CEOTI
Clinical and Experimental Ocular Trauma and Infection

Original Article

Clin Exp Ocul Trauma Infect. 2023;5(1),16-25

Does Epiphora Cause Meibomian Gland Loss and Dry Eye?

Dr Kübra Tinç[1], MD; Prof Dr Sertaç Argun Kıvanç, MD[2],3; Prof Dr Berna Akova,MD[2]

[1]MD, Health Sciences University, Erzurum Region Training and Research Hospital, Erzurum, Türkiye
[2]Prof, MD, Bursa Uludag University, School of Medicine, Department of Ophthalmology, Bursa, Türkiye
[3]PhDc, Bursa Uludag University, Health Sciences Institute, Translational Medicine, Bursa, Türkiye

Abstract

Purpose: To investigate the effects of epiphora due to primary acquired nasolacrimal duct obstruction (PANDO) and external dacryocystorhinostomy (DCR) for its treatment on meibomian glands and tear film parameters.
Methods: External DCR for unilateral PANDO in the Department of Ophthalmology, Faculty of Medicine, Bursa Uludag University between January 2018-June 2019 were reviewed. The tear film parameters and meibography measurement recorded at the preoperative and follow-up examinations were examined on both the obstructed side and the patent side. SPSS 23 was used for statistical analyzed.
Results: There was a significant difference between Schirmer-1 score before external DCR (13,1±5,0; 6,3±5,0; p=0,01) and this difference disappeared after surgery (12,0±7,3; 7,7±5,0; p=0,06). Postoperative increase in non-invasive average break-up time (niAVG-BUT) on operated side was statistically significant (10,5±4,6; 12,0±5,3; p=0,033). When the healthy and operated sides were compared with each other, no significant difference was observed in niAVG-BUT before and after surgery (p=0,907, p=0,614). Mean meibomian gland losses were decreased in both operated and patent sides postoperatively and these values were statistically significant (33,0±8,2; 27,1±6,8; p<0,001, 37,3±10,4; 31,4±9,6; p=0,01).
Conclusion: Patients with unilateral nasolacrimal duct obstruction (NLDO) had loss of meibomian gland in both NLDO side and patent side. This loss was found to be significantly reduced on both obstructed and patent sides after successful surgical removal of the epiphora.

Keywords: Epiphora, dacryocystorhinostomy, meibomian gland, meibography, ophthalmology, eye, dry eye

Introduction

The lacrimal system is responsible for tear production and drainage. Epiphora is the state of excessive tears in the eye as a result of the disruption of the balance between the production of tears on the ocular surface and the removal of tears (1). While the presence of foreign body in the eye, increased reflex tear secretion due to dry eye and various causes such as lid malposition may cause epiphora, nasolacrimal duct obstruction (NLDO) is the most common cause of epiphora (2). Tear production and drainage must be within the physiological

Corresponding Author: Dr Sertaç Argun Kıvanç,MD Bursa Uludag University, School of Medicine, Department of Ophthalmology

boundaries. Hyperosmolarity or hypoosmolarity of the eye disrupts the homeostasis of the ocular surface (3). Studies done in different cell cultures have shown that both hyperosmolarity and hypoosmolarity trigger the release of proinflammatory mediators due to volume change in the cell (4-6). Previous studies have shown that epiphora affects ocular surface homeostasis by changing osmolarity. Saleh et al. showed that tear osmolarity decreased in patients with epiphora compared to the healthy group (7). Yuksel et al. found that the tear osmolarity before dacryocystorhinostomy was lower than that of the control group (8). Similar to the osmolarity changes, changes in tear parameters before and after dacryocystorhinostomy (DCR) were investigated in previous studies (9,10). It was found that there was a significant increase in the tear lipid layer after the silicone intubation process or DCR (9,10). Previous studies also showed that epiphora secondary to PANDO had also impacts over the tear, the conjunctival flora, ocular surface epithelium (11-13). The current literature show changes in tear parameters of patients undergoing DCR due to PANDO; however, the effect of PANDO on meibomian glands, to best of our knowledge, has not been investigated before. In the present study, we evaluated the effect of epiphora on meibomian glands in patients who underwent primary DCR due to PANDO.

Materials and Methods

In this study, the records of 35 patients who underwent external DCR operation due to unilateral PANDO between January 2018 and June 2019 at the Department of Ophthalmology of the School of Medicine at Bursa Uludag University were reviewed and of those 17 were included to the study. Data of the patients regarding age, sex, complete ophthalmologic examination (refraction, visual acuity, biomicroscopic examination, tear parameters, fundus examination), meibography images performed to evaluate meibomian glands and previous surgical history were all recorded and evaluated retrospectively. A senior surgeon (SAK) performed external DCR operation of all patients with PANDO under sedoanalgesia and regional anesthesia. This study was conducted according to the criteria set by the declaration of Helsinki and was approved by Bursa Uludag University Institutional Review Board.

Patient Selection, Inclusion and Exclusion Criteria:

Adult patients with unilateral PANDO, required differential diagnostic tests done preoperatively and postoperatively and followed up regularly in the postoperative period were included in the study. Patients with history of operation for NLDO, with bilateral PANDO, with secondary NLDO, those taking topical medications before the surgery, with systemic disease that may affect ocular surface (rheumatologic diseases, connective tissue diseases, etc.), eyelid disorders (ectropion, entropion, everted punctum, etc.), contact lens wearers, patients under 18 years of age, patients who had no diagnostic tests, and patients who lost follow-up at 1st month visit.

Preoperative and Postoperative Evaluation

In all the files scanned, the most common complaint of the patients was “watery eye” in one side. All patients underwent a complete ophthalmologic examination for differential diagnosis of epiphora. Schirmer-1 test, tear break-up time (Sirius Topo Tomographer (Italy, CSO)) and lacrimal irrigation test were performed in all cases after meibography. Preoperative and postoperative tear parameters and meibography measurements were evaluated. Schirmer-1 test with anesthesia and tear break-up time measurements were used. All measurements were performed for both the operated and non-operated eyes. Data obtained from preoperative and postoperative measurements were recorded.

Meibography:

Non-contact infrared meibography system was used for scanning the meibomian

glands. Scanning was performed at the same time intervals for all patients by the same observer with the meibography module of Sirius' plasido disk-based Topo Tomographer (Italy, CSO). Scanning was repeated for the lower and upper lids on the operated and healthy eyes in all controls. 4-5 images were obtained for all lids and the images considered to be the clearest were used for evaluation. The tars area to be evaluated was marked with four points and the boundaries of the healthy observed meibomian gland were identified by the observers and the meibomian gland loss (MGL) was determined automatically in both degree and ratio by the device. It was evaluated that if the meibomian gland loss rate was <10%, grade was 0; if the loss rate was between 10% and 25%, grade was 1: if the loss rate was between 26% and 50% grade was 2; if the loss rate between 51% and 75%, grade was 3 and if the loss rate over 75%, grade was 4. In the meibography evaluations, the meibomian gland loss rates on the operated and healthy eyes, lower and upper lids were calculated by measurements made independently by two different observers from the same areas determined by 4 points without being aware of each other's measurements. The measurement results of the two observers were compared with each other. It was found that there was a high correlation between the measurements of the two observers for all repeated measurement results for the lower and upper lids in the preoperative and postoperative periods. No statistically significant difference was observed. For this reason, statistical analyzes were performed using the (KT) data of one of the observers.

Statistical Analysis:

The suitability of the data for normal distribution was investigated by the Kolomogorov Simirnov test. Nonparametric tests were applied to the data which were found to be unsuitable for normal distribution. Meibomian gland loss (MGL), Schirmer-1 score, and TBUT before and after DCR were compared using the Wilcoxon signed rank test. Mann-Whitney test was used to compare the eye with epiphora and the healthy eye and also the upper eyelid with the lower eyelid. The correlation between epiphora duration and MGL was examined by a correlation analysis and Pearson correlation coefficient was calculated. Descriptive statistical methods were used to analyze age, gender and side distributions. P <0.05 was considered statistically significant. Data were evaluated using the SPSS package program (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.).

Results

The records of 35 patients who underwent external DCR operation due to unilateral PANDO between January 2018 and June 2019 at the Department of Ophthalmology of the School of Medicine at Bursa Uludag University were retrospectively reviewed and 17 patients were included in the study. The mean age of the patients of whom 12 were female and 5 males was 46.0 ± 17.2. Demographic data of the patients were given in Table 1. Preoperative and postoperative comparisons of dry eye diagnostic tests of the patients with PANDO and healthy sides were

Table 1: Demographic Characteristics Of The Patients Included In The Study

Sex (f/m)	12/5
Age (AVG+SD)	46,0±17,2
Side (right/left)	8/9
Silicon tube entubation (+/-)	13/4
Epiphora time (year)	2,8±2,6

AVG: Average, **SD:** Standart deviation, **f**: Female, **m:** Male

Table 2: Dry Eye Diagnosis Tests Before and After Surgery

		PANDO Side	Intact Side	P value*
Schirmer-1 (AVG±SD)	-Before DCR	13,0±5,0	6,3±5,0	**0,001**
	-After DCR 1. month	12,0±7,3	7,7±5,0	0,060
	P value	0,435	0,382	
NIF-BUT (AVG±SD)	-Before DCR	9,9±5,3	9,3±5,5	0,776
	-After DCR 1. month	11,6±5,5	10,8±6,0	0,665
	P value	0,075	0,060	
NAVG-BUT (AVG±SD)	-Before DCR	10,5±4,6	10,3±5,0	0,907
	-After DCR 1. month	12,0±5,3	11,0±6,0	0,614
	P value**	**0,033**	0,082	

PANDO: Primer Acquired Nasolacrimal Duct, **DCR:** Dacryocystorhinostomy, **NIF-BUT:** Non-invasive first break up time, **NAVG-BUT:** Non-invasive average break up time, **AVG:** Average, **SD:** Standart Deviation, * Mann-Whitney test, ** Wilcoxon sign ranks test

given in Table 2. Infrared images before and after DCR of the meibomian gland status of a patient with epiphora were given in Figure 1. It was found that the Schirmer-1 test in the preoperative period was statistically significantly higher in the PANDO side compared to the healthy side (p = 0.001). This significance disappeared after surgery and no significant difference was found between the PANDO and the healthy sides in terms of the Schirmer-1 test scores in the postoperative period. The mean TBUT value was significantly higher in the PANDO side in the postoperative period compared to the preoperative period (p =0.033). There was no statistically significant difference between preoperative and postoperative results in the PANDO and healthy group with regard to nif-BUT values. Preoperative and postoperative niAVG-BUT values were similar on the PANDO and healthy sides. Preoperative and postoperative changes in the mean meibomian gland losses of the upper eyelid (UE), lower eyelid (LE) and both lids were given in Table 3. It was found that the MGL was significantly higher than the first month after the external DCR on both the PANDO and healthy sides. It was found that while the

Table 3: Meibomian Gland Loss On PANDO and Intact Side

		PANDO Side	**Intact Side**	**P value***
UE-MGL (AVG±SD)	-Before DCR	28,5±10,1	29,3±12,5	0,848
	-After DCR first month	24,9±8,4	27,9±13,5	0,364
	P value	**<0,001**	**0,02**	
LE-MGL (AVG±SD)	-Before DCR	36,7±12,6	36,5±14,7	0,952
	-After DCR first month	29,5±9,7	30,3±14,2	0,154
	P value	**<0,001**	**0,01**	
Toplam kayıp (AVG±SD)	-Before DCR	33,0±8,2	37,3±10,4	0,191
	-After DCR first month	27,1±6,8	31,4±9,6	0,151
	P value**	**<0,001**	**0,01**	

PANDO: Primary acquired nasolacrimal duct obstruction, **UE:** Upper eyelid, **LE:** Lower eyelid, **DCR:** Dacryocystorhinostomy, **MGL:** Meibomian gland loss, **AVG:** Average, **SD:** Standart Deviation, *Mann-Whitney test, ** Wilcoxon signed rank test

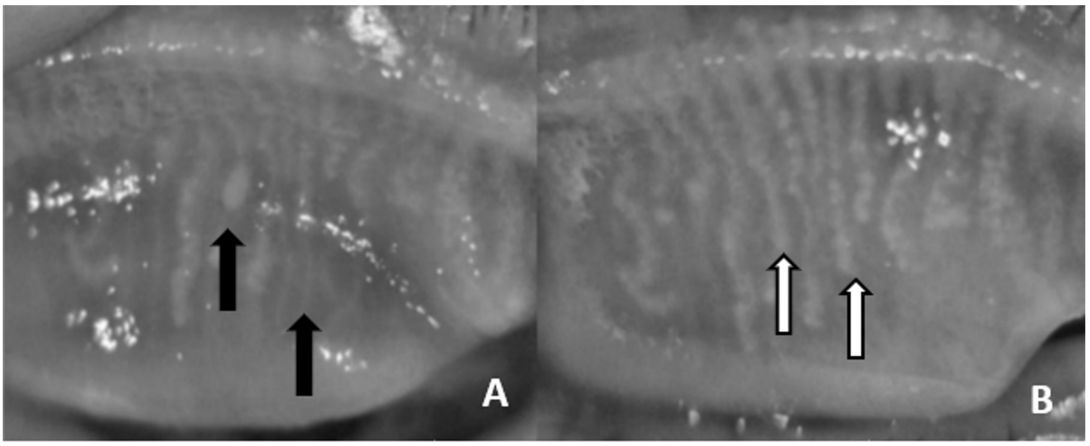

Figure 1: A) Infrared images before DCR of the meibomian gland status of a patient with epiphora, B) Status of the meibomian gland one month after DCR

total mean MGL of LE and UE was 33.0 ± 8.2 in the preoperative period, it was 27.1 ± 6.8 in the postoperative period (p <0.001). On the healthy side, these rates were 37.3 ± 10.4 and 31.4 ± 9.6, respectively (p = 0.01). There was no statistically significant difference between the MGLs in the comparison of both sides in preoperative and postoperative periods (Table 3). Table 4 shows the MGL comparison of UE with LE on the side with nasolacrimal duct obstruction and on the healthy side. It was found that LE was significantly higher than UE in terms of MGL on the PANDO side in the preoperative period (36.7 ± 12.6; 28.5 ± 10.1; p = 0.045, respectively). In the postoperative 1st month, both the PANDO and the healthy sides showed a decrease in the MGL rates in UE and LE, and this decrease was statistically significant (Table 4). In Table 5, MGL scores of patients with PANDO and healthy sides before and after DCR were given. Given the MGL levels in the UE were evaluated on the PANDO side in the preoperative period, it was found that while 29% of the patients had grade 0-1, it was 65% in the postoperative period. Given the MGL levels in the UE were evaluated on the healthy side in the preoperative period, it was found that while 30% of the patients were grade 0-1 in the preoperative period, it was 53% in the postoperative period. While the rate of patients with MGL grade 2 or 3 on the lower eyelid PANDO was 88% in the preoperative period, it was 53% after DCR. The rate of patients with grade 2 or 3 loss on the non-operated side was 82% before DCR and 59% in the postoperative period. No grade 4 loss was found in any of the patients. Infrared image of meibomian glands of a patient's eye with epiphora in the UE before and after DCR was given in Figure 1. The correlation between UE and LE in terms of the duration of epiphora and Schirmer-1 score was not statistically significant. Gender differences and cases with silicone tube intubation were not compared in terms of variables since the number of patients between the groups were not similar.

DISCUSSION

Epiphora causes blurred vision, a crying expression as a result of continuous tearing, and maceration of periocular skin and affects the visual quality and social life of a person (14). In addition to these effects, it has been shown in many studies that epiphora causes changes on the ocular surface (7,8,12,13). Yuksel et al. showed that in patients with unilateral PANDO-related epiphora, squamous metaplasia degrees were significantly higher in conjunctival epithelial cells on the epiphora side compared to the healthy side, and goblet cell density increased due to chronic inflammation and irritation12. Eshraghi et al. found growth in conjunctival bacterial samples as 100% in those with NLDO, compared to 41% in the control group with similar age and sex

Table 4: Meibomian Gland Loss On The Upper and Lower Eyelid

			UE-MGL	LE-MGL	P value*
PANDO (AVG±SD)	**Side**	-Before DCR	28,5±10,1	36,7±12,6	**0,045**
		-After DCR first month	24,9±8,4	29,5±9,7	0,154
		P value	**<0,001**	**<0,001**	
Intact (AVG±SD)	**Side**	-Before DCR	29,3±12,5	36,5±14,7	0,154
		-After DCR first month	27,9±13,5	30,3±14,2	0,640
		P value**	**0,02**	**0,01**	

PANDO: Primary acquired nasolacrimal duct obstruction, **UE:** Upper eyelid, **LE:** Lower eyelid, **DCR:** Dacryocystorhinostomy, **MGL:** Meibomian gland loss, **AVG:** Average, **SD:** Standart Deviation, *Mann-Whitney test, ** Wilcoxon signed rank test

characteristics; after DCR they found normalization time of ocular flora as 7 weeks (13). Saleh et al. found tear osmolarity in eyes with epiphora to be lower than in the control group (7). Yüksel et al. showed that this decrease in osmolarity disappeared after DCR surgery (8). To best of our knowledge, the effect of PANDO and DCR operation on MG, has not been investigated before. Even though the effect of epiphora on DCR and MG has not been shown directly, studies with interferometer and tear parameters show that mean lipid layer thickness increases after opening of the tear ducts (9-10). Kubo et al. found that tear lipid layer thickness after DCR was higher than pre-DCR measurements (9). Lee et al. found that lipid layer thickness was 72 ± 23 nm before silicone tube intubation in patients with incomplete NLDO; and they reported that this value was 92 ± 16 nm after silicone tube intubation and the difference was statistically significant(10). However, in that study, the time period when the measurement was performed after surgery was not specified (10).

Studies in the late 1980s and early 1990s showed that tear secretion decreased with compensatory mechanisms in patients with chronic dacryocystitis and epiphora; however, it was found in these studies that

Table 5: Distribution of Meibomian Gland Loss in Lower and Upper Eyelid Before and After Surgery

		MGLD	Before DCR (%)	After DCR (%)			MGLD	Before DCR (%)	After DCR (%)
PANDO Side	UE	0 or 1	29	65	**Intact Side**	UE	0 or 1	30	53
		2 or 3	71	35			2 or 3	70	47
	Total		100	100		Total		100	100
	LE	0 or 1	12	47		LE	0 or 1	18	41
		2 or 3	88	53			2 or 3	82	59
	Total		100	100		Total		100	100

MGLD: Meibomian gland loss distribution, **DCR:** Dacryocystorhinostomy, **PANDO:** Primary acquired nasolacrimal duct obstruction, **UE:** Upper eyelid, **LE:** Lower eyelid

TBUT was similar before and after the surgery (15). There is a limited number of studies examining the relationship between nasolacrimal duct obstruction and MG (16). Eom et al. measured meibography and lipid layer thickness in patients with epiphora due to obstruction of lacrimal drainage secondary to use of systemic antineoplastic agents (16). They used the data of patients who used systemic antineoplastic agent as the control group and who had signs of irritation but no epiphora. In the epiphora group, while MGL was found to be 80 ± 17% in the lower lid and 43 ± 16% in the upper lid, these values were 23 ± 13% and 17 ± 7% in the control group, respectively. It was found that MGL was statistically significant in the secondary NLDO group compared to the control group. The lipid layer thickness was 28 ± 10 nm in the epiphora group and 72 ± 23 nm in the control group, and the difference was statistically significant. In this study, the authors defined the cause of MGL in the group with secondary NLDO as obstructive meibomian gland dysfunction (MGD) caused by systemic antineoplastics causing obstruction in the MG channels (16). In this study, in which patients with secondary NLDO were investigated, even though both the epiphora group and the control group has had a history of antineoplastic drug use, the presence of a significant increase in MGL in the eyes with epiphora suggests that epiphora has contributed to this loss. In another study, MGL before silicone tube intubation in patients with partial NLDO was not statistically significant after silicone intubation. In that study, interferometry was used for the MGL measurement, patients without complete obstruction were included in the study and only silicone tube intubation was performed surgically (10). In our study, on the other hand, PANDO patients with complete obstruction were included and patients with partial NLDO were excluded. Even though the number of patients with silicone tube intubation in our study comprised 3/4 of all the patients, we believe that the inclusion of patients only with complete obstruction was the reason for obtaining different results from other studies. In our study, we did not compare the two groups statistically since the number of patients without silicone tube was low. Another reason for our results may be the use of non-contact infrared meibography for MGL measurement in our study. Recent studies have shown that different devices that measure MGL generate different results and are not suitable to be used interchangeably (17,18). Our patients had no history of antineoplastic use. However, our findings were similar to those of Eom et al. and they improved after the DCR operation. It was also shown in previous studies that there was a compensation mechanism between the ocular surface, tears and MG (19-21). In a multi-centered study, Arita et al. showed that tear secretion increased in patients with MGD to stabilize the tear film layer and compensate for loss of meibum (19). It was found that in patients with MGD, while total MGL grade in the upper and lower lids was 4.1 ± 1.3, the Schirmer score 12.5 ± 7.6 mm and the TBUT 3.5 ± 2.1 sec, the MGL score in the control group was 1.1 ± 0.8, Schirmer 10.3 ± 3.0 mm, and TBUT 6.0 ± 1.7 sec. The authors suggest that the high Schirmer scores in the MGD patients are due to the compensatory tear secretion (19). The fact that Stearoyl-CoA desaturase was an important enzyme for the healthy functioning of MG proven in animal studies (21). In another mice study in which MGD was developed through the Stearoyl-CoA desaturase enzyme deficiency model, it was shown that the amount of tear and mucin increased compensatorily (20). In a study, it was found that the number of ocular surface colonization on the healthy side was higher in patients with unilateral epiphora compared to the control group, but it was observed that flora normalized within 4 weeks after the DCR on the epiphora side (22). In our study, it was found that the effects of DCR operation were bilateral. We found that the loss of the meibomian glands was in both the side with epiphora and the healthy side in patients with PANDO-related epiphora, and the Schirmer scores were low on the healthy side. In patients with epiphora after external DCR, MGL decreased on both sides, TBUT increased on both sides, and Schirmer score increased on the healthy side. We thought that

flora change in healthy eyes was due to the decrease in the release of antibacterial substances in the tears as a result of decreased tear secretion and this was consistent with our findings. The reduction in the tear gland also explains why we have found the Schirmer score low in the healthy eyes. Meibomian glands are sebaceous glands and produce holocrine secretions. However, unlike other glands in the body, MG also has neural stimulation in addition to the hormonal stimulation (23,24). There is a dense network of nerve fibers around the acini of the tubuloacinar gland and the ductal system (22). Previous studies showed that different neurotransmitter activities occurred at the nerve endings (25,26). This shows that the autonomic system, mainly the parasympathetic system, is involved in the neural stimulation in the MB. Similar to the lacrimal gland, parasympathetic stimuli are transmitted through the pterygopalatine ganglion and sympathetic stimuli are transmitted through the superior cervical plexus and sensory conductions of the trigeminal ganglion. They also contain receptors for various hormones, including the sex hormones (27,28). This complex innervation pattern ensures that all contents of the tear film with different contents are produced in optimum composition under varying conditions (29,30). In the light of this information, we think that MG loss increased in the epiphora patients compansatorily and the reason for this bilateral loss was the bilateral reduction of neural and humoral stimuli after the feedback mechanisms from one eye.

The main limitations of this study are the retrospective nature of the study and the limited number of patients and follow-up periods. Other limitations are that tear osmolarity and lipid layer thickness measurement and blink measurements could not have been performed because they are not among our clinical facilities. The strengths of our study, on the other hand, are the comparison of the eye with the epiphora with the healthy eye and the measurements after surgery.

Acknowledgement

The thesis of Dr Kübra Tinç, MD was taken as a source for this manuscript. Authors do not have any conflict of interest. Author do not have any financial interest. There is no funding source for this manuscript.

REFERENCES

1. Nuhoglu F, Ozdemir FE, Buyrukcu AT, Eltutar K. Lacrimal Scintigraphy and Dacryocystography in Patients with Epiphora. JAREM 2012;2:68-70.

2. Mainville N, Jordan DR. Etiology of tearing: a retrospective analysis of referrals to a tertiary care oculoplastics practice. Ophthalmic Plast Reconstr Surg. 2011 May-Jun;27(3):155-157.

3. Pflugfelder SC, Liu Z, Monroy D, Li DQ, Carvajal ME, Price-Schiavi SA, Idris N, Solomon A, Perez A, Carraway KL. Detection of sialomucin complex (MUC4) in human ocular surface epithelium and tear fluid. Invest Ophthalmol Vis Sci. 2000 May;41(6):1316-1326.

4. Lang F, Busch GL, Ritter M, Völkl H, Waldegger S, Gulbins E, Häussinger D. Functional significance of cell volume regulatory mechanisms. Physiol Rev. 1998 Jan;78(1):247-306.

5. Ngezahayo A, Kolb HA. Gap junctional permeability is affected by cell volume changes and modulates volume regulation. FEBS Lett. 1990 Dec 10;276(1-2):6-8.

6. Sachs F. Mechanical transduction by membrane ion channels: a mini review. Mol Cell Biochem. 1991 May 29-Jun 12;104(1-2):57-60.

7. Saleh GM, Hussain B, Woodruff SA, Sharma A, Litwin AS. Tear film osmolarity in epiphora. Ophthalmic Plast Reconstr Surg. 2012 Sep-Oct;28(5):338-340.

8. Yuksel N, Akcay E, Ayan B, Duru N. Tear-Film Osmolarity Changes Following Dacryocystorhinostomy in Primary Acquired Nasolacrimal Duct Obstruction. Curr Eye Res. 2017 Mar;42(3):348-350.

9. Kubo M, Sakuraba T, Arai Y, Nakazawa M. Tear lipid layer interference changes after dacryocystorhinostomy. Jpn J Ophthalmol. 2001 Nov-Dec;45(6):653-656.

10. Lee SM, Chung SJ, Lew H. Evaluation of Tear Film Lipid Layer Thickness Measurements Obtained Using an Ocular Surface Interferometer in Nasolacrimal Duct Obstruction Patients. Korean J Ophthalmol. 2018 Dec;32(6):445-450.

11. Zengin N. The effect of dacryocystorhinostomy on tear film flow and stability in patients with chronic dacryocystitis. Acta Ophthalmol (Copenh). 1993 Oct;71(5):714-716.

12. Yuksel N, Mutlu M, Kilicarslan A, Akcay E. Conjunctival cytologic features in patients with unilateral primary acquired nasolacrimal duct obstruction. Int Ophthalmol. 2018 Feb;38(1):323-326.

13. Eshraghi B, Masoomian B, Izadi A, Abedinifar Z, Falavarjani KG. Conjunctival bacterial flora in nasolacrimal duct obstruction and its changes after successful dacryocystorhinostomy surgery. Ophthalmic Plast Reconstr Surg. 2014 Jan-Feb;30(1):44-46.

14. Fayers T, Laverde T, Tay E, Olver JM. Lacrimal surgery success after external dacryocystorhinostomy: functional and anatomical results using strict outcome criteria. Ophthalmic Plast Reconstr Surg. 2009 Nov-Dec;25(6):472-475.

15. Khurana AK, Moudgil SS, Ahluwalia BK, Parmar IP. Study of tear film flow and stability in chronic dacryocystitis. Acta Ophthalmol (Copenh). 1987 Jun;65(3):300-302.

16. Eom Y, Baek S, Kim HM, Song JS. Meibomian Gland Dysfunction in Patients With Chemotherapy-Induced Lacrimal Drainage Obstruction. Cornea. 2017 May;36(5):572-577.

17. Wong S, Srinivasan S, Murphy PJ, Jones L. Comparison of meibomian gland dropout using two infrared imaging devices. Cont Lens Anterior Eye. 2019 Jun;42(3):311-317.

18. Ngo W, Srinivasan S, Schulze M, Jones L. Repeatability of grading meibomian gland dropout using two infrared systems. Optom Vis Sci. 2014 Jun;91(6):658-667.

19. Arita R, Morishige N, Koh S, Shirakawa R, Kawashima M, Sakimoto T, Suzuki T, Tsubota K. Increased Tear Fluid Production as a Compensatory Response to Meibomian Gland Loss: A Multicenter Cross-sectional Study. Ophthalmology. 2015 May;122(5):925-933.

20. Miyazaki M, Man WC, Ntambi JM. Targeted disruption of stearoyl-CoA desaturase1 gene in mice causes atrophy of sebaceous and meibomian glands and depletion of wax esters in the eyelid. J Nutr. 2001 Sep;131(9):2260-2268.

21. Inaba T, Tanaka Y, Tamaki S, Ito T, Ntambi JM, Tsubota K. Compensatory increases in tear volume and mucin levels associated with meibomian gland dysfunction caused by stearoyl-CoA desaturase-1 deficiency. Sci Rep. 2018 Feb 20;8(1):3358.

22. Eshraghi B, Alemzadeh SA, Abedinifar Z. Conjunctival bacterial flora in fellow eyes of patients with unilateral nasolacrimal duct obstruction and its changes after successful dacryocystorhinostomy surgery. J Curr Ophthalmol. 2016 Dec 3;29(1):59-62.

23. Jester JV, Nicolaides N, Smith RE. Meibomian gland studies: histologic and ultrastructural investigations. Invest Ophthalmol Vis Sci. 1981 Apr;20(4):537-547.

24. Perra MT, Serra A, Sirigu P, Turno F. Histochemical demonstration of acetylcholinesterase activity in human Meibomian glands. Eur J Histochem. 1996;40(1):39-44.

25. Luhtala J, Palkama A, Uusitalo H. Calcitonin gene-related peptide immunoreactive nerve fibers in the rat conjunctiva. Invest Ophthalmol Vis Sci. 1991 Mar;32(3):640-645.

26. Hartschuh W, Weihe E, Reinecke M. Peptidergic (neurotensin, VIP, substance P) nerve fibres in the skin. Immunohistochemical evidence of an involvement of neuropeptides in nociception, pruritus and inflammation. Br J Dermatol. 1983 Jul;109 Suppl 25:14-7.

27. Sullivan DA, Sullivan BD, Ullman MD, Rocha EM, Krenzer KL, Cermak JM, Toda I, Doane MG, Evans JE, Wickham LA. Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci. 2000 Nov;41(12):3732-3742.

28. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol Scand. 2000 Apr;78(2):146-153.

29. Stern ME, Gao J, Siemasko KF, Beuerman RW, Pflugfelder SC. The role of the lacrimal functional unit in the pathophysiology of dry eye. Exp Eye Res. 2004 Mar;78(3):409-416.

30. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC. The pathology of dry eye: the interaction between the ocular surface and lacrimal glands. Cornea. 1998 Nov;17(6):584-589.