ORIGINAL ARTICLE

Evaluation the Effect of Long-term Antiglaucomatous Therapy on the Ocular Surface and Meibomian Glands

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ABSTRACT

Purpose: To evaluate the effect of long-term antiglaucomatous therapy on the meibomian glands by meibograpy.

Materials and Methods: A total of 31 patients with unilateral ocular hypertension or glaucoma receiving antiglaucomatous medical treatment for at least 1 year were included in this study. The contralateral eyes were used as the control group. Invasive tear film break-up time (TF-BUT), fluorescein staining of the ocular surface, and Schirmer II test were performed in all subjects. Total eyelid score and meibomian gland secretion score were evaluated. Non-contact meibography were performed with the Sirius corneal topographic device.

Results: There were 15 (48,4%) males and 16 (51,6%) females and the mean age was 57.9±9.8 years. While the TF-BUT ($p<0.001$) and Schirmer test ($p<0.001$) values were significantly lower in the glaucoma group compared to the control group, the ocular surface staining score ($p=0.001$), eyelid ($p<0.001$) and meibomian gland secretion ($p<0.001$) score were significantly higher. Meibomian gland loss area ($p<0.001$ for the both upper and lower eyelid) and meiboscore ($p<0.001$ for the upper and lower eyelid) were significantly higher in the glaucoma group. In correlation analysis number of antiglaucoma eye drops, daily benzalkonium chloride exposure was associated with ocular surface parameters and meiboscore. Disease duration was correlated with any of ocular surface parameters.

Conclusion: Long-term topical anti-glaucoma treatment adversely affects the ocular surface and meibomian glands. We found that long-term use of topical antiglaucomatous drugs caused significant loss of meibomian glands by meibographic evaluation, as well as decreased ocular surface scores.

Keywords: Dry eye, Glaucoma, Meibography, Meibomian gland, Ocular surface.

INTRODUCTION

Glaucoma is a multifactorial progressive optic neuropathy characterized by visual field defects. Despite the improvements in laser and surgical treatment options, antiglaucomatous drops are the most commonly used treatment. Prostaglandin analogues, beta blockers and alpha agonists are commonly used agents in medical glaucoma treatment. It is known that the most common side effect of topical antiglaucomatous therapy is the ocular surface disease (OSD), and approximate prevalence rises up to 78%.[1,2] The etiopathogenesis of OSD in glaucoma is multifactorial and affected by increasing age, long duration of glaucoma treatment, multiple antiglaucomatous drop use, use of glaucoma drops containing preservatives and the type of preservative.[3-5] OSD primarily manifests in the cornea and conjunctiva as superficial punctate keratitis (SPK), tear-film instability, and allergic manifestations. Topical glaucoma medications can cause burning, irritation, itching, tearing, and decreases in visual acuity within few months of medication initiation.[6] Cytotoxicity due to active ingredients and preservatives of glaucoma drug or direct corneal and conjunctival epithelial damage is thought to be responsible for the development of OSD.[7] Ocular surface problems not only affect the patient's life quality but also impair compliance to glaucoma treatment.[8,9] It is also known that the treatment of OSD has a positive effect on the control of glaucoma.[10,11]

Meibomian glands are modified sebaceous glands embedded in the lower and upper eyelid tarsal plates. Meibum, a lipid-rich secretion, prevents the evaporation of tearfilm and provides its stabilization. Meibomian gland dysfunction (MGD) causes disruption of the lipid layer of tear film and evaporative dry eye. Non-contact meibography is a non-invasive imaging method that allows us to evaluate the

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morphology of the meibomian glands. In recent years, it has been suggested that long-term antiglaucomatous therapy affect meibomian gland morphology and function.[12-17] These studies show methodological differences. As the ocular surface discomfort increases with advancing age, investigating the contralateral eye as a control in the same individuals will more objectively reveal the efficacy of the antiglaucomatous drops. In our study, to reveal the adverse effect of long-term use of topical antiglaucomatous drugs on the ocular surface parameters and morphology of meibomian glands, meibomian glands were evaluated by noncontact meibography method in patients who received unilateral antiglaucomatous treatment.

MATERIALS AND METHODS

Ocular hypertension (OHT) and glaucoma cases receiving unilateral antiglaucomatous medication attending the glaucoma clinic consecutively were enrolled in this prospective comparative study between August 2021 and November 2021. All study procedures were performed in accordance with the Declaration of Helsinki. The study was commenced after obtaining approval in accordance with the standards determined by the ethics committee and informed consent was obtained from the patients.

Patients diagnosed with OHT and primary open angle glaucoma (POAG) using topical antiglaucomatous drops in one eye for at least 1 year were included in the study group. Each participant underwent a complete ophthalmic examination that included gonioscopy, dilated slit-lamp biomicroscopy and fundus examination, visual field by Humphrey field analyzer (Humphrey Visual Field Analyzer, Carl Zeiss Meditec, Dublin, Ireland). Gonioscopy was performed by classic Goldmann three mirror lens and the diagnosis of OHT and POAG was confirmed by the absence of angle closure, angle recession or neovascularization, iridodialysis, pseudoexfoliative material deposition in the angle and peripheral anterior synechiae. The diagnosis of POAG was established upon the observation of IOP greater than 21 mmHg measured by applanation tonometry, signs of glaucoma-specific optic disc changes (rim thinning, excavation, and/or retinal nerve fiber layer defects) and visual field defects detected on consecutive reliable standard automated perimetry tests with the 24-2 algorithm. Patients with elevated intraocular pressure (IOP) greater than 24 mmHg and no signs of POAG on standard clinical tests are defined as OHT. The contralateral eyes of the cases that did not receive glaucoma medication were included in the control group. Exclusion criteria were history of ocular trauma, glaucoma surgery or intraocular surgery in the last 6 months, participants to report changes in anti-glaucoma medications within the preceding 1 year, ocular disease other than glaucoma (uveitis, ocular infections, optic nerve and retinal diseases), eyelid deformity or eyelid surgery, active ocular infection and allergy, contact lens use and autoimmune disease. Poor meibography image quality was also considered as exclusion criteria.

Invasive tear film break-up time (TF-BUT), fluorescein staining of the ocular surface, and Schirmer II test were performed after non-contact intraocular pressure measurement in both treated and untreated eyes of each participant, in the same session. Invasive TF-BUT was measured by evaluating the time in seconds between the last blink and the appearance of the first black spot on the tear film after instillation of fluorescein drops in the lower fornix and the average of 3 consecutive measurements was recorded. For conjunctival and corneal staining, the Oxford ocular surface staining scale which consists of 5 panels and the total score ranged from 0 to 15, was used.[18] The Schirmer II test was performed by placing a standard test paper on the outer 1/3 of the lower eyelid after the topical anesthetic drop had been instilled. The eyelids, lid margin, conjunctiva and cornea were evaluated by slit-lamp biomicroscopy. The eyelid margin was evaluated for the presence of telangiectasies, lid margin irregularity, obstructed meibomian gland orifices, and anterior or posterior displacement of the mucocutaneous junction. The eyelid score (0-4) was calculated according to the presence of these findings.[19,20] The meibum quality expressed by applying pressure to the middle part of the lower and upper eyelid with the index finger was examined. Expressed meibum was scored as: grade 0= clear; grade 1= cloudy; grade 2= cloudy with granular debris and grade 3= thick and toothpaste-like.[21]

After the biomicroscopic examination, non-contact meibography was performed with the Phoenix-Meibography module of the Sirius (CSO, Florence, Italy) corneal topography device. In both groups, at least 6 infrared tarsal conjunctival images were obtained for each eyelid by everting the upper and lower eyelids. The best quality infrared meibography image was used for analysis. The borders of tarsus was determined by marking the tarsal conjunctival borders trapezoidally. Then the examiners marked the borders of circumscribed the meibomian glands. Meibomian glands appeared as hypoilluminant grape-like clusters transversely located on the lid margins. Meibomian glands that were not lined transversely to the total tarsal plate were indicated as a “dropout” (Figure 1). The meiboscore was calculated using Phoenix-Meibography software, which semi-automatically calculates the percent of meibomian gland loss area (MGLA) (grade 0 = no loss at all, grade 1= ≤25%, grade 2 = 26 to 50%, grade 3 = 51 to 75%, and grade 4= more than 75%).[22,23] The number of drugs used in eyes with glaucoma and daily exposure to

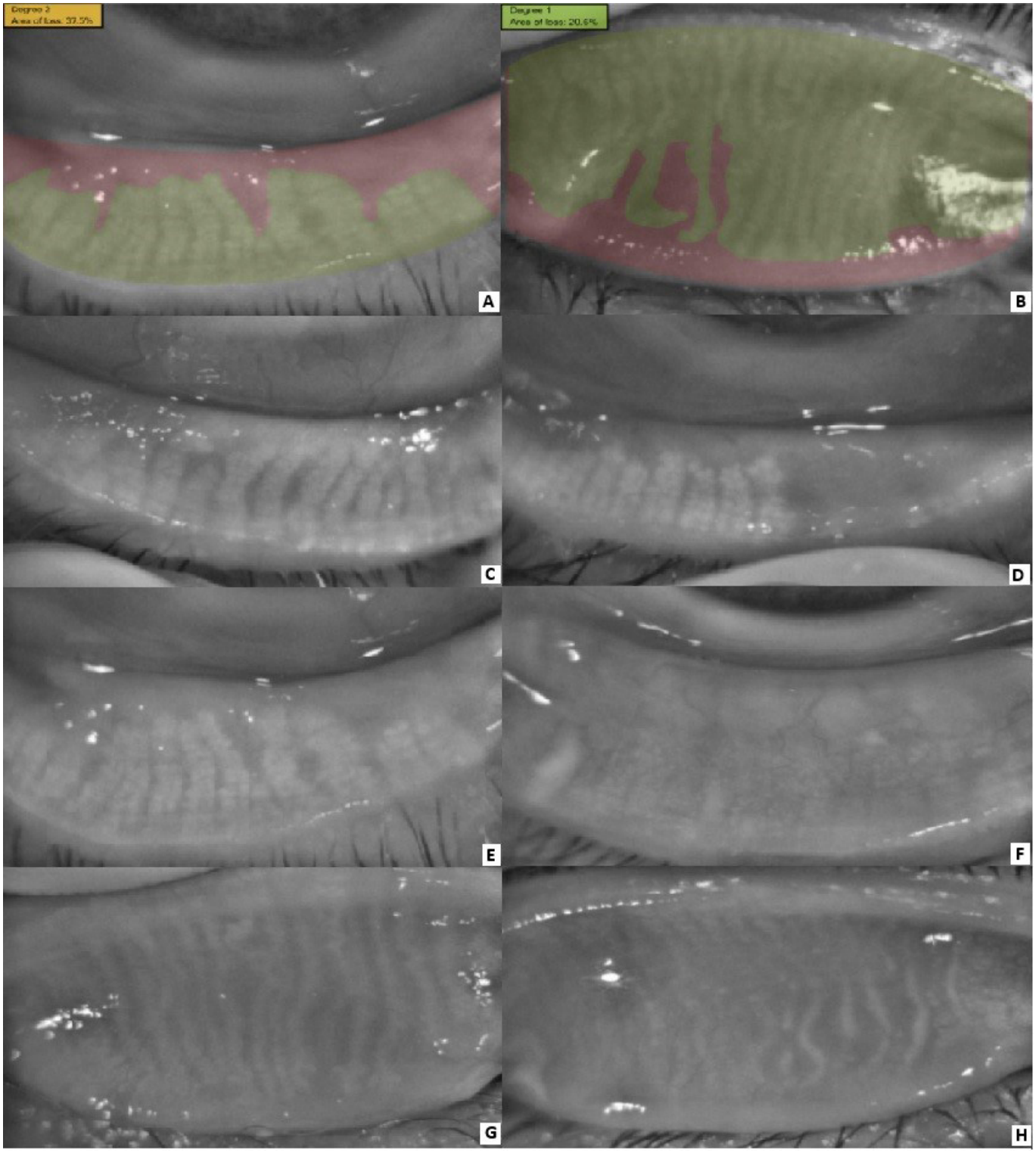

Figure 1: *Infrared imaging and visual documentation of the glands from lower (A) and upper (B) eyelid. The borders of tarsus was determined by marking the tarsal conjunctival borders trapezoidally and gland areas are traced. The meibomian gland loss area (as percentage) and meiboscore is checked on the meiboscale on the left. Comparison of meibography images of eyes that did not receive treatment (C, E, G) and meibography images of eyes that received glaucoma treatment (D, F, H).*

benzalkonium chloride (BAK) (mg/ml) was also recorded.

IBM SPSS Statistics version 24.0 (IBM Corp. Armonk, NY) was used for statistical analysis. Data were shown as mean, standard deviation, and percentage (%). The Shapiro Wilk test was used to evaluate the normality assumption of numerical variables. The -2 to +2 standard deviations of the kurtosis and skewness ranges of the variables were

considered to be normally distributed. Paired t-test was used for those with normal distribution, and Wilcoxon Signed ranks test for those who did not distribute normally. McNemar test was utilized to compare categorical variables. The groups were divided into subgroups according to the number of drugs used. Intra-group differences were investigated. One-way ANOVA was used for comparisons in terms of numerical variables in subgroup analyses. Tukey test was used for post hoc analysis of subgroups. Kruskal Wallis test was used for those who did not show normal distribution in the analysis of numerical variables or did not have homogeneity of variance in the Levene test. Chi-square test was utilized to compare categorical variables. Pearson correlation analysis was used to evaluate the relationship between normally distributed variables, and Spearman correlation analysis was used for non-normally distributed variables. A p-value of <0.05 was considered statistically significant.

RESULTS

The study consisted of 62 eyes of 31 patients with unilateral glaucoma/OHT. There were 16 (51.6%) females and 15 (48.4%) males and the mean age was 57.9±9.8 years (range, 40-71 years). The mean duration of glaucoma medication was 4.0±2.5 years (range, 1-15 years), and the mean number of used drops was 1.9±0.9 (range, 1-3). Among these 15 (48.4%) were treated with prostaglandin analogue, 25 (80.6%) were alpha agonist, 22 (71%) were carbonic anhydrase inhibitors and 20 (64.5%) were on beta-blocker medications. While the drugs used by 11 (35.5%) of the cases did not contain BAK as a preservative, 20 (64.5%) were using drops containing BAK as a preservative. The mean daily BAK exposure was 0.12±0.12 mg/dl (range, 0-0.4 mg/dl). The mean intraocular pressure, invasive TF-BUT, ocular surface staining score (OSSS), Schirmer II test, total eyelid score and meibomian gland secretion score of both groups were summarized in Table 1.

Treated eyes exhibited significantly shorter TF-BUT (6.9±3.7s versus 10.5±3,0 s, p=<0.001), lower Schirmer test values (7.1±2.0 mm versus 9.2±2.3 mm, p=<0.001) and higher Oxford OSSS (1.3±1.5 versus 0.1±0.3, p=<0.001) than untreated fellow eyes. Total eyelid score (2.0±0.9 versus 0.5±0.7, p=<0.001) and meibomian gland secretion score (1.6±0.8 versus 0.6±0.5, p=<0.001) were also statistically significant in those receiving antiglaucomatous medication. On the eyelid examination; the presence of telangiectasia (p=0.01), lid margin irregularity (p=<0.001) and obstructed meibomian glands (p=<0.001) were significantly higher in the treatment group. There was no significant difference between groups in terms of displacement of the muco-cutaneous junction. Significantly higher MGLA measurements (46.0±26.1% versus 23.0±18.5%, p=<0.001 for upper eyelid and 54.7±22.0% versus 27.5±14.6%, p=<0.001 for lower eyelid) and meiboscore (2.2±1.1 versus 1.5±0.7, p=<0.001 for upper meiboscore and 2.6±0.8 versus 1.6±0.7, p=<0.001 for lower meiboscore) were also observed in treated eyes (Table 2). In both groups, the percentage of MGLA and meiboscore were higher in the lower eyelid than the upper eyelid.

Correlation of ocular surface parameters and meiboscore with antiglaucomatous treatment parameters in the glaucoma group was shown in Table 3. The mean number of antiglaucomatous drops was positively correlated with ocular surface staining score (r=0.41, p=0.02) and lower meiboscore (r=0.46, p=0.01). The groups were divided into subgroups according to the number of drugs used. There were 13 (41.9%) cases using 1 drug, 8 (25.8%) cases using 2 drugs, and 10 (32.3%) cases using 3 drugs.

Table 1: *Comparison of ocular surface parameters, eyelid score and meibomian gland secretion score.*

	Treatment group	Control group	p
IOP (mmHg)	14.4±3.7	13.6±2.0	0.20
Invasive TF-BUT (s)	6.9±3.7	10.5±3,0	<0.001
Oxford Score	1.3±1.5	0.1±0.3	0.001 *
Schirmer II (mm)	7.1±2.0	9.2±2.3	<0.001
Total eyelid score	2.0±0.9	0.5±0.7	<0.001 *
Telangiectasia (n, %)	23 (%74.2)	13 (%41.9)	0.006**
Lid margin irregularity (n, %)	18 (%58.1)	1 (%3.2)	<0.001**
Obstructed meibomian gland (n, %)	17(%54.8)	2 (%6.5)	<0.001**
Displacement of the muco-cutaneous junction (n, %)	3 (%9.7)	-	0.25**
MG secretion score	1.6±0.8	0.6±0.5	<0.001

IOP: intraocular pressure, TF-BUT: tear film break-up time, MG: meibomian gland, * The Wilcoxon signed ranks test was used to compare groups that did not distribute normally, ** McNemar test was used to compare categorical variables.

Table 2: *Comparison of upper and lower eyelid meibomian gland loss area and meiboscore.*

	Treatment group	Control group	p
Upper meibography (%)	46.0±26.1 (7.9- 92.0)	23.0±18.5 (3.2- 66.3)	<0.001
Upper meiboscore	2.2±1.1 (1-4)	1.5±0.7 (1-3)	<0.001
Lower meibography (%)	54.7±22.0 (5.9- 95.3)	27.5±14.6 (3.2- 62.3)	<0.001
Lower meiboscore	2.6±0.8 (1-4)	1.6±0.7 (0-3)	<0.001
MG: meibomian gland			

Table 3. *Correlation of ocular surface parameters and meiboscore with antiglaucomatous treatment parameters in the glaucoma group.*

		TF-BUT	Oxford score	Schirmer	Eyelid score	Upper meiboscore	Lower meiboscore
Number of medication	r	-0.09	0.41	-0.28	0.22	0.13	0.46
	p	0.64	0.02	0.12	0.27	0.49	0.01
Duration of eye drop use*	r	-0.19	0.24	-0.30	0.07	0.28	0.10
	p	0.31	0.20	0.10	0.70	0.13	0.96
BAK	r	-0.36	0.68	-0.57	0.26	0.22	0.65
	p	0.04	0.000	0.001	0.15	0.24	<0.001
BAK: benzalkonium chloride, TF-BUT: tear film break-up time, *Spearman correlation analysis was used for nonparametric data							

In the subgroup analysis, the number of antiglaucomatous drops used did not affect TF-BUT (p=0.70), Schirmer II test (p=0.076), total eyelid score (p=0.319), meibomian gland secretion score (0.075), MGLA (p=0.143 and p=0.218 for upper and lower meibography, respectively), and meiboscore (p=0.073 and p=0.171 for upper and lower meibography, respectively). Among the ocular surface parameters, only Oxford OSSS was associated with the number of drops used (p=0.014). In post hoc analysis, while there was no difference between using one and two drops (p=0.87), the difference between using one and three (p=0.034) and using two and three (p=0.023) drops was significant. Duration of eye drop use was not associated with any ocular surface parameters. While the daily BAK exposure showed a significant negative correlation (r=-0.36, p=0.04) with invasive TF-BUT and Schirmer values (r=-0.57, p=0.001), it was positively associated with Oxford OSSS (r=0.68, p=<0.001) and lower meiboscore (r=0.65, p=<0.001).

DISCUSSION

Long-term use of antiglaucomatous eye drops leads to a chronic ocular surface inflammation with the release of inflammatory mediators and cytokines. Ocular surface inflammation begins to appear within 3 months after glaucoma medication initiation. [24] Structural and functional disorders in goblet cells, accessory lacrimal glands and meibomian glands cause tear film instability, decrease in tear film secretion, corneal anesthesia, and disruption of the corneal and conjunctival epithelial barrier.[25-31] Benzalkonium chloride is a quaternary ammonium and is the most commonly used preservative in ophthalmic preparations. Although its pathophysiological mechanism has not been fully explained, it has been shown to be toxic to the ocular surface in many laboratory, experimental and clinical studies.[32-35] It causes an increase in evaporation by disrupting the integrity of the precorneal tear lipid layer and increases the severity of OSD by triggering inflammation.[36-38]

Although the effect of drugs used in the medical treatment of glaucoma on the meibomian glands is not fully understood, it has been reported that chronic ocular surface inflammation may cause stasis in the meibomian glands and hyperkeratinization may cause plug formation in the meibomian gland orifices.[39,40] Agnifili et al.[41] reported that the mean meibomian gland acinar density and area significantly decreased in eyes that received glaucoma medications, and this decrease may be due to drug-related loss of glandular activity, decreased meibum secretion, and secondary hyperviscosity.

There are some studies in the literature evaluating the

effects of glaucoma on the ocular surface and meibomian glands.[12-17,42,43] It was observed that conjunctival hyperemia, ocular surface disease index (OSDI) questionnaire and quality of life index were worse, the height of the tear meniscus reduced and the meiboscore increased in the glaucoma group.[43] In a retrospective study evaluating 80 cases using prostaglandin analogues, it was shown that meibum score, lid margin abnormality score (presence of lid margin irregularity, vascular engorgement, glandular orifices obstruction, and anterior or posterior displacement of the mucocutaneous junction) and meiboscore increased significantly at the end of 12 months compared to baseline, and the findings were more severe in those using drops containing preservatives.[12] Mocan et al.[17] reported that 95.7% of cases using prostaglandin analogues had obstructive type MGD in a cross-sectional study including 70 eyes of 70 patients. In this study MGD was evaluated by the presence of signs consistent with meibomian gland terminal duct obstruction with or without accompanying resistance to meibum expressibility as observed with slit-lamp biomicroscopy.[17]

In our study, we found that the TF-BUT and Schirmer test values were decreased and the OSSS was higher in the eyes of the cases who received glaucomatous medical treatment for at least 1 year compared to the control eyes. The total eyelid score and meibomian gland secretion score were also significantly higher. In the meibographic examination, the percentage of MGLA and meiboscore were significantly higher in the glaucoma treatment group. The percentage of MGLA and meiboscore was higher in lower meibography than the upper meibography. Arita et al.[16] reported that lid margin abnormality, superficial punctate keratopathy, meiboscore obtained by non-contact meibography, and meibum scores were significantly higher in glaucoma patients than healthy volunteers. In subgroup analysis, they also reveal no significant difference between patients receiving prostaglandin and those receiving b-blockers, or among receiving one or more type of antiglaucoma eye drops.[16] In a study including 31 patients with glaucoma treated with topical anti-glaucoma drugs in only one eye for more than 1 year, untreated contralateral eyes served as controls. In this cross-sectional observational case series, the mean duration of medical treatment was 7.9±6.0 years and all antiglaucomatous agents (13 receiving prostaglandin analogues alone, eight receiving β-blockers alone, and ten receiving multiple treatments) contained BAK. Similar to our study, it was found that tear break-up time (p=0.001) and Schirmer test values (p= 00.0039) were lower; lid margin abnormality (p=0.001), superficial punctate keratitis (p=<0.001), and meiboscore (p=<0.001) were higher than the control group. [14] In the subgroup analysis of the same study, it was reported that meiboscore was higher in those using prostaglandin analogues compared to those using beta-blockers.[14] In our study, we did not perform a subgroup analysis according to antiglaucomatous agents type, since most of the cases had multiple drug use and sample size is relatively small.

Cho et al.[13] investigated the cumulative dosage effect under long-term IOP lowering agents by using a scoring system called **b**urden of **a**nti-**g**laucoma regimen score (BAG score). They found that patients with a higher BAG score had more unstable tear films and more severe MG dropout.[13] In a study, it was observed that the meibomian gland loss rate increased as the medical treatment burden increased.[12] There was a significant negative correlation between the duration of antiglaucomatous treatment and TF-BUT. When glaucoma/OHT cases were grouped according to the number of antiglaucomatous drops used, it was reported that as the number of drugs increased, meiboscore increased, and meiboscore was associated with the duration of treatment in those using 3 drugs. [12] In our study, Oxford OSSS and lower meiboscore were associated with the mean number of antiglaucomatous drops. Contrary to expectations, the duration of antiglaucomatous treatment usage was not associated with any ocular surface parameters and meiboscore. The fact that not all of the antiglaucomatous drops used in the study did not contain BAK, the wide variety of agents used, and the relatively small sample size may have caused the duration of the antiglaucomatous treatment usage to not affect the ocular surface parameters. In the current study, when the subgroup analysis was performed according to the number of drugs used the Oxford OSSS was found to be significantly higher in those using 3 drugs compared to those using 1 or 2 drugs. Daily BAK exposure was associated with both ocular surface parameters (TF-BUT, Oxford OSSS and Schirmer test) and lower meiboscore. While the daily BAK dose and the number of drugs used were statistically correlated with the lower meiboscore, the upper meiboscore relationship was not significant. This situation may be explained by the lower eyelid being exposed to antiglaucomatous drops for a longer period than upper eyelid. The daily dose of BAK exposure was not calculated and its relationship with MGLA and meiboscore was not evaluated in any of the studies. In our study, we found that there was a significant relationship between daily BAK exposure and ocular surface parameters and meiboscore. In a study by Wong et al.[15] comparing the treated and untreated eyes of the cases, it was found that non-invasive tear break-up time, tear osmolarity, bulbar conjunctival hyperemia, lid margin score, tear meniscus height and Schirmer test values were worse in treated eyes; dry eye symptoms and OSSS were not different. Contrary to our study, while the lower and upper eyelid meiboscore values were higher in those treated eyes, the difference was not statistically significant in this study. [15] According to these data, the number of

drugs and daily BAK exposure adversely affect the ocular surface rather than the duration of glaucoma drug use.

In the current study, the use of the contralateral eyes of the same subjects as a control group enabled the exclusion of other individual parameters that may affect the ocular surface and meibomian glands. By eliminating the effect of individual differences, the effect of antiglaucomatous treatment was evaluated more accurately, and this is the strength of our study. In addition, in our study, the lower and upper MGLA and meiboscore were evaluated separately and it was seen that lower meibography parameters were more affected. Studies with a similar design are very limited in the literature. In this respect, our study is valuable and we believe that its contribution to the literature is important. The limitations of our study are relatively small sample size, heterogeneity of medical treatments and the lack of ocular surface parameters of the cases before glaucoma treatment initiation. Cases of POAG and OHT are mostly bilateral, and cases receiving long-term unilateral antiglaucomatous therapy are rare. The relatively small number of cases in our study may be related to this situation. Although the pathophysiological mechanism has not been fully elucidated, our study is consistent with some previous studies suggesting the adverse effects of chronic antiglaucomatous use on meibomian gland structure and function. Differences in results may be due to the methodological heterogeneity of the studies. On the other hand, various factors such as age, gender, ethnicity, disease duration, hormonal disorders, drugs and environmental exposure may potentiate or alter the susceptibility of meibomian glands to the effects of antiglaucomatous drugs.

CONCLUSION

We found that chronic antiglaucomatous drug use leads to pathological changes in meibomian glands as well as disruption of the ocular surface parameters. Increased number of topical antiglaucomatous drops and the drops containing BAK adversely affect the ocular surface and meibomian glands. Future long-term, large-sample, longitudinal and drug-grouped experimental and clinical studies will provide information to better reveal the effect of chronic antiglaucomatous therapy on the ocular surface, meibomian gland morphology and function. Recognizing the risk factors for OSD in glaucoma and restoring the ocular surface homeostasis will reduce the patients' complaints and increase compliance to treatment.

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