

Proposal of a simple grading system integrating cosmetic and tonometric aspects of prostaglandin-associated periorbitopathy

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Abstract

The distribution of prostaglandin-associated periorbitopathy (PAP) graded using the Shimane University PAP Grading System (SU-PAP) among glaucoma/ocular hypertension subjects using a topical FP or EP2 receptor agonist was reported. A 460 consecutive Japanese subjects (211 men, 249 women; mean age \pm standard deviation, 69.9 \pm 14.5 years) who had used either a FP agonist (0.005% latanoprost, 0.0015% tafluprost, 0.004% travoprost, 0.03% bimatoprost, or fixed combinations of these) or EP2-agonist (0.002% omidenepag isopropyl) for more than 3 months in at least 1 eye were retrospectively enrolled. Age, sex, prostaglandin, intraocular pressure (IOP) measured by Goldmann applanation tonometry (IOP_{GAT}) and iCare rebound tonometry (IOP_{RBT}), difference between IOP_{GAT} and IOP_{RBT} (IOP_{GAT-RBT}), PAP grade, and PAP grading items were compared among groups stratified by PAP grade or prostaglandins. Of the study patients, 114 (25%) had grade 0 (no PAP), 174 (38%) grade 1 (superficial cosmetic PAP), 141 (31%) grade 2 (deep cosmetic PAP), and 31 (7%) grade 3 (tonometric PAP). The IOP_{GAT} was significantly higher in grade 3 (17.5 \pm 5.4 mm Hg) than grades 0 (15.0 \pm 5.1 mm Hg, $P = .032$) and 1 (14.5 \pm 4.2 mm Hg, $P = .008$), and the IOP_{GAT-RBT} was significantly higher in grade 3 (5.8 \pm 3.2 mm Hg) than the other 3 grades (1.3–1.9 mm Hg, $P < .001$ for all comparisons); the IOP_{RBT} was equivalent among the 4 grades. The PAP grade was significantly higher associated with travoprost (2.0 \pm 0.8) and bimatoprost (2.0 \pm 0.7) than latanoprost (1.0 \pm 0.8, $P < .001$ for both comparisons) and tafluprost (1.0 \pm 0.7, $P < .001$ for both comparisons), but significantly lower associated with omidenepag (0.0 \pm 0.0, $P < .001$ for all comparisons) than the other 4 prostaglandins. Multivariate analyses showed older age (standard $\beta = 0.11$), travoprost (0.53, referenced by latanoprost) and bimatoprost (0.65) were associated with higher PAP grades, while tafluprost (−0.18) and omidenepag (−0.73) were associated with lower PAP grades. The PAP graded using SU-PAP reflects the degree of overestimation of the IOP_{GAT} and different severities of PAP among the different prostaglandins. SU-PAP, the grade system constructed based on the underlining mechanisms of PAP, is a simple grading system for PAP that is feasible for use in a real-world clinical situation.

Abbreviations: DUES = deepening of the upper eyelid sulcus, IOP = intraocular pressure, IOP_{GAT} = IOP measured by Goldmann applanation tonometry, IOP_{RBT} = IOP measured by iCare rebound tonometry, PAP = prostaglandin-associated periorbitopathy, SU-PAP = Shimane University PAP Grading System.

Keywords: adverse effect, deepening of upper eyelid sulcus, EP2-agonist, FP agonist, goldmann applanation tonometer, grading system, iCARE rebound tonometer, prostaglandin-associated periorbitopathy

1. Introduction

Lowering intraocular pressure (IOP) using prostaglandin F2 α -derived prostanoid FP receptor agonists such as latanoprost, tafluprost, travoprost, and bimatoprost, is the current standard

of care for patients with glaucoma and ocular hypertension.^[1] FP agonists have few systemic side effects; however, frequent local side effects known as prostaglandin-associated periorbitopathy (PAP) occur,^[2,3] including skin hyperpigmentation, eyelash

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elongation, iris color changes, dermatochalasis involution, deepening of the upper eyelid sulcus (DUES), loss of lower lid steatoblepharon, upper lid ptosis, lower lid retraction, and enophthalmos.^[4,5] In the US, users of prostaglandin agonists have variety of signs of PAP including DUES (69%), hypertrichosis (91%), periocular erythema (69%), and meibomian gland dysfunction (51%).^[6] In Asian populations, 53.4% of prostaglandin users have at least 1 PAP sign; the most common being DUES (24.1%), eyelid pigmentation (19.0%), eyelid erythema (19.0%), dermatochalasis involution (10.3%), eyelid retraction (5.2%), and ptosis (3.4%).^[7] PAP affects patient care in many ways, such as cosmetic concerns, difficulty in IOP measurement, and intraoperative difficulty.^[2,8]

Hypertrichosis has been linked to the ability of FP agonists to prolong anagen in resting hair follicles while inducing hypertrophic changes in the involved follicles^[9] and elongated eyelashes by changing the hair follicle cycles.^[9] The mechanisms of prostaglandin-associated periocular skin pigmentation has not been explored fully; however, the FP-agonists' effects on melanogenesis^[10] and melanocyte proliferation^[11] are considered the key events. On the other hand, DUES resulting from current antiglaucoma FP agonists likely follows inhibition of adipogenesis around the eyelid followed by atrophy of orbital fat.^[12] Histologic analysis of upper eyelid adipose tissue excised intraoperatively indicated that adipocyte density was higher in eyelids treated with travoprost and bimatoprost than in the untreated contralateral eyes but not for latanoprost-treated eyes.^[13] FP agonists negatively modulate the size of three-dimensional organoids from human orbital fibroblasts in vitro.^[14] Magnetic resonance imaging showed decreased orbital adipose tissue after long-term use of prostaglandins;^[15] thus, DUES is induced by atrophy of orbital fat.^[13] Accordingly, although lid pigmentation and DUES are considered negative cosmetic effects of FP-agonist treatments, these may occur through different mechanisms.

Regarding DUES, a mechanical insult to the eyelids causing levator dehiscence or reduction in collagens leading to Müller's muscle degeneration may explain deepening of the eyelid sulcus and upper lid ptosis.^[16] Thus, further remodeling of the extracellular matrix of the orbital/deeper lid tissue^[17] can be associated with ptosis and hardening of lid skin. With ptosis and tight eyelids due to PAP, IOP measurement can be challenging. With a deep upper eyelid sulcus and no preseptal fat, lifting a tight lid without applying pressure to the globe is difficult.^[4] Performing surgery for these patients presents a unique challenge, beginning with placement of the lid speculum and the less-than-optimal exposure as a result of the enophthalmos and tight eyelids.^[4] The presence of DUES was associated with surgical failure of trabeculectomy; and presurgical use of bimatoprost was associated with a high risk of recurrent IOP elevation up to 2 years post-trabeculectomy.^[18] Accordingly, not only the cosmetic concerns but also the periorbital tissue changes associated with PAP make the management and treatment of glaucoma in these patients particularly difficult.

We recently started to use our in house PAP grading system (Shimane University PAP Grading System, SU-PAP), which considers the previously mentioned mechanisms involved in the development of cosmetic PAPs (i.e., superficial and deep), and the effect of PAP in glaucoma management (i.e., difficult IOP measurement). Omidenedap isopropyl (Eybelis, Santen Pharmaceutical Co., Ltd., Osaka, Japan), a selective prostanoid EP2 agonist,^[19] a new class of ocular hypotensive agent that was

approved in 2018 in Japan, can be used as a first-line drug for glaucoma and ocular hypertension like a FP agonist. Omidenedap 0.002% was found to be non-inferior to latanoprost 0.005% in reducing IOP in patients with ocular hypertension or primary open-angle glaucoma and was well tolerated.^[20] We report the distributions of SU-PAP gradings among subjects who used FP and EP2 agonists.

2. Subjects and methods

2.1. Subjects and data collection

The study adhered to the tenets of the Declaration of Helsinki; the institutional review board of Shimane University Hospital reviewed and approved the research (No. 20200404-1). The institutional review board approval did not require each patient provide written informed consent for publication; instead the study protocol was posted at the study institutions to notify participants about the study. This descriptive cross-sectional study included 460 consecutive 460 eyes (sides) of 460 Japanese subjects (211 men, 249 women; mean age \pm standard deviation, 69.9 ± 14.5 years) who fulfilled the inclusion criteria: 1) subjects who presented to Shimane University Hospital between March and April 2020; 2) use of either topical FP-agonist (0.005% latanoprost, 0.0015% tafluprost, 0.004% travoprost, 0.03% bimatoprost, or those containing fixed-combination drugs) or EP2-agonist (0.002% omidenedap isopropyl) for more than 3 months in at least 1 eye; 3) PAP severity graded by Shimane University PAP Grading System (SU-PAP) and recording of the grade in the medical chart; and 4) IOP measured by both Goldmann applanation tonometer (IOP_{GAT}) and the iCARE rebound tonometer (M.E. Technica, Tokyo, Japan) (IOP_{RBT}) on the same day (in our glaucoma clinic, both IOP_{GAT} and IOP_{RBT} were recorded routinely at patients' initial visits). If both eyes were eligible, the eye with the higher PAP score was included to highlight the effects of PGs on PAP formation; if the scores were the same in both eyes, the left eye was included. The following data were collected from the medical charts: age, sex, prostaglandin, IOP_{GAT}, IOP_{RBT}, difference between the IOP_{GAT} and IOP_{RBT} (IOP_{GAT-RBT}), PAP grade, and PAP grading items. The prostaglandin used for the longest time during the previous 3 years was regarded as the prostaglandin used by each subject.

2.2. Shimane university PAP grading system

Our in-house PAP grading system (Table 1), which we began to use in March 2020, classifies the severities of PAP into 4 grades based on the appearance and difficulty performing GAT. The grades were constructed based on the underlining mechanisms of each PAP items as described in the Introduction section. Grade 0 (no PAP) is defined as no prostaglandin-associated cosmetic changes by macroscopic or slit-lamp observation; grade 1 (superficial cosmetic PAP) as the presence of eyelid hyperpigmentation and/or eyelash growth; grade 2 (deep cosmetic PAP) as the presence of at least 1 component of DUES, blepharochalasis involution, periorbital fat loss, or enophthalmos (Fig. 1); and grade 3 (tonometric PAP) as difficulty performing GAT and/or reduced reliability of IOP_{GAT} due to the presence of PAP-related DUES, hardening of eyelids, ptosis, or enophthalmos. The difficulty or the reduced reliability was based on the subjective judgement of the examiners.

Table 1
Shimane university prostaglandin-associated periorbitopathy grading system.

Grade	0	1	2	3
Grade Name	No PAP	Superficial cosmetic PAP	Deep cosmetic PAP	Tonometric PAP
Definition	No cosmetic change	Cosmetic change(s) including eyelid pigmentation and/or eyelash growth	Cosmetic change(s) with at least one sign of PAP including DUES, blepharochalasis involution, periorbital fat loss, or enophthalmos	Difficulty performing GAT and/or reduced reliability of GAT-measured IOP due to PAP-related DUES, hardening of eyelids, ptosis, or enophthalmos

DUES = deepening of upper eyelid sulcus, GAT = Goldmann applanation tonometry, IOP = intraocular pressure.

2.3. Statistical analysis

The statistical comparisons among groups stratified by PAP grade or prostaglandins were performed using one-way analyses of variance for continuous data and the exact Cochran-Armitage trend test (comparisons of PAP grade-stratified groups) or G test (comparisons of prostaglandin-stratified groups) for categorical data. If the one-way analyses of variance was significant, the pairs were compared using the Tukey-Kramer honestly significant test. IOP values were compared between the presence and absence of each PAP items using the *t*-test. The correlations between the PAP grades and prostaglandins were analyzed by multiple regression analysis with adjustment for age. All continuous data are expressed as the mean \pm SD. All statistical analyses were performed using the JMP Pro version 14.2 statistical software (SAS Institute, Inc., Cary, NC). $P < .05$ was considered significant.

3. Results

Subject demographic data, IOP, and prostaglandins stratified by PAP grade are shown in Table 2. PAP was graded as follows: grade 0, 114 (25%) patients; grade 1, 174 (38%) patients; grade 2, 141 (31%) patients; and grade 3, 31 (7%) patients. The IOP_{GAT} was significantly higher in grade 3 than grades 0 and 1, and in grade 2 than grade 1; the IOP_{RBT} was equivalent among the 4 grades. IOP_{GAT} was not available in 2 eyes from Grade 3 eyes because of inability of IOP measurement, while IOP_{RBT} was available in all subjects. As a result, the IOP_{GAT-RBT} was significantly higher in grade 3 than in the other 3 grades, and in grade 2 than grade 1.

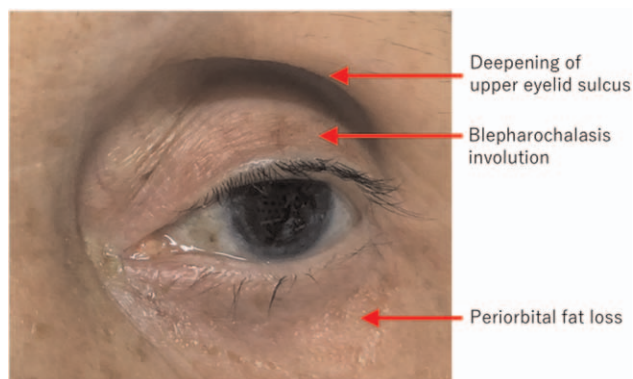


Figure 1. Representative findings of deep cosmetic prostaglandin-associated periorbitopathy (left eye). The figure is used with the permission of the patient.

The difference of IOP_{GAT-RBT} between the presence and absence of each item in the PAP grading was less than 1 mm Hg for grade 1 items, 1 to 2 mm Hg for grade 2 items, and 4.3 mm Hg for grade 3 items (Table 3).

Subject demographic data, IOP, and PAP grade stratified by prostaglandin are shown in Table 4. Latanoprost was used by 240 (52%) patients, tafluprost by 97 (21%), travoprost by 45 (10%), bimatoprost by 58 (13%), and omidenepag by 20 (4%). The PAP grade was significantly higher in those who used travoprost and bimatoprost than in those who used latanoprost and tafluprost but was significantly lower in omidenepag than the other 4 prostaglandins. The IOP_{GAT-RBT} was significantly higher in those using travoprost and bimatoprost than latanoprost.

By multivariate analysis (Table 5) showed that older age was significantly associated with a higher PAP grade. Even after adjustment for age, compared with latanoprost, travoprost and bimatoprost were associated with higher PAP grades, while tafluprost and omidenepag were associated with lower PAP grades.

4. Discussion

Using the SU-PAP, we graded PAP in patients who visited our glaucoma clinic. With this grading system, the cosmetic aspects of PAP were classified as superficial or deep based on the differences in the underlying pathogenesis.^[9-17] Previously, grading or subjective measurement of PAP had been attempted in each PAP component such as conjunctival hyperemia (0 to 3),^[21] eyelash changes,^[22] DUES (0 to 4),^[7] dermatochalasis (-3 to +2), steatoblepharon (-1 to +2), marginal reflex distance (0 to 4), and levator muscle excursion (0 to 4).^[5] Rabinowitz et al published an objective PAP grading system for monocular FP agonist users in a prospective study.^[23] That grading system stratified eyelids and adnexa into 3 categories: grade 1, relative fat atrophy without superior sulcus deformity and grade 3, positivity for severe fat atrophy and sulcus deformity.^[23] Although these are useful to quantify PAP for clinical trials, they may be too complex to use in real-world situations. Incorporation of the difficulty performing IOP measurement into the grading system is the unique feature of SU-PAP. In our subjects, patients with grade 3 had the highest discrepancy between IOP_{GAT} and IOP_{RBT} (5.8 mm Hg). GAT was reported to overestimate the IOP by 8.6 ± 5.3 mm Hg compared with the RBT in glaucomatous eyes associated with tight orbit syndrome (mostly due to PAP).^[24] RBT's elimination of the need for the examiner to open the patient's upper lid when measuring the IOP can be associated with preventing overestimation. Therefore, RBT is a suitable alternative device for use in patients with SU-PAP grade 3 in whom the IOP may be overestimated by GAT.

In our subjects, the PAP grades were higher, and the GAT overestimation was greater with travoprost and bimatoprost

Table 2
Demographic data, IOP, and prostaglandins stratified by PAP grade.

Parameters	Total	Grade 0	Grade 1	Grade 2	Grade 3	P value [†]
Subjects						
n (%)	460 (100)	114 (25)	174 (38)	141 (31)	31 (7)	
Age (yr)						
Mean ± SD	69.9 ± 14.5	67.5 ± 17.3	68.2 ± 14.8	72.6 ± 11.6	76.4 ± 10.3	<.001**
95% CI	68.6–71.3	64.3–70.7	66.0–70.4	70.7–74.5	72.6–80.2	
P value [‡] , vs grade 0		–	0.970	0.024*	0.011*	
vs grade 1		–	–	0.037*	0.019*	
vs grade 2		–	–	–	0.534	
Sex						
Male, n (%)	211 (46)	46 (40)	86 (49)	69 (49)	10 (32)	.818
Female, n (%)	249 (54)	68 (60)	88 (51)	72 (51)	21 (68)	
Prostaglandin, n (%)						
Latanoprost	240 (52)	67 (59)	107 (61)	62 (44)	4 (13)	
Tafluprost	97 (21)	23 (20)	48 (28)	26 (18)	0 (0)	
Travoprost	45 (10)	3 (3)	7 (4)	24 (17)	11 (35)	
Bimatoprost	58 (13)	1 (1)	12 (7)	29 (21)	16 (52)	
Omidenepag	20 (4)	20 (18)	0 (0)	0 (0)	0 (0)	
IOP _{GAT} (mm Hg)						
Mean ± SD	15.2 ± 5.6	15.0 ± 5.1	14.5 ± 4.2	15.8 ± 7.1	17.5 ± 5.4	.025*
95% CI	14.7–15.7	14.1–16.0	13.9–15.1	14.6–17.0	15.4–19.5	
P value [‡] , vs grade 0		–	0.447	0.265	0.032*	
vs grade 1		–	–	0.041*	0.008**	
vs grade 2		–	–	–	0.135	
IOP _{RBT} (mm Hg)						
Mean ± SD	13.4 ± 5.5	13.6 ± 5.3	12.5 ± 4.1	13.2 ± 4.6	11.7 ± 3.9	.220
95% CI	12.9–13.9	12.6–14.5	11.7–13.3	12.5–13.9	10.2–13.1	
IOP _{GAT-RBT} (mm Hg)						
Mean ± SD	1.8 ± 2.8	1.5 ± 2.4	1.3 ± 2.6	1.9 ± 2.5	5.8 ± 3.2	<.001**
95% CI	1.6–2.1	1.0–1.9	0.9–1.7	1.5–2.3	4.6–7.0	
P value [‡] , vs grade 0		–	0.545	0.175	<0.001**	
vs grade 1		–	–	0.032*	<0.001**	
vs grade 2		–	–	–	<0.001**	
Eyelids pigmentation						
No, n (%)	204 (44)	114 (100)	65 (37)	22 (16)	3 (10)	<.001**
Yes, n (%)	256 (56)	0 (0)	109 (63)	119 (84)	28 (90)	
Eyelashes growth						
No, n (%)	176 (38)	114 (100)	29 (17)	26 (18)	7 (23)	<.001**
Yes, n (%)	284 (62)	0 (0)	145 (83)	115 (82)	24 (77)	
DUES						
No, n (%)	310 (67)	114 (100)	174 (100)	20 (14)	2 (6)	<.0001**
Yes, n (%)	150 (33)	0 (0)	0 (0)	121 (86)	29 (94)	
Blepharochalasis involution						
No, n (%)	404 (88)	114 (100)	174 (100)	105 (74)	11 (35)	<.0001**
Yes, n (%)	56 (12)	0 (0)	0 (0)	36 (26)	20 (65)	
Periorbital fat loss						
No, n (%)	357 (78)	114 (100)	174 (100)	65 (46)	4 (13)	<.0001**
Yes, n (%)	103 (22)	0 (0)	0 (0)	76 (54)	27 (87)	
Enophthalmos						
No, n (%)	416 (90)	114 (100)	174 (100)	115 (82)	13 (42)	<.0001**
Yes, n (%)	44 (10)	0 (0)	0 (0)	26 (18)	18 (58)	
Difficulty performing GAT and/or reduced reliability of IOP _{GAT}						
No, n (%)	429 (93)	114 (100)	174 (100)	141 (100)	0 (0)	<.0001**
Yes, n (%)	31 (7)	0 (0)	0 (0)	0 (0)	31 (0)	

[†] P values are calculated using one-way analysis of variance (ANOVA) for continuous data and the exact Cochran–Armitage trend test for categorical data.

[‡] For continuous data, if ANOVA is significant ($P < .05$), Tukey–Kramer honestly significant difference tests are used for each pair comparison. * and ** indicate significance levels of 5% and 1%, respectively. CI = confidence interval, DUES = deepening of upper eyelid sulcus, GAT = Goldmann applanation tonometry, IOP = intraocular pressure, IOP_{GAT} = IOP measured by Goldmann applanation tonometry, IOP_{GAT-RBT} = difference between IOP_{GAT} and IOP_{RBT} (IOP_{GAT} minus IOP_{RBT}), IOP_{RBT} = IOP measured by rebound tonometry, n = number, PAP = prostaglandin-associated periorbitopathy, SD = standard deviation.

than latanoprost and tafluprost. It is well established that bimatoprost and travoprost are associated with a higher risk of dermatochalasis and DUES^[5] or with more frequent and more

severe PAP.^[25] A cross-sectional study found that the frequencies of presenting enophthalmos, DUES, proptosis, dermatochalasis involution, and periorbital fat loss differed among bimatoprost,

Table 3
Effect of PAP grading items on IOP.

Items	IOP _{GAT} (mm Hg)			IOP _{RBT} (mm Hg)			IOP _{GAT-RBT} (mm Hg)		
	No	Yes	P value [†]	No	Yes	P value [†]	No	Yes	P value [†]
Eyelid pigmentation									
Mean ± SD	15.1 ± 4.7	15.3 ± 6.2	.711	13.8 ± 5.1	13.1 ± 5.9	0.155	1.3 ± 2.4	2.2 ± 3.0	<.001**
95% CI	14.5–15.8	14.5–16.1		13.1–14.5	12.4–13.8		1.0–1.6	1.8–2.6	
Eyelash growth									
Mean ± SD	15.2 ± 5.3	15.2 ± 5.7	.948	13.4 ± 5.3	13.4 ± 5.7	0.946	1.8 ± 2.6	1.8 ± 2.9	.826
95% CI	14.4–16.0	14.6–15.9		12.6–14.2	12.7–14.1		1.4–2.2	1.5–2.2	
DUES									
Mean ± SD	14.9 ± 5.2	15.9 ± 6.1	.033*	13.5 ± 5.4	13.3 ± 5.9	0.680	1.4 ± 2.5	2.6 ± 3.1	<.001**
95% CI	14.3–15.5	14.9–16.9		12.9–14.1	12.3–14.2		1.1–1.7	2.1–3.1	
Blepharochalasis involution									
Mean ± SD	15.1 ± 5.6	16.3 ± 5.3	.144	13.5 ± 5.7	12.6 ± 4.4	0.240	1.6 ± 2.6	3.6 ± 3.5	<.001**
95% CI	14.5–15.6	14.8–17.7		13.0–14.1	11.4–13.8		1.3–1.8	2.7–4.6	
Periorbital fat loss									
Mean ± SD	14.9 ± 5.2	16.4 ± 6.5	.016*	13.5 ± 5.4	13.1 ± 5.9	0.493	1.4 ± 2.6	3.3 ± 3.1	<.001**
95% CI	14.3–15.4	15.1–17.7		12.9–14.1	11.9–14.2		1.1–1.7	2.7–3.9	
Enophthalmos									
Mean ± SD	15.1 ± 5.6	16.4 ± 4.9	.140	13.5 ± 5.6	13.0 ± 4.4	0.599	1.6 ± 2.7	3.4 ± 3.4	<.001**
95% CI	14.6–15.6	14.9–17.9		12.9–14.0	11.7–14.3		1.4–1.9	2.3–4.4	
Difficulty performing GAT and/or reduced reliability of IOP _{GAT}									
Mean ± SD	15.1 ± 5.5	17.5 ± 5.4	.023*	13.5 ± 5.6	11.7 ± 3.9	0.034*	1.5 ± 2.5	5.8 ± 3.2	<.001**
95% CI	14.5–15.6	15.4–19.5		13.0–14.1	10.2–13.1		1.3–1.8	4.6–7.0	

[†] P values are calculated by using t-test. The * and ** indicate significance levels of 5% and 1%, respectively. CI = confidence interval, DUES = deepening of upper eyelid sulcus, GAT = Goldmann applanation tonometry, IOP = intraocular pressure, IOP_{GAT} = IOP measured by Goldmann applanation tonometer, IOP_{GAT-RBT} = difference between IOP_{GAT} and IOP_{RBT} (IOP_{GAT} minus IOP_{RBT}), IOP_{RBT} = IOP measured by rebound tonometer, N = number, PAP = prostaglandin-associated periorbitopathy, SD = standard deviation.

latanoprost, and travoprost; overall, the signs of PAP were present in 93.3% with bimatoprost, 70% with travoprost, and 41.4% with latanoprost.^[2,5] A retrospective Japanese study showed that DUES occurred most frequently after bimatoprost use (60%), followed by travoprost (50%), latanoprost (24%), and tafluprost (18%).^[2,6] Prospective studies have reported that the rate of DUES induced by tafluprost was 14% at 4 months^[2,7] and by travoprost 53%.^[2,8] Switching from latanoprost to bimatoprost induced DUES in 60% of patients after 3 months.^[2,9] Thus, our system successfully detected differences in PAP frequency and severity derived from different FP agonists.

The PAP grade was zero for the omidenepag users in this study. Bimatoprost increased the eyelash number and thickness and the percentage of dermal papilla in the anagen phase, while omidenepag did not affect eyelash growth in mice.^[30] FP agonists, including latanoprost, tafluprost, travoprost, and bimatoprost, inhibited adipogenesis by stimulating the FP receptor in preadipocyte 3T3-L1 cells,^[31,32] while omidenepag did not affect the adipocyte differentiation in these cells.^[12] Some PAP signs such as DUES and flattening of the lower eyelid bags induced by FP agonists improved after switching to omidenepag.^[33] Based on the chart review, all patients taking omidenepag were treatment-naïve before starting the drug. Collectively, our results confirmed the PAP-free character of EP2-agonist users.

Multivariate analyzes showed that other than the types of prostaglandins, older age was associated with a higher PAP grade. Previous studies have suggested that a longer duration of bimatoprost use was associated with a higher risk of PAP,^[5] older age and the duration of prostaglandin administration were

correlated with DUES,^[7] and older age and use of bimatoprost and travoprost were risk factors for PAP, while latanoprost and tafluprost were not.^[8] Accordingly, our results agreed with those previous observations.

The limitations of the current study included the absence of a control group, lack of sample size calculation, retrospective design, absence of medical and surgical treatment history, and inclusion of eyes with various treatment durations. Retrospective study design explains the large variations in numbers of subjects between old-released (i.e., latanoprost) and new-released (i.e., omidenepag) drugs. Our subjects used other topical medications in addition to the prostaglandins. While other medications are less likely to be associated with PAP, allergic reactions and follicular conjunctivitis are not uncommon side effects of glaucoma medications, and might have had some impact on the outcomes seen in this study. We considered the prostaglandin used for the longest time during the previous 3 years as the prostaglandin of each subject. Accordingly, the current PAP grades are not the only PAP caused by 1 prostaglandin; the absence of the exact medical history regarding switched use of prostaglandins was another study limitation.

PAP can be classified into 4 grades, that is, 0 (no PAP), 1 (superficial cosmetic PAP), 2 (deep cosmetic PAP), and 3 (tonometric PAP). The grade reflects the degree of overestimation of IOP measured by GAT and different severities of PAP among different prostaglandins. Since the SU-PAP is much simpler than grading systems reported previously, and unique in respect to unite cosmetic and tonometric aspects of PAP, SU-PAP is a grading system for PAP that can be useful in a regular clinical situation.

Table 4
Demographic data, IOP, and PAP grade stratified by prostaglandins.

	Latanoprost	Tafuprost	Travoprost	Bimatoprost	Omidenepag	P value [†]
Subjects						
n (%)	240 (52)	97 (21)	45 (10)	58 (13)	20 (4)	
Age (yr)						
Mean ± SD	70.2 ± 14.5	70.8 ± 12.5	74.2 ± 11.7	69.5 ± 14.0	54.4 ± 21.7	<.001**
95% CI	68.4–72.0	68.3–73.3	70.7–77.7	65.8–73.2	44.2–64.5	
P value [‡] , vs latanoprost	–	.997	.417	.997	<.001**	
vs tafuprost	–	–	0.671	0.982	<0.001**	
vs travoprost	–	–	–	0.458	<0.001**	
vs bimatoprost	–	–	–	–	<0.001**	
Sex						
Male, n (%)	115 (48)	46 (47)	21 (47)	22 (38)	7 (35)	.569
Female, n (%)	125 (52)	51 (53)	24 (53)	36 (62)	13 (65)	
IOP _{GAT} (mm Hg)						
Mean ± SD	15.0 ± 5.6	14.2 ± 4.0	15.2 ± 4.7	17.9 ± 7.8	15.5 ± 4.1	.002**
95% CI	14.3–15.7	13.4–15.0	13.8–16.7	15.8–20.0	13.5–17.4	
P value [‡] , vs latanoprost	–	.237	.773	<.001**	.717	
vs tafuprost	–	–	0.295	<0.001**	0.356	
vs travoprost	–	–	–	0.017*	0.889	
vs bimatoprost	–	–	–	–	0.090	
IOP _{RBT} (mm Hg)						
Mean ± SD	13.6 ± 5.8	12.5 ± 4.1	12.2 ± 4.1	15.0 ± 7.2	13.7 ± 4.6	.041*
95% CI	12.9–14.3	11.7–13.3	10.9–13.4	13.1–16.9	11.5–15.8	
P value [‡] , vs latanoprost	–	0.457	0.513	0.409	1.000	
vs tafuprost	–	–	0.998	0.049*	0.905	
vs travoprost	–	–	–	0.077	0.851	
vs bimatoprost	–	–	–	–	0.888	
IOP _{GAT} – _{RBT} (mm Hg)						
Mean ± SD	1.4 ± 2.5	1.7 ± 2.6	3.1 ± 3.2	2.8 ± 3.5	1.8 ± 2.6	<.001**
95% CI	1.1–1.7	1.2–2.2	2.1–4.0	1.8–3.7	0.6–3.0	
P value [‡] , vs latanoprost	–	0.8671	0.002**	0.007**	0.976	
vs tafuprost	–	–	0.051	0.155	1.000	
vs travoprost	–	–	–	0.982	0.402	
vs bimatoprost	–	–	–	–	0.638	
PAP Grade						
Mean ± SD	1.0 ± 0.8	1.0 ± 0.7	2.0 ± 0.8	2.0 ± 0.7	0	<.001**
95% CI	0.9–1.1	0.9–1.2	1.7–2.2	1.8–2.2	0	
P value [‡] , vs latanoprost	–	.838	<.001**	<.001**	<.001**	
vs tafuprost	–	–	<0.001**	<0.001**	<0.001**	
vs travoprost	–	–	–	0.596	<0.001**	
vs bimatoprost	–	–	–	–	<0.001**	
PAP Grade, n (%)						
0 (No PAP)	67 (28)	23 (24)	3 (7)	1 (2)	20 (100)	
1 (Superficial cosmetic PAP)	107 (45)	48 (49)	7 (16)	12 (21)	0 (0)	
2 (Deep cosmetic PAP)	62 (26)	26 (27)	24 (53)	29 (50)	0 (0)	
3 (Tonometric PAP)	4 (2)	0 (0)	11 (24)	16 (28)	0 (0)	
Eyelids pigmentation						
No, n (%)	127 (53)	42 (43)	9 (20)	6 (10)	20 (100)	<.001**
Yes, n (%)	113 (47)	55 (57)	36 (80)	52 (90)	0 (0)	
Eyelashes growth						
No, n (%)	101 (42)	38 (39)	5 (11)	12 (21)	20 (100)	<.001**
Yes, n (%)	139 (58)	59 (61)	40 (89)	46 (79)	0 (0)	
DUES						
No, n (%)	182 (76)	75 (77)	13 (29)	20 (34)	20 (100)	.001**
Yes, n (%)	58 (24)	22 (23)	32 (71)	38 (66)	0 (0)	
Blepharochalasis involution						
No, n (%)	227 (98)	95 (98)	29 (64)	33 (57)	20 (100)	<.001**
Yes, n (%)	13 (5)	2 (2)	16 (36)	25 (43)	0 (0)	
Periorbital fat loss						
No, n (%)	210 (88)	89 (92)	16 (36)	22 (38)	20 (100)	<.001**
Yes, n (%)	30 (13)	8 (8)	29 (64)	36 (62)	0 (0)	
Enophthalmos						
No, n (%)	229 (95)	95 (98)	31 (69)	41 (71)	20 (100)	<.001**
Yes, n (%)	11 (5)	2 (2)	14 (31)	17 (29)	0 (0)	
Difficulty performing GAT and/or reduced reliability of IOP _{GAT}						
No, n (%)	236 (98)	97 (100)	34 (76)	42 (72)	20 (100)	<.001**
Yes, n (%)	4 (2)	0 (0)	11 (24)	16 (28)	0 (0)	

[†] P values are calculated by using one-way analysis of variance (ANOVA) for continuous data and by using G-test for categorical data.

[‡] For continuous data, if ANOVA is significant ($P < .05$), Tukey–Kramer honesty significant difference tests are used for each pair comparison. * and ** indicate significance levels of 5% and 1%, respectively. CI = confidence interval, DUES = deepening of upper eyelid sulcus, GAT = Goldmann applanation tonometry, IOP = intraocular pressure, IOP_{GAT} = IOP measured by Goldmann applanation tonometer, IOP_{GAT}–_{RBT} = difference between IOP_{GAT} and IOP_{RBT} (IOP_{GAT} minus IOP_{RBT}), IOP_{RBT} = IOP measured by rebound tonometer, N = number, PAP = prostaglandin-associated periorbitopathy, SD = standard deviation.

Table 5
Age-adjusted association of prostaglandins with the PAP grade.

	Estimates	95% CI	P value	Standard β
Age (yr)	0.006	0.002–0.011	.009**	0.11
Prostaglandins (/latanoprost)				
Tafloprost	–0.19	–0.34–0.05	.011*	–0.18
Travoprost	0.71	0.51–0.90	<.001**	0.53
Bimatoprost	0.82	0.64–0.99	<.001**	0.65
Omidenepag	–1.12	–1.40–0.84	<.001**	–0.73

The PAP score is set as a dependent variable in this multiple regression analysis model. * and ** indicate significance levels of 5% and 1%, respectively. PAP = prostaglandin-associated periorbitopathy, CI = confidence interval.

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