ORIGINAL RESEARCH ORİJİNAL ARAŞTIRMA

DOI: 10.5336/ophthal.2024-103210

Ocular Surface After Trabeculectomy: Association Between Bleb and Dry Eye Disease: Cross Sectional Study

Trabekülektomi Sonrası Oküler Yüzey: Bleb ve Kuru Göz Hastalığı Arasındaki İlişki: Kesitsel Çalışma

İbrahim UZAR[a], İhsan ÇAKIR[a], Gülay YALÇINKAYA ÇAKIR[a], Çiğdem ALTAN[a], Seren PEHLİVANOĞLU[a], Tekin YAŞAR[a]

[a]University of Health Sciences Beyoğlu Eye Training and Research Hospital, Department of Ophthalmology İstanbul, Türkiye

ABSTRACT Objective: To evaluate the frequency of dry eye disease (DED) and the relationship between the morphology of the filtering bleb and ocular surface instability in patients with functional filtering blebs. **Material and Methods:** Patients who had undergone trabeculectomy and had a functional filtering bleb and healthy individuals were included in the study and control groups, respectively. The bleb morphology, tear break-up time (TBUT), meibomian gland dysfunction, fluorescein corneal staining, Schirmer's test, and results of an ocular symptom questionnaire were evaluated. The coexistence of TBUT<10 seconds and superficial punctate keratitis was considered DED. **Results:** Thirty-seven eyes with functional filtering blebs and 40 healthy eyes were analyzed. TBUT was significantly lower (p=0.01) and the corneal staining score was significantly higher in the study group (p=0.01). Schirmer's test were similar in both groups (p=0.30). DED was more prevalent in the study group (p=0.02). The study group exhibited higher occurrences of dryness (p=0.007), feeling grittiness (p=0.005), watering and tearing (p=0.04), and itching (p=0.02). The height of bleb and microcystic structure scores were significantly higher in the DED group (p=0.03 and p<0.001, respectively). Microcystic structure in the bleb and height of bleb were positively correlated with the presence of DED (r=0.590, p=0.009 and r=0.355, p=0.03, respectively). **Conclusion:** DED is more common in eyes with functional filtering bleb following trabeculectomy and is associated with the height of the bleb and microcystic structure. The evaluation of the patients in terms of ocular surface and DED may be more important in eyes with these types of blebs.

Keywords: Bleb morphology; corneal staining; dry eye disease; ocular surface; trabeculectomy

ÖZET Amaç: Fonksiyonel filtran blebi olan hastalarda kuru göz hastalığı (KGH) sıklığını ve filtran bleb morfolojisi ile oküler yüzey instabilitesi arasındaki ilişkiyi değerlendirmek. **Gereç ve Yöntemler:** Trabekülektomi geçirmiş ve fonksiyonel filtran blebi olan hastalar ve sağlıklı bireyler sırasıyla çalışma grubuna ve kontrol gruplarına dâhil edildi. Bleb morfolojisi, gözyaşı kırılma zamanı (GKZ), meibomian bez disfonksiyonu, floresein kornea boyama, Schirmer testi ve oküler semptom anketinin sonuçları değerlendirildi. GKZ<10 sn ve yüzeyel punktat keratit birlikteliği KGH olarak kabul edildi. **Bulgular:** Fonksiyonel filtran blebi olan 37 göz ve 40 sağlıklı göz analiz edildi. GKZ çalışma grubunda anlamlı derecede düşüktü (p=0,01) ve korneal boyanma skoru anlamlı derecede yüksekti (p=0,01). Schirmer testi her iki grupta benzerdi (p=0,30). KGH çalışma grubunda daha yaygındı (p=0,02). Çalışma grubunda kuruluk (p=0,007), kumlu his (p=0,005), sulanma ve yaşarma (p=0,04) ve kaşıntı (p=0,02) daha sık görüldü. Bleb yüksekliği ve mikrokistik yapı skorları KGH grubunda anlamlı derecede yüksekti (sırasıyla p=0,03 ve p<0,001). Blebdeki mikrokistik yapı ve bleb yüksekliği KGH varlığı ile pozitif korelasyon gösterdi (sırasıyla r=0,590, p=0,009 ve r=0,355, p=0,03). **Sonuç:** KGH, trabekülektomi sonrası fonksiyonel filtran blebi olan gözlerde daha yaygındır ve bleb yüksekliği ve mikrokistik yapı ile ilişkilidir. Bu tip blebleri olan hastaların oküler yüzey problemleri ve KGH açısından değerlendirilmesi önemlidir.

Anahtar Kelimeler: Bleb morfolojisi; korneal boyanma; kuru göz hastalığı; oküler yüzey; trabekülektomi

Correspondence: İbrahim UZAR
University of Health Sciences Beyoğlu Eye Training and Research Hospital, Department of Ophthalmology İstanbul, Türkiye
E-mail: uzar7912@gmail.com

Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 04 Apr 2024 ***Received in revised form:*** 28 Jul 2024 ***Accepted:*** 15 Aug 2024 ***Available online:*** 23 Aug 2024

Dry eye disease (DED) is a prevalent disorder, and awareness has increased significantly around the world in the last three decades.[1] DED can be brought on by a variety of reasons, such as aging, hormonal alterations, environmental variables, topical/systemic medications, autoimmune diseases, surgery, and meibomian gland dysfunction (MGD).[2] The link between DED and surgical procedures has recently become a focal point of interest. In earlier research, it has been reported that some surgical interventions, such as corneal refractive procedures and phacoemulsification surgery, may lead to DED.[3,4] However, there are very few studies evaluating the relationship between DED and glaucoma surgery.[5-7]

Trabeculectomy is one of the standard surgical interventions for patients with glaucoma that cannot be controlled by medical therapy.[8] With this filtering surgery, it is planned to reduce the intraocular pressure (IOP) by forming a connection between the anterior chamber and the subconjunctival area.[8] Through this connection, it forms a bulge on the conjunctiva called a bleb.[9] Patients with functional filtering blebs often complain of bleb dysesthesia.[10]

The aim of this research was to assess the occurrence of DED and examine the connection between the morphology of the filtering bleb and instability of the ocular surface among individuals with functional filtering blebs subsequent to trabeculectomy.

MATERIAL AND METHODS

This cross-sectional and comparative study was performed between January 2023 and June 2023. All procedures were conducted in accordance with the principles outlined in the Declaration of Helsinki. It was approved by the Health Sciences University Hamidiye Scientific Research Ethics Committee (date: June 17, 2022, no: 16/7). All patients provided written informed consent.

Consecutive patients who were followed up in the glaucoma unit of Health Sciences University Beyoğlu Eye Training and Research Hospital, with the diagnosis of primary open angle glaucoma (POAG) and who had undergone trabeculectomy surgery with mitomycin C (MMC) (0.2 mg/mL for two minutes) and had a functional filtering bleb were included in the study. Patients who had undergone trabeculectomy surgery at least six months ago were included to abolish the effect of MMC on the ocular surface. As the control group, 40 eyes of 40 healthy participants (matched for age and gender) who came to the outpatient clinic for routine examinations were included. Participants who underwent any ocular surgery other than a trabeculectomy, had an IOP>21 mmHg, had any systemic disease that could affect the ocular surface, used contact lenses, were pregnant, and used any topical medication were excluded.

In postoperative treatment, topical antibiotics were used 5 times daily for two weeks, and prednisolone acetate was used 6 times daily for two weeks, followed by a gradual tapering over the course of six weeks. Additionally, cyclopentolate hydrochloride ophthalmic solution was started once a day for two weeks. Subjects using topical treatments other than this treatment were excluded from the study.

Patients with an IOP≤21 mmHg without any antiglaucomatous drug and a morphology of filtering bleb were considered to have functional filtering bleb.[11]

An eight-question questionnaire on ocular symptoms was given to each patient.[12] Symptoms included feelings of dryness, grittiness, burning, sticky feeling, watering and tearing, redness, crusting and discharge of eyelashes, and difficulty opening eyes in the morning.[5] Responses were categorized using a scale from “never” (0) to “always” (4).[5]

Bleb morphology was performed with respect to Wuerzburg bleb classification score criteria.[13] According to this classification, vascularization, corkscrew-like vessels, encapsulation, microcystic structure, and height of bleb were evaluated (Table 1).[13]

The meibomian glands’ condition was assessed by inspecting the lid margin with a biomicroscopy. The dysfunction of the meibomian glands was classified on a scale from 0 to 3: 0 indicating no dysfunction, 1 for glands that were occluded with a clear, serous discharge upon compression of the lid margin, 2 for glands that were blocked with a thick or waxy

TABLE 1: Morphology of bleb.	
Vascularization (It was determined by reference to the conjunctiva other than the bleb.)	3- avascular, 2- similar to adjacent conjunctiva, 1- increased, 0- massive
Corkscrew-like vessels	3- no, 2- in 1/3 of the bleb, 1- in 2/3 of the bleb, 0- throughout the bleb
Encapsulation	3- no, 2- in 1/3 of the bleb, 1- in 2/3 of the bleb, 0- throughout the bleb
Microcystic structure	3- whole bleb, 2- medial or lateral of the bleb, 1- above the scleral flap, 0- no

Height of bleb: Calculated in multiples of corneal thickness. Calculated as the distance from the scleral surface to the highest point of the bleb using a slit lamp microscope (How many times higher the bleb height compared to the corneal thickness).

white discharge, and 3 for glands with no discharge at all when the lid margin was pressed.[14] Fluorescein corneal staining was graded on a scale from 0 to 3, with 0 meaning no staining, 1 representing mild staining (a few punctate spots covering less than 10% of the corneal surface), 2 indicating moderate staining (10%-50% coverage), and 3 denoting severe staining (>50% coverage). Observing ≥1 dot of fluorescent staining on the corneal surface indicated the presence of superficial punctate keratitis.[15]

To calculate the tear break-up time (TBUT), 2% fluorescein drops were instilled into the lower bulbar conjunctiva. Patients were requested to blink repeatedly. The time taken for the 1st black line after blinking to seem was considered TBUT. The measurement was made in a slit lamp biomicroscope using a cobalt blue filter. TBUT<10 seconds was considered abnormal.[16,17]

For the Schirmer's test, one drop of 0.5% proparacaine (Alcaine, Alcon Laboratories, Inc, Belgium) was instilled into the eye. The tear at the lower fornix or eyelid margin was absorbed with a swab. A Schirmer's test strip (5 mm×35 mm Whatman no. 41 filter paper) was then positioned in the temporal inferior conjunctival sac for five minutes. Results were evaluated after five minutes. Less than 5 mm at 5 minutes was considered clinically abnormal.[18]

The coexistence of TBUT<10 seconds and superficial punctate keratitis was considered DED.[5]

STATISTICAL ANALYSIS

The statistical analysis utilized SPSS Statistics 20 (Armonk, NY, USA) for data processing. The Shapiro-Wilk test was utilized to assess normality. The mean and standard deviation were used to represent data with a normal distribution, whereas the median or interquartile range was used to describe data that were not normally distributed. For continuous data in group comparisons, an independent sample t-test or Mann-Whitney U test was used. A chi-square test was conducted to analyze categorical data. The relationship between bleb morphology and ocular findings was evaluated by Pearson and Spearman correlation analyses. The cutoff point for statistical significance was 0.05.

RESULTS

Thirty-seven eyes of 37 patients with functional filtering blebs and 40 eyes of 40 healthy individuals as a control group were evaluated. There were no significant differences detected between the groups in terms of age (p=0.48) or gender (p=0.53). All patients in the study group (n=37) had POAG. The diagnosis of all individuals in the control group was refractive error. Clinical and demographic features are demonstrated in Table 2. The mean time between trabeculectomy surgery and examination was 29.02±8.91 months.

The best corrected visual acuity (logMAR) of the study group was significantly higher (p<0.001). IOP was significantly lower in the study group (p=0.004). While TBUT was significantly lower in

TABLE 2: Demographic and clinical characteristics.			
	Study group (n=37)	Control group (n=40)	
	$\bar{X}$±SD	$\bar{X}$±SD	p value
Age (year)	57.86±13.53	55.53±10.67	0.48*
Gender (male/female)	8/29	16/24	0.53**
Primary diagnosis	POAG: 37	Refractive error: 40	

*Independent sample t test; **Chi-square test; POAG: Primary open angle glaucoma; SD: Standard deviation.

the study group, Schirmer's test values were similar in both groups (p=0.01 and p=0.30, respectively). The MGD score and corneal staining score were significantly higher in the study group (p=0.01 for both). DED was more prevalent in the study group (p=0.02) (Table 3).

Table 4 illustrates the symptoms of the patients in both groups. The study group exhibited higher occurrences of dryness (p=0.007), feeling grittiness (p=0.005), watering and tearing (p=0.04), and itching (p=0.02). Conversely, there was no significant difference in other symptoms between the two groups (p>0.05).

The bleb morphology scores in patients with and without DED are shown in Table 5. In the DED group, both the height of the bleb and the microcystic structure scores were significantly higher (p=0.03 and p<0.001, respectively).

The relation between bleb morphology and ocular surface findings in the study group is demonstrated in Table 6. The microcystic structure in the bleb was positively correlated with the corneal staining score (r=0.370, p=0.03). The height of the bleb showed a negative correlation with TBUT (r=-0.688, p<0.001) and a positive correlation with corneal staining score (r=0.375, p=0.02). Additionally, there

TABLE 1: Ocular surface findings in the study and the control groups.

	Study group (n=37) $\bar{X}$±SD	Control group (n=40) $\bar{X}$±SD	p value
BCVA (logMAR)	0.52±1.10	0.05±0.6	**<0.001***
IOP (mmHg)	11.38±4.12	18.47±3.98	**0.004***
TBUT (second)	5.78±1.75	7.65±2.76	**0.01***
Schirmer test (mm)	10.13±3.88	11.92±5.71	0.30*
Meibomian gland occlusion score	1.62±0.82	1.02±0.85	**0.01***
Corneal staining score	2.37±0.89	1.85±0.83	**0.01***
DED	24 (76%)	16 (40%)	**0.02****

*Independent sample t test; **Chi-square test; BCVA: Best corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; IOP: Intraocular pressure; TBUT: Tear break-up time; DED: Dry eye disease; SD: Standard deviation.

TABLE 4: Ocular surface symptoms in the study and the control groups.

	Study group (n=37)	Control group (n=40)	p*
Feeling of dryness	2 (1-3)	0 (0-2)	**0.007**
Feeling grittiness	2 (1-2)	1 (0-2)	**0.005**
Burning	1 (0-2)	1 (0-2)	0.14
Sticky	0 (0-1)	0 (0-0)	0.29
Watering and tearing	1 (0.5-2)	0 (0-2)	**0.04**
Redness	1 (0-2)	0 (0-2)	0.06
Crusting on eyelashes	0 (0-1)	0 (0-0)	0.14
Itching	2 (0-2)	0 (0-0.75)	**0.02**

*Mann-Whitney U test; Values are shown as median (interquartile range).

TABLE 5: Bleb morphology in the study group with and without DED.

	Eyes with DED (n=24) $\bar{X}$±SD	Eyes without DED (n=13) $\bar{X}$±SD	p*
Vascularization	2.07±0.6	2.22±0.66	0.51
Corkscrew-like vessels	2.75±0.44	2.88±0.33	0.39
Encapsulation	2.28±0.93	2.55±0.88	0.37
Microcystic structure	1.91±0.93	0.33±0.50	<0.001
Height of bleb	2.12±0.6	1.00±0.22	0.03

*Independent sample t test; DED: Dry eye disease; SD: Standard deviation.

TABLE 6: The correlation between bleb morphology and ocular surface parameters in the study group.

	Vascularization	Corkscrew-like vessels	Encapsulation	Microcystic structure	Height of bleb
TBUT (second)	r=0.074	r=0.086	r=-0.021	r=-0.260	r=-0.688
	p=0.66	p=0.61	p=0.90	p=0.12	**p<0.001**
Schirmer test (mm)	r=0.180	r=0.088	r=-0.174	r=-0.151	r=-0.237
	p=0.29	p=0.61	p=0.30	p=0.37	p=0.16
Corneal staining	r=-0.127	r=-0.147	r=-0.234	r=0.370	r=0.375
	p=0.45	p=0.39	p=0.16	**p=0.03**	**p=0.02**
Meibomian gland occlusion	r=-0.254	r=-0.243	r=0.289	r=0.139	r=0.289
	p=0.06	p=0.15	p=0.08	p=0.41	p=0.08
DED	r=0.109	r=0.145	r=0.150	r=0.590	r=0.355
	p=0.52	p=0.39	p=0.38	**p=0.009**	**p=0.03**

TBUT: Tear break-up time; DED: Dry eye disease.

was a positive correlation between the presence of DED and both the microcystic structure in the bleb (r=0.590, p=0.009) and the height of the bleb (r=0.355, p=0.03).

DISCUSSION

The influences of topical antiglaucomatous medications on the ocular surface in glaucoma patients have been investigated in different studies.[19,20] However, there are very few studies on the ocular surface in subjects with functional filtering blebs in the literature.[5-7] In this study, DED was found to be more common in eyes with functional filtering blebs and not using topical medication after trabeculectomy surgery. Dryness, feeling grittiness, watering and tearing, and itching were significantly higher in subjects with functional filtering blebs. The microcystic structure of the bleb and the height of the bleb were associated with the presence of DED.

According to some researchers, individuals with functional filtering blebs may suffer burning, a feeling of a foreign body, tearing, and discomfort.[10,21] In our study, we observed that the symptoms of dryness, feeling grittiness, itching, watering, and tearing were significantly higher in patients with functional filtering blebs, which was consistent with the literature.

Neves Mendes et al. reported that they found the Schirmer's test significantly higher in eyes with functional filtering bleb than the control group.[6] However, Schirmer's test scores were similar in two groups in our study. They performed the Schirmer's test without topical anesthesia in their study.[6] However, the Schirmer's test was done with topical anesthesia in our study. The Schirmer's test with anesthesia measures basal secretion level only.[22] The increase in reflex secretion in the postoperative period may be the reason for the significant difference in the study of Neves Mendes et al. Consistent with our study, Ji et al. reported that the Schirmer's test performed with topical anesthesia was similar in patients with functional bleb and in the control group.[5,6]

In this study, superficial punctate keratitis and a concurrent TBUT<10 seconds were considered DED. The Tear Film and Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) report's primary objective was to develop an evidence-based definition and a contemporary classification system for DED.[1] According to TFOS DEWS II, dry eye is characterized as a multifactorial disorder of the ocular surface accompanied by a loss of tear film equilibrium and symptoms.[1] Etiologically, instability and hyperosmolarity of the tear film, inflammation of the ocular surface, and neurosensorial disorders are contributing factors. The TFOS DEWS II report classifies DED into aqueous-deficient and evaporative subtypes.[1] According to the TFOS DEWS II report, the diagnosis of DED begins with the use of one of two questionnaires that inquire about symptoms [the Dry Eye Questionnaire-5 or the Ocular Surface Disease Index (OSDI)].[1] Many pathophysiological mechanisms of DED stimulate the sensory neurons of the cornea, and DED is sometimes defined as a "symptomatic disease".[23-25] However, one study showed that

there was a 40% discordance between symptoms and clinical signs.[26] Therefore, in this study, ocular symptoms were not used when diagnosing DED.

In our study, the microcystic structure score in the bleb was significantly elevated in patients with DED in the study group. In addition, the microcystic structure score in the bleb was positively correlated with the corneal staining score and the presence of DED. Shields et al. performed histopathological analysis of functional filtering blebs and observed that the blebs were of irregular thickness and contained many microcysts.[27] Moreover, an in vivo confocal microscopy study reported the presence of multiple epithelial microcysts in eyes with functional filter blebs.[28] In another histopathological study, it was stated that microcystic blebs contained significantly fewer goblet cells, unlike normal conjunctival epithelium.[29] Mucin, which is the innermost layer of the tear film, is synthesized by goblet cells and is necessary for the protection of the ocular surface.[30] We think that decreased goblet cells and mucin production in eyes with filtering blebs cause abnormalities in the tear film.

The height of the bleb was inversely correlated with TBUT, corneal staining score, and the presence of DED in our study. Large blebs have been linked by many researchers to impaired eyelid function, which may change the distribution of the tear film in the bleb area.[31] This leads to dryness of the cornea, epithelial defects, corneal dellen, and pain. Neves Mendes et al. reported that the height of the bleb was highly correlated with the fluorescein corneal staining score and TBUT, consistent with our study.[6] Budenz et al. described the clinical characteristics of filtrate bleb dysesthesia and thought that this was due to the uneven distribution of secretion of the meibomian gland on the tear film because the large functional filtering bleb impedes upper eyelid movement.[10] The results of our study support this hypothesis.

There are few studies evaluating MGD after trabeculectomy.[5] In our study, the MGD score was significantly higher in the study group. Meibomian glands, by secreting lipid, both reduce friction between the palpebral and bulbar conjunctiva and protect the ocular surface by preventing the evaporation of tears.[32] Thus, MGD may be linked to problems with tear film and the ocular surface after trabeculectomy. One of the limitations of our study is the lack of information on how long topical antiglaucomatous medications were used before surgery. Our hospital is a tertiary reference hospital. Most of the patients were followed up in different hospitals and referred to us for glaucoma surgery. It has been reported that mild-to-moderate MGD is frequently encountered in glaucoma patients using topical medications.[33] Therefore, the mechanism of MGD remains controversial. Is the surgery itself causing meibomian dysfunction, or was it present at the time of surgery due to previous glaucoma medications? This needs to be investigated in future investigations. Based on the findings of our study, we think that MGD might be a contributing factor to the development of DED in patients with functional filtering bleb.

The success rate has increased with the use of MMC in trabeculectomy surgery.[34] However, the use of MMC can cause abnormalities in tear film and complications on the ocular surface, including deformities in the conjunctival epithelium over the functional filtering bleb.[7] In the early period after surgery, MMC may affect the ocular surface. However, at 6-month follow-up, it was reported that MMC (0.2 mg/mL) did not contribute to the deterioration of the tear film and ocular surface.[35] Therefore, subjects who had undergone trabeculectomy with MMC at least six months ago were evaluated in our study.

The current study includes a few limitations. The first is a cross-sectional study, so data on the condition of the ocular surfaces before trabeculectomy surgery could not be obtained. The variation of the parameters during the follow-up period was also not examined. Second, age, gender, work environment, and hormonal changes can also affect the ocular surface. Although there was no gender or age difference between the groups, it was impossible to evaluate other factors in this study. Third, in this study, dry eye symptoms were assessed with reference to the Shihpai Eye Study.[12] It may be suggested that the OSDI questionnaire is more appropriate for the population included in the current study. The OSDI is regarded as a more recent and universally applicable

questionnaire for assessing dry eye symptoms. However, OSDI consists of 12 questions, with 6 specifically related to visual function. We considered that the OSDI questionnaire might not be appropriate, as the majority of glaucoma patients are elderly and have low visual acuity.

CONCLUSION

In conclusion, besides the evaluation of the bleb morphology after trabeculectomy surgery in glaucoma patients, the evaluation of the patients in terms of ocular surface and DED may be important for starting the necessary treatments without delay to ensure the stability of the ocular surface and increasing the standard of living of the patient.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Çiğdem Altan, Tekin Yaşar;* ***Design:*** *İhsan Çakır, Seren Pehlivanoğlu;* ***Control/Supervision:*** *İhsan Çakır, Gülay Yalçınkaya;* ***Data Collection and/or Processing:*** *İbrahim Uzar, Gülay Yalçınkaya;* ***Analysis and/or Interpretation:*** *İhsan Çakır, İbrahim Uzar;* ***Literature Review:*** *Gülay Yalçınkaya, Seren Pehlivanoğlu;* ***Writing the Article:*** *İbrahim Uzar, İhsan Çakır;* ***Critical Review:*** *Çiğdem Altan, Tekin Yaşar;* ***References and Fundings:*** *Gülay Yalçınkaya, Seren Pehlivanoğlu;* ***Materials:*** *İbrahim Uzar.*

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276-83. PMID: 28736335.
2. Rouen PA, White ML. Dry eye disease: prevalence, assessment, and management. Home Healthc Now. 2018;36(2):74-83. PMID: 29498987.
3. Miura M, Inomata T, Nakamura M, Sung J, Nagino K, Midorikawa-Inomata A, et al. Prevalence and characteristics of dry eye disease after cataract surgery: a systematic review and meta-analysis. Ophthalmol Ther. 2022;11(4):1309-32. PMID: 35534685; PMCID: PMC9253209.
4. Dohlman TH, Lai EC, Ciralsky JB. Dry eye disease after refractive surgery. Int Ophthalmol Clin. 2016;56(2):101-10. PMID: 26938341.
5. Ji H, Zhu Y, Zhang Y, Li Z, Ge J, Zhuo Y. Dry eye disease in patients with functioning filtering blebs after trabeculectomy. PLoS One. 2016;11(3):e0152696. PMID: 27032098; PMCID: PMC4816306.
6. Neves Mendes CR, Hida RY, Kasahara N. Ocular surface changes in eyes with glaucoma filtering blebs. Curr Eye Res. 2012;37(4):309-11. Erratum in: Curr Eye Res. 2012;37(8):759. PMID: 22440162.
7. Ono T, Yuki K, Ozeki N, Shiba D, Tsubota K. Ocular surface complications after trabeculectomy: incidence, risk factors, time course and prognosis. Ophthalmologica. 2013;230(2):93-9. PMID: 23774034.
8. Koike KJ, Chang PT. Trabeculectomy: a brief history and review of current trends. Int Ophthalmol Clin. 2018;58(3):117-33. PMID: 29870414.
9. Güven Yılmaz S, Değirmenci C, Palamar M, Yağcı A. Evaluation of filtering bleb function after trabeculectomy with mitomycin C using biomicroscopy, anterior segment optical coherence tomography and in vivo confocal microscopy. Turk J Ophthalmol. 2015;45(4):132-7. PMID: 27800219; PMCID: PMC5082269.
10. Budenz DL, Hoffman K, Zacchei A. Glaucoma filtering bleb dysesthesia. Am J Ophthalmol. 2001;131(5):626-30. PMID: 11336938.
11. Shigeeda T, Tomidokoro A, Chen YN, Shirato S, Araie M. Long-term follow-up of initial trabeculectomy with mitomycin C for primary open-angle glaucoma in Japanese patients. J Glaucoma. 2006;15(3):195-9. PMID: 16778640.
12. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. Ophthalmology. 2003;110(6):1096-101. PMID: 12799232.
13. Klink T, Schrey S, Elsesser U, Klink J, Schlunck G, Grehn F. Interobserver variability of the Würzburg bleb classification score. Ophthalmologica. 2008;222(6):408-13. PMID: 18849624.
14. Jie Y, Xu L, Wu YY, Jonas JB. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. Eye (Lond). 2009;23(3):688-93. PMID: 18309341.
15. Rossi GC, Pasinetti GM, Scudeller L, Raimondi M, Lanteri S, Bianchi PE. Risk factors to develop ocular surface disease in treated glaucoma or ocular hypertension patients. Eur J Ophthalmol. 2013;23(3):296-302. PMID: 23335308.
16. Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II Diagnostic Methodology report. Ocul Surf. 2017;15(3):539-74. PMID: 28736342.
17. Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. Effect of fluorescein instillation on the pre-corneal tear film stability. Curr Eye Res. 1985;4(1):9-12. PMID: 3979093.
18. Su TY, Ho WT, Lu CY, Chang SW, Chiang HK. Correlations among ocular surface temperature difference value, the tear meniscus height, Schirmer's test and fluorescein tear film break up time. Br J Ophthalmol. 2015;99(4):482-7. PMID: 25297654.
19. Inoue K, Okugawa K, Kato S, Inoue Y, Tomita G, Oshika T, et al. Ocular factors relevant to anti-glaucomatous eyedrop-related keratoepitheliopathy. J Glaucoma. 2003;12(6):480-5. PMID: 14646683.

20. Küsbeci T, Öztürk F, Yavaş G, Aktepe F, Ermiş SS, İnan ÜÜ. Topikal travoprost % 0,004 ve bimatoprost % 0,03 kullanımının oküler yüzey üzerine etkisi [The effect of travoprost 0,004% and bimatoprost 0,03% on ocular surface]. Turk J Ophthalmol. 2007;37(5):359-66. https://d2v96fxpocvxx.cloudfront.net/new/bda9171a-fae8-4995-8276-2138323f1e16/articles/2834/TJO-37-359-En.pdf
21. Hoskins HD, Kass M. Introduction and classification of the glaucomas. In: Klein EA, ed. Becker-Shaffers Diagnosis and Therapy of the Glaucomas. 6th ed. Baltimore: The CV Mosby Company; 1989. p.1-9.
22. Cho P, Yap M. Schirmer test. I. A review. Optom Vis Sci. 1993;70(2):152-6. PMID: 8446379.
23. Belmonte C, Acosta MC, Gallar J. Neural basis of sensation in intact and injured corneas. Exp Eye Res. 2004;78(3):513-25. PMID: 15106930.
24. Begley CG, Chalmers RL, Abetz L, Venkataraman K, Mertzanis P, Caffery BA, et al. The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity. Invest Ophthalmol Vis Sci. 2003;44(11):4753-61. PMID: 14578396.
25. Rosenthal P, Borsook D. The corneal pain system. Part I: the missing piece of the dry eye puzzle. Ocul Surf. 2012;10(1):2-14. PMID: 22330055.
26. Lemp MA, Baudouin C, Amrane M, Ismail D, Garrigue JS, Buggage RR. Poor correlation between dry eye disease signs and symptoms in a phase III randomized clinical trial. Invest Ophthalmol Vis Sci. 2011;52(14):3821. https://iovs.arvojournals.org/article.aspx?articleid=2355968
27. Shields MB, Scroggs MW, Sloop CM, Simmons RB. Clinical and histopathologic observations concerning hypotony after trabeculectomy with adjunctive mitomycin C. Am J Ophthalmol. 1993;116(6):673-83. PMID: 8250068.
28. Morita K, Gao Y, Saito Y, Higashide T, Kobayashi A, Ohkubo S, et al. In vivo confocal microscopy and ultrasound biomicroscopy study of filtering blebs after trabeculectomy: limbus-based versus fornix-based conjunctival flaps. J Glaucoma. 2012;21(6):383-91. PMID: 21423030.
29. Francis BA, Du LT, Najafi K, Murthy R, Kurumety U, Rao N, et al. Histopathologic features of conjunctival filtering blebs. Arch Ophthalmol. 2005;123(2):166-70. PMID: 15710811.
30. Kessing SV. Mucous gland system of the conjunctiva. A quantitative normal anatomical study. Acta Ophthalmol (Copenh). 1968:Suppl 95:1+. PMID: 4170134.
31. Palmberg P. Surgery for complications. In: Albert DM, ed. Ophthalmic Surgery: Principles and Techniques. Vol 1. London: Blackwell Science; 1999. p.476-91.
32. Binotti WW, Bayraktutar B, Ozmen MC, Cox SM, Hamrah P. A review of imaging biomarkers of the ocular surface. Eye Contact Lens. 2020;46 Suppl 2(Suppl 2):S84-S105. PMID: 31833999; PMCID: PMC7354708.
33. Uzunosmanoglu E, Mocan MC, Kocabeyoglu S, Karakaya J, Irkec M. Meibomian gland dysfunction in patients receiving long-term glaucoma medications. Cornea. 2016;35(8):1112-6. PMID: 27055218.
34. Kitazawa Y, Kawase K, Matsushita H, Minobe M. Trabeculectomy with mitomycin. A comparative study with fluorouracil. Arch Ophthalmol. 1991;109(12):1693-8. PMID: 1841578.
35. Mohammadi SF, Ashrafi E, Norouzi N, Abdolahinia T, Mir-AbouTalebi M, Jabbarvand M. Effects of mitomycin-C on tear film, corneal biomechanics, and surface irregularity in mild to moderate myopic surface ablation: preliminary results. J Cataract Refract Surg. 2014;40(6):937-42. PMID: 24726159.