ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Short-Term Effect of Prostaglandin Group Antiglaucomatous Drugs on Choroid Thickness

Prostaglandin Grubu Antiglokomatöz İlaçların Koroid Kalınlığı Üzerine Kısa Dönem Etkisi

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ABSTRACT

Aim: *To evaluate the effects of patients with whom we started prostaglandin analogues for primary open-angle glaucoma (POAG) by measuring the choroidal thickness with Enhanced-Depth Imaging - Optical Coherence Tomography (EDI-OCT).*

Material and Method: *Thirty-two eyes of 32 patients (Group 1) in whom prostaglandin analogues antiglaucomatous drops were initiated, 32 eyes of 32 patients (Group 2) who were initiated with different groups of antiglaucomatous drugs, and 32 eyes of 32 healthy individuals (control group) were included in the study. Before the drug, these groups' submacular choroidal thickness (CT) and intraocular pressure (IOP) were measured with EDI-OCT. Submacular CT of the same groups was measured in the 1st week, the 1st month, and the 3rd month after starting the drug..*

Results: *A significant increase was detected in mean submacular CT thickness measurements with drug use in both Group 1 and Group 2 (p<0.001). Although the choroidal thickness was thinner in pre-treatment glaucoma groups, there was no significant difference in CT (p=0.072). There was no statistically significant difference between the mean Submacular CT groups of all groups at three months (p=0.198). The decrease in IOP in the glaucoma groups was statistically significant (p<0.001, p<0.001, respectively).*

Conclusion: *A significant increase in submacular CT values was detected in patients who started prostaglandin or non-prostaglandin antiglaucomatous due to POAG. In addition, no statistically significant difference was found between the glaucoma groups regarding choroidal change.*

Key words: *choroidal thickness; optical coherence tomography; prostaglandin analogues; intraocular pressure*

ÖZET

Amaç: *Primer açık açılı glokom (PAAG) nedeni ile prostaglandin analogu başladığımız hastaların koroid kalınlığını Enhanced-Depth Imaging - Optical Coherence Tomography (EDI-OCT) ile ölçerek etkilerini değerlendirmek.*

Materyal ve Metot: *Prostaglandin analogu antiglokomatöz damla başlanan 32 hastanın 32 gözü (Grup 1), farklı grup antiglokomatöz ilaç başlanan 32 hastanın 32 gözü (Grup 2), 32 sağlıklı bireyin 32 gözü (kontrol grubu) çalışmaya dâhil edildi. İlaç öncesi bu grupların EDI-OCT ile submaküler koroid kalınlığı (KK) ve göz içi basıncı (GİB) ölçüldü. İlaç başlandıktan sonra 1. hafta, 1. ay ve 3. ayda submaküler KK'ları incelendi.*

Bulgular: *Hem Grup 1 hem de Grup 2'de ilaç kullanımı ile ortalama submaküler KK ölçümlerinde anlamlı artış saptandı (p<0,001). Tedavi öncesi glokom gruplarında koroid kalınlığı daha ince olmasına rağmen gruplar arasında KK'da anlamlı fark yoktu (p=0,072). Submaküler KK ölçümlerinde 3. ayda gruplar arasında istatiksel olarak anlamlı fark tespit edilmedi (p=0,198). Glokom gruplarında GİB'deki düşüş istatistiksel olarak anlamlı bulundu (sırasıyla p<0,001, p<0,001).*

Sonuç: *PAAG nedeniyle prostaglandin veya prostaglandin dışı antiglokomatöz başlanan hastalarda submaküler KK değerlerinde anlamlı artış saptandı. Ayrıca koroid değişikliği açısından glokom grupları arasında istatistiksel olarak anlamlı fark bulunmadı.*

Anahtar kelimeler: *koroid kalınlığı; optik kohorens tomografi; prostoglandin analogları; göz içi basıncı*

Introduction

Glaucoma is a chronic progressive optic neuropathy resulting in permanent loss of vision[1]. Medical treatment in which prostaglandins play an important role is generally effective. Prostaglandin analogues are a frequently employed drug group in glaucoma due to their efficacy in monotherapy, ease of use in a single dose, and lack of impact on quality of life[2]. Several studies have proved the effectiveness of medications from this group in lowering intraocular pressure (IOP), the most critical risk factor in glaucoma[3]. Prostaglandin analogues reduce IOP by increasing the outflow of aqueous humor via the uveoscleral route and the trabecular meshwork[1,4].

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Several studies have shown that these prostaglandin analogues used in the treatment of glaucoma increase ocular perfusion pressure and blood flow, which is reported to be positively correlated with the choroidal thickness (CT)[5]. However, some studies have suggested that this increase is associated with a decrease in IOP[6]. In addition, the regulatory capacity of changes in ocular perfusion pressure in the human choroid has recently been shown to be capable of alteration in line with changes in arterial blood pressure and IOP[7]. Prostaglandin group medications have a known potential pro-inflammatory effect and have been linked to ocular inflammation in some cases[8]. There have also been case reports of prostaglandin analogues causing choroidal detachment[9].

The fact that optic neuropathy also develops in the case of normal IOP suggests that factors other than IOP elevation may be involved in the pathogenesis of glaucoma. Enhanced-depth imaging (EDI) is a new optical coherence tomography (OCT) technique permitting detailed evaluation of the choroid layer. Evaluating CT in glaucomatous eyes using this new method will also contribute to a greater understanding of the relationship between glaucoma and the choroid and the effect on the choroid of the drugs used in medical treatment. A limited number of studies have examined changes in the choroid coat developing with anti-glaucomatous treatment, and we think that studies in this area will contribute to a better understanding of the effect of topical anti-glaucomatous medications on the choroid.

The present study aimed to investigate CT using EDI-OCT in patients started on prostaglandin analogues due to primary open-angle glaucoma (POAG).

Materials and Methods

This prospective study was conducted with patients who presented to the Harran University Faculty of Medicine Eye Clinic Glaucoma Unit between September 2018 and March 2021. The research commenced following receipt of permission from the Harran University Medical Surgery and Drug Research Ethics Committee. Thirty-two eyes of 32 patients aged 50–70 were diagnosed with POAG. They started on prostaglandin analog anti-glaucoma drops (Group 1), 32 eyes of 32 patients started on different anti-glaucomatous group medications (Group 2), and 32 eyes of 32 healthy individuals from a similar age group but without glaucoma representing the control group were included in the study.

Patients with visual acuity of 0.2 or worse, retinal sensitivity affected by environmental turbidity, and any condition capable of affecting retinal sensitivity or the visual field (such as cataract, corneal turbidity, vitreous turbidity, or age-related macular degeneration), diabetes mellitus, systemic diseases affecting retinal sensitivity such as uveitis or Behçet's disease, a previous history of ocular surgery, refractive error exceeding ±1.0 diopters (D), or patients with problematic choroidal-scleral differentiation at OCT were excluded from the study.

Patients in the first group were started on one of the prostaglandin analogues latanoprost (Xalatan®), travoprost (Travatan®), or bimatoprost (Lumigan®). In contrast, those in Group 2 were started on one of the carbonic anhydrase inhibitors, beta-blockers, or alpha-adrenergic agonists. The individuals in the third group had no ocular disease. The patients were not using any medication other than the anti-glaucomatous agents. Corrected near and far visual acuity, anterior segment, and fundus examination, angle examination using a Goldmann three-mirror contact lens, IOP measurement using a Goldmann applanation tonometer, axial length measurement using an ultrasonic biometer (NIDEK US-4000 Echoscan Gamagori, Japan), topographic pachymetry using a Pentacam, and central corneal thicknesses measurements were performed at the first examination and follow-ups at the first week and the first and third months. Perimetric tests (central 30–2 threshold test with the SITA-Fast strategy) were conducted using a Humphrey Field Analyzer (Humphrey Field Analyzer-750; Carl Zeiss Meditec, Dublin, CA, USA), and mean deviation (MD) and pattern standard deviation (PSD) values were recorded. The POAG group consisted of patients with IOP exceeding 21 mmHg without medication, with an open and normal anterior segment angle at gonioscopic examination, with glaucoma-specific optic nerve head damage and visual field defect. In addition, all patients' submacular CT was measured using spectral domain OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany), and enhanced-depth imaging (EDI) mode was used for CT. A single technician performed imaging without knowledge of the research, and thickness measurements were carried out by a single evaluator blinded to the study groups. The first measurement point on the macular cross-section at OCT was beneath the fovea, and subsequent measurements were taken in the nasal and temporal directions. This measurement was based on the distance between the posterior edge of the retinal pigment epithelium

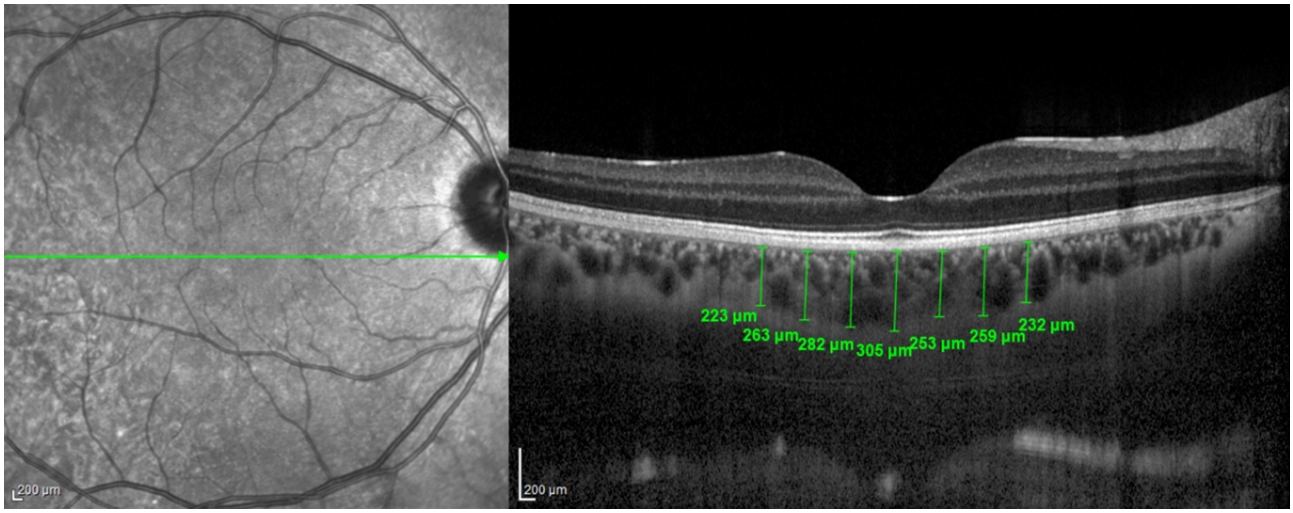

Figure 1. *Seven choroidal thickness measurements from the macular region.*

Table 1. *Demographic and clinical characteristics of the participants in the study groups*

	Group 1	Group 2	Control	p
Age (years)	58.60±6.54	58.80±5.34	57.66±5.65	0.850
Sex(F/M)	14/18	15/17	16/16	0.915
Perimetric MD (dB)	-8.47±1.38	-8.44±1.40	-0.54±0.30	**<0.001**
Perimetric PSD (dB)	8.47±1.19	8.51±1.28	1.81±0.41	**<0.001**
Corneal thickness (µm)	524.83±5.34	525.56±5.97	524.73±3.36	0.782
Axial length (mm)	22.69±0.94	22.86±0.96	22.84±0.96	0.962

MD: Mean deviation; **PSD:** Pattern standard deviation

(RPE) and the choroid sclera junction. The user manually measured the vertical distance between these two points in microns with the assistance of the device's ruler function. This first measurement was recorded with the abbreviation SF (subfoveal). Six further measurement points, three nasal and three temporal, were then established at 500-micron intervals, with the first measurement point being fixed. These points in the nasal region were referred to as N1, N2, and N3 from the center toward the periphery, and those in the temporal regions were referred to as T1, T2, and T3 from the center toward the periphery (Fig. 1).

Statistical Analysis

The data obtained were analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 23.0 (IBM Inc., Chicago, IL, USA) software. When parametric conditions were met, the Mann-Whitney U-test was used to compare measurement data between the two glaucoma groups. Analysis of variance (ANOVA) was applied to compare measurement data among the three groups when parametric conditions were established and the Kruskal-Wallis test if parametric conditions were not met. Repeated measures ANOVA was applied for consecutive measurements, while descriptive data were compared using the chi-square test. Measurement data were expressed as mean ± standard deviation and descriptive data as numbers and percentages. p values <0.05 were regarded as statistically significant.

Results

No significant difference was determined among the three groups regarding age, sex, axial length, or corneal thickness (p>0.05 for all). The demographic characteristics and clinical findings of all three groups are shown in Table 1. Mean deviation values in groups 1 and 2, the glaucoma groups, differed significantly from those in the control group p<0.001 for both).

There was no significant difference between the glaucoma groups regarding MD, PSD, IOP, or corneal thickness values (p=0.871, p=0.863, p=0.964, and p=0.782, respectively).

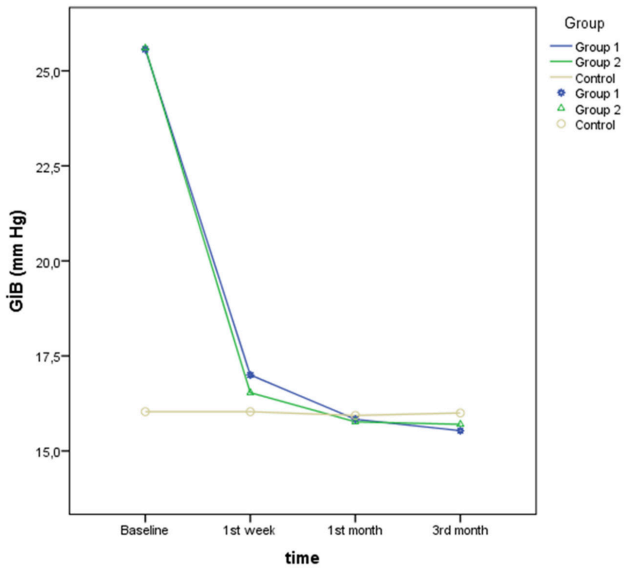

Figure 2. *Changes in IOP values in the study groups.*

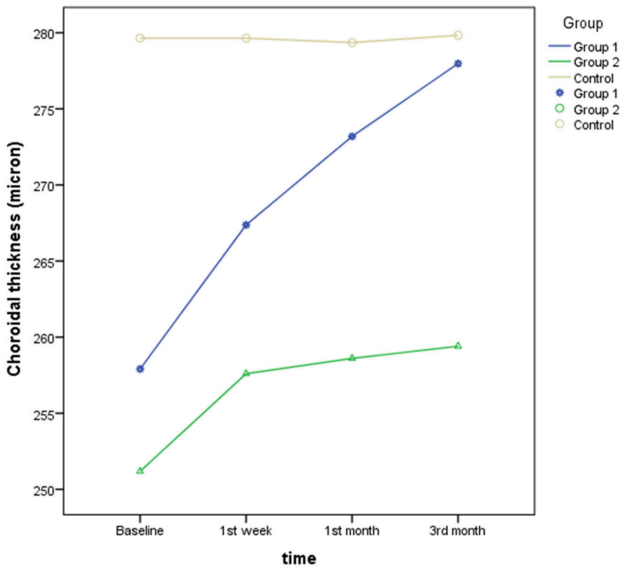

Figure 3. *Changes in mean choroidal thickness values in the study groups.*

Table 2. *Distribution of eyes. IOP and submacular choroidal thickness in the groups*

		Baseline	1st week	1st month	3rd month	p
Group 1	IOP (mm Hg)	25.5±1.6	17.0±1.3	15.8±1.2	15.5±1.2	**<0.001**
	CT (µm)	257.9±53.3	267.3±52.0	273.1±52.0	277.9±52.0	**<0.001**
Group 2	IOP (mm Hg)	25.6±1.8	16.5±0.9	15.7±1.5	15.7±1.2	**<0.001**
	CT (µm)	251.1±44.1	257.6±44.6	259.4±42.9	259.4±42.9	**<0.001**
Control	IOP (mm Hg)	16.0±2.6	16.0±2.4	15.9±2.1	16.0±2.4	0.964
	CT (µm)	279.6±47.7	279.6±47.7	279.3±47.2	279.8±47.4	0.268

IOP: Intraocular pressure; **CT:** Choroidal thickness (µm).

Twelve cases in the prostaglandin group were started on latanoprost, ten on travoprost, and ten on bimatoprost. Mean CT and IOP values by groups at baseline, one week, and one and three months are shown in Table 2.

Comparison of baseline IOP levels with those at one week and one and three months revealed significant decreases in both Group 1 and Group 2. In contrast, a substantial increase was determined in CT values ($p<0.001$). Changes in IOP and mean CT at consecutive measurements in all three study groups are shown in Figures 2 and 3.

Although there was no statistically significant difference in pre-treatment CT between the two glaucoma groups (Groups 1 and 2) and the control group, CT was lower in the glaucoma groups ($p=0.072$). In the third month, the mean CT in the control group was 279.8±47.4 µm, compared to 277.9±52.0 µm in Group 1 and 259.4±42.9 µmin Group 2. Mean CT values at submacular measurements in the third month were highest in the control group, followed by Group 1 and Group 2. However, there was no statistically significant difference among the three groups ($p=0.198$).

No statistically significant difference was observed between the glaucoma groups regarding changes in IOP or CT ($p=0.715$ and $p=0.341$, respectively). Changes in submacular CT at the seven measurement points at the end of the third month compared to baseline values are shown in Table 3.

The subfoveal measurements were the highest mean values among the seven measurements taken from the macular region. At the same time, CT on the temporal side was greater than on the nasal side. CT other than SF at all times points in groups 1 and 2 and the control group, from highest to lowest, were at T1, N1, T2, N2, T3, and N3. Statistical analysis showed that CT increased significantly in groups 1 and 2 at all seven points. At the same time, no significant difference was found in the control group.

Table 3. *Changes in choroidal thickness at the seven submacular measurement points*

	Group 1			Group 2			Control		
	Baseline CT (µm)	3rd month CT (µm)	p	Baseline CT (µm)	3rd month (µm)	p	Baseline CT (µm)	3rd month CT (µm)	P
T3	240.9±53.8	264.4±53.1	<0.001	233.9±42.8	241.7±43.2	<0.001	264.1±47.5	264.3±47.4	0.165
T2	258.3±54.0	279.5±52.3	<0.001	246.7±45.4	256.0±44.5	<0.001	281.5±47.3	281.9±47.4	0.167
T1	269.5±52.3	291.9±51.1	<0.001	269.8±45.4	278.0±43.8	<0.001	295.5±48.1	296.0±48.1	0.164
SF	296.5±52.3	317.1±50.7	<0.001	295.3±46.1	305.0±43.9	<0.001	322.4±50.9	322.9±50.1	0.326
N1	269.6±54.7	291.3±53.8	<0.001	263.1±50.7	271.8±48.7	<0.001	283.2±52.9	282.8±52.3	0.502
N2	248.2±59.8	266.8±58.5	<0.001	241.6±53.3	248.8±52.9	<0.001	268.3±54.4	268.7±54.4	0.163
N3	222.0±59.8	234.6±56.4	<0.001	207.7±50.8	214.2±50.6	<0.001	242.2±55.5	241.9±54.4	0.502

CT: Choroidal thickness (µm).

Discussion

The choroid is a highly vascularized structure with considerable blood flow. The thickness may change in line with variations in IOP[10]. Although there have been various studies of the relationship between glaucomatous optic neuropathy and impaired choroidal circulation or optic nerve head blood flow, the role of the choroid in glaucomatous optic neuropathy is still unclear[11].

Recent advances in the imaging of the ocular posterior segment, particularly the entry into EDI OCT, have permitted a more detailed examination of the choroid layer and have again raised the question of the relationship between glaucoma and CT. The present study aimed to assess the effect of prostaglandin-group anti-glaucoma drug use on submacular CT.

Mwanza et al. reported no significant differences in CT measurements taken from the macula region using EDI OCT in cases with glaucoma and normal individuals[12]. Maul et al. also reported no significant difference in a similar study[13]. Song et al. reported a thinner submacular choroid in patients with glaucoma, although the difference was not statistically significant[14]. In the present study, while there was no significant difference in pre-treatment CT between the glaucoma groups (groups 1 and 2) and the control group, the choroid was thinner in the glaucoma groups.

Any topical glaucoma medication will alter ocular perfusion pressure due to its ocular hypotensive effect. The ocular perfusion pressure of the human choroid has been shown to vary in association with arterial blood pressure or IOP[7,15]. Since choroidal venous pressure and IOP are closely interrelated, any decrease in IOP will lead directly to an increase in ocular perfusion[16]. Latanoprost has been found to positively affect ocular perfusion pressure, ocular blood flow, and choroidal blood flow[5,6]. Most studies have shown that blood flow increases significantly following treatment, including latanoprost. Based on the findings of studies involving B-receptor antagonists and carbonic anhydrase inhibitors, the vasomotor effect contributes directly to changes in ocular perfusion pressure[17]. Intraocular pressure levels play a crucial role in changes in CT. Moreover, any decrease in IOP is thought to have an improving effect on ocular blood flow regulation[18].

Çalişkan et al. examined CT and axial length changes following mannitol infusion in patients with high IOP. They reported that a decrease in IOP following infusion in such patients caused an increase in CT values[19]. Similarly, Akahori et al. observed that the more significant the decrease in IOP, the more remarkable the increase in CT[20]. The change in CT after treatment in our glaucoma groups may, therefore, be related to a decrease in IOP. In addition, no significant difference was observed in IOP changes between Group 1 and Group 2. The greater increase in CT in the cases using prostaglandin, even though both glaucoma treatments produced a decrease in IOP, may derive from the different effect mechanisms of the two medications.

In contrast to other anti-glaucoma agents, prostaglandins increase the outflow of aqueous humor via the uveoscleral route. Aqueous humor passes from there to the suprachoroidal space via the vortex veins that drain the choroid and thus enter the circulation. Prostaglandins can, therefore, raise CT more than non-prostaglandin anti-glaucoma medications. In addition, a slight increase in CT in the non-prostaglandin anti-glaucoma medication group may also occur as a result of a decrease in IOP[21].

Kola et al. reported a significantly greater CT in cases of ankylosing spondylitis, an inflammatory disease than in a healthy control group. Those authors suggested that this difference might be due to the inflammatory effect of prostaglandins[22]. Boyraz et al. observed

a significant increase in foveal thickness and foveal volume in patients using prostaglandin for three years or longer. They suggested that since prostaglandins exert an inflammation-triggering effect, they may also increase foveal and macular thickness by exacerbating subclinical inflammation[23]. The increased CT observed in patients receiving prostaglandin analog therapy may be due to these inflammation-triggering effects.

Glaucoma is a focal disease that usually affects the inferotemporal or superotemporal nerve fiber layers. Due to its focal nature, there is a strong likelihood of a link between the choroidal layer and the area around the optic disk, known as the peripapillary zone. Nakakura et al. observed no significant difference between normal individuals and those with glaucoma in their comparison of macular CT in cases of POAG[24]. Similarly, both Hirata et al. and Mawanza et al.'s studies reported greater thicknesses in the temporal part of the macula than in the nasal part[25,12]. The present study supports the idea that the macula's temporal region is thicker than the nasal region in cases of POAG. The highest of the seven measurements in the macular region in the present study were those from the subfoveal region. When the six measurements other than SF were compared at all time points, the mean CT values were highest to lowest in groups 1 and 2, and the control group was in T1, N1, T2, N2, T3, and N3. Statistical analysis revealed a significant increase in CT in the seven measurement points in Group 1 and Group 2 but no significant difference in the control group.

Akyol et al. investigated the effects on CT of bimatoprost against those of a brinzolamide/timolol maleate fixed combination. They observed a statistically significant difference between the two groups, the increase in thickness being greater in the bimatoprost group[26]. No significant difference was observed in the present study between prostaglandin and non-prostaglandin anti-glaucoma therapy, although consistent with that study, the increase in CT was greater in patients using prostaglandin.

Aksoy et al. confirmed that CT is affected by several factors. For example, they observed 30–60 μm changes in diurnal CT and that intravenous acetazolamide use led to increased CT[27]. We therefore measured CT values within a limited time frame (09:00–12:00 hours), and patients using oral carbonic anhydrase inhibitor (acetazolamide) were excluded. In addition, systolic blood pressure values and hypercholesterolemia are also known to affect CT[28]. However, these parameters were not investigated in this study. Other limitations of this study are the low case number, the short follow-up period, and the fact that CT was measured manually.

In conclusion, examination of submacular CT in patients started on prostaglandin or non-prostaglandin anti-glaucoma therapies due to POAG in this study revealed a significant increase in both groups. No significant difference was determined between the glaucoma groups and the control group at the end of three months. No significant difference was found between the glaucoma groups regarding IOP or choroidal changes. Our study supports the idea that anti-glaucoma medications increase submacular CT. Further, more extensive studies are now needed to determine the role of choroidal circulation in the pathogenesis of glaucoma.

Funding

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Data Availability

All data are available; please contact the corresponding author.

Compliance with Ethical Standards

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Harran University Institutional Evaluation Committee and Ethical Committee (Protocol Number 10/08/2018-E. 31565).

Informed consent

Informed consent was obtained from all participants in the study.

Consent for publication

It was obtained from all individual participants included in the study.

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