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Periocular changes in topical bimatoprost and latanoprost use

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Background/aim: To evaluate the periocular changes due to topical bimatoprost and latanoprost use and to investigate their effects on the lacrimal drainage system.

Materials and methods: All participants (69 eyes of 43 patients, 52 eyes of 26 controls) were classified into three groups: bimatoprost (0.03%) users, latanoprost (0.005%) users, and healthy controls. Each patient was examined before prostaglandin therapy, and then at the first, third, sixth, and twelfth month of therapy. Palpebral fissure height, upper eyelid crease, and levator function were measured, and lacrimal system drainage irrigation was performed. Periocular hyperpigmentation and upper eyelid sulcus were also examined.

Results: No significant change was identified in palpebral fissure height or levator function in any group. However, in upper eyelid crease, among bimatoprost users, a statistically significant increase was observed when compared to the control group (P < 0.001). Patients with skin type II and III, in bimatoprost users, and patients with skin type III, in latanoprost users, had statistically significant hyperpigmentation (P < 0.001) after the third month of therapy. During follow-up, no lacrimal drainage system obstruction was seen.

Conclusion: Topical bimatoprost therapy causes more periocular changes than latanoprost therapy. Thus, in unilateral cases, patients should be well informed about these probable changes before therapy.

Key words: Bimatoprost, eyelids, lacrimal drainage, latanoprost

1. Introduction
In ophthalmology practice, topical prostaglandin analogues are often used in antiglaucomatous treatment. The potent efficacy, ease of use, and single dose application of these drugs make them advantageous over other medical therapy agents in glaucoma. They decrease the intraocular pressure by 20%–35%, increasing the uveoscleral outflow (1).

Despite the advantages mentioned above, numerous side effects of prostaglandin analogues are reported in the literature. Indeed, conjunctival hyperemia (2,3), increased iris pigmentation (4–6), hypertrichosis (7–10), periocular hyperpigmentation (11,12), and poliosis (13) are common side effects of these drugs. In addition, uncommon as they are, cystoid macular edema, herpetic keratitis activation, and lash ptosis are observed (6). On top of all this, particularly in bimatoprost use, periorbital fat atrophy, deepening in upper eyelid sulcus, and regression in dermatochalasis have been recently reported (14,15).

Few studies exist in the literature examining eyelid motility and position in prostaglandin use. In recent years, these orbital and adnexal changes have been described under a separate heading, ‘prostaglandin associated periorbitopathy’ (16).

The purpose of the present study was to evaluate the periocular changes due to topical bimatoprost and latanoprost therapy and to investigate its effects on the lacrimal drainage system.

2. Materials and methods
A total of 121 eyes of 69 participants were examined between May 2009 and February 2011 at Ankara University Faculty of Medicine, Department of Ophthalmology. Of the 43 patients, 21 patients (35 eyes) received bimatoprost (0.03%) therapy, and 22 patients (34 eyes) latanoprost (0.005%) therapy. The remaining 26 participants (52 eyes) were healthy and constituted the control group. The control group and glaucoma patients were selected from the outpatient polyclinic and glaucoma sections. All of the participants were Turkish. Informed consent, including a detailed explanation of the procedures, was obtained for every patient in the experiment and control groups. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Our study was a prospective, comparative, open-label, nonrandomized study of the effect of two different prostaglandins on periocular measures. All participants were examined before the prostaglandin therapy and then at the first, third, sixth, and twelfth months of the therapy. On ophthalmological examination, the anterior and posterior segments of all the subjects were evaluated, and intraocular pressure (IOP) was measured with Goldmann applanation tonometry. Criteria for inclusion in normal subjects were having an IOP less than 22 mmHg, normal visual fields, no evidence of glaucomatous changes in the optic disc, and no history of glaucoma or ocular hypertension in first-degree relatives. On every examination, palpebral fissure height, upper eyelid crease, and levator function were measured by a ruler and by the same researcher. Upper eyelid sulcus asymmetry was noted when observed. Periocular hyperpigmentation and deepening of upper eyelid sulcus were checked at every visit. The close-up photographs were taken by the same researcher using the same camera. The parameters were evaluated by a second researcher who was blinded as to whether the patients had had the therapy or not.

The Fitzpatrick Skin-Type Chart was used to assess the genetic disposition, reaction to sun exposure, and tanning habits of the participants (17). By using this questionnaire, the skin type can be quickly and easily determined by adding up the score for each question. It entails six skin-type categories: Type I, highly sensitive, always burns, never tans; Type II, fairly sensitive, burns easily, tans minimally; Type III, sun sensitive skin, sometimes burns, slowly tans to light brown; Type IV, minimally sensitive, burns minimally, always tans to moderate brown; Type V, fairly insensitive skin, rarely burns, tans well; Type VI, sun insensitive, never burns, deeply pigmented. For example, pale skinned, fair haired Caucasians can be classified as Type II, darker Caucasians as Type III, and Mediterranean-type Caucasians and some Hispanics as Type IV.

To investigate the effects of the prostaglandin analogue therapy on the lacrimal drainage system, lacrimal system irrigation was performed in all patients at each examination.

All applicable institutional and governmental regulations were followed concerning the ethical use of human volunteers in this research.

2.1. Statistical analysis
Definitive data for continuous variables were estimated by mean ± standard deviation (SD) or median (minimum–maximum). Discrepant variables were processed by means of the Mann–Whitney U test, Pearson’s chi-square test, or Fischer’s exact chi-square test. The periocular changes observed during the follow-up were qualified according to presence/absence. To analyze these parameters, Cochran’s test (with the Bonferroni procedure) was used. P < 0.025 and P < 0.008 values were significant for the results. The data were analyzed using SPSS version 15.0. In addition, for the potential changes in eyelid motility and position between the groups throughout the follow-up, a statistical model was established, and mixed effect analysis of variance (ANOVA) test was used. ANOVA is a tool used to separate the analyzed variance in a specific variable into components attributable to different sources of variation. Our study uses this model, which is one of the functions of XLSTAT 2006 for Microsoft Excel. P < 0.05 was significant for the results.

3. Results
A total of 121 eyes of 69 participants (43 patients, 26 healthy controls) were classified into three groups. Group 1 was composed of 35 eyes of 21 patients on bimatoprost, Group 2 was composed of 34 eyes of 22 patients on latanoprost, and Group 3 included 52 eyes of 26 healthy controls. Table 1 shows the analysis of participants according to demographic data, diagnosis, and skin type. There was no significant difference between the groups in terms of age (P = 0.163), sex (P = 0.884), or skin type distribution (P = 0.369).

Palpebral fissure and levator function changes recorded during the follow-up were insignificant in all groups (in Group 1, P = 0.086, P = 0.348, respectively; in Group 2, P = 0.592, P = 0.455, respectively). In terms of upper eyelid crease, in Group 1, a statistically significant increase was observed compared to the control group (P < 0.001). However, in patients who used latanoprost, there was no significant change (P = 0.297). Tables 2 and 3 show the comparison of eyelid position and motility in subjects on prostaglandin therapy and healthy controls.

At the end of the follow-up, significant periocular changes including deepening of upper eyelid sulcus and periocular hyperpigmentation were found in patients who used bimatoprost (0.03%). They became obvious at the 3rd month of therapy (P < 0.001). However, in latanoprost (0.005%) use, only periocular hyperpigmentation formation was statistically significant, which occurred at the 3rd month of therapy (P < 0.001).

This study also investigated the potential relation between periocular hyperpigmentation and skin types. A statistically significant increase in pigmentation took place in Group 1, the patients with skin types II and III (P < 0.001), and in Group 2, patients with skin type III (P < 0.001), after the 3rd month of therapy. Tables 4 and 5 show this relationship.

Lacrimal drainage system irrigation was performed in every patient before and after the treatment. During the follow-up, no lacrimal drainage system obstruction was recorded in this series.
### Table 1. Analysis of patients on topical prostaglandin analogue and healthy controls according to demographic data, diagnosis, and skin type.

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 21 (30.4%)</td>
<td>N = 22 (31.9%)</td>
<td>N = 26 (37.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td></td>
<td></td>
<td>0.163 &lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean age ± SD</td>
<td>63.9 ± 9.3</td>
<td>58.1 ± 11.6</td>
<td>59.1 ± 10.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>66 (46–78)</td>
<td>60.5 (37–76)</td>
<td>60.5 (40–79)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td>0.884 &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Female</td>
<td>12 (57.1%)</td>
<td>12 (54.5%)</td>
<td>16 (61.5%)</td>
</tr>
<tr>
<td>Male</td>
<td>9 (42.9%)</td>
<td>10 (45.5%)</td>
<td>10 (38.5%)</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td></td>
<td></td>
<td>0.000 &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>POAG</td>
<td>14 (40%)</td>
<td>19 (55.9%)</td>
<td>-</td>
</tr>
<tr>
<td>PXG</td>
<td>17 (48.6%)</td>
<td>10 (29.4%)</td>
<td>-</td>
</tr>
<tr>
<td>OHT</td>
<td>4 (11.4%)</td>
<td>5 (14.7%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Skin type</strong></td>
<td></td>
<td></td>
<td>0.369 &lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Type II</td>
<td>6 (28.6%)</td>
<td>2 (9.1%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>Type III</td>
<td>13 (61.9%)</td>
<td>18 (81.8%)</td>
<td>16 (61.5%)</td>
</tr>
<tr>
<td>Type IV</td>
<td>2 (9.5%)</td>
<td>2 (9.1%)</td>
<td>5 (19.2%)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mann–Whitney U test; <sup>b</sup>Pearson chi-square test; N, number; SD, standard deviation; P < 0.05 is statistically significant. POAG, primary open-angle glaucoma; PXG, pseudoexfoliative glaucoma; OHT, ocular hypertension.

### Table 2. Comparison of patients on bimatoprost (0.03%) therapy and healthy controls throughout follow-up in terms of eyelid position and motility.

<table>
<thead>
<tr>
<th>Bimatoprost (0.03%) therapy (N = 35)</th>
<th>Healthy controls (N = 52)</th>
<th>P value &lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF change (mm) ± SE</td>
<td>0.83 ± 0.18</td>
<td>−0.06 ± 0.15</td>
</tr>
<tr>
<td>ULC change (mm) ± SE</td>
<td>1.17 ± 0.36</td>
<td>−0.06 ± 0.15</td>
</tr>
<tr>
<td>LF change (mm) ± SE</td>
<td>−0.26 ± 0.27</td>
<td>0.32 ± 0.22</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mixed effect ANOVA test; P < 0.05 is statistically significant; SE, standard error. PF, palpebral fissure; ULC, upper eyelid crease; LF, levator function, N, number.

### Table 3. Comparison of patients on latanoprost (0.005%) therapy and healthy controls throughout follow-up in terms of eyelid position and motility.

<table>
<thead>
<tr>
<th>Latanoprost (0.005%) therapy (N = 34)</th>
<th>Healthy controls (N = 52)</th>
<th>P value &lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF change (mm) ± SE</td>
<td>0.44 ± 0.18</td>
<td>−0.06 ± 0.15</td>
</tr>
<tr>
<td>ULC change (mm) ± SE</td>
<td>0.29 ± 0.37</td>
<td>−0.06 ± 0.15</td>
</tr>
<tr>
<td>LF change (mm) ± SE</td>
<td>0.38 ± 0.27</td>
<td>0.32 ± 0.22</td>
</tr>
</tbody>
</table>

<sup>a</sup>Mixed effect ANOVA test; P < 0.05 is statistically significant; SE, standard error. PF, palpebral fissure; ULC, upper eyelid crease; LF, levator function, N, number.
4. Discussion
Clinical pharmacokinetic studies on male cynomolgus monkeys have proved that, after 0.1% bimatoprost application, ocular tissue concentration of eyelids were 2000 times greater than aqueous humor and were 16 times greater than iris and ciliary body concentration (18). Therefore, this information is of great importance in periorbital prostaglandin absorption in topical antiglaucomatous therapy.

The deepening of upper eyelid sulcus and regression of dermatochalasis were first reported by Peplinski et al. in three patients who used unilateral topical bimatoprost therapy (19). They reported these side effects throughout the first and ninth months of the treatment. Additionally, the authors observed the reversibility of these effects in one patient, 6 weeks after the cessation of the therapy.

Prostaglandin associated periorbitopathy was first defined by Filippopoulos et al. in 2008, including periorbital fat atrophy, deepening upper eyelid sulcus, and regression of dermatochalasis (16). They investigated 5 glaucoma patients using unilateral bimatoprost for 7 months and 4 years, and observed these periocular changes in all patients. The authors also observed that these changes were reversed after the termination of therapy at the 3rd or 6th months.

Periorbital fat atrophy was initially documented by Jayaprakasam et al. on magnetic resonance imaging in a patient who used unilateral bimatoprost for 2 years (14). This study recorded the deepening of upper eyelid sulcus and 2 mm relative enophthalmos by fat atrophy. Nine months after the cessation of the treatment, fat atrophy was almost completely reversed. According to investigators, the inhibition of adipocyte production and differentiation, and production by prostaglandins may be responsible for the resultant fat atrophy. Therefore, the reversal of fat atrophy after cessation may be due to the removal of this inhibiting agent.

Histological changes in prostaglandin analogue users were first shown by Park et al. in 2011 by orbital fat tissue biopsy (15). In addition to bimatoprost, they studied latanoprost and travoprost. They observed deep superior sulcus in all three prostaglandin groups and compared the orbital fat tissue between the treated and untreated eyes. A careful analysis of histological preparations revealed decreased intracellular lipid volume in adipocytes. Because of the displacement of adipocyte nuclei, a relative increase in mean adipocyte density per unit area was observed in three prostaglandin analogue-treated eyes.

Tan et al. reported three patients who had latanoprost-induced prostaglandin associated periorbitopathy via photo documentation, retrospectively. The deepening of upper eyelid sulcus, blepharoptosis, involution of dermatochalasis, and flattening of lower eyelid bags were seen after a mean consumption time of 6 years (3 to 8 years). The researchers drew attention to the lower risk and longer latency of onset of these changes with latanoprost than with bimatoprost or travoprost (20).

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**Table 4.** The relationship between periocular hyperpigmentation and skin type among bimatoprost (0.03%) users.

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Topical bimatoprost (0.03%) use (N = 35)</th>
<th>Periocular hyperpigmentation (+)</th>
<th>Periocular hyperpigmentation (–)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II</td>
<td>7 (20%)</td>
<td>3 (8.6%)</td>
<td>0.000 (3rd Mo)</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>11 (31.4%)</td>
<td>11 (31.4%)</td>
<td>0.000 (3rd Mo)</td>
<td></td>
</tr>
<tr>
<td>Type IV</td>
<td>3 (8.6%)</td>
<td>0</td>
<td>0.037</td>
<td></td>
</tr>
</tbody>
</table>

*Cochran’s test (with Bonferroni procedure); P < 0.008 is statistically significant; N, number; Mo, month.

**Table 5.** The relationship between periocular hyperpigmentation and skin type among latanoprost (0.005%) users.

<table>
<thead>
<tr>
<th>Skin type</th>
<th>Topical latanoprost (0.005%) use (N = 34)</th>
<th>Periocular hyperpigmentation (+)</th>
<th>Periocular hyperpigmentation (–)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type II</td>
<td>1 (2.9%)</td>
<td>1 (2.9%)</td>
<td>0.406</td>
<td></td>
</tr>
<tr>
<td>Type III</td>
<td>8 (23.5%)</td>
<td>20 (58.8%)</td>
<td>0.000 (3rd Mo)</td>
<td></td>
</tr>
<tr>
<td>Type IV</td>
<td>0</td>
<td>4 (11.8%)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*Cochran’s test (with Bonferroni procedure); P < 0.008 is statistically significant; N, number; Mo, month.
In the present study, 34.3% of the patients on bimatoprost therapy ($P < 0.001$) and 2.9% of the patients on latanoprost therapy ($P = 0.406$) developed upper eyelid sulcus deepening. Because the therapy continued, it was not possible to observe reversibility.

Altieri et al. examined 182 patients who were on bilateral prostaglandin therapy and 191 age-matched healthy controls (21). The patients and healthy controls did not differ significantly according to eyelid position or motility. They also investigated bimatoprost, latanoprost, and travoprost separately and found no significant difference among the groups.

Conversely, Wang et al. reported a patient with right upper eyelid ptosis 2 months after starting topical bimatoprost (0.03%) therapy. Evidently, the patient’s right levator muscle became less able to function. After the termination of therapy, levator muscle resection was performed. The authors noted that this side effect may not be completely reversible even after the therapy was terminated (22).

The results of our study revealed no significant change in terms of vertical palpebral fissure height or levator function ($P = 0.086$ and $P = 0.348$, respectively) in bimatoprost or latanoprost therapy ($P = 0.592$ and $P = 0.455$, respectively) compared to the control group. A significant increase in the upper eyelid crease was determined in patients who used bimatoprost ($P < 0.001$). This change was insignificant in the latanoprost group ($P = 0.297$).

Prostaglandins are potent stimulators in melanogenesis (23). After melanin is produced in dermal melanocytes, it is transferred to keratocytes neighboring the epidermal basal membrane (24). Melanin laden keratocytes are thrown out by the epidermal cell cycle (25). Thus, the normal epidermal cell cycle accounts for the reversibility of pigmented changes.

Periocular hyperpigmentation due to topical prostaglandin use was first reported by Wand et al. in a 75-year-old woman who had undergone binocular latanoprost therapy for 15 months (12). Two months after the cessation of the treatment, periocular pigmentation significantly decreased.

In our study, the incidence of periocular hyperpigmentation was 60% ($P < 0.001$) in bimatoprost users and 26.5% ($P < 0.001$) in latanoprost users.

The research also focused on the potential relation between the periocular hyperpigmentation and skin types. Of the 69 participants, 13 had (18.8%) skin type II, 47 (68.1%) skin type III, and 9 (13%) skin type IV. In Group 1, skin type II and III ($P < 0.001$) patients, and in Group 2, skin type III ($P < 0.001$) patients displayed a statistically significant increase in pigmentation after 3 months of therapy. To the best of our knowledge, this is the first study using the Fitzpatrick Skin-Type Chart to analyze the relation between the periocular pigmentation and skin type of patients using topical prostaglandin analogues.

Additionally, our study is the first prospective research to investigate the effects of topical prostaglandin therapy on lacrimal drainage system. It seems that a single article exists by Artunay et al. about nasolacrimal canal obstruction and antiglaucomatous therapy (26). They analyzed the participants retrospectively. Two hundred and five eyes of 110 glaucoma patients and 184 eyes of 94 untreated glaucoma suspects were evaluated. In the treatment group using an antiglaucomatous agent, the incidence of nasolacrimal canal obstruction was 13.7%, and in the untreated group it was 7.1%. The difference between the groups was statistically significant ($P < 0.05$). The authors also reviewed patients who suffered from nasolacrimal canal obstruction according to antiglaucomatous drug subtypes. Of the patients who had nasolacrimal canal obstruction, 28.5% were using timolol maleate, 21.5% were using prostaglandin analogues, and 50% were using a combination of them. The time that elapsed from the initial treatment to the nasolacrimal canal obstruction was estimated to be $4.8 \pm 2.4$ years.

No lacrimal drainage system obstruction developed during the follow-up phase of our study. Studies with larger series and longer follow-up are needed for more conclusive results.

In conclusion, topical bimatoprost therapy causes more marked periocular changes than topical latanoprost therapy. For instance, our study revealed a significant deepening of upper eyelid sulcus and periocular hyperpigmentation after bimatoprost use ($P < 0.001$). Moreover, upper eyelid crease significantly increased in the bimatoprost group ($P < 0.001$). Finally, in the latanoprost group, significant periocular hyperpigmentation ($P < 0.001$) was observed.

As a result, ophthalmologists, particularly glaucoma specialists should be aware of the potential periocular changes due to topical prostaglandin analogues and should inform their patients properly about it. Especially when treating unilateral cases, physicians should behave much more cautiously.

Acknowledgment
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References


