Evaluation of Tear Film Layer and Meibomian Gland Morphology in Glaucoma Patients

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ABSTRACT

Purpose: This study aims to investigate the changes in meibomian gland (MG) morphology and tear film layer in glaucoma patients.

Materials and Methods: The study included 88 eyes of 44 glaucoma patients and 166 eyes of 83 healthy subjects. Noncontact meibography and noninvasive tear break-up time (TBUT) tests were performed with the Sirius Scheimpflug camera.

Results: The total meiboscore, first and mean noninvasive TBUT, invasive TBUT, and OSDI scores were 3.57 ± 1.57, 9.24 ± 5.86, 10.76 ± 4.81, 7.62 ± 3.04, and 14.11 ± 10.48, respectively, for the glaucoma group and 2.43 ± 1.42, 11.17 ± 5.72, 12.30 ± 4.65, 9.56 ± 3.39, and 8.17 ± 7.17, respectively, for the control group.

Conclusion: Morphological changes in the MG, decreases in TBUT tests and increases in OSDI scores were observed in glaucoma patients. The changes in the MG occurring in glaucoma patients may be associated with long-term use of topical antiglaucoma medication.

Keywords: Meibography, Tear Break-up Time, Meibomian Gland, Glaucoma.

INTRODUCTION

Glaucoma is one of the most important causes of blindness in the world.[1,2] The necessity of treatment in glaucoma has been accepted by all authorities. Medical and surgical treatment methods are used as treatment options, but medical treatment is usually recommended as the first choice.[3,4]

In the treatment of glaucoma, several different antiglaucoma eye drops are widely used, such as b-blockers, a-adrenergic stimulants, carbonic anhydrase inhibitors, and prostaglandin analogs (PGA). Although the choice of treatment with these drugs has expanded, the risk of drug-induced side effects and complications has also increased. Glaucoma treatment is usually long-term, and drug-related chronic side effects are the major problems. Ocular surface disease (OSD) is associated with long-term use of topical antiglaucoma agents and is one of the most important condition affecting patients' quality of life. Patients with long-term antiglaucoma medication have symptoms of OSD, including dry eye symptoms, conjunctival hyperemia, and abnormal tear functions, ranging from 48% to 59%.[5,6] OSD not only decreases the quality of life but also may negatively affect glaucoma treatment compliance.[7,8] One of the predicted mechanisms for the occurrence of OSD is the direct toxic effect of active drugs, and the other is preservative toxicity.[9] Most of the commercially available antiglaucoma eye drops contain preservatives, which have a detergent effect on the tear lipid layer and increases evaporation of tear film. Benzalkonium chloride (BAC) is commonly used as a preservative. The side effects of BAC on the tear film and ocular surface have been shown in previous studies.[10-13]

On the other hand, OSD is usually seen with meibomian gland dysfunction (MGD). MGD is a chronic and common eyelid margin disease associated with tear film instability, inflammation, and OSD.[14] MGD is known as the most common cause of evaporative dry eye disease, which is

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Received: 11.09.2021
Accepted: 16.06.2021

Glo-Kat 2021; 16: 188-193

DOİ: 10.37844/glauc.cat.2021.16.32

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frequently observed in between 30% and 70% of the general population.[15]

Glaucoma is more common in elderly patients.[16] In addition, MGD and OSD are also increase with age. The antiglaucoma drugs used in elderly patients may cause further deterioration in MGD and OSD, making the condition even more serious.[17] Changes in meibomian gland (MG) functions and tear film layer in glaucoma patients have been demonstrated by biomicroscopic examination.[18-21] Mocan et al.[17] showed that long-term use of topical PGA is associated with an obstructive type of MGD. Arita et al.[22] also found that MG morphology and function were negatively affected by long-term use of antiglaucoma medication. There are limited studies showing the effects of antiglaucoma eye drops on the tear film layer and MG morphology.[22,23]

This study was designed to investigate the changes in the tear film layer and MG morphology in patients with glaucoma using long-term topical antiglaucoma medication. In addition, we aimed to investigate the effects of these changes on quality of life.

MATERIALS AND METHODS

This study was conducted to the provisions of the Declaration of Helsinki, and the local institutional ethics committee reviewed and approved the study. The study included 88 eyes of 44 patients with primary bilateral open-angle glaucoma using the same type of topical antiglaucoma medication at least 3 years and 166 eyes of 83 healthy subjects as the control group. The control group consisted of healthy individuals with no clinical symptoms. All patients used BAC containing antiglaucoma eye drops. All patients were requested to answer a symptom questionnaire [OSD index scores (OSDI)], which measures dry eye disease severity on a scale of 0 (no symptoms) to 100 (severe symptoms). Noncontact meibography and noninvasive tear break-up time (TBUT) tests were performed using the Sirius Scheimpflug camera (Costruzione Strumenti Oftalmici, Florence, Italy). Noninvasive TBUT was automatically detected with the Sirius Scheimpflug camera (Figure 1). The first and mean noninvasive TBUT were recorded. The noninvasive TBUT measurements were performed first based on the assumption that the use of fluorescein drops in patients may affect TBUT duration. Invasive TBUT was performed 1 min after a single drop of fluorescein was used in all patients. The invasive TBUT was performed using a slit lamp with a cobalt blue exciter filter. Finally, noninvasive meibography was performed in all patients. The lipids can be discharged from the MG orifices to the ocular surface by manipulating the lid during noninvasive meibography. This manipulation could have led to errors in TBUT measurement. Therefore, non-invasive meibography was performed after TBUT measurements. Meibography scoring (meibomian gland atrophy score or meiboscore) in the upper and lower lids of both eyes was performed for all patients. First, the MG of the upper eyelid was examined and graded. The grading was based on the criteria proposed by Arita et al.[24,25], wherein MG atrophy is graded as follows: 0 = no atrophy, 1 = less than one-third atrophy, 2 = more than one-third

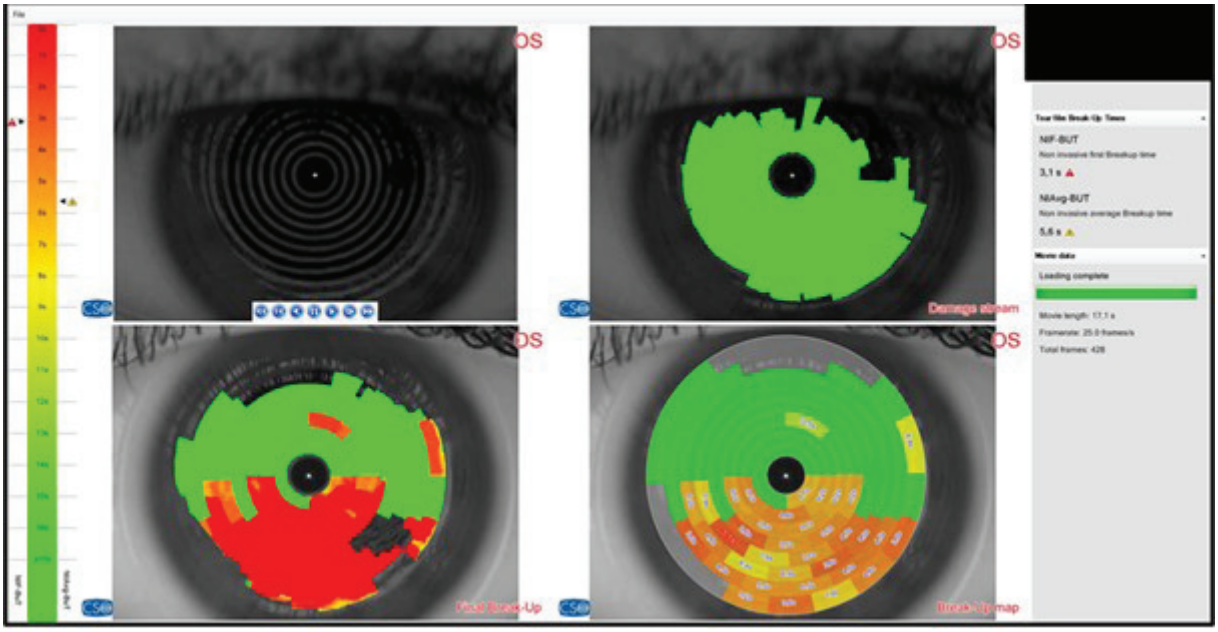

Figure 1: *Sirius Scheimpflug camera imaging in a representative patient; non-invasive first and mean tear film break-up time.*

atrophy, and 3 = more than two-third atrophy. All eyelids were examined and graded in the same way (Figure 2). The scores of the upper and lower eyelids were then added to obtain a total meiboscore (ranging from 0 to 6). Patients who were suffering from chronic blepharitis; using contact lens; undergoing eyelid surgery; or having rosacea, chronic ocular disease, eyelid abnormalities, and systemic disease with dry eyes were excluded from the study.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL, USA). Normal distribution was assessed using the Kolmogorov–Smirnov test. Independent samples *t*-test was used to test statistical significance, and a *p*-value of <0.05 was considered statistically significant.

RESULTS

The glaucoma group was composed of 35 (79.5%) women and 9 (20.5%) men, whereas the control group had 63 (75.9%) women and 20 (24.1%) men. The mean ages of the patients included in the study were 67.81 ± 10.71 and 66.14 ± 10.68 years in the glaucoma and control groups, respectively. No statistically significant difference was found regarding sex and age between the groups ($p = 0.64$ and 0.403, respectively).

The results for the glaucoma and control groups were, respectively, as follows: total meiboscores 3.57 ± 1.57 and 2.43 ± 1.42 ($p < 0.001$), first noninvasive TBUT durations 9.24 ± 5.86 and 11.17 ± 5.72 s ($p = 0.006$), mean noninvasive TBUT durations 10.76 ± 4.81 and 12.30 ± 4.65 s ($p = 0.008$), invasive TBUT durations 7.62 ± 3.04 and 9.56 ± 3.39 s ($p < 0.001$), and OSDI scores 14.11 ± 10.48 and 8.17 ± 7.17 ($p = 0.001$). A statistically significant difference was found for all scores between the two groups. The results obtained are summarized in Table 1.

A subgroup analysis was performed based on three categories. First, the patients were classified according to the number of drugs they used. It was observed that 17 patients (38.7%) used one drug, and 27 patients (61.3%)

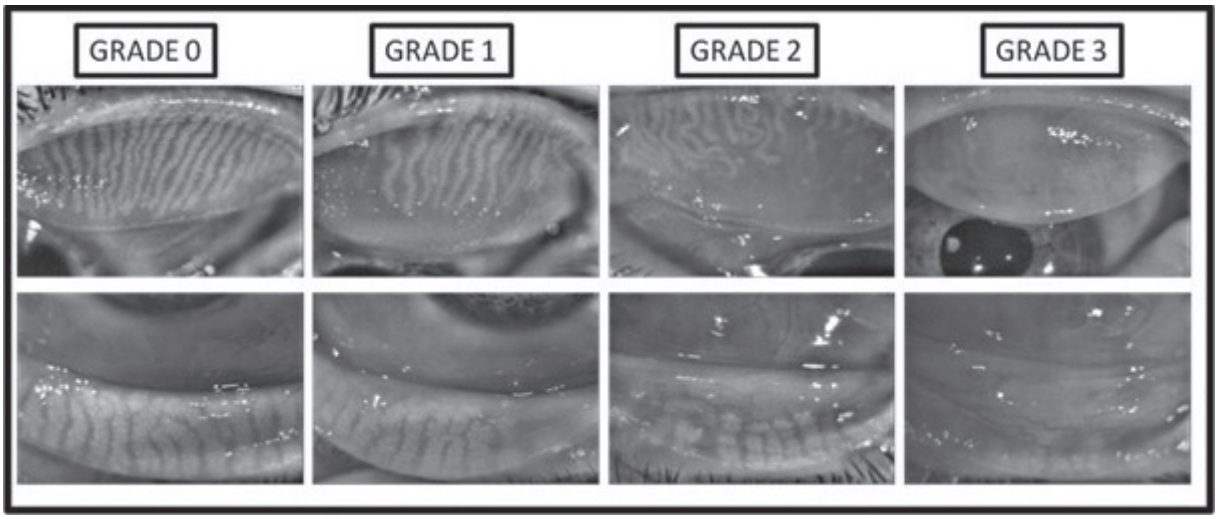

Figure 2. Non-contact meibography grading.

Table 1. *The results of the study and meibography subgroup analysis are summarized.*

	Glaucoma group	Control group	P
Non-invasive first TBUT	9.24 ± 5.86	11.17 ± 5.72	0.006
Non-invasive mean TBUT	10.76 ± 4.81	12.30 ± 4.65	0.008
Invasive TBUT	7.62 ± 3.04	9.56 ± 3.39	0.000
OSDI scores	14.11 ± 10.48	8.17 ± 7.17	0.001
Total meiboscore	3.57 ± 1.57	2.43 ± 1.42	0.000
Right upper eyelid meiboscore	1.77 ± 1.00	1.07 ± 0.89	0.000
Right lower eyelid meiboscore	1.72 ±0.84	1.33 ± 0.80	0.012
Left upper eyelid meiboscore	1.77 ± 0.93	1.08 ± 0.84	0.000
Left lower eyelid meiboscore	1.88 ± 0.89	1.48 ± 0.96	0.023

TBUT: Tear break-up time, **OSDI**: Ocular surface disease index. *P = Independent samples, t-test was used.

used two or more drugs [21 patients (47.7%) used two drugs, 3 (6.8%) patients used three, and 3 (6.8%) patients used four]. It was found that the patients used these drugs for an average of 8.65 ± 7.05 (between 3 and 30) years. The results of patients using one and more drugs were compared with the healthy group. In particular, the meiboscore of both groups was significantly different from that of the healthy group. The results obtained are summarized in Table 2. Second, the patients were classified according to whether they used PGA-containing drugs. There were 31 (70.5%) patients who used PGA-containing drugs and 13 (29.5%) patients used other groups of medication. There was a significant difference in the meiboscore of both groups using PGA-containing drugs and other groups of medication compared with that of the healthy group. However, there was a significant difference in all TBUT parameters (first noninvasive, mean noninvasive, and invasive TBUT) in patients using PGA-containing drugs but not in patients taking other groups of medication. The results of the subgroup analysis are summarized in Table 2. Third subgroup analysis was performed for each eyelid meiboscore in both the glaucoma and control groups. All eyelid meiboscores were significantly different between the two groups. The results obtained are summarized in Table 1.

DISCUSSION

In this study, we investigated the effects of the long-term use of topical antiglaucoma drugs on the MG, TBUT, and quality of life. The results showed that patients using topical antiglaucoma drugs for a long time had significantly worse outcomes in terms of meiboscore, TBUT, and quality of life than the control group. As seen in the subgroup analysis, all topical antiglaucoma drugs had negative effects on OSDI score, TBUT, and meiboscore parameters, but PGA-containing drugs affect the ocular surface more. These findings show that the function and morphology of MG have been changed by the long-term use of topical antiglaucoma drugs. This change in MG function may explain the tear film problems, which were reported in patients using antiglaucoma eye drops.[5,26,27] The mechanism of changes in MG caused by antiglaucoma eye drops is not known.[28,29] Several studies have shown that long-term treatment with multiple eye drops can lead to subclinical inflammation of the conjunctiva.[28]

Previous studies have shown that topical antiglaucoma medications increase the number of inflammatory cells and decrease the number of goblet cells of the conjunctiva.[30,31] Increased expression of inflammatory markers have been demonstrated even without clinical inflammation.[32,33] Chronic recurrent inflammation of ocular surface may stimulate accumulation of meibum and keratinization of the MG orifices.[34] Arita et al. showed MG duct distortion in patients with allergic conjunctivitis.[35] Chronic subclinical inflammation and allergic reaction resulting from prolonged use of antiglaucoma eye drops may lead to lid margin abnormalities, meibum accumulation, and ultimately changes in the MGs adjacent to the conjunctiva. Biomicroscopic changes in the MG in patients using antiglaucoma medication have been shown previously in the literature.[17,18] However, there are only a few studies showing these morphological changes by meibography. To the best of our knowledge, only Arita et al.[22,23] have shown the morphological changes on the meibography in the MG in patients using topical antiglaucoma medications. Our results also support the previous literature in prolonged uses of antiglaucoma eye drops.

The main limitation of our study was its retrospective design. In addition, a limited number of cases were found in accordance with the study criteria. Finally, meibography was used for the evaluation of MGD, TBUT for the tear film layer, and OSDI score for the daily effects. The Schirmer test was not evaluated in this study because of its high variability, low reproducibility, and poor correlation with clinical manifestations of the dry eye, which have been previously shown in numerous articles.[36,37]

The strength of our study is that the patients included were using long-term topical antiglaucoma medication. In our study, the mean duration of medication was 8.65 ± 7.05 years. To our knowledge, there are limited publications showing the effects of multiple antiglaucoma drugs use on tear parameters and MG morphology. In the literature, Arita et al.[23] showed the effects of PGA and b-blocker monotherapy on MG morphology. Mocan et al.[17] showed the effects of PGA monotherapy on MGD. Lee et al.[19] also showed the effects of PGA monotherapy on MGD in normotensive glaucoma patients. In our study, we found that both monotherapy and multiple drug use may affect tear parameters and MG morphology in the subgroup analysis (Table 2).

In our study, the loss of the MG was observed mostly in the lower eyelids of the healthy population and all the eyelids of the glaucoma group. This suggests that antiglaucoma medications may adversely affect all ocular surface and adjacent tissues.

The results of our study showed that OSDI scores, meiboscores were significantly increased,and TBUT values were significantly decreased in patients using topical antiglaucoma medications. These changes lead to serious

Table 2. *Subgroup analysis results.*

	Total meiboscore	Non-invasive first TBUT	Non-invasive mean TBUT	Invasive TBUT	OSDİ
Control group	**2.43±1.42**	**11.17±5.72**	**12.30±4.65**	**9.56±3.39**	**8.17±7.17**
Glaucoma group, using one drug	3.26±1.62	8.71±5.31	10.20±4.49	7.85±3.68	15.76±9.36
Glaucoma group, using multiple drugs	3.70±1.44	9.83±6.38	11.43±4.97	7.85±2.64	12.36±10.42
Respectively P	**0.003 / 0.000**	**0.022 / 0.225**	**0.017 / 0.331**	**0.009 / 0.006**	**0.000 / 0.014**
Prostaglandin containing drugs	3.50±1.68	8.21±5.50	10.03±4.46	7.25±3.14	14.67±10.15
Other group medication	3.79±1.25	11.99±6.03	12.73±5.24	8.62±2.55	12.60±11.20
Respectively P	**0.000 / 0.000**	**0.000 / 0.514**	**0.001 / 0.677**	**0.000 / 0.193**	**0.000 / 0.078**

TBUT: Tear break-up time, **OSDI**: Ocular surface disease index. *P = Independent samples, t-test was used.

limitations in patients' daily activities. We believe that the changes in MG and TBUT values may be associated with long-term use of topical antiglaucoma medication in these patients. In the future, prospective randomized and large series of studies will be useful to increase the experience.

Declaration of interest statement: No conflict of interest

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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