness in patients with choroidal and retinal diseases[15].

Many clinical studies have evaluated subfoveal and peripapillary choroidal thickness in various types of glaucoma[16]. The common finding in many of these studies is that there is no significant change in choroidal thickness in POAG and no correlation between choroidal thickness and glaucoma severity[16]. Similar studies, though fewer in number, have investigated PEX glaucoma and PEX syndrome[17-24], but yielded varying results. Some studies have identified choroidal thinning in PEX syndrome and PEX glaucoma[17-20], whereas in others, no such changes were observed[21,22,25].

The aim of the present study was to evaluate the effect of PEX on choroidal thickness in two groups of glaucoma patients with similar degrees of damage and similar demographical characteristics. We also investigated whether there was a correlation between choroidal thickness and indicators of glaucoma severity, such as the thickness of the retinal nerve fiber layer (RNFL) and mean deviation (MD) value, in these two glaucoma types.

METHODS

The study included 30 eyes of 30 patients diagnosed with POAG and 30 eyes of 30 patients diagnosed with PEX glaucoma who presented to the Glaucoma Unit of İzmir Katip Çelebi University Atatürk Training and Research Hospital (Izmir, Turkey) between August 2014 and February 2015. The control group included 30 eyes of 30 healthy individuals with a similar age distribution.

The study protocol was approved by the Ethics Committee of İzmir Katip Çelebi University Medical School Atatürk Training and Research Hospital. Detailed informed consent forms were obtained from each of the study participants. The authors have no financial interest to declare.

All procedures in this study involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study included subjects aged >18 years with best corrected visual acuity of 0.5 or better, transparent optic medium, at least two reliable visual field tests, and reliable spectral domain (SD)-OCT (signal strength ≥7/10) and EDI-OCT images (signal strength ≥6/10).

Information pertaining to systemic diseases and chronic medication use was recorded. Patients with diabetes mellitus, systemic arterial hypertension, renal failure, hemodialysis history, chronic medication use, or smoking habit were excluded. In addition, those with retinal and neuro-ophthalmological diseases, amblyopia, active or previous uveitis, previous ocular trauma, intraocular surgery within the last 6 months, previous trabeculectomy, or refractive error with a spherical equivalent > ± 3.0 D were also excluded from the study. In order to minimize the effect of IOP on choroidal thickness, patients with IOP >21 mmHg at the time of OCT image acquisition were also excluded from the study. The number of glaucoma medications was noted.

POAG was diagnosed based on high IOP (>21 mmHg) at the time of diagnosis, typical glaucomatous optic disk and visual field changes, and a normal anterior chamber angle. PEX glaucoma diagnosis was based on similar diagnostic criteria along with the presence of PEX material at the pupillary margins or the anterior lens on anterior segment examination after pupil dilation. The control group consisted of healthy individuals with normal anterior and posterior segment findings and IOP <21 mmHg.

All subjects underwent a detailed ophthalmologic examination. Axial length was measured using the intraocular lens Master optic biometry device (Carl Zeiss Meditec, Dublin, CA, USA). The visual field was assessed with the Swedish Interactive Threshold Algorithm standard central 24-2 test using the Humphrey II Perimetry Visual Field Analyzer (Carl Zeiss Meditec). Tests with fixation loss of <20% and false negative and false positive response rates of <33% were considered reliable. Patients with at least two reliable visual field tests were included in the study. MD values were obtained.

Optic disk images were obtained with the Cirrus 4000 HD-OCT (Carl Zeiss Meditec) SD OCT device. Mean RNFL thickness and vertical cup-to-disk (c/d) ratios were noted. Choroidal imaging was performed after pupil dilation using the EDI-OCT model. In order to minimize the effect of diurnal choroidal thickness variation on the measurements, choroidal thickness measurements of all patients were made between 09:00 and 11:00 am, after a resting period of 30 min. The macular field was scanned in the horizontal plane in high-resolution one-line raster mode. Patients were asked to focus on the instrument's internal fixation light until the retinal image was acquired. Images with a signal strength of 6/10 or better were eligible for assessment. Patients with at least two reliable high-resolution foveal and choroidal images were included in the study.

The fovea centralis was determined by identifying the point of maximum depression in the central 500 μm-diameter area. The internal and external choroidal margins were determined manually in the section passing through the fovea centralis and were drawn based on the criteria defined by Boonarpha et al.[11]. The posterior edge of the hyperreflective band corresponding to the retinal pigment epithelium-Bruch's membrane complex was determined as the anterior border of the choriocapillaris. The posterior border of the choriocapillaris was demarcated as the hyperreflective band corresponding to the sclerochoroidal interface or the hyporeflective line corresponding to suprachoroidal space. In cases where these two anatomic structures could not be visualized, measurements were made using the prominent straight line corresponding to the posterior margin of the large choroidal vessels. Patients for whom choroidal margins could not be clearly distinguished were also excluded from the study.

High-resolution retinal choroidal images with distinct choroidal margins were transferred to ImageJ software[26]. The high-resolution EDI-OCT images were 6000 μm in width and 2000 μm in height, as indicated in the manufacturer's user's manual. EDI-OCT images to be measured were opened using ImageJ software. The Scale command was selected in the Image tab of the ImageJ software menu. Using the Scale menu, width (pixels) was defined as 6000 and height (pixels) as 2000. The distance to be measured was marked on the new image of 6000 × 2000 pixels and measurements were made using the Measure command in the Analyze tab. The choroidal margins were drawn using this software according to the specified criteria, followed by manual measurements. Measurements were taken vertically at the fovea centralis and in the nasal and temporal quadrants at distances of 1500 and 2500 μm from the fovea centralis. The same researcher repeated the measurements at different times using the double-blind method, and intraobserver and intervisit measurement repeatability were assessed.

The Kolmogorov-Smirnov Z test was performed to test for normal distribution of the parameters. Continuous parameters with normal distributions were tested with analysis of variance (ANOVA), the independent t-test, and Pearson's correlation analysis. Changes in subfoveal choroidal thickness (as a dependent parameter) were identified by mixed model multivariate analysis with the use of age and all glaucoma severity parameters (vertical c/d, RNFL thickness, MD, and IOP) together to determine the fixed effect on the diagnosis groups (control, PAOG, and PEX). Repeatability analysis of the study parameters, as measured with the Cirrus 4000 HD-OCT instrument, was evaluated using the coefficient of variation (CV). For CV calculation of choroidal thickness, as measured with the Cirrus 4000 HD-OCT instrument, 10 consequential measurements of the same eye of the subject were obtained by the same operator. CV is defined as the ratio of the standard deviation to the mean, as $CV = \sigma/\mu$.

RESULTS

The study included 30 POAG patients and 30 PEX glaucoma patients, with 30 eyes of 30 healthy individuals as the control group. The demographic and clinical characteristics of the subjects are summarized in table 1.

Age, sex, and axial length values were similar among the three groups (p>0.05). RNFL thickness, vertical c/d ratio, and MD values were similar in the POAG and PEX glaucoma groups. However, the values of the control group were significantly different from those in both the POAG and PEX glaucoma groups. The average number of glaucoma medications was 1.8 ± 0.89 in the PEX glauco-

ma group and 2.1 ± 0.89 in the POAG group (p=0.147, Mann-Whitney *U* test).

Comparisons of mean choroidal thicknesses at nasal 2500 µm, nasal 1500 µm, subfoveal, temporal 1500 µm, and temporal 2500 µm in the three groups are presented in table 2. Of the three groups, choroidal thickness was lowest in the PEX glaucoma group. The difference was statistically significant in all quadrants when compared with the POAG group, but was only significant at temporal and nasal 1500 µm and the subfoveal zone when compared with the control group.

Correlation analysis of choroidal thickness values and other variables revealed a significant correlation between age and subfoveal choroidal thickness (r=-0.44, p<0.001). No such correlation was noted with other variables (Table 3). In the subgroup analysis, negative correlations were observed between subfoveal choroidal thickness and age in both the PEX glaucoma and POAG groups. Choroidal thickness was not correlated with mean RNFL thickness, vertical c/d ratio, or MD values in the PEX glaucoma or POAG group (Table 4).

Mixed model multivariate analysis showed that age and glaucoma severity parameters had no significant effects on subfoveal choroidal thickness among the study groups, whereas the only significant parameter was PEX diagnosis, as determined by correlation analysis (p<0.001).

Table 1. Demographic and clinical characteristics of subjects by groups

	Control	POAG	PEX	P value	PEX-Control	POAG-Control	POAG-PEX
n	30	30	30				
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	ANOVA	Independent t	Independent t	Independent t
Mean age (years)	65.40 ± 6.62 (55-81)	64.13 ± 8.72 (51-81)	67.07 ± 7.40 (53-80)	0.332	0.361	0.529	0.165
Sex (M/F)	15/15	15/15	15/15	1.000			
Mean IOP (mmHg)	13.77 ± 2.33 (9-18)	14.50 ± 2.30 (11-19)	14.17 ± 2.77 (10-20)	0.519	0.547	0.225	0.614
Axial length (mm)	23.53 ± 0.61 (22.07-24.32)	23.34 ± 0.87 (21.65-25.06)	23.26 ± 0.75 (21.85-24.98)	0.341	0.119	0.322	0.687
Mean deviation	-0.88 ± 1.27 (-3.38-2.09)	-5.92 ± 4.77 (-20.10-1.19)	-5.54 ± 4.49 (-20.37-0.87)	<0.001	<0.001	<0.001	0.751
RNFL thickness (µm)	93.93 ± 9.35 (78-117)	71.73 ± 14.90 (51-102)	73.13 ± 11.96 (45-101)	<0.001	<0.001	<0.001	0.69
Vertical c/d	0.44 ± 0.16 (0.06-0.70)	0.68 ± 0.13 (0.45-0.87)	0.62 ± 0.14 (0.41-0.90)	<0.001	<0.001	<0.001	0.107

POAG= primary open-angle glaucoma; PEX= pseudoexfoliation glaucoma; SD= standard deviation; IOP= intraocular pressure; RNFL= retinal nerve fiber layer; c/d= cup-to-disk ratio

Table 2. Choroidal thickness measurements by groups

	Control	POAG	PEX	P value	PEX-Control	POAG-Control	POAG-PEX
n	30	30	30				
	Mean ± SD (range)	Mean ± SD (range)	Mean ± SD (range)	ANOVA	Independent t	Independent t	Independent t
Nasal 2500 µm	179.83 ± 24.87 (128-220)	187.50 ± 25.64 (125-234)	169.60 ± 25.57 (114-215)	**0.027**	0.122	0.245	**0.009**
Nasal 1500 µm	221.03 ± 31.95 (176-336)	226.57 ± 25.14 (148-270)	203.70 ± 27.48 (140-256)	**0.007**	**0.028**	0.459	**0.001**
Subfoveal	268.03 ± 24.50 (207-300)	271.80 ± 19.96 (220-300)	241.43 ± 32.47 (180-290)	**<0.001**	**0.001**	0.516	**<0.001**
Temporal 1500 µm	238.40 ± 20.78 (200-270)	244.97 ± 24.25 (176-282)	222.03 ± 27.78 (160-264)	**0.002**	**0.012**	0.265	**0.001**
Temporal 2500 µm	203.60 ± 22.04 (146-250)	213.97 ± 22.32 (150-246)	199.03 ± 25.51 (150-238)	**0.045**	0.461	0.075	**0.019**

POAG= primary open-angle glaucoma; PEX= pseudoexfoliation glaucoma; SD= standard deviation.

Repeatability analysis of the study parameters measured with the Cirrus 4000 HD-OCT instrument showed that the CV of choroidal thickness was 1.20%. Because the CV was less than the statistical significance threshold of 5%, the variation introduced by the instrument was considered insignificant.

DISCUSSION

The choroid is a vascular tissue that nourishes the optic nerve head and outer retinal layer and has the highest level of blood flow in the body. In addition to ocular nutrition, it has important functions including volume and temperature regulation. Many of the major ocular pathologies are known to be based on structural or functional anomalies of the choroid[27]. Despite these important functions, until recently, there was no technique that allowed *in vivo* sectional analysis of the choroid. The EDI-OCT method developed in 2008 by Spaide et al.[14] made it possible to conduct *in vivo* sectional analysis to measure the thickness of the choroid.

Several variables influencing choroidal thickness have been described in the literature. Previous studies have shown that choroidal thickness changes throughout the day and is influenced by many factors, including axial length, IOP, systolic and diastolic blood pressure, Valsalva maneuver, and exercise[28,29]. In the present study, we tried to minimize the effect of these factors on choroidal thickness. Patient groups had similar axial length values and were also subjected to choroidal thickness measurements at the same time of the day. As a prerequisite,

the IOP values obtained just before measurement were less than 21 mmHg.

In the present study, measurements were made manually using the software of the Cirrus 4000 HD-OCT device, which did not have an automatic segmentation and measurement mode. In order to obtain reliable measurements, only those cases in which the posterior choroidal margin was clearly visible were included in the study, even if this meant having a limited number of cases.

Studies analyzing choroidal thickness in healthy individuals have shown that the choroid is thickest in the subfoveal zone and becomes thinner with increasing distance from the fovea, with the nasal periphery being the thinnest[12,13]. On the other hand, the mean subfoveal choroidal thickness of healthy subjects obtained with different OCT devices showed high variation, ranging from 236.63 to 311.8 µm[17-20,22,23]. This difference may arise from the use of different instruments and the fact that EDI-SD OCT image analysis is examiner-dependent. Choroid limits are manually determined and after that, measured with image software in which areas of interest are once more manually chosen. Despite this variability, the results of the present study and a study by Manjunath et al.[12] obtained with the same instrument are very similar. Manjunath et al.[12] used Cirrus HD-OCT to measure subfoveal choroidal thickness in 34 eyes of 34 healthy individuals with a mean age of 51.1 years, and reported a mean subfoveal choroidal thickness of 272 ± 81 µm. The authors noted a negative correlation between

Table 3. Correlation analysis between subfoveal choroidal thickness and age, RNFL thickness, vertical cup-to-disk ratio, axial length, mean deviation, and IOP

Pearson correlation analysis	Age	RNFLT	Vertical c/d	AL	MD	IOP
Subfoveal ChT n=90	r=-0.44	r=0.207	r=-0.133	r=-0.092	r=0.014	r=0.147
	p<0.001	p=0.051	p=0.210	p=0.391	p=0.893	p=0.165

RNFLT= retinal nerve fiber layer thickness; c/d= cup-to-disk ratio; AL= axial length; MD= mean deviation; ChT= choroidal thickness; IOP= intraocular pressure.

Table 4. Correlation analysis between subfoveal thickness in subgroups and age, RNFL, vertical c/d, AL, and MD

		Age	RNFL	Vertical c/d	AL	MD
Subfoveal ChT	Pearson correlation coefficient POAG	-0.668**	0.066	-0.282	-0.289	-0.126
n=30	P value	0.000	0.729	.131	0.122	0.507
Subfoveal ChT	Pearson correlation coefficient PEX	-0.406*	0.226	-0.145	-0.023	-0.046
n=30	P value	0.026	0.229	0.444	0.905	0.811
Subfoveal ChT	Pearson correlation coefficient Control	-0.248	0.171	0.016	-0.254	-0.252
n=30	P value	0.187	0.365	0.935	0.176	0.179

POAG= primary open-angle glaucoma; PEX= pseudoexfoliation glaucoma; RNFL= retinal nerve fiber layer; c/d= cup-to-disk ratio; AL= axial length; MD= mean deviation; ChT= choroidal thickness.

age and choroidal thickness. In the current study, the mean subfoveal choroidal thickness in the control group was found to be 268.03 ± 24.50 μm. Furthermore, as in previous studies, we observed a negative correlation between age and choroidal thickness.

It is known that axial length is negatively correlated with choroidal thickness[30]. In the present study, we found no association between choroidal thickness and axial length. In our study, mean axial length in the control, POAG, and PEX glaucoma groups were 23.53 ± 0.61, 23.34 ± 0.8, and 23.26 ± 0.7 mm, respectively. Our patient and control groups had a relatively narrower range of axial length values, as compared with previously mentioned studies, which might have resulted in a lack of correlation between axial length and choroidal thickness.

Many clinical studies have used EDI-OCT to evaluate the relation between choroidal thickness and glaucoma. Most of these clinical studies reached the common conclusion that choroidal thickness in POAG patients was not different from that of healthy individuals and that the glaucoma severity and choroidal thickness were not significantly correlated[16].

Relatively fewer studies have been conducted to analyze choroidal thickness in PEX glaucoma and PEX syndrome[17-24]. The results of these few studies have been contradictory. Macular choroidal thickness was found significantly less in clinically affected eyes compared to both unaffected eyes and the healthy control group in the study of Eroğlu et al.[19]. Vural et al.[23] reported macular choroidal thinning and reduced ocular perfusion pressure in all quadrants in PEX syndrome. However, other studies yielded opposite results[24,25].

Similar results have been described for PEX glaucoma. In a study by Bayhan et al.[17], choroidal thickness in the nasal 1500- and 3000-μm zones of the macula was found to be less in PEX glaucoma patients than in healthy subjects. Demircan et al.[18] compared PEX syndrome patients, PEX glaucoma patients, and healthy individuals, and reported that choroidal thickness was less in all quadrants in the PEX group. In a study by Özge et al.[22], choroidal thickness of the PEX glaucoma group was not different from that of the control group.

In the present study, the PEX glaucoma group had lower macular choroidal thickness values than both the control and POAG groups. When compared with the control group, this difference was significant at the subfoveal, nasal, and temporal 1500-μm points, whereas the difference was significant at all points in comparison to the POAG group. However, despite the tendency for the greater thickness of the choroid in the POAG group, there was no statistically significant difference between the POAG and control group, which might have resulted from the limited number of patients included in this study. On the other hand, several studies similarly failed to find any significant difference[16].

There were some limitations to this study. The number of patients included in the study was relatively small. The inability to obtain reliable EDI-OCT images due to lens opacity, and particularly the inability to clearly visualize the sclerochoroidal margin, were factors limiting the number of patients included in the study. In addition, the exclusion criteria aimed at ruling out other factors that affect choroidal thickness, thereby further limiting the number of patients. Our patient group had glaucomatous damage ranging from early to an advanced stage, yet the majority of cases had an early stage of glaucoma. Hence, our results may not be applicable to patients with more advanced stages of glaucomatous damage. Manual drawing of choroidal margins may have introduced some measurement errors. However, the measurements were statistically confirmed to have high intraobserver repeatability.

To the best of our knowledge, this is the first study in the literature to compare choroidal thickness in POAG and PEX glaucoma patients in groups with comparable degrees of glaucomatous damage. We found that among glaucoma patients with similar glaucomatous damage, those with PEX material had thinner choroids. Besides, our findings indicate that subfoveal choroidal thickness is reduced in PEX glaucoma cases, but there was no correlation between choroidal thickness and glaucoma damage. The fact that choroidal thickness does not change in POAG glaucoma, but decreases in PEX glaucoma, may be attributable to hemodynamic changes resulting from the effect of exfoliative material on vascular structures. This theory may be supported by studies indicating less variability of retrobulbar blood flow in POAG versus a significant reduction in PEX glaucoma[8,9]. On the other hand, the EDI-OCT imaging method may be inadequate for the analysis of dynamic tissue.

In brief, our findings indicate that macular choroidal thickness is lower in PEX glaucoma as compared with both healthy individuals and POAG patients with similar degrees of glaucomatous damage. The clinical implications of the reduced choroidal thickness in PEX glaucoma and its effect on glaucomatous optic nerve damage have yet to be clarified. Hence, further extensive research on this topic is warranted.

REFERENCES

1. Anastasopoulos E, Founti P, Topouzis F. Update on pseudoexfoliation syndrome pathogenesis and associations with intraocular pressure, glaucoma and systemic diseases. Curr Opin Ophthalmol. 2015;26(2):82-9.

2. Andrikopoulos GK, Alexopoulos DK, Gartaganis SP. Pseudoexfoliation syndrome and cardiovascular diseases. World J Cardiol. 2014;6(8):847-54.

3. Ritch R, Schlotzer-Schrehardt U. Exfoliation syndrome. Surv Ophthalmol. 2001;45(4):265-315.

4. Konstas AG, Stewart WC, Stroman GA, Sine CS. Clinical presentation and initial treatment patterns in patients with exfoliation glaucoma versus primary open-angle glaucoma. Ophthalmic Surg Lasers. 1997;28(2):111-7.

5. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E; Early Manifest Glaucoma Trial Group. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. Arch Ophthalmol. 2003;121(1):48-56.

6. Parrish RK, 2nd. Thessaloniki eye study: the importance of recognizing pseudoexfoliation. Am J Ophthalmol. 2009;148(4):482-3. Comment in: Am J Ophthalmol. 2009;148(4):606-13.

7. Schlotzer-Schrehardt U, Kuchle M, Naumann GO. Electron-microscopic identification of pseudoexfoliation material in extrabulbar tissue. Arch Ophthalmol. 1991;109(4):565-70.

8. Dayanir V, Topaloglu A, Ozsunar Y, Keceli M, Okyay P, Harris A. Orbital blood flow parameters in unilateral pseudoexfoliation syndrome. Int Ophthalmol. 2009;29(1):27-32.

9. Yuksel N, Karabas VL, Arslan A, Demirci A, Caglar Y. Ocular hemodynamics in pseudoexfoliation syndrome and pseudoexfoliation glaucoma. Ophthalmology. 2001;108(6):1043-9.

10. Banitt M. The choroid in glaucoma. Curr Opin Ophthalmol. 2013; 24(2):125-9.

11. Boonarpha N, Zheng Y, Stangos AN, Lu H, Raj A, Zanner G, Harding SP, et al. Standardization of choroidal thickness measurements using enhanced depth imaging optical coherence tomography. Int J Ophthalmol. 2015;8(3):484-91.

12. Manjunath V, Taha M, Fujimoto JG, Duker JS. Choroidal thickness in normal eyes measured using Cirrus HD optical coherence tomography. Am J Ophthalmol. 2010;150(3):325-9 e1.

13. Margolis R, Spaide RF. A pilot study of enhanced depth imaging optical coherence tomography of the choroid in normal eyes. Am J Ophthalmol. 2009;147(5):811-5.

14. Spaide RF, Koizumi H, Pozzoni MC. Enhanced depth imaging spectral-domain optical coherence tomography. Am J Ophthalmol. 2008;146(4):496-500. Erratum in: Am J Ophthalmol. 2009; 148(2):325.

15. Sezer T, Altinisik M, Koytak IA, Ozdemir MH. The choroid and optical coherence tomography. Turk J Ophthalmol. 2016;46(1):30-7.

16. Zhang Z, Yu M, Wang F, Dai Y, Wu Z. Choroidal thickness and open-angle glaucoma: a meta-analysis and systematic review. J Glaucoma. 2016;25(5):e446-54.

17. Bayhan HA, Bayhan SA, Can I. Evaluation of the macular choroidal thickness using spectral optical coherence tomography in pseudoexfoliation glaucoma. J Glaucoma. 2016;25(2):184-7.

18. Demircan S, Yilmaz U, Kucuk E, Ulysoy MD, Atas M, Gulhan A, et al. The effect of pseudoexfoliation syndrome on the retinal nerve fiber layer and choroid thickness. Semin Ophthalmol. 2017; 32(3):341-7.

19. Eroglu FC, Asena L, Simsek C, Kal A, Yilmaz G. Evaluation of choroidal thickness using enhanced depth imaging by spectral-domain optical coherence tomography in patients with pseudoexfoliation syndrome. Eye (Lond). 2015;29(6):791-6.

20. Goktas S, Sakarya Y, Ozcimen M, Sakarya R, Bukus A, Ivacik IS, et al. Choroidal thinning in pseudoexfoliation syndrome detected by enhanced depth imaging optical coherence tomography. Eur J Ophthalmol. 2014;24(6):879-84.

21. Moghimi S, Mazloumi M, Johari M, Abdi P, Fakharaie G, Mohammadi M, et al. Evaluation of lamina cribrosa and choroid in nonglaucomatous patients with pseudoexfoliation syndrome using spectral-domain optical coherence tomography. Invest Ophthalmol Vis Sci. 2016; 57(3):1293-300.

22. Ozge G, Koylu MT, Mumcuoglu T, Gundogan FC, Ozgonul C, Ayyildiz O, et al. Evaluation of retinal nerve fiber layer thickness and choroidal thickness in pseudoexfoliative glaucoma and pseudoexfoliative syndrome. Postgrad Med. 2016;128(4):444-8.

23. Turan-Vural E, Yenerel N, Okutucu M, Yukduz E, Dikmen N. Measurement of subfoveal choroidal thickness in pseudoexfoliation syndrome using enhanced depth imaging optical coherence tomography. Ophthalmologica. 2015;233(3-4):204-8.

24. You QS, Xu L, Wang YX, Yang H, Ma K, Li JJ, et al. Pseudoexfoliation: normative data and associations: the Beijing eye study 2011. Ophthalmology. 2013;120(8):1551-8.

25. Zengin MO, Cinar E, Karahan E, Tuncer I, Yilmaz S, Kocaturk T, et al. Choroidal thickness changes in patients with pseudoexfoliation syndrome. Int Ophthalmol. 2015;35(4):513-7.

26. Abramoff MD, Magalhaes PJ, Ram SJ. Image processing with ImageJ. Biophotonics Int [Internet]. 2004 [cited 2017 Jul 27];11:36-42. Available from: https://imagescience.org/meijering/publications/download/bio2004.pdf

27. Riva CE, Alm A. Ocular circulation. In: Levin LA, Nilsson SF, Hoeve JV, Wu S, Kaufman P, Alm A (eds). Adler's physiology of the eye. 11th ed. China: Elsevier; 2011.

28. Usui S, Ikuno Y, Akiba M, Maruko I, Sekiryu T, Nishida K, et al. Circadian changes in subfoveal choroidal thickness and the relationship with circulatory factors in healthy subjects. Invest Ophthalmol Vis Sci. 2012;53(4):2300-7.

29. Kinoshita T, Mitamura Y, Shinomiya K, Egawa M, Iwata A, Fujihara A, et al. Diurnal variations in luminal and stromal areas of choroid in normal eyes. Br J Ophthalmol. 2017;101(3):360-4.

30. Maul EA, Friedman DS, Chang DS, Boland MV, Ramulu PY, Jampel HD, et al. Choroidal thickness measured by spectral domain optical coherence tomography: factors affecting thickness in glaucoma patients. Ophthalmology. 2011;118(8):1571-9.