Shortening of Interpupillary Distance after Instillation of Topical Prostaglandin Analog Eye Drops

ICHIYA SANO, HIDENORI TAKAHASHI, SATORU INODA, SHINICHI SAKAMOTO, YUSUKE ARAI, YUJI TAKAHASHI, AKIRA OHKUBO, HIDETOSHI KAWASHIMA, AND CHIHIRO MAYAMA

• PURPOSE: To investigate changes in the interpupillary distance (IPD) after continual instillation of topical prostaglandin analogs (PGAs) in glaucoma patients as an objective indicator of prostaglandin-associated periorbitopathy (PAP).

• DESIGN: Retrospective, comparative case series.

• METHODS: A total of 152 institutional patients with glaucoma were enrolled in this study. Inclusion criteria were visual acuities exceeding 10/20 bilaterally and no intraocular surgery during observation. INTERVENTION/OBSERVATION PROCEDURES: First-time bilateral instillation of bimatoprost, travoprost, latanoprost, or tafluprost and IPDs measured by automatic refractometry. IPDs, intraocular pressures (IOPs), and refractive errors were measured before and after continual drug administration (treatment, 2-24 months). MAIN OUTCOME MEASUREMENTS: Post-treatment changes in IPDs. A total of 61 untreated patients served as controls.

• RESULTS: The IPDs shortened significantly ($P < 0.001$) after treatment (−0.80 ± 2.1 mm); the IPDs of control subjects remained unchanged (0.05 ± 0.96 mm; $P = 0.69$). The IPD change after bimatoprost instillation (−2.20 ± 0.97 mm) was significantly ($P < 0.001$) greater than with other PGAs (−0.65 ± 2.09 mm). The IOPs decreased significantly ($P < 0.001$) (−3.7 ± 4.3 mm Hg); the refractive errors did not change significantly ($P < 0.099$) (−0.07 ± 0.69 diopter) post-treatment. The percentages of subjects with 2-mm or greater decreases in IPD after bimatoprost, travoprost, latanoprost, or tafluprost were 85.7%, 20.0%, 18.2%, and 17.2%, respectively, and with 3-mm or greater decreases in IPD 35.7%, 12.0%, 14.5%, and 12.1%, respectively. The specificities were 93.4% and 100% in the control group, respectively, with IPD threshold changes of 2 and 3 mm or more, respectively.

• CONCLUSIONS: The IPD decreased significantly after topical PGAs within 24 months. The effect was significantly greater with bimatoprost than with other PGAs. The noninvasive, immediate automatic refractometry measurement may be an objective numerical indicator of PAP. (Am J Ophthalmol 2019;206:11–16. © 2019 Elsevier Inc. All rights reserved.)

TOPICAL PROSTAGLANDIN ANALOGS (PGAS) ARE used widely as the first-line therapy for glaucoma to achieve substantial intraocular pressure (IOP) decreases without major systemic side effects. However, the drugs cause some local side effects, such as lid pigmentation and lengthening of eyelashes. Long-term use of PGAs can cause periorbital cosmetic problems such as upper eyelid ptosis, deepening of the upper eyelid sulcus (DUES), enophthalmos, flattening of lower eyelid bags, inferior scleral show, and dermatochalasis. Several symptoms that occur simultaneously are recognized as prostaglandin-associated periorbitopathy (PAP).[1] A volume reduction in orbital adipose tissue is considered the mechanism of PAP,[2,3] which is seen on magnetic resonance imaging after long-term use of PGAs.[3]

PAP has emerged recently as a notable local side effect of PGAs, but the assessment procedures for PAP are not standardized. Several studies have focused on DUES. The incidence rates of DUES in patients treated with bimatoprost, travoprost, latanoprost, and tafluprost[4–8] have been investigated, and some studies have reported recovery from DUES after discontinuing PGAs or switching to other drugs.[9] However, in all those studies, the occurrence of DUES was assessed subjectively based on a series of photographs, and the procedures lacked objectivity and quantification. Magnetic resonance imaging or other modalities are superior in those respects, but they are invasive, time consuming, and/or costly and inadequate for repeated assessments. Considering the large number of patients with glaucoma who use topical PGAs in a clinical situation, noninvasive and less time-consuming assessments for PAP are needed.

The aims of the current study were to determine the changes in the interpupillary distance (IPD) of patients with glaucoma before and after continual administration

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From the Department of Ophthalmology, Jichi Medical University (I.S., H.T., S.I., S.S., Y.A., Y.T., A.O., H.K.), Tochigi, Japan; Department of Ophthalmology, Japan Community Health Care Organization Tokyo Shinjuku Medical Center (H.T., C.M.), Tokyo, Japan; Takahashi Eye Clinic (Y.T.), Tochigi, Japan; and the Ohkubo Eye Clinic (A.O.), Tochigi, Japan.

Inquiries to Hidenori Takahashi, Department of Ophthalmology, Jichi Medical University, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi 329-0431, Japan; e-mail: takahah-tky@umin.ac.jp

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of topical PGAs and whether the IPD may be an objective indicator of PAP. The authors speculated that enophthalmos and DUES, which are the major manifestations of PAP, are at least caused partly by dorsal movement of the eyeballs. Thus, the IPD would shorten simultaneously, because the distance between the bilateral eye sockets lengthens toward the anterior opening (Figure). To the best of the present authors' knowledge, the current study is the first to shed light on the suitability of the IPD for monitoring PAP. The IPD is measured frequently by automatic refractometry during routine clinical examinations, and it would be useful for clinicians if the measurement could serve as a quantitative indicator of PAP in clinical practice and research.

SUBJECTS AND METHODS

• **STUDY DESIGN:** The institutional review board of Jichi Medical University and Japan Community Healthcare Organization (JCHO) Tokyo Shinjuku Medical Center approved this multicenter retrospective, comparative case series study, which adhered to the tenets of the Declaration of Helsinki (IRB 17-111). Patient consent to review their medical records was not required because the collected data analyzed in this study did not contain personal information that could result in the identification of individuals. The procedures in this study followed all institutional guidelines, and all data were obtained during routine clinical examinations. No subjects underwent additional examinations, interventions, or dosage changes in medications for the purposes of this study.

• **SUBJECTS:** The medical records of patients with glaucoma at the Jichi Medical University Hospital, JCHO Tokyo Shinjuku Medical Center, Takahashi Eye Clinic, and Okubo Eye Clinic were retrospectively reviewed between 2004 and 2017. The subjects (152 patients) with glaucoma who began instilling topical PGAs, bimatoprost, travoprost, latanoprost, or tafluprost for the first time bilaterally were enrolled in this study. The following demographic and clinical data were collected: age, sex, IOP, and the kinds of PGAs administered.

Glaucoma was diagnosed in 1 or both eyes based on the presence of glaucomatous optic nerve head damage with corresponding visual field damage, except for the presence of other ocular abnormalities or a history of other ocular diseases that may affect the optic nerve or visual fields.

The inclusion criteria were 25 to 75 years of age, a visual acuity of 10/20 or higher in each eye without loss of the central visual field, bilateral topical PGA administration for the first time that continued for 2 months or more, and an IPD routinely obtained at 2 time points, that is, at 0 to 2 months before the start of PGA administration (preadministration) and 3 to 24 months after drug administration of the same antiglaucoma medication (post-administration). Use of antiglaucoma drugs or eye drops other than the PGAs was permitted.

The exclusion criteria included the use of topical or systemic steroid or nonsteroidal anti-inflammatory drugs; intraocular, ocular surface, eyelid, or periocular surgeries during the observation period; and a history of disorders that might have affected the ocular position including strabismus, abnormal thyroid function, and central nervous system dysfunction.

Similar data were collected from 61 control subjects who did not have glaucoma and who fulfilled the inclusion criteria but did not use topical antiglaucoma medications.

• **PARAMETERS ASSESSED:** The IOP was measured routinely at each visit using Goldmann applanation tonometry. The distance refractive error and IPD were measured simultaneously using the following automatic refractometers avoiding convergence: Tonoref RKT-7700, Tonoref III, ARK-560A (all from Nidek, Inc, Aichi, Japan), and RK-F1 (Canon, Inc, Tokyo, Japan), at Jichi Medical University, JCHO Tokyo Shinjuku Medical Center, Takahashi Eye Clinic, and Ohkubo Eye Clinic, respectively. Each subject was examined using the same apparatus in the same institution during all measurements. The IPDs, IOPs, and refractive errors obtained from 0 to 2 months before the start of PGAs therapy were collected as the preadministration data. Similar post-administration data were obtained 2 to 24 months after the continual administration of the same PGAs. If there were several repeated measures during a short period, a representative value was adopted with any outliers excluded. The IPDs also were obtained in the control group in the same fashion; the interval between the 2 time points of the IPD measurements ranged from 2 to 60 months.

• **STATISTICAL ANALYSIS:** All statistical analyses were performed using JMP 14 software (SAS Institute, Inc, Cary, North Carolina, USA). The parameters were analyzed using the paired *t*-test, Student *t*-test, analysis of variance, or Fisher exact test. A P value <0.05 with Bonferroni correction when needed was considered significant.

RESULTS

SUBJECT DEMOGRAPHICS ARE SHOWN IN TABLE 1. A TOTAL of 152 patients (64 men, 88 women) were included in this study. The mean ± standard deviation age was 60.9 ± 10.6 years (range, 29-75 years).

Among the PGAs, 14, 25, 55, and 58 subjects instilled bimatoprost, travoprost, latanoprost, or tafluprost drugs bilaterally, respectively. The mean period of PGA administration between the preadministration and post-administration measurements was 12.0 ± 5.6 months, and the mean periods

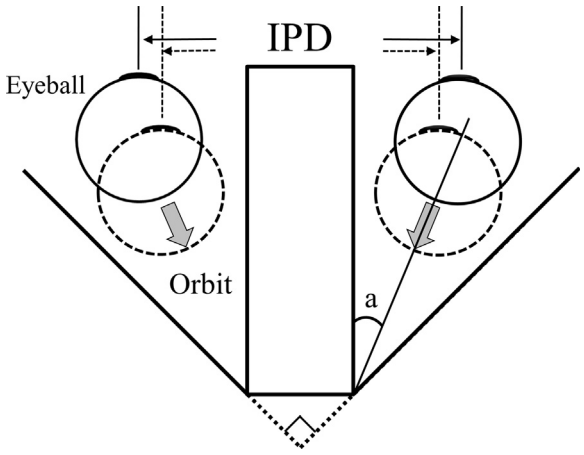

FIGURE. The principle of shortening of the interpupillary distance (IPD) is shown in the standardized model of orbits on the transverse plane.[23] The medial walls of the orbits are parallel and set apart by the ethmoid sinuses, and the lateral walls are related to each other at a 90-degree angle. The angle at which each orbital axis deviates from the parasagittal plane (angle a) is 22.5 degrees.

TABLE 1. General Characteristics and Number of Subjects Using Each PGA

Number of subjects	152
Men/women	64/88
Median ± SD age range (y)	60.9 ± 10.6 (29–75)
Median ± SD refractive error range (D)	−2.8 ± 4.0 (−13.9 to +3.8)
Median ± SD IOP range (mm Hg)	18.0 ± 5.4 (8.5–36)
Subjects receiving PGAs	
Bimatoprost	14
Travoprost	25
Latanoprost	55
Tafluprost	58

IOP = interocular pressure; PGAs = prostaglandin analogs; SD = standard deviation.

were 13.5 ± 7.0, 11.9 ± 4.5, 12.1 ± 6.2, and 10.8 ± 5.2 months, respectively, among the subjects using bimatoprost, travoprost, latanoprost, and tafluprost. No significant ($P = 0.38$) differences in the administration periods were seen among the 4 PGAs.

The IPDs are expressed as integral numbers. The mean IPDs of the subjects were 63.1 ± 3.0 mm and 62.3 ± 3.2 mm at the preadministration and post-administration time points, respectively, with a significant ($P < 0.001$) change of −0.80 ± 2.1 mm. The IPD changes in the patients using bimatoprost, travoprost, latanoprost, and tafluprost were −2.20 ± 0.97 mm ($P < 0.001$), −0.84 ± 1.6 mm ($P = 0.008$), −0.74 ± 2.4 mm ($P = 0.012$), and −0.49 ± 2.0 mm ($P = 0.035$), respectively (Table 2). The decrease in the IPD resulting from the use of bimatoprost was significantly ($P = 0.007$) greater than those resulting from the use of all other PGAs (−0.65 ± 2.09 mm).

The IPD decrease after PGA instillation was correlated positively with age ($P = 0.006$) and the preadministration IPD value ($P = 0.005$), but the correlation coefficients were very small ($\beta = -0.04$, and $\beta = -0.16$, respectively; 10 years accounted for −0.4 mm; and 10 mm of preadministration IPD accounted for a 1.6-mm IPD change). These results were not correlated with sex ($P = 0.25$).

The IOP decreased significantly ($P < 0.001$) (−3.7 ± 4.3 mm Hg), and the refractive error did not change significantly ($P = 0.099$) (−0.07 ± 0.69 diopter) after PGA instillation among all patients.

In the control group, the mean age was 63.0 ± 3.9 years (range, 55-71 years), and the mean interval of the IPD measurements was 22.0 ± 15.0 months (range, 2-52 months). The IPDs were 63.0 ± 3.9 mm and 63.0 ± 3.9 mm at the first and last measurements, respectively, a difference (0.05 ± 0.96 mm) that did not reach significance ($P = 0.69$).

The percentages of subjects fulfilling different thresholds of IPD change (ie, 1 mm or more, 2 mm or more, and 3 mm or more) are shown in Table 3. After bimatoprost administration, 85.7% and 35.7% of the subjects fulfilled the thresholds of 2 mm or more and 3 mm or more, respectively. The mean percentages were 18.1% and 13.0% of the subjects using the other PGAs, which were significantly ($P < 0.001$ and $P = 0.040$, respectively) smaller than those of bimatoprost. The specificities were 93.4% and 100%, respectively, in the control group with the thresholds of IPD changes of 2 mm or more and 3 mm or more, respectively.

DISCUSSION

AMONG THE SEVERAL SYMPTOMS OF PAP, DUES AND PTOSIS have been attracting increased attention as cosmetic problems because they cause significant concerns about facial expression and the patients' perceptions of themselves. One study evaluated PGA-induced enophthalmos by using a Hertel exophthalmometer,[10] and most other studies diagnosed DUES by using a series of facial photographs.[4–6,9–18] The exophthalmometer provides numerical results through noninvasive examination; however, the accuracy and reproducibility of the results depend on the skills of the examiners. Obtaining photographs is an easier procedure for recording lid and facial appearances, but the procedure is completely subjective and lacks quantitative values. It is difficult to standardize exposure or other conditions when obtaining photographs, especially among different examiners or institutions, and the facial expression around the orbit is affected easily by makeup or physiological age-related changes. Standardized digital cameras and display monitors or printers are needed to study the photographs, and the image data must be

TABLE 2. Changes in IPDs after Use of PGA

PGAs	IPD Change (mm)	*P* Value
Total	−0.80 ± 2.1	<0.001[a]
Bimatoprost	−2.20 ± 0.97	<0.001[a]
Travoprost	−0.84 ± 1.6	0.008[a]
Latanoprost	−0.74 ± 2.4	0.012
Tafluprost	−0.49 ± 2.0	0.035

IPD = interpupillary distance; PGAs = prostaglandin analogs.
[a]$P < 0.01$ after Bonferroni correction.

TABLE 3. Percentages of Subjects Fulfilling Different Thresholds of IPD Change

	Threshold of IPD Change		
	≥1 mm (n/N)	≥2 mm (n/N)	≥3 mm (n/N)
All PGAs	78/152 (51.3)	37/152 (24.3)	23 (15.1)
Bimatoprost	13/14 (92.9)	12/14 (85.7)	5/14 (35.7)
Travoprost	17/25 (68.0)	5/25 (20.0)	3/25 (12.0)
Latanoprost	22/55 (40.0)	10/55 (18.2)	8/55 (14.5)
Tafluprost	26/58 (44.8)	10/58 (17.2)	7/58 (12.1)
Control	17/61 (27.9)	4/61 (6.6)	0/61 (0)

IPD = interpupillary distance; PGAs = prostaglandin analogs.

recorded and stored. Furthermore, both of those methods have theoretical difficulties when diagnosing bilateral changes rather than hemilateral changes compared with the other eye, although most patients with glaucoma treated with PGAs instill the drugs bilaterally.

To the best of the present authors' knowledge, the current study is the first to demonstrate the usefulness of the IPD as an index of the symptoms of PAP in patients with glaucoma using topical PGAs. This methodology enables numerical evaluation of enophthalmos caused by PAP using automatic refractometry during routine examinations and results in usual medical records without the need for specific skills or additional equipment. The current tested methodology is an instantaneous and noninvasive procedure that is suitable for assessing bilateral changes associated with PAP.

No topical antiglaucoma drugs other than the PGAs have been reported to be associated with the symptoms of PAP. Concomitant use of topical drugs other than PGAs was not considered in the current study, which included 45 subjects treated with adjunctive drugs, mainly beta-blockers. The study confirmed that the use of adjunctive drugs had no significant effects on IPD according to multivariate analysis, and it was confirmed that the IPD did not change significantly ($P > 0.43$) after use of only beta-blockers or unoprostone in another small group of patients.

The mechanism of PAP is thought to be decreased fat production in the orbital fat tissues through activation of the prostaglandin F receptor resulting from topically instilled PGAs.[19–21] A previous study that investigated the effects of orbital decompression surgery for treating IPD in patients with thyroid-associated orbitopathy[22] suggested the possibility of evaluating PAP using the IPD. The decreased orbital fat may induce simultaneous dorsal movement of the eyeballs and shortening of the IPD because the distance between the bilateral eye sockets shortens toward the posterior orbital apexes (Figure). Based on the assumption of the standardized model of orbits,[23] the angle at which each orbital axis deviates from the sagittal plane is 22.5 degrees. According to this model and trigonometric calculations, that is 2 mm and 3 mm of IPD decreases which are threshold values suggested in the current study, corresponded to 2.4 mm and 3.6 mm of enophthalmic shift, and 2 mm of enophthalmic shift corresponded to 1.7 mm of an IPD decrease. Actually, the incidence rates of enophthalmos after hemilateral use of bimatoprost, latanoprost, or travoprost were reported to be 80%, 7.1%, and 35%, respectively, in a previous study in which enophthalmos was defined by a 2-mm or greater difference between both eyes, using Hertel exophthalmometry measurements.[10] Those results agreed with the current findings (Table 3).

The current results showed significant shortening of the IPD after topical PGA instillation and significant differences in the degree of the IPD changes among the different PGAs. The average IPD change after bimatoprost instillation was −2.2 mm, which was significantly ($P < 0.001$) greater than that of the other PGAs (−0.49 to −0.84 mm), although there were no significant ($P = 0.38$) differences in the lengths of the treatment periods among the PGAs.

A previous study reported that the incidence rates of DUES were 60%, 50%, 24%, and 18%, respectively, in subjects treated with bimatoprost, travoprost, latanoprost, and tafluprost and determined by using photographs.[11] Other studies have found that patients with PAP caused by bimatoprost or travoprost recovered after the drugs were switched to latanoprost,[14,17] suggesting that the magnitudes of the pharmacologic effects that cause PAP and/or individual susceptibility to the PGAs regarding PAP differed among the PGAs. In the current study, a similar trend also was seen in the extent of IPD shortening, which supported the usefulness of this methodology by quantifying PAP using the IPD.

Individual variability of the expression of PAP is a noteworthy issue. The mechanism of variability has not been clarified, and there likely are several complex factors involved, including the amount or composition of the local adipose tissues, treatment duration of the PGAs, subject compliance with the treatment regimen, amount of the

eye drops actually instilled, and behaviors after the instillation, such as wiping or washing of eyelids, which were difficult to standardize or evaluate in this retrospective investigation. Those issues were beyond the scope of the current study. A future prospective study may identify important information. The methodology using IPD is also valuable in such conditions.

Based on the analysis, using the different thresholds of the IPD changes (ie, 2 mm or more or 3 mm or more) may be clinically acceptable. The percentages of subjects after PGA administration who fulfilled those thresholds of IPD decreases were comparable to the incidence rates of DUES diagnosed through facial photographs. Additionally, the high specificity found in the control group with the thresholds of IPD changes suggested the possible acceptability of this methodology for distinguishing the PAP symptoms from age-related changes.

Another previous study in which facial photographs were used reported that the incidence rates of DUES were 44% and 60%, respectively, at 1 and 3 months after the start of PGA administration,[9] suggesting that PAP can occur after several months in clinical cases. In the current study, IPD shortening was seen after an average of 12 months of PGA instillation according to the retrospectively collected data. Another prospective study is needed to elucidate the possibility of using the IPD to detect PAP in the early period and assess progress or recover of PAP quantitatively.

Age-related factors cannot be excluded from the IPD changes over a long period. Several cross-sectional studies have reported that the IPD increases with skeletal growth in young patients, that the increase is slight in middle-aged patients,[24–27] and that the increase may decrease slightly in older patients.[24,27] The effect of aging on the assessment of PAP also is present and is even significant in the methodology that uses facial photographs. Several of those studies have reported that the incidence rates of DUES increase significantly with age.[9,13] The effects of individual, racial, or sexual differences are inevitable to some extent, because PAP affects the cosmetic facial expression. IPD shortening was correlated significantly with age, which suggests that the IPD shortening in the current subjects may have been due partly to aging; however, the effect was very small and clinically negligible in the short observation period (average, 12.0 months). According to the correlation coefficient found in this study, the effect of age was as small as −0.04 mm annually, and there was no significant change in the IPD in the control patients who were older (55-71 years of age) and during the longer measurement interval (22.0 ± 15.0 months) compared with the patients with glaucoma.

Another limitation of this study was the accuracy of the IPD measurements. In this study, the IPD was measured by automatic refractometry; however, the instrument manufacturers did not officially release the detailed mechanism and accuracy data of the measurements. In addition, the IPD data in this retrospective study were obtained during routine visual acuity measurements without the intention to measure the IPD itself. However, the adequate reproducibility of the measurement was assured to some degree by the control data obtained in this study, and the measurement error, ± standard deviation, of the data obtained from the other 3 normal subjects during measurements repeated 10 times using each apparatus and compared among different institutions was <1 mm, the minimal scale of the IPD value (data not shown). Actually, the accuracy and performance of the IPD measurement used to monitor PAP potentially can be improved by greater attention to the IPD measurement.

When looked at from another clinical point of view, the significant shortening of the IPD after topical PGAs use found in this study may induce not only cosmetic problems but also functional disorders. Some patients may need their spectacle prescriptions adjusted, and the IPD change may affect the binocular vision. Further research should focus on the effect of topical PGAs on visual function.

The current study investigated whether the IPD can be used as an objective index of PAP. The results showed a significant decrease in the IPD after topical PGA instillation, and the change after bimatoprost use was significantly greater than that after the other PGAs, which supported the objective and quantified advantage of this methodology. The noninvasive and instantaneous measurement of the IPD using automatic refractometry enables objective monitoring of PAP in patients using PGAs and is useful both clinically and experimentally.

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REFERENCES

1. Shah M, Lee G, Lefebvre DR, et al. A cross-sectional survey of the association between bilateral topical prostaglandin analog use and ocular adnexal features. *PLoS One* 2013; 8(5):e61638.
2. Taketani Y, Yamagishi R, Fujishiro T, Igarashi M, Sakata R, Aihara M. Activation of the prostanoid FP receptor inhibits adipogenesis leading to deepening of the upper eyelid sulcus in prostaglandin-associated periorbitopathy. *Invest Ophthalmol Vis Sci* 2014;55(3):1269–1276.
3. Jayaprakasam A, Ghazi-Nouri S. Periorbital fat atrophy: an unfamiliar side effect of prostaglandin analogs. *Orbit* 2010; 29(6):357–359.
4. Peplinski LS, Albiani Smith K. Deepening of lid sulcus from topical bimatoprost therapy. *Optom Vis Sci* 2004;81(8): 574–577.
5. Sakata R, Shirato S, Miyata K, Aihara M. Incidence of deepening of the upper eyelid sulcus in prostaglandin-associated periorbitopathy with a latanoprost ophthalmic solution. *Eye (Lond)* 2014;28(12):1446–1451.
6. Sakata R, Shirato S, Miyata K, Aihara M. Incidence of deepening of the upper eyelid sulcus on treatment with a tafluprost ophthalmic solution. *Jpn J Ophthalmol* 2014;58(2):212–217.
7. Ung T, Currie ZI. Periocular changes following long-term administration of latanoprost 0.005%. *Ophthalmic Plast Reconstr Surg* 2012;28(2):e42–e44.
8. Yang HK, Park KH, Kim TW, Kim DM. Deepening of eyelid superior sulcus during topical travoprost treatment. *Jpn J Ophthalmol* 2009;53(2):176–179.
9. Aihara M, Shirato S, Sakata R. Incidence of deepening of the upper eyelid sulcus after switching from latanoprost to bimatoprost. *Jpn J Ophthalmol* 2011;55(6):600–604.
10. Kucukevcilioglu M, Bayer A, Uysal Y, Altinsoy HI. Prostaglandin associated periorbitopathy in patients using bimatoprost, latanoprost and travoprost. *Clin Exp Ophthalmol* 2014; 42(2):126–131.
11. Inoue K, Shiokawa M, Wakakura M, Tomita G. Deepening of the upper eyelid sulcus caused by 5 types of prostaglandin analogs. *J Glaucoma* 2013;22(8):626–631.
12. Kim HW, Choi YJ, Lee KW, Lee MJ. Periorbital changes associated with prostaglandin analogs in Korean patients. *BMC Ophthalmol* 2017;17(1):126.
13. Maruyama K, Shirato S, Tsuchisaka A. Incidence of deepening of the upper eyelid sulcus after topical use of travoprost ophthalmic solution in Japanese. *J Glaucoma* 2014;23(3): 160–163.
14. Nakakura S, Tabuchi H, Kiuchi Y. Latanoprost therapy after sunken eyes caused by travoprost or bimatoprost. *Optom Vis Sci* 2011;88(9):1140–1144.
15. Nakakura S, Terao E, Nagatomi N, et al. Cross-sectional study of the association between a deepening of the upper eyelid sulcus-like appearance and wide-open eyes. *PLoS One* 2014;9(4):e96249.
16. Nakakura S, Yamamoto M, Terao E, et al. Prostaglandin-associated periorbitopathy in latanoprost users. *Clin Ophthalmol* 2015;9:51–56.
17. Sakata R, Shirato S, Miyata K, Aihara M. Recovery from deepening of the upper eyelid sulcus after switching from bimatoprost to latanoprost. *Jpn J Ophthalmol* 2013;57(2):179–184.
18. Tan J, Berke S. Latanoprost-induced prostaglandin-associated periorbitopathy. *Optom Vis Sci* 2013;90(9): e245–e247. discussion 1029.
19. Casimir DA, Miller CW, Ntambi JM. Preadipocyte differentiation blocked by prostaglandin stimulation of prostanoid FP2 receptor in murine 3T3-L1 cells. *Differentiation* 1996; 60(4):203–210.
20. Miller CW, Casimir DA, Ntambi JM. The mechanism of inhibition of 3T3-L1 preadipocyte differentiation by prostaglandin F2alpha. *Endocrinology* 1996;137(12):5641–5650.
21. Serrero G, Lepak NM. Prostaglandin F2alpha receptor (FP receptor) agonists are potent adipose differentiation inhibitors for primary culture of adipocyte precursors in defined medium. *Biochem Biophys Res Commun* 1997;233(1):200–202.
22. Yeo JH, Park SJ, Chun YS, Kim JT, Moon NJ, Lee JK. The effect of orbital decompression surgery on interpupillary distance and angle kappa in patients with thyroid-associated orbitopathy. *Graefes Arch Clin Exp Ophthalmol* 2017;255(4): 825–830.
23. Moore KL, Agur AMR. Clinically Oriented Anatomy. 8th edition. Philadelphia: Lippincott Williams & Wilkins; 2018.
24. Alanazi SA, Alanazi MA, Osuagwu UL. Influence of age on measured anatomical and physiological interpupillary distance (far and near), and near heterophoria, in Arab males. *Clin Ophthalmol* 2013;7:711–724.
25. Fesharaki H, Rezaei L, Farrahi F, Banihashem T, Jahanbkhshi A. Normal interpupillary distance values in an Iranian population. *J Ophthalmic Vis Res* 2012;7(3):231–234.
26. Pointer JS. The far interpupillary distance. A gender-specific variation with advancing age. *Ophthalmic Physiol Opt* 1999; 19(4):317–326.
27. Yildirim Y, Sahbaz I, Kar T, et al. Evaluation of interpupillary distance in the Turkish population. *Clin Ophthalmol* 2015;9: 1413–1416.