Original Article

The Effect of Conjunctiva-Müller Muscle Resection on Tear Oxidative Stress Levels in Patients with Blepharoptosis

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Abstract

Objectives: To examine changes in tear oxidative stress levels and tear film functions in patients with blepharoptosis and dermatochalasis following conjunctiva-Müller muscle resection (CMMR) and blepharoplasty surgeries.

Materials and Methods: This prospective study included 32 healthy controls and 62 patients with blepharoptosis or dermatochalasis. CMMR surgery was performed in 20 eyes and upper blepharoplasty was performed in 42 eyes. Tear oxidative stress markers (8-hydroxy-2'-deoxyguanosine [8-OHdG] and 4-hydroxy-2-nonenal [4-HNE]) were quantified by enzyme-linked immunosorbent assay and tear film functions were evaluated preoperatively and at 1 and 6 months postoperatively. The same assessments were performed in the control group at the same time points.

Results: Preoperative tear 8-OHdG and 4-HNE levels were lower in healthy controls (52.8±13.5 ng/mL and 27.8±6.4 ng/mL, respectively) compared to patients with dermatochalasis (86.1±37.2 ng/mL and 29.8±11.1 ng/mL, respectively) and blepharoptosis (90.4±39.3 ng/mL and 43.1±4.2 ng/mL, respectively) ($p<0.001$). 8-OHdG levels were increased at 1 month after CMMR, while both markers were decreased 1 month postoperatively in the blepharoplasty group ($p=0.034$). Schirmer 1 and OSDI scores did not change throughout the visits in both patient groups, but a temporary decrease in tear break-up time (TBUT) was observed after CMMR ($p=0.017$).

Conclusion: Dermatochalasis and blepharoptosis were associated with higher tear oxidative stress levels. CMMR surgery caused a temporary decrease in TBUT scores and an increase in oxidative stress in the first postoperative month.

Keywords: Blepharoptosis, blepharoplasty, dermatochalasis, oxidative stress, tear film

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Introduction

Dermatochalasis is the loss of elasticity in the eyelid skin and the formation of excess skin folds due to aging.[1] Blepharoptosis is an abnormally low positioning of the upper eyelid due to various etiologies.[2]

Conjunctiva-Müller muscle resection (CMMR) is a surgery performed for acquired moderate ptosis that responds positively to the phenylephrine test, and it works by strengthening the Müller muscle.[3,4,5,6,7] Upper blepharoplasty is a surgery performed to treat dermatochalasis associated with age-related loss of skin elasticity in the upper eyelid and the development of excessive skin folds.[1]

8-hydroxy-2'-deoxyguanosine (8-OHdG) and 4-hydroxy-2-nonenal (4-HNE) are byproducts of DNA oxidation and lipid peroxidation, respectively, and are used as biomarkers to evaluate oxidative damage to the ocular surface.[8,9,10]

A study in the literature found that dermatochalasis causes dry eye related to meibomian gland dysfunction.[11] Oxidative stress is one of the factors involved in the dry eye mechanism.[12] The relationship between tear oxidative stress values and tear film function has been examined in previous studies.[10,12,13,14] The effects of CMMR and blepharoplasty surgeries on the tear film have also been examined previously.[7,15,16,17,18,19,20,21,22,23,24,25,26] Our study examines tear film functions and levels of oxidative stress in the tear film in patients with blepharoptosis and dermatochalasis and the effects of CMMR and blepharoplasty surgeries on these levels.

Materials and Methods

Participants

This prospective study included 20 patients with blepharoptosis who underwent CMMR surgery and 42 patients with dermatochalasis who underwent blepharoplasty in the Oculoplastic Surgery Clinic of the İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine from May 2018 to March 2020. The control group consisted of 32 healthy individuals matched for age and gender. The İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee approved the study (approval number: 83045809-604.01.02, date: 07.08.2018). All patients and controls provided written informed consent.

The operated eye in unilateral surgeries and one random eye in bilateral surgeries were included.

The blepharoplasty group comprised individuals with dermatochalasis but with a margin reflex distance-1 (MRD-1) of 3 mm or greater. The CMMR group consisted of patients with MRD-1 less than 3 mm, levator function greater than 10 mm, and a positive 2.5% phenylephrine test. For this test, MRD-1 was measured preoperatively, before and 5 minutes after instilling 2.5% phenylephrine into the superior fornix. A change in MRD-1 greater than 1.5 mm was accepted as a positive result. The control group included healthy participants who did not meet any of the exclusion criteria and were similar in age and gender distribution to both of the two patient groups. The exclusion criteria for all groups were as follows: (1) having dry eye, (2) smoking and alcohol consumption, (3) a history of ocular or systemic disease and topical or systemic medication that may lead to dry eye, (4) contact lens use, and (5) any eye surgery or trauma.

Surgical Interventions

All surgeries were performed by one of the authors (C.A.).

Blepharoplasty

Marking was done with dye according to the "skin pinch" technique. The skin incisions were made and the excrescent skin tissue was removed, preserving the preseptal orbicularis muscle. The eyelid skin was sutured using 6/0 propylene.

CMMR

A 4-0 silk suture was passed along the upper eyelid edge to provide traction. A retractor was utilized to flip the upper eyelid inside out to expose the conjunctiva and upper portion of the upper tarsal plate. The distance planned to be resected was measured. The retractor was displaced. The Müller muscle and the conjunctiva were clamped simultaneously. Continuous suturing was performed from the lateral side to the medial side using 6-0 propylene. The Müller muscle and conjunctiva were excised at the same time. The suture was tied on the eyelid skin with a few throws.

Visit Schedule

The examination done before the surgery was regarded as day 0. Follow-up evaluations were performed at 1 and 6 months after surgery.

Clinical Assessments

Tear specimens were collected from the participants at each visit to quantify tear 8-OHdG and 4-HNE values. Schirmer 1 test was performed without using anesthetic drops. Schirmer tear test strips (35x5 mm; Liposic-Schirmer-Test-Streifen; Dr. Mann Pharma, Berlin, Germany) were placed in the outer third of the inferior fornix and the wetted distance was recorded after 5 minutes. For the tear break-up time (TBUT) test, 5 µL of unpreserved 2% sodium fluorescein was dropped into the inferior fornix. The biomicroscopic examination was performed under a cobalt blue filter. The seconds from the last blink to the occurrence of the first break in the dye were recorded. The influence of dry eye complaints on vision was evaluated subjectively using the Ocular Surface Disease Index (OSDI) questionnaire.

The same interventions were performed at the same time points in the control group.

Tear Collection and Quantification of 8-OHdG and 4-HNE

Tear specimens were collected according to the previously described eye wash method.[27] With the help of an Eppendorf pipette, 60 µL of unpreserved saline was dropped into the lower cul-de-sac with special care not to irritate the ocular surface. Then the subjects were told to close their eyes without squeezing and to rotate them twice. Samples were collected by microcapillary tube within 1 minute at the latest to prevent reflex tearing. Tear specimens were placed in 1-mL Eppendorf microtubes and stored at -80 °C until analysis. Levels of 8-OHdG and 4-HNE were quantified using commercially available 8-OHdG and 4-HNE enzyme-linked absorbent assays (ELISA; Bioassay Technology Laboratory) and following the manufacturer's recommendations. The concentration of the markers was quantified by comparing their absorption with known standard curves. The lowest measurable levels of 8-OHdG and 4-HNE were 0.5 ng/mL and 10 ng/L, respectively.

Statistical Analysis

The findings were analyzed using SPSS version 20.0 (IBM Corp., Armonk, NY, USA). The sample size was determined based on the following parameters using the G-Power software: type of analysis: ANOVA, significance level (α): 0.05, desired statistical power: 0.80, number of groups: 3, effect type: f, and effect size: 0.4. After conducting the power analysis, it was found that a sample size of 51 would yield a statistical test power of 0.803. More than 17 patients were included in each group to meet the desired level of power. Values were shown as mean ± standard deviation. The Shapiro-Wilk test was utilized to analyze the distribution of data. The chi-square test was utilized to compare frequencies. Mann-Whitney U test was utilized to compare the values of two independent groups. Friedman test was utilized in the analysis of repeated measures. For post-hoc comparison of groups with significant differences, the p value was determined by performing the Wilcoxon test with Bonferroni correction. Comparisons of three independent groups were made using Kruskal-Wallis test followed by post-hoc Mann-Whitney U test with Bonferroni correction. Spearman correlation coefficients were determined to analyze correlations between variables. P values <0.05 were considered statistically significant.

Results

Characteristics of the Participants

Table 1 presents the demographic characteristics of the patients and controls included in the study. All of the groups were homogenous in terms of age (p=0.52) and gender (p=0.62).

The mean MRD-1 was significantly increased at 1 month after CMMR (1.6±0.5 mm vs. 3.5±0.7 mm, p<0.001) and remained high at 6 months (3.4±0.7 mm, p=1.0).

Tear Function Test Results and Changes Between Visits

Table 2 shows the differences in Schirmer, TBUT, and OSDI scores between visits in the three groups and Table 3 shows the results of post-hoc pairwise comparisons. In the preoperative period, there was no difference among the three groups in terms of Schirmer test and TBUT scores (p=0.874 and p=0.535, respectively), but OSDI scores were lower in the control group compared to the blepharoplasty group (p=0.033).

In the analysis of repeated measures, the three groups showed no significant difference at postoperative 1 and 6 months compared to baseline values in terms of Schirmer test (p=0.779, p=0.248, and p=0.08, respectively) or OSDI scores (p=0.502, p=0.573, and p=0.793, respectively). While TBUT scores did not change in the control and blepharoplasty groups, in the CMMR group they decreased between the baseline visit and 1 month (p=0.017) and increased again between 1 and 6 months (p=0.001).

Changes in Tear Oxidative Stress Levels Between Visits

The tear 8-OHdG and 4-HNE values measured preoperatively in the three groups are presented in Figure 1 and changes in these values between visits are presented in Figure 2 and Figure 3, respectively.

Table 1. Demographic characteristics of controls and patients

		Controls	Blepharoplasty	Conjunctiva-Müller muscle resection
Age (years)		53.0±6.9	55.0±7.2	52.4±15.4
Range		33-64	40-71	24-76
Gender	**Female**	19 (59.3%)	23 (54.7%)	14 (70.0%)
	Male	13 (40.7%)	19 (45.3%)	6 (30.0%)
Total		32	42	20

Table 2. Comparison of the three groups using Kruskal-Wallis test

		Control (n=32)			Blepharoplasty (n=42)			CMMR (n=20)			p
		Mean	**SD**	**Range**	**Mean**	**SD**	**Range**	**Mean**	**SD**	**Range**	
Age		53.0	6.9	33-64	55.0	7.2	40-71	52.4	15.4	24-76	0.628
Schirmer (mm)	**Baseline**	14.6	4.5	7-23	14.3	5.1	7-27	14.4	4.4	7-22	0.874
	1 month	15.0	4.5	8-24	14.0	4.1	8-26	12.2	4.4	7-24	0.057
	6 months	14.9	4.6	8-23	14.7	5.4	8-31	14.0	4.5	8-24	0.807
TBUT (s)	**Baseline**	11.7	2.3	8-17	11.5	2.4	8-16	12.0	2.5	6-16	0.535
	1 month	11.4	2.1	9-17	11.0	1.8	8-15	9.3	2.2	6-14	0.006*
	6 months	11.5	2.2	9-17	10.9	2.0	8-16	12.2	2.7	7-17	0.085
OSDI	**Baseline**	3.6	5.7	0-19	11.2	15.2	0-60	9.7	15.1	0-50	0.042*
	1 month	4.2	5.1	0-16	8.9	10.1	0-42	10.7	10.5	0-33	0.054
	6 months	4.2	5.1	0-16	9.7	13.4	0-56	9.9	12.1	0-33	0.201
8-OHdG (ng/mL)	**Baseline**	52.8	13.5	31-84	86.1	37.2	22-156	90.4	39.3	16-163	<0.001*
	1 month	50.7	28.9	14-123	54.6	30.5	13-217	118.2	48.5	17-200	<0.001*
	6 months	56.3	29.5	14-115	66.4	29.4	13-135	95.5	36.1	20-191	<0.001*
4-HNE (ng/mL)	**Baseline**	27.8	6.4	18-48	29.8	11.1	13-65	43.1	4.2	33-52	<0.001*
	1 month	29.2	7.7	15-48	15.2	4.5	10-29	45.2	7.9	36-73	<0.001*
	6 months	29.7	6.2	18-41	15.0	4.0	10-24	43.9	6.2	36-68	<0.001*

*Statistically significant (p<0.05), CMMR: Conjunctiva-Müller muscle resection, SD: Standard deviation, TBUT: Tear break-up time, OSDI: Ocular Surface Disease Index, 8-OHdG: 8-hydroxy-2'-deoxyguanosine, 4-HNE: 4-hydroxy-2-nonenal

In the preoperative period, the mean tear 8-OHdG level was higher in the CMMR (90.4±39.3 ng/mL) and blepharoplasty groups (86.1±37.2 ng/mL) compared to the control group (52.8±13.5 ng/mL) ($p<0.001$), with no statistical difference between the CMMR and blepharoplasty groups ($p=1.0$). At the 1-month visit, 8-OHdG levels were significantly higher in the CMMR group (118.2±48.5 ng/mL) when compared to the control (50.7±28.9 ng/mL) and blepharoplasty groups (54.6±30.5 ng/mL) ($p<0.001$ for both), with no difference observed between the control and blepharoplasty groups ($p=1.0$). Similarly, at the 6-month visit, tear 8-OHdG levels were higher in the CMMR group compared to the control and blepharoplasty groups ($p<0.001$ and $p=0.003$, respectively). While no significant changes in tear 8-OHdG levels were observed between different visits in the control group ($p=0.064$), there was a significant decrease in the blepharoplasty group ($p<0.001$) and a significant increase in the CMMR group ($p=0.034$) between the baseline and 1-month visits. No significant change was found in terms of 8-OHdG levels between the baseline and 6-month visits or between the 1- and 6-month visits in the CMMR group.

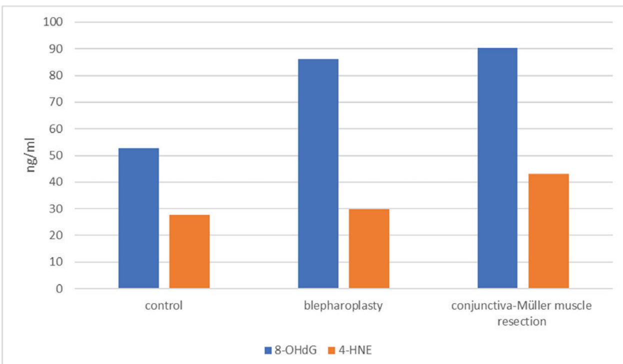

Figure 1. Baseline mean tear 8-hydroxy-2'-deoxyguanosine (8-OHdG) and 4-hydroxy-2-nonenal (4-HNE) levels in the three groups

In the preoperative period, tear 4-HNE levels were lower in the control (27.8±6.4 ng/mL) and blepharoplasty groups (29.8±11.4 ng/mL) compared to the CMMR group (43.1±4.2 ng/mL) ($p<0.001$ for both). At the 1-month visit, tear 4-HNE levels were higher in the CMMR group (45.2±7.9 ng/mL) compared to the control group (29.2±7.7 ng/mL) and lower in the blepharoplasty group (15.3±4.5 ng/mL) compared to the control group ($p<0.001$ for both). Similarly, tear 4-HNE levels at 6 months were also higher in the CMMR group and lower in the blepharoplasty group when compared to the control group ($p<0.001$ for both). While no significant change in 4-HNE levels was observed in the control and CMMR groups between visits ($p=0.061$ and $p=0.58$, respectively), the blepharoplasty

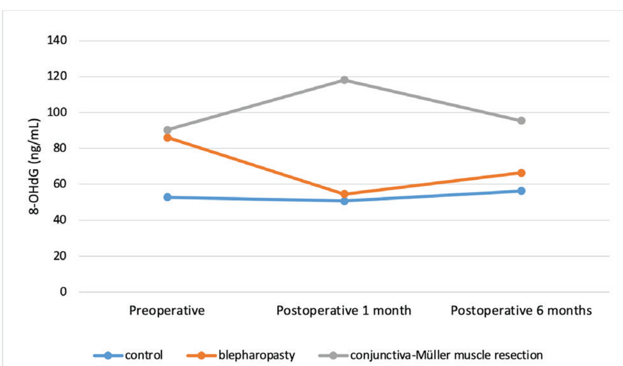

Figure 2. Changes in mean tear 8-hydroxy-2'-deoxyguanosine (8-OHdG) concentration between consecutive visits in the three groups

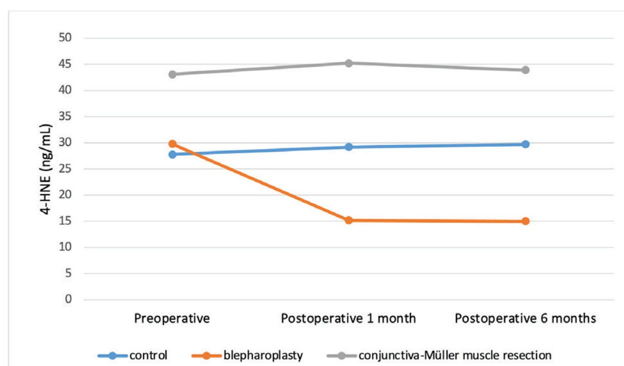

Figure 3. Changes in mean tear 4-hydroxy-2-nonenal (4-HNE) concentration between consecutive visits in the three groups

Table 3. The results (p values) of pairwise comparisons of the study groups using the Mann-Whitney U test with Bonferroni correction

	Control vs. blepharoplasty group	Control vs. CMMR group	Blepharoplasty vs. CMMR group
TBUT - 1 month	1.0	0.009*	0.015*
OSDI - baseline	0.033*	0.504	1.0
8-OHdG - baseline	<0.001*	<0.001*	1.0
8-OHdG - 1 month	1.0	<0.001*	<0.001*
8-OHdG - 6 months	0.477	<0.001*	0.003*
4-HNE - baseline	1.0	<0.001*	<0.001*
4-HNE - 1 month	<0.001*	<0.001*	<0.001*
4-HNE - 6 months	<0.001*	<0.001*	<0.001*

*Statistically significant ($p<0.05$), CMMR: Conjunctiva-Müller muscle resection, TBUT: Tear break-up time, OSDI: Ocular Surface Disease Index, 8-OHdG: 8-hydroxy-2'-deoxyguanosine, 4-HNE: 4-hydroxy-2-nonenal group showed a significant decrease between the baseline and 1-month visits and between the baseline and 6-month visits ($p<0.001$ for both).

Correlation of Tear Oxidative Stress Levels to Tear Function Parameters

In the correlation analysis performed with all patients at the baseline visit, tear 8-OHdG and 4-HNE values were found to be positively correlated ($p=0.001$, $r=0.338$). Although 8-OHdG did not show a correlation with any tear parameter, 4-HNE showed a positive correlation only with Schirmer test results ($p=0.012$, $r=0.258$).

At postoperative 1 month, tear 8-OHdG and 4-HNE values were found to be positively correlated ($p<0.001$; $r=0.384$). 8-OHdG values were negatively correlated with Schirmer test ($p=0.039$; $r=-0.214$) and TBUT scores ($p=0.017$; $r=-0.246$) and positively correlated with OSDI score ($p=0.048$; $r=0.205$). 4-HNE values were found to be negatively correlated with TBUT scores ($p=0.006$; $r=-0.281$).

At postoperative 6 months, neither oxidative stress marker was correlated with any tear parameter.

Discussion

Although blepharoptosis and dermatochalasis sometimes occur together, patients with dermatochalasis without accompanying blepharoptosis were included in our study. Even though the influence of CMMR and blepharoplasty surgeries on tear function has been researched in the past,[7,15,16,17,18,19,20,21,22,23,24,25,26] the influence of these surgeries on tear oxidative stress levels has not been investigated. Our study reveals important findings about the role of these surgeries on tear oxidative stress markers and tear film function.

We observed that tear 8-OHdG values were higher in patients with dermatochalasis and both tear 8-OHdG and 4-HNE levels were higher in patients with blepharoptosis compared to controls. This may be due to impaired blinking dynamics. It has been previously found that blinking functions are impaired in patients with blepharoptosis.[28] Similarly, blinking dynamics may be impaired in patients with dermatochalasis due to increased mechanical weight on the eyelid.[29] The effective blinking which ensures the release of lipids from the meibomian glands is the principal factor in the generation of the lipid layer of the tear film.[30] In cases of impaired blinking, the lipid layer thickness of the tear film becomes thinner, causing the aqueous layer of the tear film to evaporate and leading to instability of the tear film.[31,32] Hollander et al.[29] hypothesized that excess tissue in the upper eyelid may cause mechanical eyelid dysfunction and increase dry eye complaints. The high OSDI score in dermatochalasis patients in the preoperative period may be due to this mechanical weight on the eyelid. In addition, it has also been reported that dermatochalasis causes dry eyes due to meibomian gland dysfunction.[10]

The higher tear 8-OHdG levels and lower TBUT scores 1 month after CMMR might be explained by several factors. First, inflammation is known to increase reactive oxygen products.[33] The increase of 8-OHdG and decrease of TBUT scores may have occurred due to transient inflammation on the ocular surface after CMMR, probably associated with conjunctival surgical manipulations and suturing. A previous study showed that levels of 4-HNE and malondialdehyde in the tear film were higher in patients with dry eye and were negatively correlated with Schirmer and TBUT scores.[14] Similarly, we observed a negative correlation between 8-OHdG and TBUT in our study. Therefore, we speculate that oxidative stress may cause temporary tear film dysfunction after CMMR surgery. Zloto et al.[17] also reported significant decreases in Schirmer and TBUT test results and significant increases in OSDI scores and corneal staining 90 days after CMMR. In terms of the possible causes of these findings, it has been suggested that the loss of accessory lacrimal glands might lead to aqueous tear deficiency, increased MRD-1 might result in increased tear evaporation, and the palpebral conjunctival scar might lead to increased dry eye complaints. Actually, significant loss of accessory glands and goblet cells is not expected after CMMR because the glands of Wolfring are located at the superior edge of the tarsus, the glands of Krause are located in the fornices, and goblet cells are located mostly in the bulbar conjunctiva and fornices.[15,18] In this study, observing no change in Schirmer test results after CMMR supports the hypothesis that CMMR might not cause a reduction in tear production. However, some reports have claimed the opposite.[18,19] The increased oxidative stress might also be explained by greater exposure to ultraviolet (UV) radiation due to an increase in MRD-1. It has previously been found that photooxidative reactions associated with UV light cause dry eye, and in a study conducted with rabbits, oxidation increased in corneal epithelial cells due to UV light.[34] In our previous study, we found that 8-OHdG in the tear film increased in patients whose blepharoptosis was corrected by an anterior approach.[25] The increase in tear 8-OHdG levels despite less conjunctival manipulation and thus less ocular surface inflammation can be explained by the increased UV exposure due to an increase in MRD-1. Another explanation for the increase in tear oxidative stress markers that were seen after blepharoptosis surgery performed via the anterior or posterior approach is the increase in evaporation due to the increase in MRD-1.[23]

In the blepharoplasty group, the decrease in 8-OHdG and 4-HNE levels in the tears at 1 month after surgery may be related to a possible decrease in the mechanical weight on the eyelid and the resulting reduction in the muscle strength needed to open the eyelid. However, this theory has to be verified by further studies with electrophysiological tests. We observed no change in Schirmer, TBUT, or OSDI scores between visits in this group. The lack of change in MRD-1 and the preservation of the orbicularis muscle may have ensured the stability of tear function parameters. Floegel et al.[35] previously found that there were no significant changes in Schirmer and TBUT tests 3 months after blepharoplasty but there were improvements in subjective symptoms and a decrease in the inflammatory reaction. Similar to our findings, previous studies revealed no significant change in Schirmer, TBUT, and OSDI scores 90 days after surgery or in TBUT scores 6 weeks after blepharoplasty.[17,21,22] Another study also demonstrated no difference in tear volume 6 months after blepharoplasty.[23] Prior use of artificial tears, hypothyroidism, and diabetes are risk factors that may cause dry eyes after blepharoplasty.[36,37] Therefore, such patients were not included in our study. Some authors have suggested that excising the eyelid skin conservatively and not excising the orbicularis muscle reduces the deterioration of tear function after blepharoplasty.[24,33,34,38,39,40,41] However, other authors claim that resection of the preseptal orbicularis muscle does not impair blinking function.[42,43] In this study, the orbicularis muscle was preserved in blepharoplasty surgery and we observed no tear film dysfunction.

Study Limitations

One of the limitations of our study is that tear film functions were examined only with Schirmer, TBUT, and OSDI tests. The assessment of dry eye is complex; a single test is insufficient and the correlation between different tests is limited.[44] Objective and subjective assessments of dry eye are reported to show weak correlation,[45] and this discrepancy may be affected by various factors such as age, personal perceived health, and mental health.[46] Although we used more than one test to increase specificity and sensitivity in our study, the use of more additional tests such as non-invasive TBUT, tear osmolarity measurement, meniscal height measurement, meibography, and interferometry will be more useful in evaluating the results and understanding the mechanism. The evaluation of oxidative stress only with 8-OHdG and 4-HNE is also a limitation of this study. Further studies evaluating changes in other oxidative stress markers would offer a deeper understanding of the influence of blepharoplasty and CMMR on oxidative stress in the tear film.

Conclusion

In conclusion, we found that oxidative stress markers in the tear film of patients with dermatochalasis or blepharoptosis were higher than in healthy controls. We demonstrated that blepharoplasty and CMMR did not cause any differences in Schirmer and OSDI scores at postoperative 1 and 6 months, but CMMR caused a temporary decrease of TBUT and an increase in tear oxidative stress levels. Furthermore, at the postoperative 1-month visit, tear oxidative stress markers were negatively correlated with Schirmer and TBUT scores and positively correlated with OSDI. The findings suggest that dry eye after CMMR surgery may be caused by oxidative stress. Additional studies are needed to better reveal the relationship between tear oxidative stress status and dry eye syndrome.

Ethics

Ethics Committee Approval: İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine Ethics Committee approved the study (approval number: 83045809-604.01.02, date: 07.08.2018).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: C.A., Concept: S.S., C.A., B.M., Ö.B.E., Design: S.S., C.A., B.M., Ö.B.E., Data Collection or Processing: S.S., C.A., B.M., Ö.B.E., Analysis or Interpretation: S.S., C.A., B.M., Ö.B.E., Literature Search: S.S., C.A., Ö.B.E., Writing: S.S., C.A., B.M., Ö.B.E.

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

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