

# Posterior Segment Effects of Prostaglandin Analogues

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## ABSTRACT

**Purpose:** Prostaglandin (PG) analogues are commonly used in the treatment of glaucoma. In this study, we aimed to investigate the posterior segment effects of the drug with long-term use of topical PG analogue monotherapy in patients with the diagnosis of primary open angle glaucoma (POAG).

**Materials and Methods:** Patients diagnosed with POAG and treated for 1 to 3 years were included in the study. A total of 25 patients treated with latanoprost monotherapy formed the 1<sup>st</sup> group, 25 patients who received dorzolamide timolol combination monotherapy constituted the 2<sup>nd</sup> group, 25 patients with brimonidine monotherapy formed the 3<sup>rd</sup> group and 31 healthy volunteers made up the 4<sup>th</sup> group. Routine ophthalmological examination, intraocular pressure (IOP) measurement and fundus examinations were performed thoroughly. Central macular and choroidal thicknesses were measured by optical coherence tomography (OCT).

**Results:** There was no significant difference in the mean macular thickness between the groups. The mean choroidal thickness was significantly higher in patients using PG analogue than the other groups. None of the patients had intraocular inflammation or cystoid macular edema (CME).

**Conclusion:** The choroidal thickness was significantly higher in the group receiving topical latanoprost monotherapy than the other groups. None of the patients had CME or inflammation. PG analogue monotherapy can be used safely in POAG cases. PG analogue therapy should be kept in mind in clinical conditions where choroidal thickness is significant.

**Key Words:** Latanoprost, Macular thickness, Choroidal thickness, Cystoid macular edema

## INTRODUCTION

Glaucoma is characterized by progressive optic neuropathy and loss of peripheral visual field (PGF). It is one of the major causes of irreversible vision loss. Intraocular pressure is the most important, modifiable risk factor. In glaucoma treatment, primary goal is to reduce intraocular pressure.<sup>1</sup>

In glaucoma treatment, it is aimed to protect integrity of visual function and quality of life by preventing loss of retinal ganglion cell via reduction in IOP.<sup>2,3</sup>

Topical PG analogues are first-line treatment in glaucoma. These agents are preferred due to their effectiveness and ease of once a daily use. In addition, these agents are highly effective in the control of daily IOP fluctuations. PG analogues primarily exert their effect by enhancing uveoscleral outflow of aqueous humor; however, it is seen that PG analogues facilitate aqueous humor passage by acting on trabecular network.<sup>4</sup>

PG analogues are pro-inflammatory mediators. There are published evidence suggesting that they are associated to increased intraocular inflammation, CME, increased permeability of choroidal vessels and choroidal detachment.<sup>5-10</sup>

The OCT is a non-invasive, high-resolution imaging technique that can assess macula in detail. It also enables cross-sectional imaging of choroid tissue. The most beneficial application of choroidal imaging by enhanced-depth OCT technique reflecting in clinical practice is measurement of choroidal thickness. It has good inter-visit agreement, providing highly reliably measurements, inter-observer and inter-system. In current practice, subfoveal choroidal thickness is the most commonly used measurement. It is used in clinical conditions such as macular degeneration, central serous retinopathy and Harada where choroidal thickness is relevant.<sup>11</sup>

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## METHODS

The study included 50 eyes of 25 patients receiving latanoprost, 50 eyes of 25 patients receiving drozolamid plus timolol combination and 50 eyes of 25 patients receiving brimonidin, who presented to Glaucoma outpatient clinic. In addition, 62 eyes of 31 healthy volunteers presented for routine control were included as controls.

The study was approved by Ethics Committee. All participations gave written informed consent. The diagnosis of POAG was made in the absence of findings indicating open angle and secondary glaucoma in gonioscopy.

All patients had well-controlled IOP in both eyes for at least one year. The patients with regular follow-up were included to the study while patients not attending to control visits were excluded. Study population included glaucoma patients with early-to-intermediate stage who had no progression during follow-up of at least 1-3 years.

For glaucoma cases, inclusion criteria were: age between 45 and 74; no history of previous maculopathy, uveitis, optic nerve pathology or ocular surgery; no corneal opacity, cataract, vitreal opacity; no refractive error  $> \pm 3$  D; no systemic disease such as diabetes mellitus, uncontrolled hypertension, Raynaud disease or metabolic disorders.

As healthy controls, individuals aged 45-74 years who had no anterior or posterior segment pathology were included.

The subjects were assessed using Spectralis Optic Coherence Tomography (SD-OCT, Heidelberg

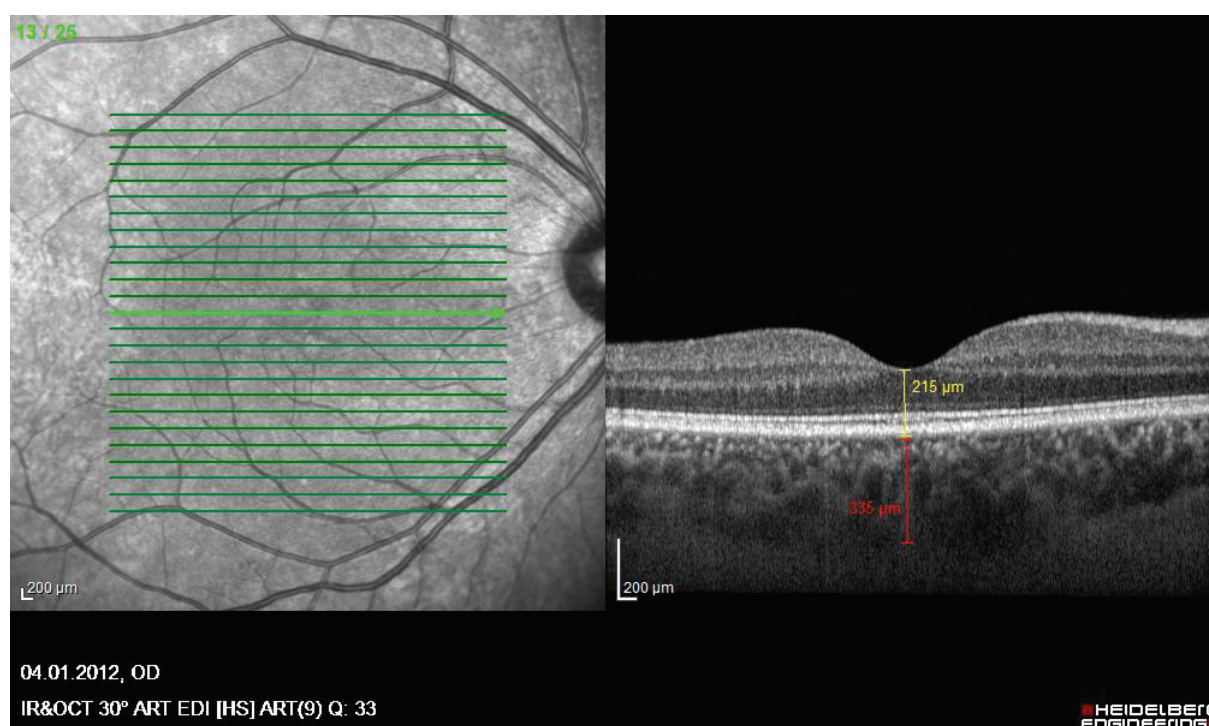
Engineering, Germany). Choroid imaging was performed using EDI (Enhanced Depth Imaging) mode. Choroid thickness was assessed by manual measurement of perpendicular distance between outer margin of RPE hyper-reflectivity (Figure 1).

## Statistical Analysis

Measurement data are expressed as mean  $\pm$  standard deviation. Data were analyzed using SPSS (Statistical Package for Social Sciences) version 22.0 (SPSS Inc. Chicago IL, USA). Pearson correlation test was used to assess relationship among independent variables. Student's t test was used to compare groups. In all analyses, p value  $< 0.05$  was considered as statistically significant. Age-adjusted values were estimated for patient and control groups and data were re-analyzed.

## RESULTS

In the study, we assessed 50 eyes of 25 glaucoma patients (13 women, 12 men) using PG analogues, 50 eyes 25 glaucoma patients (11 women, 14 men) using dorzolomid plus timolol, 50 eyes of 25 glaucoma patients (13 women, 12 men) using brimonidin and eyes of healthy volunteers (16 women, 15 men). Mean age was  $57.68 \pm 8.5$  years in group 1,  $58.82 \pm 7.83$  years in group 2,  $56.34 \pm 7.46$  years in group 3 and  $56.61 \pm 7.65$  years in the control group. Duration of drug use was 1-3 years in the patient group. No significant difference was detected in age and gender among groups. Table 1 presents demographic characteristics of groups.



**Figure 1:** ED-OCT image and choroid measurement.

**Table 1: Demographic characteristics of groups.**

	Group 1 n=25	Group 2 n=25	Group 3 n=25	Group 4 n=31	P value
Male: Female	13:12	14:11	13:12	16:15	>0,05
Age (years)	57,68 ± 8,5	58,82± 7,83	56,34± 7,46	56,61 ± 7,65	>0,05
Baseline IOP (mmHg)	24,5±4,2	23,4±2,9	22,8±2,3	16,1±2,9	>0,05
Post-treatment IOP (mm Hg)	18,4±2,8	17,1±3,1	17,3±2,4	16,1±2,9	>0,05

Based on data screened in patient files, mean IOP values were 24.5±4.2 in group 1, 23.4±2.9 in group 2 and 22.8±2.3 in group 3 at baseline. The mean IOP was found as 18.4±2.8 in group 1, 17.1±2.5 in group 2 and 17.3±2.4 in group 3 after treatment. In group 4, mean IOP was found as 16.1±2.9 in healthy volunteers. The patients showed no progression with effective reduction in IOP.

A decrease was seen in parameters by advancing age. Thus, age-adjusted values were calculated and all parameters were compared among groups. It was found that central choroid thickness was significantly higher in the group using PG analogues when compared to controls.

Mean central macular thickness (CMT) was found as 231.43 ± 22.38 μ in group 1, 220.35± 20.51 μ in group 2, 227.85± 26.45 in group 3 and 218.90 ± 19.59 μ in controls, indicating no significant difference among groups.

Mean central choroid thickness was found as 300.59 ± 68.82 μ in group 1, 269.81±63.37 μ in group 2, 272.42±48.56μ in group 3 and 283.25 ± 51.88 μ in the control group. When groups were compared, a significant difference was detected in G analogue group (p <0.05). Table 2 summarizes results.

## DISCUSSION

The PGs are metabolic derivatives of arachidonic acid, which play role in inflammatory process. They are involved in induction of inflammation and in the pathogenesis of edema via increased vascular permeability in eyes and other tissue. It is known that PGs/prostamides exert potential pro-inflammatory effect and are associated with ocular inflammation.<sup>5-7</sup>

We think that PG analogues will affect choroidal flow by pro-inflammatory effects and increasing vascular

permeability and uveoscleral outflow. Thus, we aimed to assess intraocular inflammation and macular and choroidal changes by comparing patients using long-term PG analogues, those using other anti-glaucomatous agents and healthy volunteers.

There are studies suggesting that PG analogues, used as ocular hypotensive agents, lead macular structural changes and CME development when endogenous PG release disrupts blood-humor aqueous barrier and functions. In almost all cases reported, there were risk factors for CME development such as intraocular surgery, aphakia, pseudoexfoliation, posterior capsule rupture and cataract surgery complicated by vitreous loss.<sup>12-15</sup> In a retrospective review of 225 eyes with aphakia or pseudoaphakia which were treated with topical latanoprost, Lima et al. found that all three of patients with CME had posterior capsule rupture requiring anterior vitrectomy and history of cystoid macular edema diagnosed 3 years before onset of latanoprost in one patient. Authors suggested that CME incidence with latanoprost treatment is rather low even if there is a causal relationship between latanoprost treatment and CME.<sup>12</sup> Furuichi et al. assessed foveal thickness by OCT in case of normal functioning blood-ocular barrier and found that latanoprost did not induced CME development.<sup>16</sup>

In a similar study, it was reported that bimatoprost did not cause clinical or structural macular changes in phakic glaucoma patients. In the study, bimatoprost resulted in effective reduction in IOP without causing macular disorder such as CME on OCT during 3-months follow-up.<sup>17</sup> Chang et al. retrospectively reviewed 84 cases with uveitic glaucoma which had at least 3 months of follow-up. Authors compared patients treated with PG analogues and non-PG analogues and found no significant difference in frequency of uveitis episodes and CME development.<sup>18</sup>

**Table 2: Mean central macular and choroid thickness in groups.**

	Group 1 n=25	Group 2 n=25	Group 3 n=25	Group 4 n=31	P value
Central macular thickness (micron)	231,43±22,38	220,35±20,51	227,85±26,45	218,90±19,59	p>0,05
Central choroid thickness (micron)	300,59±68,82	269,81±63,37	272,42±48,56	283,25±51,88	p<0,05

In another study, 121 eyes of 73 cases with glaucoma and 36 eyes of 18 healthy controls were evaluated for CME. The patients with glaucoma were assigned into 3 groups to receive medical treatment including timolol maleate, latanoprost and bimatoprost.

At 12-months follow-up, a significant, mild-to-moderate increase was detected in central macular thickness with no effect on vision in bimatoprost and latanoprost groups. No CME was detected in study population.<sup>19</sup> In our study, age-adjusted values were calculated for all parameters and comparisons were made by using these values. Although central macular thickness was higher in the group receiving topical latanoprost treatment no significant difference was detected when compared to remaining groups and no CME was observed in any of the patients. In our patients, there was no history of ocular pathology, ocular surgery, and systemic pathology such as diabetes mellitus which may be risk factor for CME. We think that PG analogues can be used safely as monotherapy or combination in patients having no risk factor.

Choroid tissue supports metabolic requirements of outer retina and retinal pigment epithelium. It is known that macrophages and dendritic cells in choroid are important in the homeostasis of retina and choroid, and that they play important roles in the inflammation. Thus, choroid tissue has a major function in case of uveoretinitis and is active in case of inflammation.<sup>20</sup> There are studies regarding thickening of choroidal layers in posterior uveitis. It was reported that increased choroidal thickness was detected as a result of inflammatory infiltration in these cases.<sup>21-23</sup> In a study comparing 84 ankylosing spondylitis cases without ocular involvement and 63 healthy individuals, it was found that choroid tissue was significantly thicker although there was no significant difference in retinal thickness. It was concluded that the difference may be due to chronic inflammation caused by disease.<sup>24</sup> In another study, Kim et al. reported that there was choroidal thickening during active phase of Behcet disease-related posterior uveitis. In addition, subfoveal choroidal thickness was significantly higher during ictal period in addition to active phase. It was found that the reduction in choroidal thickness was significantly correlated to improvement in retinal vessel leakage as detected by fluorescein angiography.<sup>25</sup>

In the literature, central serous chorioretinopathy (CSC) cases were reported with PG analogue use. It is thought that PG analogues cause CSC by acting on choroidal circulation via increase vascular permeability. Choroid tissue is a part of uveoscleral pathway and uveoscleral outflow may contribute to CSC. The clinical picture was recovered by withdrawal of drug in reported cases.<sup>8,10</sup> There are case reports suggesting a relationship between

PG analogue use and choroid detachment. It is thought that PG analogue treatment play role in the pathogenesis of complication by IOP lowering and pro-inflammatory effect in case of choroid detachment together with hypotonia and visual impairment.<sup>26-29</sup>

In another study, 40 cases who had asymmetric, unilateral IOP >40 mmHg were assessed. In the study, IOP was decreased by 14.23 mmHg in average with systemic mannitol infusion; reduction in axial length and increase in choroid thickness was detected following decrease in IOP. The increase in choroidal thickness was found to be correlated with decrease in IOP.<sup>30</sup> In their study, Bolt et al. showed that latanoprost enhanced choroidal flow despite alteration in ocular.<sup>31</sup> Authors suggested that the result might be due to hypotensive effect of latanoprost. In a similar study, bimatoprost and fixed brinzolamid plus timolol combination were compared. Choroid thickness was found to be significantly increased in bimatoprost group despite comparable decrease in IOP among groups.<sup>32</sup>

In our study, we showed that choroid was thicker in patients receiving PG analogue over >1 year when compared to other anti-glaucomatous groups and controls. The increased choroidal thickness may be due to reduction IOP demonstrated in previous studies; however, the fact that choroidal thickness was higher when compared to other anti-glaucomatous agents which achieve comparable decreases in IOP suggest that the thickening may be due to pro-inflammatory effects of PG analogues, increased vascular permeability and uveoscleral flow.

This study has some limitations. We compared controls with patient groups receiving anti-glaucomatous agents; thus, we did not obtain serial measurements in PG analogue group. More relevant data can be obtained by serial measurements and follow-up visits.

## CONCLUSION

No structural change was detected in macula in patients receiving PG analogues for more than one year. Choroid was found to be thicker when compared to controls. The findings should be taken into account in order to improve success of medical and surgical treatment and during surgery.

## REFERENCES

1. Shah R, and Wormald RP. Glaucoma. *BMJ Clin. Evid.* 2011; 06: 703-710.
2. Fajgenbaum M and Ansari E. Prescribing Trends in a Glaucoma Clinic and Adherence to EGS Guidelines. A Retrospective, Non- Interventional, Single-Center UK Study. *Adv Ther.* 2017; 34: 2033-2044.

3. Mastropasqua R, Fasanella V, Agnifili L, Fresina M, Di Staso S, Di Gregorio A, Marchini G, and Ciancaglini M. Advance in the pathogenesis and treatment of normal-tension glaucoma. *Prog Brain Res.* 2015; 221: 213-232.
4. Konstas A.G, Maltezos A.C, Gandi S, Hudgins AC and Stewart WC. Comparison of 24-hour intraocular pressure reduction with two dosing regimens of latanoprost and timolol maleate in patients with primary open-angle glaucoma. *Am. J. Ophthalmol.* 1999; 128: 15–20.
5. Parentin F. Granulomatous anterior uveitis associated with bimatoprost: a case report. *Ocul Immunol Inflamm* 2003; 11: 67–71.
6. Packer ., Fine IH, Hoffman RS. Bilateral nongranulomatous anterior uveitis associated with bimatoprost. *J Cataract Refract Surg.* 2003; 29: 2242–2243.
7. Kroll DM, Schuman JS. Reactivation of herpes simplex virus keratitis after initiating bimatoprost treatment for glaucoma. *Am J Ophthalmol* 2002; 133:401–403.
8. Artunay O, Senel A, Sengul A, Rasier R, Bahcecioglu H. Central serous chorioretinopathy associated with topical latanoprost therapy. *Ocul Immunol Inflamm* 2011; 19(6):453–455.
9. Ozdemir H, Karacorlu M, Karacorlu SA. Serous detachment of macula in cystoid macular edema associated with latanoprost. *Eur J Ophthalmol.* 2008; 18(6):1014.
10. Krishnamurthy R, Senthil S, Garudadri CS. Late postoperative choroidal detachment following an uneventful cataract surgery in a patient on topical latanoprost. *BMJ Case Rep.* 2015.
11. Sezer T, Altinisik M, Koytak IA, Ozdemir MH. Koroid ve Optik Koherens Tomografi. *Turk J Ophthalmol* 2016; 46: 30-37.
12. Lima MC, Paranhos A Jr, Salim S. Visually significant cystoid macular edema in pseudophakic and aphakic patients with glaucoma receiving latanoprost. *J Glaucoma* 2000; 9: 317–21.
13. Halpern DL, Pasquale LR. Cystoid macular edema in aphakia and pseudophakia after use of PG analogs. *Semin Ophthalmol.* 2002; 17: 181–6.
14. Yeh PC, Ramanathan S. Latanoprost and clinically significant cystoid macular edema after uneventful phacoemulsification with intraocular lens implantation. *J Cataract Refract Surg* 2002; 28: 1814–8,
15. Kruse P, Rieck P, Sherif Z, Liekfeld A. Cystoid macular edema in a pseudophakic patient after several glaucoma procedures. Is local therapy with bimatoprost the reason? *Klin Monatsbl Augenheilkd* 2006; 223:534–7
16. Furuichi M, Chiba T, Abe K, Kogure S, Iijima H, Tsukahara S, and Kashiwagi K. Cystoid macular edema associated with topical latanoprost in glaucomatous eyes with a normally functioning blood-ocular barrier. *J. Glaucoma.* 2001; 10: 233–236.
17. Yeom HY, Hong S, Kim SS, Kim CY, Seong GJ. Influence of topical bimatoprost on macular thickness and volume in glaucoma patients with phakic eyes. *Can J Ophthalmol.* 2008; 43(5):563-6.
18. Chang, JH, McCluskey P, Missotten T, Ferrante P, Jalaludin B, and Lightman S. Use of ocular hypotensive PG analogues in patients with uveitis: does their use increase anterior uveitis and cystoid macular oedema? *Br. J. Ophthalmol.* 2008; 92: 916–921
19. Selen F, Tekeli O, Yanik O. Assesment of the Anterior Chamber Flare and Macular Thickness in Patients Treated with Topical Antiglaucomatous Drugs. *J Ocular Pharmacol Ther.* 2017; 33(3): 170-175
20. Terasaki H, Kase S, Shirasawa M. TNF- $\alpha$  decreases VEGF secretion in highly polarized RPE cells but increases it in non-polarized RPE cells related to crosstalk between JNK and NF- $\kappa$ B pathways. *PLoS One.* 2003; 8:e69994
21. Nakayama M, Keino H, Okada AA, Watanabe T, Taki W, Inoue M, Hirakata A. Enhanced depth imaging optical coherence tomography of the choroid in Vogt-Koyanagi-Harada disease. *Retina.* 2012; 32(10):2061–2069
22. Maruko I, Iida T, Sugano Y, Oyamada H, Sekiryu T, Fujiwara T, Spaide RF. Subfoveal choroidal thickness after treatment of Vogt-Koyanagi-Harada disease. *Retina.* 2011; 31(3):510–517
23. Aoyagi R, Hayashi T, Masai A, Mitooka K, Gekka T, Kozaki K, Tsuneoka H. Subfoveal choroidal thickness in multiple evanescent white dot syndrome. *Clin Exp Optom.* 2012; 95:212–217
24. Kola M, Kalkisim A, Karkucak M. Evaluation of choroidal thickness in ankylosing spondylitis using optical coherence tomography. *Ocul Immunol Inflamm.* 2014; 22(6):434-8
25. Kim M, Kim H, Kwon HJ. Choroidal thickness in Behcet's uveitis: an enhanced depth imaging-optical coherence tomography and its association with angiographic changes. *Invest Ophthalmol Vis Sci.* 2013; 54: 6033–6039
26. Cheggour M, Gambrelle J. Massive choroidal detachment secondary to topical use of bimatoprost: Report of two cases. *J Fr Ophtalmol* 2012; 35:176–80
27. Nakakura S, Noguchi A, Tabuchi H, Kiuchi Y. Bimatoprost-induced late-onset choroidal detachment after trabeculectomy: A case report and review of the literature. *Medicine (Baltimore).* 2017; 96(5):e5927
28. Krishnamurthy R, Senthil S, Garudadri CS. Late postoperative choroidal detachment following an uneventful cataract surgery in a patient on topical latanoprost. *BMJ Case Rep.* 2015; July 14
29. Coban DT, Erol MK, Yucel O. Hemorrhagic choroidal detachment after use of anti-glaucomatous eye drops: case report. *Arq Bras Oftalmol.* 2013; 76(5):309-10
30. Caliskan S, Ugurbas SC, Alpay A, Ugurbas SH. Changes in the choroidal thickness and axial length upon mannitol infusion in patients with asymmetric intraocular pressure. *J Glaucoma* 2016; 25: 891–895.
31. Boltz A, Schmidl D, Weigert G, et al. Effect of latanoprost on choroidal blood flow regulation in healthy subjects. *Invest Ophthalmol Vis Sci.* 2011; 52: 4410-5.
32. Akyol N, Kalkisim A, Turk A, Kola M, Imamoglu H.I. Evaluation of the effects on choroidal thickness of bimatoprost 0.03% versus a brinzolamide 1.0%/ timolol maleate 0.5% fixed combination *Cutan Ocul Toxicol,* 2017; 36(4): 397–403