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Comparison of Choroidal Thickness in Patients with Pseudoexfoliation Syndrome and Pseudoexfoliative Glaucoma with Normal Subjects

Psödoeksfoliasyon Sendromu ve Psödoeksfoliasyon Glokomu Olan Hastalarda Koroid Kalınlığının Normal Olgularla Karşılaştırılması

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ABSTRACT Objective: To compare the choroidal thickness in pseudoexfoliation syndrome (PES) and pseudoexfoliative glaucoma (PEG) cases with healthy individuals. **Material and Methods:** We included 31 eyes of 31 patients with PES, 31 eyes of 31 patients with PEG, and 33 eyes of 33 healthy individuals in this study. All patients underwent choroidal thickness measurement at the subfoveal, nasal 500 µm, nasal 1000 µm, temporal 500 µm, and temporal 1000 µm areas by using the optical coherence tomography (3D OCT-2000, Topcon, Japan) device. **Results:** There was no difference between the groups for gender and axial length (p>0.05). The subfoveal, nasal 500 µm and temporal 500 µm choroidal thickness values of the PEG cases were statistically significantly lower than the PES cases and the healthy group (p<0.05). Although the choroidal thickness values in the subfoveal and nasal 500 µm regions in the PES cases was lower than in the healthy group, this difference was not found to be statistically significant (p>0.05). **Conclusion:** We found the subfoveal, nasal 500 µm and temporal 500 µm choroidal thicknesses to be significantly lower in the PEG cases than the other two groups. Choroidal thicknesses at the subfoveal and nasal 500 µm areas were also lower in the PES group than the control group but without statistical significance.

Keywords: Choroid; exfoliation syndrome; optical coherence tomography

ÖZET Amaç: Psödoeksfoliasyon sendromu (PES) ve psödoeksfoliasyon glokomu (PEG) olan olgularda koroid kalınlığının sağlıklı bireylerle karşılaştırılması. **Gereç ve Yöntemler:** 31 PES'li hastanın 31 gözü, 31 PEG'li hastanın 31 gözü ve 33 sağlıklı bireyin 33 gözü çalışmaya dahil edildi. Tüm hastalara optik koherens tomografi (3D OCT-2000, Topcon, Japan) cihazı ile koroid kalınlığı ölçümleri subfoveal, nazal 500 µm, nazal 1000 µm, temporal 500 µm ve temporal 1000µm mesafeden yapıldı. **Bulgular:** Gruplar arasında cinsiyet ve aksiyel uzunluk açısından anlamlı farklılık tespit edilmedi (p>0,05). PEG'li olguların subfoveal, nazal 500 µm ve temporal 500 µm'luk koroidal kalınlık değerleri, PES'li olgular ve sağlıklı gruba göre istatistiksel olarak anlamlı olarak daha ince bulundu (p<0,05). PES'li olgular, sağlıklı gruba göre subfoveal ve nazal 500 µm bölgelerdeki koroidal kalınlık değerleri için daha ince olsalar da bu fark istatistiksel olarak anlamlı bulunmadı (p>0,05). **Sonuç:** Bu bulgulara göre PEG'li olgularda subfoveal, nazal 500 µm ve temporal 500 µm'luk koroid kalınlık ölçümü diğer iki gruba göre anlamlı olarak ince saptandı. Ayrıca PES grubunda subfoveal ve nazal 500 µm'deki koroid kalınlığı da kontrol grubuna göre istatistiksel olarak anlamlı olmamakla birlikte daha ince bulundu.

Anahtar Kelimeler: Koroid; eksfoliasyon sendromu; optik koherens tomografi

Pseudoexfoliation syndrome (PES) is characterized by pseudoexfoliative material (PEM) accumulation in both ocular and systemic tissues and is considered to be a systemic disease. PEM is a grayish-white microfibrillary protein structure. PES is often seen in Scandinavian countries and in older ages, especially over the age of 60.[1,2] A study from our country has reported the PEX prevalence as 7.2% for the 50-60 years age group and 11.2% for those above 60 years.[3] The substance progressively accumulates in ocular tissues, mainly at the pupillary edge and lens anterior capsule, iridocorneal angle, ciliary

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body, zonules, anterior hyaloidal face, trabecular mesh, and corneal endothelium, in addition to the palpebral conjunctiva. PEM can even be found on the vascular wall of the posterior ciliary artery, vortex veins and the central retinal veins.[4] These findings indicate that PES may be an ischemic ophthalmic disorder.[5]

There is more pigment distribution from the iris during pupil movements in PES compared to normal subjects. Both the PEM and this distributed pigment are thought to accumulate in the trabecular mesh due to aqueous humor dynamics and then to decrease outflow and cause increased intraocular pressure.[6] Glaucomatous damage in eyes with PES is characterized by higher intraocular pressure (IOP) and wider IOP fluctuations compared to primary open angle glaucoma (POAG) patients, resulting in rapid progression and a worse prognosis.[7-9] The presence of PEM has been found to be an important risk factor independent of progression and to double the progression rate in the Early Manifest Glaucoma Study Group.[10] In addition to the role of high IOP in glaucoma progression and optic nerve injury, Martinaz et al. have emphasized that decreased retrobulbar hemodynamic characteristics may contribute to the damage in PEG cases.[11]

The choroid is one of the tissues with the highest vascular supply in the human body and constitutes 95% of the ocular circulation.[12] Its vascularization is mainly by the long and short posterior ciliary arteries and to a smaller extent by the anterior ciliary artery.[13] Gugleta et al. have shown that an abnormal choroidal blood supply could play a role in the development of glaucomatous optic neuropathy.[14] An attempt has been made to elucidate the relationship between choroidal circulation and glaucoma pathogenesis in patients with normotensive glaucoma, POAG, PEG and PES and conflicting results have been reported in the literature.[15-20]

The Enhanced Deep Imaging (EDI) mode of the Spectral domain optical coherence tomography (SD-OCT) device, has now provided an opportunity to investigate the deep posterior segment structures (lamina cribrosa, choroidal thickness) as it minimizes light loss due to scatter and provides high resolution.

We aimed to compare the choroidal thickness of PES and PEG cases and healthy subjects by using the EDI mode of the SD-OCT device and also to compare our results with those from other studies in the literature. Our aim was to detect whether the choroidal vascular structure was modified in glaucomatous eyes and its effect on the etiopathogenesis.

MATERIAL AND METHODS

The patients with PES, with PEG, and randomly selected healthy individuals who presented to the Amasya Sabuncuoğlu Şerefeddin Training and Research Hospital's Ophthalmic Outpatient Department between December 2017 and December 2018 were included in this cross-sectional and prospective study. Ethics committee approval was obtained from Amasya University (2019/44). The Helsinki Declaration principles were adhered to. All patients provided informed consent.

All subject underwent a full ocular examination that included measuring the logarithmic (logMAR) equivalent of the minimal angle of vision of best corrected visual acuity (BCVA) values with the Snellen chart, anterior segment and dilated fundus examination under biomicroscopy, intraocular pressure (IOP) measurement with Goldman applanation tonometry, gonioscopic angle examinations and measurement of axial length (Nidek US-800 Echo-Scan, Japan) in addition to a Humphrey 24-2 visual field test (Zeiss Humprey Field Analyzer 2 745I, Germany) with the SITA standard program. PEM at the lens anterior capsule or iris edge, a translocation defect in the iris, or PEM accumulation and/or increase in pigmentation at the angle were looked for in the anterior segment examination. PES was defined as presence of PEM, IOP <21 mmHg without using any medication, and a normal-appearing optic nerve and visual field. PEG was defined as PEM and IOP >21 mmHg without medication, glaucomatous optic nerve damage (especially thinning or notching in the superior and/or inferior quadrant), and loss of visual field (a cluster of points with sensitivity loss, with at least one at the $p<0.1$ level on the pattern deviation map).[21,22] Glaucoma stage was determined by using the visual field MD values. Patients with an MD value ≥ -6 dB were considered early glaucoma, -6 dB to -12 dB as middle stage glaucoma and ≤-12dB as advanced glaucoma. None of our cases with PEG had undergone glau-

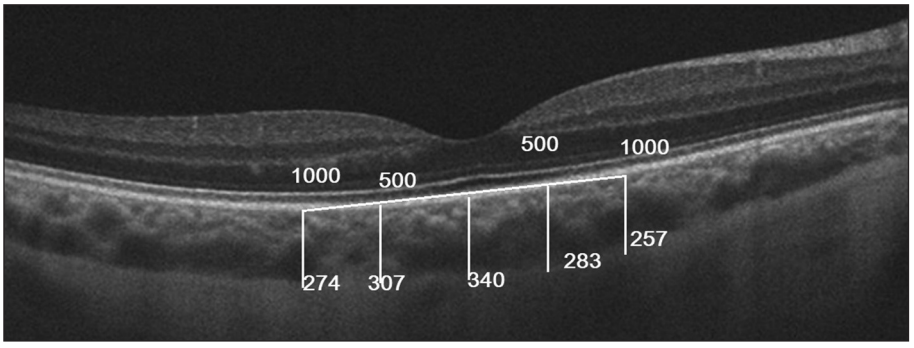

FIGURE 1: Optical coherence tomography scan, showing the macular choroidal thicknesses at five locations (subfoveal, 500 μm nasal to the fovea, 1000 μm nasal to the fovea, 500 μm temporal to the fovea, 1000 μm temporal to the fovea).

coma surgery. The control group was selected from healthy individuals who presented to our outpatient department with no PEM and an IOP <21 mmHg, normal optic disc and visual field, and no systemic disease or medication use.

We excluded subjects <18 years of age and patients who had previously undergone intraocular surgery, those who had inflammatory eye disease or an opacity of the cornea or lens that could affect the image acquisition, those who could not fixate on the target beam of the device, in addition to patients found to have retinal pathologies such as age-related macular degeneration, central serous chorioretinopathy, diabetic retinopathy, epiretinal membrane, or macular dystrophy, patients who had systemic diseases such as hypertension, diabetes or vasculitis that could affect choroidal vascular circulation; and those with a history of drug (analgesic, decongestant, antihistaminic) use and smokers from the study.

Choroidal thickness measurements were conducted at the subfoveal, nasal 500 μm, nasal 1000 μm, temporal 500 μm, and temporal 1000 μm areas by using the SD-OCT (3D OCT-2000, Topcon, Japan) device after pupil dilation. The images were obtained by using the linear mode of the SD-OCT device after placing the patient's head on the device and approximating the device to the relevant eye to produce an inverted image at the top of the screen. All measurements were performed by the same clinician with the groups masked and between 09.00 and12.00 in the morning so that the choroidal circulation would not be affected by diurnal variation.[23] Sections below the signal strength index of 6/10 were not evaluated. Choroidal thickness measurement was performed manually by two independent physicians (MT, NA) at different times with the groups masked and with the help of digital calipers by determining the retinal pigment epithelium outer border and the sclera inner border. In addition to the subfoveal area, the choroidal thickness was measured at areas 500 and 1,000 μm nasal and temporal to the fovea (Figure 1). The measurements were repeated when there was a difference of more than 10 μm between two measurements.

STATISTICAL ANALYSIS

The SPSS 22.0 software (SPSS, Inc., an IBM Company, Chicago, IL, USA) was used for the statistical analyses. Mean ± standard deviation was used to express descriptive statistics. The normality was evaluated by using the One Sample Kolmogorov Smirnov Test and the Shapiro-Wilk Test. The chi-square test was used to compare categorical variables. Parameters with a normal distribution were compared with the one-way ANOVA test while those without a normal distribution were compared with the Kruskal-Wallis test. One-way analysis of covariance (ANCOVA) was used to compare choroidal thickness values between groups after adjusting for confounding factors including IOP, age, sex and axial length. The Bonferroni post hoc test was used for pairwise comparisons between groups. Multiple linear regression analyses were used to evaluate the relationship between the choroidal thickness values with the other parameters. Statistical significance was defined as a p value less than 0.05.

RESULTS

A total of 95 patients, consisting of 31 PES patients (17 female, 14 male), 31 patients with PEG (21 female, 10 male), and 33 randomly selected healthy individuals (15 female, 16 male) in the control group included in the study. The visual field results of the glaucoma patients revealed early glaucoma in 14 (45%), middle stage glaucoma in 10 (32%) and advanced glaucoma in 7 (23%).

No statistically significant difference was found between the three groups in terms of gender and axial length (for gender p=0.256 and for axial length p=0.150). The mean age was 71±5 (63-80) years in the PES group, 69±6 (60-79) years in the PEG group, and 67±6 (53-76) years in the control group. There was no statistically significant difference between the PES group and PEG group and also between the PEG group and the control group in terms of age (p=0.399 and p=0.795, respectively). However, a statistically significant difference was present for age when the PES group and the control group were compared, with the mean age statistically significantly higher in the PES group (p=0.028). The mean visual acuity values of the control, PES and PEG groups were 0.16±0.09 logMAR, 0.17±0.09 logMAR and 0.09±0.07 logMAR, respectively. The control group had statistically better visual acuity as defined by BCVA LogMAR value than the PES and PEG groups (Control vs. PES p=0.01, Control vs. PEG p<0.001), but there was no such difference between the PES and PEG groups (p=1.00).

The mean IOP values of the control, PES and PEG groups were 16.94±2.62, 21.03±4.06 and 15.23±2.95, respectively. Cases with PEG had a statistically significantly higher mean IOP value when compared with the other groups (p<0.001 for both comparisons) and there was no difference between control group and PES group in terms of IOP (p=0.133). Demographic characteristics and clinical findings of the groups are summarized in Table 1.

The effect of age, gender and axial length on the choroidal thickness has been the subject of other studies in the literature.[16,24] The effect of the choroidal thickness was analyzed after correction as the mean age was higher in our PES group. Accordingly, the mean choroidal thickness values in the PEG group were 275.13±22.15 µm in the subfoveal region, 253.35±25.31µm in the temporal 500 µm region, and 238.77±27.31µm in the nasal 500 µm region. The subfoveal, nasal 500 µm and temporal 500 µm choroidal thickness values of the PEG cases were found to be significantly lower than in the PES cases and the healthy group (p=0.002 for the subfoveal region, p=0.03 for the temporal 500 µm, and p=0.023 for the nasal 500 µm between the PEG and PES groups and p<0.0001, p=0.02 and p=0.02, respectively, between the PEG and control groups). No statistically significant difference was seen in choroidal thickness values between the PEG group and the other two groups for the nasal 1000 µm and temporal 1000 µm in PEG group (p>0.05). The mean choroidal thickness was 293.42±13.87 µm in the PES group and 300.68±17.39 µm in the control group in the subfoveal region while the respective values were 255.58±22.01 µm and 257.58±20.06 µm for the nasal 500 µm. Although the choroidal thickness values in the subfoveal area and nasal 500 µm region were lower in PES cases than in the healthy group, this dif-

TABLE 1: Demographic characteristics and clinical findings of the groups.

Parameters	PES	PEG	Control	p value
Number	31 (32.6%)	31 (32.6%)	33 (34.7%)	
Gender (Female/male)	17/16	10/21	15/16	0.256[a]
Age	71±5	69±6	67±6*	0.033[b]
IOP (mmHg)	16.94±2.62	21.03±4.06**	15.23±2.95	<0,001[c]
VA (logMAR)	0.16±0.09	0.17±0.09	0.09±0.07**	<0.001[c]
AXL (mm)	22.12±1.33	21.64±1.83	21.34±1.81	0.150[c]

[a]: Chi-square test, [b]: Analysis of Variance, [c]: Kruskal-Wallis test, PES: Pseudoexfoliation syndrome, PEG: Pseudoexfoliation glaucoma, IOP: Intraocular pressure, VA: Visual acuity, AXL: Axial length *: significant at p<0.05, **: significant at p<0.001.

ference was not found to be statistically significant (p=0.876 for subfoveal thickness, p=1.0 for nasal 500 µm). Choroidal thickness values of the groups and p values for pairwise comparisons are shown in Table 2 and Table 3, respectively.

In multiple linear regression analysis, with potential confounder adjusting, a negative association was found between subfoveal choroidal thickness and the IOP values (β=-0.312, p=0.020) and a positive relationship was found between BCVA

TABLE 2: Comparison of choroidal thickness between pseudoexfoliation syndrome, pseudoexfoliative glaucoma and control groups.

	PES	PEG	Control	p value
F	293.42±13.87	275.13±22.15	300.68±17.39	<0.001
N1	255.58±22.01	238.77±27.31	257.58±20.06	0.019
N2	222.12±26.43	214.26±25.21	220.29±21.90	0.603
T1	272.45±16.84	253.35±25.31	272.39±19.7	0.003
T2	240.15±22.75	226.42±27.45	237.77±22.54	0.620

PES: Pseudoexfoliation syndrome, PEG: Pseudoexfoliation glaucoma, F: Choroidal thickness at fovea, N1: Choroidal thickness at 500 µm nasal to the fovea, N2: Choroidal thickness at 1000 µm nasal to the fovea, T1: Choroidal thickness at 500µm temporal to the fovea, T2: Choroidal thickness at 1000µm temporal to the fovea.

TABLE 3: The results of Bonferroni post-hoc test for pairwise comparisons.

Variable	Group (I)	Group (J)	Mean Difference (I-J)	SE	p value	(95% CI)
F	PES	PEG	18.953*	5.283	.002	(6.058-31.848)
		Control	-5.389	5.083	.876	(-17.794-7.016)
	PEG	PES	-18.953*	5.283	.002	(-31.848--6.058)
		Control	-24.342*	5.869	.000	(-38.666--10.017)
	Control	PES	5.389	5.083	.876	(-7.016-17.794)
		PEG	24.342*	5.869	.000	(10.017-38.666)
N1	PES	PEG	18.287*	6.713	.023	(1.903-34.671)
		Control	.671	6.458	1.000	(-15.091-16.433)
	PEG	PES	-18.287*	6.713	.023	(-34.671--1.903)
		Control	-17.616	7.458	.061	(-35.817-0.585)
	Control	PES	-.671	6.458	1.000	(-16.433-15.091)
		PEG	17.616	7.458	.061	(-0.585-35.817)
T1	PES	PEG	20.377*	6.052	.003	(5.607-35.146)
		Control	1.662	5.822	1.000	(-12.547-15.871)
	PEG	PES	-20.377*	6.052	.003	(-35.146--5.607)
		Control	-18.714*	6.723	.020	(-35.122--2.307)
	Control	PES	-1.662	5.822	1.000	(-15.871-12.547)
		PEG	18.714*	6.723	.020	(2.307-35.122)
N2	PES	PEG	6.621	7.162	1.000	(-10.859-24.1)
		Control	4.894	6.890	1.000	(-11.923-21.71)
	PEG	PES	-6.621	7.162	1.000	(-24.1-10.859)
		Control	-1.727	7.956	1.000	(-21.145-17.691)
	Control	PES	-4.894	6.890	1.000	(-21.71-11.923)
		PEG	1.727	7.956	1.000	(-17.691-21.145)
T2	PES	PEG	16.769	7.008	.057	(-0.334-33.872)
		Control	5.032	6.742	1.000	(-11.422-21.485)
	PEG	PES	-16.769	7.008	.057	(-33.872-0.334)
		Control	-11.737	7.785	.406	(-30.737-7.262)
	Control	PES	-5.032	6.742	1.000	(-21.485-11.422)
		PEG	11.737	7.785	.406	(-7.262-30.737)

PES: Pseudoexfoliation syndrome; PEG: Pseudoexfoliation glaucoma; SE: Standard error, CI: Confidence interval,* significant at the 0.05 level.

and subfoveal choroidal thickness (β=-0.197, p= 0.031).

DISCUSSION

PEG is the most common type of secondary open-angle glaucoma and constitutes 25% of all glaucoma cases.[6] It may develop in 5 years in 5.3% and in 10 years in 15.4% of the patients with PES.[25] PEG is characterized by a high IOP and potentially faster progression.[26,27] However, the role of impaired ocular and retrobulbar blood flow regardless of the IOP elevation is also considered in the etiopathogenesis.[28] Abnormal retinal and choroidal circulation and optic nerve head supply are thought to play a role in the etiology of the related glaucoma.[29-31] We aimed to measure the choroidal thickness of PES cases without glaucoma and PEG cases by using EDI-OCT and to compare these results with a healthy control group in this study.

Choroidal thickness values in the subfoveal, nasal 500 µm and temporal 500 µm area in cases with PEG were found to be significantly lower than in the PES and control groups in this study. The choroidal thickness values in the subfoveal and nasal 500µm areas were also lower in PES patients than the healthy control group but this difference was not found to be statistically significant. We believe that this difference that is present in PEG patients but not PES patients points toward an effect of choroidal ischemia on glaucoma development or could itself be a result of glaucomatous damage. Considering the macular anatomy, the presence of thinning involving the fovea and parafoveal region at the posterior pole within the subfoveal and 500 µm areas could be a result of the progressive course of the disease in these patients.

No difference was present between the subfoveal and temporal choroidal thicknesses but the nasal 3000 µm measurement was significantly lower in PEG cases compared to healthy individuals in the study conducted by Bayhan et al. Choroidal thicknesses were measured from the subfoveal, 1500 µm and 3000 µm nasal and temporal regions and were significantly lower in all regions compared to the control group in both the PEG and PES groups in the study of Dursun et al. who reported that choroidal thickness was lower in the PEG group than in the PES group but with no statistical significance.[17,18] On the other hand, Demircan et al. found choroidal thickness measurements taken from the subfoveal, 1500 µm temporal and nasal regions in the control group to be significantly higher than in both the PEG and PES groups but with no significant difference between the PES and PEG groups.[20] We believe these varying results could be due to glaucomatous patients' at different stages being included, measurements being taken at different distances from the fovea, and the studies being conducted with various numbers of patient groups.

Moghimi et al. showed subfoveal choroidal thickness in PES cases to be significantly lower than in the control group.[19] Göktaş et al. found choroidal thickness in the PES group to be significantly lower than in the control group in their study where they measured choroidal thickness in the subfoveal area and nasal and temporal areas 3000 µm away from the fovea in 34 PES cases and 30 healthy individuals.[32]

There are several studies in the literature reporting changes in retrobulbar blood flow in PES and PEG. Detorakis et al. found the end-diastolic velocity (EDV) in the long posterior ciliary artery to be significantly lower in PES and PEG patients than the POAG and control groups. Additionally, EDV in the short posterior ciliary artery was found to be significantly lower and the residual index (RI) to be significantly higher in the PEG group than the PES group.[33] Considering the role of the long and short posterior ciliary arteries in the choroidal circulation, the increased vascular resistance and decreased blood flow rate will result in decreased perfusion pressure. Ophthalmic artery peak systolic velocity (PSV) and end-diastolic velocity (EDV) were found to be lower in cases with unilateral PES than the control group in the study of Dayanır et al.[34] Such changes in retrobulbar blood flow have also been shown to potentially affect the choroidal circulation. Novais et al. showed an inverse relationship between the short posterior ciliary artery RI parameter and subfoveal choroidal thickness in a study on healthy individuals. They stated that the change in the short posterior ciliary artery, which plays a role in the choroidal blood circulation, may decrease choroidal blood flow and lead to low choroidal thickness.[35] The results of our study

and the others mentioned above indicate that the cause of choroidal thinning shown in PES and PEG may be the accumulation of exfoliative material in the vessel wall, decreasing the retrobulbar blood flow rate and affecting the choroidal circulation.[17,32]

Our results in the PEG group are similar to the literature but differ by the lack of a statistically significant decrease in the choroidal thickness in the PES group. However, taking into account the inverse relationship of the subfoveal choroidal thickness with the IOP value as detected in our study, we believe that the choroid is affected more prominently in PEG and that choroidal ischemia may play a role in glaucoma progression or could appear as a result of glaucomatous damage.

Choroidal thickness has been shown to be affected by age, gender and axial length in various studies. An inverse relationship has been proven to be present between choroidal thickness and axial length.[17,24] This effect was avoided in our study by the lack of a significant difference between the groups in terms of axial length. Goldenberg et al. showed that choroidal thickness decreased with age.[24] While the mean age of the PES group was significantly higher than the control group in our study, no significant difference was observed between the PES group and PEG group in this respect. A recent study has reported that choroidal thickness measurements show diurnal changes with a variability detected especially in the laminar choroidal layer.[36] In order to avoid this effect, all choroidal measurements were made between 09.00 and 12.00 to prevent diurnal change.

There are some missing aspects in our study, and the most important of these is that the choroidal thickness measurements were conducted manually. However, all measurements were performed independently by two physicians for confirmation. When there was a difference of more than 10 µm between the measurements, we tried to avoid such a result by repeating the measurements at different times. The second deficiency was that the patients in the PEG group were receiving anti-glaucomatous treatment. Some studies suggest that anti-glaucomatous agents may affect choroidal thickness.[37] The lack of an evaluation of the relationship between retinal nerve fiber layer thickness, which indicates the severity of glaucomatous injury, and choroidal thickness is another missing point of our study.

CONCLUSION

Subfoveal, nasal 500 µm and temporal 500 µm values of the PEG group were found to be significantly lower than in the other two groups in our study. Choroidal thickness at the subfoveal and nasal 500 µm regions were also lower in the PES group than the control group but without statistical significance. These results showed that PEM may affect choroidal thickness by influencing retrobulbar blood flow. The detection of this condition in patients with PEG indicates that choroidal ischemia may have an effect on the glaucomatous developmental stage or may occur as a result of glaucomatous damage. We therefore believe that further studies supported by larger clinical and histopathological series are required to determine the effect of PEM on the choroidal layer.

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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

Idea/Concept: *Melek Tüfek, Nihat Aydın;* ***Design:*** *Melek Tüfek, Nihat Aydın;* ***Control/Supervision:*** *Melek Tüfek, Nihat Aydın;* ***Data Collection and/or Processing:*** *Melek Tüfek, Nihat Aydın, Pınar Nalçacıoğlu;* ***Analysis and/or Interpretation:*** *Melek Tüfek, Pınar Nalçacıoğlu, Caner Kara;* ***Literature Review:*** *Melek Tüfek, Pınar Nalçacıoğlu, Caner Kara;* ***Writing the Article:*** *Melek Tüfek, Pınar Nalçacıoğlu;* ***Critical Review:*** *Pınar Nalçacıoğlu.*

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